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14. ABSTRACT

The purpose of the research is to characterize patterns of care, utilization, and outcomes of treatments for localized prostate cancer such as surgery, external beam radiation, and brachytherapy. In particular, the research characterizes the patterns of care, utilization and outcomes of minimally invasive radical prostatectomy (MIRP) versus open retropubic radical prostatectomy (RRP). MIRP utilization increased from 9% to 43% from 2003 to 2007. Lengths of stay, transfusions, and stricture rates are lower for MIRP vs. RRP. However, erectile dysfunction and incontinence were more frequently diagnosed postoperatively. Additionally positive surgical margins were similar by surgical approach. While higher RRP surgeon volume was associated with fewer complications, this was not observed for MIRP surgeon volume and outcomes. In addition, MIRP was $293 more costly than RRP. Finally, pelvic lymph node dissection was performed less frequently with MIRP vs. RRP.

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INTRODUCTION

The objective of this 4-year study is to characterize the use and outcomes of competing therapies for treating localized prostate cancer. Moreover, this project will evaluate utilization trends, patterns of care, costs and outcomes of minimally invasive radical prostatectomy (MIRP), i.e. laparoscopic radical prostatectomy (LRP) and robotic assisted laparoscopic radical prostatectomy (RALP), compared to open radical prostatectomy (ORP), external beam radiotherapy (XRT), and brachytherapy (BRCY). The findings of this project will guide men with prostate cancer weighing treatment options, employers and policy makers implementing healthcare coverage, and providers seeking to deliver cost-effective, high quality care. This project will be the first national, population-based study to evaluate patterns of care and outcomes for treatments of localized prostate cancer in a wide range of health care settings. In particular, we assessed the impact of LRP, RALP, XRT, and BRCY provider volume on complications, and cancer control, and health care costs. Although this was originally a 4-year study, the principal investigator moved from Brigham and Women's Hospital to UCLA, and therefore the Department of Defense granted a 1-year extension.

BODY

Original Statement of Work tasks are italicized below, followed by the disposition of each task.

Didactics of Training Program

a. *Summer Program in Clinical Effectiveness (7 weeks / summer) in 2008 and 2009.* Completed
b. *Coursework at University of Minnesota to be taken in 2008: (1) CMS 102, Conducting Research with Medicaid Claims Data; (2) CMS 302, Conducting Economic Research using Medicare Data.* completed CMS 102. CMS 302 has not been offered recently.

Task 1: Use of 20% Medicare sample to address specific aims 1-3

I (Months 1-12)

a. *Data license user agreement and institutional contract to obtain 20% Medicare sample from CMS (1 month*). Instead of obtaining the 20% Medicare sample, we worked with the 100% Medicare sample from the Center for Medicare and Medicaid Services. In addition, we used SEER-Medicare linked data from the National Cancer Institute and the Nationwide Inpatient Sample from the Agency for Healthcare Research and Quality (AHRQ). Finally, in order to examine the use of outpatient prescription medications for analgesic use after surgery and the use of erectile dysfunction medications, such as sildenafil, we used the Marketscan Medstat database. assessed utilization and outcomes of minimally invasive versus open radical prostatectomy and published the findings in European Journal of Urology.[1] We found that during 2003 to 2007, MIRP increased from 4.9% to 44.5% of radical prostatectomies. Additionally, we showed that MIRP versus RRP subjects were younger ($p < 0.001$) and had fewer comorbidities ($p < 0.001$). Decreased MIRP genitourinary complications (6.2–4.1%; $p = 0.002$), miscellaneous surgical complications (4.7–3.7%; $p = 0.030$), transfusions (3.5–2.2%; $p = 0.005$), and postoperative cystography utilization (40.3–34.1%; $p < 0.001$) were observed over time. Conversely, overall RRP perioperative complications increased (27.4–32.0%; $p < 0.001$), including an increase in perioperative mortality (0.5–0.8%, $p = 0.009$). Late RRP complications increased, with the exception of fewer anastomotic strictures (10.2–8.8%; $p = 0.002$). In adjusted analyses, RRP versus MIRP was associated with increased 30-d mortality (odds ratio [OR]: 2.67; 95% confidence

interval [CI], 1.55–4.59; p < 0.001) and more perioperative (OR: 1.60; 95% CI, 1.45–1.76; p < 0.001) and late complications (OR: 2.52; 95% CI, 2.20–2.89; p < 0.001).

b. *Obtain and clean 20% Medicare sample (3 months).* See above.
c. *To address specific aim 3, Institutional Review Board Approval to acquire unencrypted identifying information (name and address) of a 5% sample of Medicare beneficiaries (25% of the 20% file) to mail questionnaires containing validated health related quality of life instruments. This results in a survey of approximately 6,300 men with an estimated response rate of 80% (based on similar surveys by Fowler and Barry of Medicare beneficiaries), or 5,040 respondents.* Due To budget constraints, this was not performed.
d. *Identify cohort of men undergoing open and minimally invasive radical prostatectomy, external beam radiotherapy, and brachytherapy. Eliminate men who are not enrolled in Medicare throughout the study period. (1 month)*. Completed
e. Define geographic regions consistent with U.S. Census. Completed
f. *Calculate procedure specific utilization rates over the 4-year study period.* Completed, see above.
g. *Calculate Klabunde modification of Charlson co-morbidity index for each Medicare beneficiary to classify co-morbid illness.* Completed
h. Match beneficiary zip code data to U.S. Census data to define education and income. Completed
i. *Classify subjects by age, race, co-morbid illness, geographic region, education, and income level.* Completed
j. *Perform univariate analyses to identify differences in men by treatment type.* Completed
k. *Create a longitudinal history for each beneficiary to identify post-treatment, urinary, and bowel complications, impotence, incontinence, salvage therapies.* Completed
l. *For men undergoing surgery, identify blood transfusion rates, resection of lymph nodes, lengths of stay, conversion rates from laparoscopic to open surgery.* Completed
m. *Compare outcomes of minimally invasive to open radical prostatectomy*. Completed
n. *Aggregate to the provider level to define physician and hospital volumes over the four-year study period.* Completed
o. Classify physician volume as a categorical and continuous variable and compare to outcomes of interest using Chi-square test and ANOVA. Completed
p. Identify physician age from the R file. Completed
q. *Perform adjusted analyses to identify determinants of post-treatment outcomes.* Completed

II (Months 13-24)

a. *Analysis and manuscript preparation for specific aims 1-2 using the*

20% sample. Completed using the 100% sample – see above.

b. *CMS contractor surveys Medicare beneficiaries to participate in the proposed study. Identifier file delivered from CMS contractor, containing name and address for beneficiaries who agree to participate. (6 months).* See above.

c. *Subjects are assigned a unique identifier on a secure workstation and identifying information is separated and securely stored.* See above.

III (Months 25-36)

a. *Surveys are mailed. Those not responding are mailed a second survey. (3 months).* The survey was not performed.
Data from returned surveys are entered. (6 months) A survey was not performed. Instead, to identify robotic assisted from laparoscopic radical prostatectomy, we acquired the Nationwide Inpatient Sample from the Agency for Healthcare Research and Quality (AHRQ). International Classification of Disease, 9th Edition Code 17.4x designates robotic assisted surgery. We characterized robot-assisted laparoscopic radical prostatectomy outcome by hospital volume using the Nationwide Inpatient Sample during the last quarter of 2008. Propensity scoring methods were used to assess outcomes and costs. At high volume hospitals robot-assisted laparoscopic radical prostatectomy was more likely to be done on men who were white with an income in the highest quartile and age less than 50 years than at low volume hospitals (each $p < 0.01$). Hospitals at above the 50th volume percentile were less likely to show miscellaneous medical and overall complications ($p < 0.01$). Low vs. high volume hospitals had longer mean length of stay (1.9 vs. 1.6 days) and incurred higher median costs ($12,754 vs. $8,623, each $p < 0.01$).[2]

b. Validation study of diagnosis and procedure codes for incontinence and impotence compared to urinary and sexual function from survey analysis. No survey conducted.

IV (Months 36-48).

a. Unadjusted analysis of urinary, sexual, and bowel function and cancer control obtained from surveys by provider volume and treatment type

b. Adjusted analyses controlling for patient and provider characteristics

c. Manuscript preparation

Again, a survey was not conducted

Task 2. *Use of Medstat to address specific aims 1 and 2. (Months 13-36)*

a. *Similar steps to Task 1, a through q; however, Institutional Review Board Approval (step C) is unnecessary since subject identity is encrypted, and identifying data of subjects is not available in Medstat. (12 months).* Completed
b. Analysis and manuscript preparation for specific aims 1-2 using Medstat. (12 months). We published 2 papers using Marketscan Medstat data.[3, 4] First, we evaluated outpatient prescription data after minimally

invasive, retropubic and perineal radical prostatectomy from 2003 to 2006.[3] Baseline and postoperative narcotic prescriptions were identified using the National Drug Code. Total prescribed narcotic strength in morphine sulfate equivalents, the number of prescriptions filled and costs were compared. We performed multivariate analysis adjusted for surgical approach, age, comorbidity, baseline narcotic use, health plan and geographic region. We identified 2,206 minimally invasive, 8,037 retropubic and 463 perineal radical prostatectomies with no differences in baseline narcotic prescription use. Perineal and retropubic operations were associated with greater total morphine sulfate equivalent use than the minimally invasive operation. Perineal prostatectomy was associated with more narcotic refills than minimally invasive and retropubic prostatectomy (42.3% vs. 20.2% and 28.9%, respectively, $p < 0.001$). Median narcotic costs were lower for minimally invasive than for perineal and retropubic prostatectomy. On adjusted analysis perineal radical prostatectomy, younger age, baseline narcotic use and preferred provider organization health plan were associated with greater morphine sulfate equivalents and narcotic refills while minimally invasive surgery was associated with fewer refills and lower costs but not with total morphine sulfate equivalents. There was significant geographic variation in narcotic use and costs.

Second, we identified 38,958 men who underwent definitive treatment for localized prostate cancer during 2003–2006 from the MarketScan Medstat data.[4] We compared the use of ED pharmacotherapy at baseline (up to 3 months prior) and up to 30 months following radical prostatectomy (RP) or radiotherapy (RT) for localized prostate cancer by utilizing National Drug Classification codes for phosphodiesterase-5 inhibitors (PDE5I), intracavernosal inject- able therapies (IT), urethral suppositories and vacuum erection devices (VED). In adjusted analyses, we controlled for the effect of age, comorbidity, type of treatment, health plan and use of adjuvant hormone therapy on the use of pharmacotherapies. Men undergoing RP vs. RT were younger with less co-morbid conditions. Utilization of PDE5I was up to three times greater for men undergoing RP vs. RT, 25.6% vs. 8.8%, ($P < 0.0001$) in the first post-treatment year, and usage of these agents was greatest for men undergoing minimally-invasive RP procedures. A higher percentage of men also used IT, suppositories and VED after RP vs. RT ($P < 0.001$). However, more men in the RT group received adjuvant hormonal therapy (39.53% vs. 5.25% for RP, $P < 0.01$). In adjusted analyses, men undergoing RP vs. RT were more than two times likely (OR 2.1, 95% CI 1.98, 2.26) to use PDE5I post-treatment while men on adjuvant hormonal therapy were less likely to use PDE5I (OR 0.74, 95% CI 0.70–0.79, $P < 0.0001$).

a. *Analyze and compare use of prescription medications in men treated for localized prostate cancer.* See Above

Task 3. Use of SEER-Medicare to address specific aims 1 and 2 (Months 25-48)

a. *Similar steps to Task 1, a through q; however, Institutional Review Board Approval (step C) is unnecessary since subject identity is encrypted (12 months).* Completed

b. *Analysis and manuscript preparation for specific aims 1-2 using SEER-Medicare. (12 months).* Completed. The first publication using SEER-Medicare was published in JAMA in 2009.[5] This was the first population-based comparative effectiveness of open versus minimally invasive radical prostatectomy. We identified men with prostate cancer who underwent MIRP (n = 1938) vs. RRP (n = 6899) from 2003-2007. We compared postoperative 30-day complications, anastomotic stricture 31 to 365 days postoperatively, long-term incontinence and erectile dysfunction more than 18 months postoperatively, and postoperative use of additional cancer therapies, a surrogate for cancer control. We found that among men undergoing prostatectomy, use of MIRP increased from 9.2% (95% confidence interval [CI], 8.1%-10.5%) in 2003 to 43.2% (95% CI, 39.6%-46.9%) in 2006-2007. Men undergoing MIRP vs. RRP were more likely to be recorded as Asian (6.1% vs. 3.2%), less likely to be recorded as black (6.2% vs. 7.8%) or Hispanic (5.6% vs. 7.9%), and more likely to live in areas with at least 90% high school graduation rates (50.2% vs. 41.0%) and with median incomes of at least $60 000 (35.8% vs. 21.5%) (all $P < .001$). In propensity score–adjusted analyses, MIRP vs. RRP was associated with shorter length of stay (median, 2.0 vs. 3.0 days; $P<.001$) and lower rates of blood transfusions (2.7% vs. 20.8%; $P < .001$), postoperative respiratory complications (4.3% vs. 6.6%; $P = .004$), miscellaneous surgical complications (4.3% vs. 5.6%; $P = .03$), and anastomotic stricture (5.8% vs. 14.0%; $P < .001$). However, MIRP vs. RRP was associated with an increased risk of genitourinary complications (4.7% vs. 2.1%; $P = .001$) and diagnoses of incontinence (15.9 vs. 12.2 per 100 person-years; $P = .02$) and erectile dysfunction (26.8 vs. 19.2 per 100 person-years; $P = .009$). Rates of use of additional cancer therapies did not differ by surgical procedure (8.2 vs. 6.9 per 100 person- years; $P = .35$). In conclusion, men undergoing MIRP vs. RRP experienced shorter length of stay, fewer respiratory and miscellaneous surgical complications and strictures, and similar post- operative use of additional cancer therapies but experienced more genitourinary complications, incontinence, and erectile dysfunction.

c. *Identify tumor stage and grade for each beneficiary treated for localized prostate cancer.* Completed. We also partitioned variance to discern whether tumor or demographic characteristics were associated with the choice of minimally invasive versus open radical prostatectomy.[6] We identified 11,732 men who underwent radical prostatectomy from 2003 to 2007. We assessed the contribution of

patient, surgeon and hospital characteristics to the likelihood of undergoing minimally invasive radical prostatectomy vs. radical retropubic prostatectomy using multi-level logistic regression mixed models.

We found that patient factors (36.7%) contributed most to the use of minimally invasive radical prostatectomy vs. radical retropubic prostatectomy, followed by surgeon (19.1%) and hospital (11.8%) factors. Among patient specific factors Asian race (OR 1.86, 95% CI 1.27–2.72, p = 0.001), clinically organ confined tumors (OR 2.71, 95% CI 1.60 – 4.57, p <0.001) and obtaining a second opinion from a urologist (OR 3.41, 95% CI 2.67– 4.37, p <0.001) were associated with the highest use of minimally invasive radical prostatectomy while lower income was associated with decreased use of minimally invasive radical prostatectomy. Among surgeon and hospital specific factors, higher surgeon volume (OR 1.022, 95% CI 1.015–1.028, p <0.001), surgeon age younger than 50 years (OR 2.68, 95% CI 1.69 – 4.24, p <0.001) and greater hospital bed size (OR 1.001, 95% CI 1.001– 1.002, p <0.001) were associated with increased use of minimally invasive radical prostatectomy, while solo or 2 urologist practices were associated with decreased use of minimally invasive radical prostatectomy (OR 0.48, 95% CI 0.27– 0.86, p = 0.013).

In summary, the adoption of minimally invasive radical prostatectomy vs. radical retropubic prostatectomy is multifactorial, and associated with specific patient, surgeon and hospital related factors. Obtaining a second opinion from another urologist was the strongest factor associated with opting for minimally invasive radical prostatectomy.

d. *Define active surveillance cohort as a beneficiary who does not receive definitive or hormonal therapy within 12 months of prostate needle cancer diagnosis.* We are preparing to submit a manuscript regarding factors associated with the choice of active surveillance versus definitive therapies. The abstract is below, and the manuscript is appended.

Overtreatment of indolent prostate cancer is associated with significant detriments of quality of life and increased health care expenditures. Without a better understanding of the mutable agents and predictors of treatment types, diffusion of widespread adoption of active surveillance will be slow. Therefore we sought to characterize the determinants and variance of treatments for men diagnosed with prostate cancer.

We used Surveillance, Epidemiology, and End Results (SEER)–

Medicare linked data to identify 510,031 men diagnosed with prostate cancer from 1991–2007 and were followed until December 31, 2009.[7] The final cohort consisted of 37,621 men. We used mixed-effects logistic regression analysis to determine the predictors aggressive treatment and utilization of active surveillance for men with prostate cancer.

We found that the most common treatment type is radiation therapy (57.9%), followed by radical prostatectomy (19.1%), and watchful waiting or active surveillance (9.6%). Moreover, patients and providers significantly integrate proxies for life expectancy (age and comorbidities) when determining radical prostatectomy, while regional variation and referral patterns influence the utility of radiation therapy. Patient demographics and tumor characteristics significantly account for 43% of patients undergoing prostatectomy, 14% of men choosing watchful waiting or active surveillance, and only 3% undergoing radiotherapy.

In conclusion**,** there is increased utilization of radiotherapy among all risk groups with limited to no correlation with proxies of life expectancy or tumor biology. Active surveillance is underutilized and a significant proportion of the variance is unexplained. Further research into qualitatively describing the contributing factors that drive decision-making recommendations for prostate cancer patients are needed.

e. Analyze utilization trends of definitive therapies and watchful waiting for localized prostate cancer. See above.

KEY RESEARCH ACCOMPLISHMENTS

- Publication or acceptance of 21 papers. Additionally, there is currently one manuscript under consideration at the Journal of Clinical Oncology and another that we've been asked to revise at the same journal. Similarly, there is a manuscript regarding the use of testosterone replacement therapy that we've been asked to revise at the Journal of Sexual Medicine. We have also submitted a fourth paper to the Journal of Urology regarding a observation study of the effect of PSA screening in elderly Americans, and a fifth manuscript, mentioned above, regarding factors associated with the use of active surveillance.
- The Physician Training Award also allowed the principal investigator to complete the Harvard Program in Clinical Effectiveness and become enriched in statistical and methodological concepts critical to conducting health services research.
- The research springing from this award also allowed the applicant to successfully compete for two challenge grants from the National Cancer Institute as part of the American Recovery and Reinvestment Act. Finally, the principal investigator applied for a DoD Prostate Cancer Population Impact Award using preliminary data developed from this grant and should learn about the outcome in spring of 2014.
- Most importantly, this award has allowed the principal investigator to transition to an independent investigator.

REPORTABLE OUTCOMES

First, we will summarize papers and manuscripts that examined the use of healthcare resources before prostate cancer diagnosis and/or treatment, followed by comparisons of outcomes during or shortly after treatment. We will conclude with papers comparing long-term treatment outcomes.

Studies to assess patterns of care and treatments prior to the diagnosis or treatment of prostate cancer

Testosterone replacement prior to prostate cancer diagnosis

At present, there is a large and growing demand for the use of testosterone replacement therapy to combat the effects of male aging, i.e. andropause. However, the subsequent risk of testosterone replacement therapy on the diagnosis and outcomes of prostate cancer remain under-studied. Therefore the purpose of our study was to assess utilization trends and determine the effect of testosterone replacement therapy on outcomes in men who subsequently developed prostate cancer. This was published in *Urology* in 2013.[8] We used linked Surveillance, Epidemiology, and End Results Medicare data to identify 149,354 men diagnosed with prostate cancer from 1992 to 2007. Of those, 2,237 men (1.5%) underwent testosterone replacement therapy before their prostate cancer diagnosis. Propensity scoring methods were used to assess cancer-specific outcomes of testosterone replacement vs. no replacement therapy. We found that testosterone replacement was associated with older age at cancer diagnosis, nonwhite race, and higher comorbidity (P <.001). No testosterone vs. testosterone before the prostate cancer diagnosis was associated with higher grade (34% vs. 30%, P <.0001) and more T4 (6.5% vs. 4.3%, P <.0001) tumors. Mortality was decreased in men with 2 prostate-specific antigen (PSA) tests in the year before their cancer diagnosis. No significant difference was found between groups in overall survival, cancer-specific survival, or use of salvage androgen-deprivation therapy after initial treatment.

Through our observational study design, we show that testosterone use was low throughout the study period. Testosterone use was not associated with aggressive prostate cancer and did not affect overall or disease-specific mortality. Although our findings support growing evidence that testosterone replacement is safe with respect to prostate cancer, confirmatory prospective studies are needed.

The effect of depression on the diagnosis, treatment and mortality of men with prostate cancer

While demographic, clinicopathologic, and socioeconomic differences may affect treatment and outcomes of prostate cancer, the effect of mental health disorders remains unclear. We assessed the effect of previously diagnosed depressive disorders on outcomes of men with newly diagnosed prostate cancer.[9]

We performed a population-based observational cohort study using Surveillance, Epidemiology and End Results-Medicare linked data of 41,275 men diagnosed with

prostate cancer from 2004-2007. We identified 1,894 men with a depressive disorder in the two years prior to prostate cancer diagnosis and used regression analysis to determine its effect on treatment and survival.

Men with depressive disorder were older, white or Hispanic, unmarried, resided in non-metropolitan areas and areas of lower median income, and had more co-morbidities ($p<0.05$ for all), but there was no variation in clinicopathologic characteristics. In adjusted analyses, men with depressive disorder were more likely to undergo expectant management (watchful waiting or active surveillance) (OR 1.29; 95%CI 1.19-1.47, $p<0.001$) or androgen deprivation therapy (OR 1.23; 95%CI 1.08-1.40, $p=0.002$) versus definitive therapy (radical prostatectomy and radiation therapies) and experienced increased overall mortality across risk strata (low [RR 1.86; 95%CI 1.48-2.33, $p<0.001$]; intermediate [RR 1.25; 95%CI 1.06-1.49, $p=0.01$]; high [RR 1.16; 95%CI 1.03-1.32, $p=0.02$]).

Men with a recent diagnosis of depressive disorders are less likely to undergo definitive treatments for prostate cancer and experience worse overall survival independent of treatment. The effect of depression disorders on prostate cancer treatment and survivorship warrants further study, as they are relatively common in U.S. men.

<u>Population-based observational study regarding the frequency of PSA screening and prostate cancer outcomes</u>

Given the recent controversy regarding the U.S. Preventative Services Task Force recommendations against PSA screening, we performed a population-based analysis to characterize the effect of PSA screening on oncologic outcomes in men diagnosed with prostate cancer.[10] We used Surveillance, Epidemiology, and End Results (SEER)–Medicare linked data to identify 98,883 men diagnosed with prostate cancer from 1996–2007. We stratified frequency of PSA testing as none, 1–2, 3–5, and ≥6 in the 5-years prior to prostate cancer diagnosis. We used propensity scoring methods to assess the effect of frequency of PSA screening on likelihood of: (1) metastases at diagnosis; (2) overall and prostate-cancer specific mortality.

In adjusted analyses, the likelihood of being diagnosed with metastatic prostate cancer decreased with greater frequency of PSA screening (none, 10.6; 1–2, 8.3; 3–5, 3.7; ≥6, 2.5 events per 100 person years, $p<0.001$). Additionally, greater frequency of PSA screening was associated with improved overall and prostate cancer specific survival ($p<0.001$ for both). In summary, greater frequency of PSA screening in the 5 years prior to prostate cancer diagnosis is associated with lower likelihood of being diagnosed with metastatic prostate cancer, improved overall and prostate cancer-specific survival.

Recently, there has been controversy regarding urologist self-referral for the use of intensity modulated radiation therapy. Certificate of need programs are a primary mechanism to regulate the use and cost of health care services at the state level. The effect of certificate of need programs on the use of intensity modulated radiation

therapy and the increasing costs of prostate cancer care is unknown. We compared the use of intensity modulated radiation therapy and change in prostate cancer health care costs in regions with vs. without active certificate of need programs.[11]

Certificate of Need Programs and the Diffusion of Intensity Modulated Radiation Therapy

We performed a population based, observational study using SEER (Surveillance, Epidemiology, and End Results)-Medicare linked data from 2002 through 2009 was comprised of 13,814 men treated for prostate cancer in 3 regions with active certificate of need programs (CON Yes) vs 44,541 men treated for prostate cancer in 9 regions without active certificate of need programs (CON No). We assessed intensity modulated radiation therapy use relative to other prostate cancer definitive therapies and overall prostate cancer health care costs with respect to certificate of need status.

In propensity score adjusted analyses, intensity modulated radiation therapy use increased from 2.3% to 46.4% of prostate cancer definitive therapies in CON Yes regions vs 11.3% to 41.7% in CON No regions from 2002 to 2009. Furthermore, we observed greater intensity modulated radiation therapy use with time in CON Yes vs No regions ($p < 0.001$). Annual cost growth did not differ between CON Yes vs No regions ($p = 0.396$).

Certificate of need programs were not effective in limiting intensity modulated radiation therapy use or attenuating prostate cancer health care costs. There remains an unmet need to control the rapid adoption of new, more expensive therapies for prostate cancer that have limited cost and comparative effectiveness data.

Use of imaging to stage prostate cancer prior to treatment

Routine imaging for staging low risk prostate cancer is not recommended according to current guidelines. We characterized patterns of care and factors associated with imaging overuse.[12] We used SEER-Medicare linked data to identify men diagnosed with low risk prostate cancer from 2004 to 2005, and determined if imaging (computerized tomography, magnetic resonance imaging, bone scan, abdominal ultrasound) was obtained following prostate cancer diagnosis before treatment.

Of the 6,444 men identified with low risk disease 2,330 (36.2%) under- went imaging studies. Of these men 1,512 (23.5%), 1,710 (26.5%) and 118 (1.8%) underwent cross-sectional imaging (computerized tomography or magnetic resonance imaging), bone scan and abdominal ultrasound, respectively. Radiation therapy vs surgery was associated with greater odds of imaging (OR 1.99, 95% CI1.68 –2.35, $p < 0.01$), while active surveillance vs surgery was associated with lower odds of imaging (OR 0.44, 95% CI 0.34 – 0.56, $p < 0.01$). Associated with increased odds of imaging was median household income greater than $60,000 (OR 1.41, 95% CI 1.11–1.79, $p < 0.01$), and men from New Jersey vs San Francisco (OR 3.11, 95% CI 2.24 – 4.33, $p < 0.01$) experienced greater odds of imaging. Men living

in areas with greater than 90% vs less than 75% high school education experienced lower odds of imaging (OR 0.76, 95% CI 0.6 – 0.95, p = 0.02).

There is widespread overuse and significant geographic variation in the use of imaging to stage low risk prostate cancer. Moreover treatment associated variation in imaging was noted with the greatest vs lowest imaging use observed for radiation therapy vs active surveillance.

Inappropriate Utilization of Radiographic Imaging in Men With Newly Diagnosed Prostate Cancer in the United States

The use of radiographic imaging (bone scan and computerized tomography) is only recommended for men diagnosed with high-risk prostate cancer characteristics. We sought to characterize utilization patterns of imaging in men with newly diagnosed prostate cancer.[13]

The authors performed a population-based observational cohort study using the US Surveillance, Epidemiology, and End Results-Medicare linked data to identify 30,183 men diagnosed with prostate cancer during 2004 to 2005. RESULTS: Thirty-four percent of men with low-risk and 48% with intermediate-risk prostate cancer underwent imaging, whereas only 60% of men with high-risk disease received imaging before treatment. Radiographic imaging utilization was greater for men who were older than 75 years (odds ratio [OR], 1.28; 95% confidence interval [CI], 1.20-1.37; P < .001), were black (OR, 1.11; 95% CI, 1.01-1.21; P . .030), resided in wealthier areas (OR, 1.19; 95% CI, 1.08-1.32 for median income >$60,000 vs <$35,000; P < .001), lived in rural regions (OR, 1.23; 95% CI, 1.12-1.36; P < .001), or underwent standard radiation therapies (OR, 1.71; 95% CI, 1.60-1.84; P < .001). Imaging utilization was less for men living in areas with greater high school education (OR, 0.83; 95% CI, 0.75-0.91 between highest and lowest graduation rates; P < .001) or opting for active surveillance (OR, 0.17; 95% CI, 0.15-0.19 vs radical prostatectomy; P < .001). The estimated cost of unnecessary imaging over this 2-year period exceeded $3.6 million. CONCLUSIONS: In the United States, there is widespread overutilization of imaging for low-risk and intermediate-risk prostate cancer, whereas a worrisome number of men with high-risk disease did not receive appropriate imaging studies to exclude metastases before therapy.

Comparative effectiveness studies regarding the treatment of localized prostate cancer

Perineal Radical Prostatectomy

While perineal radical prostatectomy has been largely supplanted by retropubic and minimally invasive radical prostatectomy, it was the predominant surgical approach for prostate cancer for many years. In our population based study we compared the use and outcomes of perineal radical prostatectomy vs retropubic and minimally invasive radical prostatectomy.[14]

We identified men diagnosed with prostate cancer from 2003 to 2005 who underwent perineal (452), minimally invasive (1,938) and retropubic (6,899) radical prostatectomy using Surveillance, Epidemiology and End Results-Medicare linked data through 2007. We compared postoperative 30-day and anastomotic stricture complications, incontinence and erectile dysfunction, and cancer therapy (hormonal therapy and/or radiotherapy).

We found that perineal radical prostatectomy comprised 4.9% of radical prostatecto- mies during our study period and use decreased with time. On propensity score adjusted analysis men who underwent perineal vs retropubic radical prostatec- tomy had shorter hospitalization (median 2 vs. 3 days, p <0.001), received fewer heterologous transfusions (7.2% vs. 20.8%, p <0.001) and required less additional cancer therapy (4.9% vs. 6.9%, p = 0.020). When comparing perineal vs minimally invasive radical prostatectomy men who underwent the former required more heterologous transfusions (7.2% vs. 2.7%, p = 0.018) but experienced fewer miscellaneous medical complications (5.3% vs 10.0%, p = 0.045) and erectile dysfunction procedures (1.4 vs 2.3/100 person-years, p = 0.008). The mean and median expenditure for perineal radical prostatectomy in the first 6 months postoperatively was $1,500 less than for retropubic or minimally invasive radical prostatectomy (p <0.001).

In summary, men who undergo perineal vs retropubic and minimally invasive radical prostatectomy experienced favorable outcomes associated with lower expenditure. Urologists may be abandoning an underused but cost-effective surgical approach that compares favorably with its successors.

Radical Prostatectomy Operative time

The assessment of operative time is inherent in defining surgeon learning curves and evaluating quality of care. While many single-institution series report open radical retropubic prostatectomy (RRP) and robotic-assisted radical prostatectomy (RARP) operative times, population-based determinants of radical prostatectomy operative time have not been studied.

To determine factors that influence radical prostatectomy operative times, we performed a population-based observational cohort study using US Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data of men diagnosed with prostate cancer during 2003-2007 who underwent RARP (n=3,458) and RRP (n= 6,993) through 2009.[15] We obtained median operative time using anesthesia administrative data for radical prostatectomies and assessed the contribution of patient, surgeon, and hospital factors to operative times using linear regression models.

Median operative time for RARP decreased from 315 minutes to 247 minutes (min) from 2003 through 2008-09 (p<0.001) while the operative time for RRP stayed constant (median 195 min vs. 197 min, p=0.90), and in adjusted analysis, RARP vs. RRP was associated with longer operative times (parameter estimate [PE] 70.9;

95% confidence interval [CI] 58, 84; p<0.001). Obesity was associated with longer operative times (PE 15; 95% CI 7, 23; p<0.001). Very high (PE -42.43; 95% CI -53.3, -31.55; p<0.001), high (PE -26.04; 95% CI -35.4, -16.68; p<0.001), and intermediate (PE -10.6; 95% CI -18.66, -2.53; p=0.010) vs. low surgeon volumes were associated with shorter operative times. Prostatectomies performed by surgeons employed by group and non-government vs. government facilities were associated with shorter operative times (PE -22.76; 95% CI -38, -7.49; p=0.004 and PE -35.59; 95% CI -68.15, -3.03; p=0.032, respectively). Likewise, non-profit vs. government owned hospitals were associated with shorter operative times (PE -21.85; 95% CI -32.28, -11.42; p<0.001). Finally, there was significant geographic operative time variation.

During our study period, RARP operative times decreased by 68 minutes indicating continuing maturation of a novel approach while RRP operative times remained stagnant.

The effect of surgeon volume on minimally invasive and open radical prostatectomy outcomes

In order to determine the effect of minimally invasive radical prostatectomy (MIRP) surgeon volume on outcomes, we performed an observational population-based study of 8,831 men undergoing MIRP and ORP by 1,457 low, medium, and high volume surgeons from SEER-Medicare linked data from 2003 to 2007.[16] After stratifying by surgeon ORP and MIRP volume, the following outcomes were studied: length of stay, transfusions, post-operative 30-day and anastomotic stricture complications, and use of additional cancer therapies.

We found that men undergoing MIRP with high and medium vs. low volume surgeons were less likely to require additional cancer therapies (4.5% and 4.7% vs. 7%, $P = 0.020$). Similarly, men undergoing ORP with high vs. medium and low volume surgeons were less likely to require additional cancer therapies (5.7% vs. 6.8% and 7.1%, $P = 0.044$). Men undergoing ORP with high vs. medium and low volume surgeons experienced shorter lengths of stay (2.9 vs. 3.3 and 3.6 days, $P < 0.001$), and fewer transfusions (15.4% vs. 21.3% and 22.7% $P = 0.017$), 30-day complications (18.4% vs. 25.6% and 25.7%, $P < 0.001$), and anastomotic strictures (10.1% vs. 15.6% and 16.3%, $P = 0.003$). However, MIRP surgeon volume did not affect these outcomes.

Men undergoing MIRP or ORP with high volume surgeons were less likely to require additional cancer therapies. Additionally, patients of high volume ORP surgeons were more likely to experience shorter hospital stays, fewer transfusions, 30-day complications, and anastomotic strictures, while MIRP surgeon volume did not affect these peri-operative outcomes.

Population-based determinants of radical prostatectomy positive surgical margins

We sought to characterize factors associated with positive surgical margins (PSMs) and derive population-based PSM cutoffs to evaluate surgeon performance in radical prostatectomy. We used SEER-Medicare data were used to identify 4247

men diagnosed with prostate cancer during 2004–2005 who underwent RP up to 2006.[17] We performed logistic regression to assess the impact of tumor characteristics, surgeon volume and surgical approach on the likelihood of PSMs for pT2 and PT3a disease. Moreover, we derived 25th and 10th percentile cutoffs from binomial distribution equations.

We found that 19.4% of men experienced PSMs with a pT2 vs pT3a PSM rate of 14.9% vs 42% ($P < 0.001$). Extrapolating from our population-based results, a surgeon incurring more than three PSMs in 10 cases of pT2 disease performed below the 25th percentile. There was a trend for fewer PSMs with minimally invasive vs open RP (17.4% vs 20.1%, $P = 0.086$), and the PSM rate also decreased over the study period from 21.3% in 2004 to 16.6% in 2006 ($P = 0.028$) with significant geographic variation ($P < 0.001$).

In adjusted analyses, temporal and geographic variation in PSM persisted, and men with high (odds ratio 3.68, 95% CI 2.82–4.81) and intermediate (odds ratio 2.52, 95% CI 2.03–3.13) vs low-risk disease were at greater odds to experience PSMs. Notably, neither surgical approach nor surgeon volume was significantly associated with PSMs.

Our population-based PSM benchmarks allow identification of under-performing outliers who may seek courses or video self- study to improve outcomes. There was significant temporal and geographic variation in PSMs but neither surgeon volume nor surgical approach was associated with PSMs.

Cryotherapy versus Brachytherapy to treat Localized Prostate Cancer

There are few studies to compare prostate cryotherapy vs brachytherapy outcomes and costs, beyond single-center studies. Therefore we performed an observational study of 10 928 men who underwent primary cryotherapy (943 patients) or brachytherapy (9985) with ≥2 years of follow-up using USA Surveillance, Epidemiology, and End Results (SEER-) Medicare linked data.[18] Weighted propensity score methods were used.

Use of cryotherapy increased four-fold whereas brachytherapy utilization remained the same from 2001 to 2005 ($P < 0.001$). Men who underwent cryotherapy vs brachytherapy were older ($P < 0.001$), more likely to be Black ($P < 0.001$), less likely to live in areas of higher education ($P < 0.001$), less likely to live in areas with greater income ($P < 0.001$), and were more likely to live in urban vs rural areas ($P = 0.007$). In propensity score-weighted analyses, cryotherapy was associated with more urinary (41.4% vs 22.2%, $P < 0.001$) and erectile dysfunction (ED) complications (34.7% vs 21.0%, $P < 0.001$) while brachytherapy was associated with more bowel complications (19.0% vs 12.1%, $P <0.001$). Cryotherapy was associated with greater use of salvage androgen deprivation therapy (ADT; 1.4 vs 0.5 per 100 person- years, $P < 0.001$), suggesting worse cancer control. Finally costs

were significantly greater for brachytherapy vs cryotherapy ($16 887 vs $12 629 USA dollars, $P < 0.001$).

In summary, although less costly, cryotherapy was associated with more urinary and ED complications and greater need for salvage androgen deprivation therapy. Conversely, cryotherapy was associated with fewer bowel complications. Patients and providers alike should consider these population-based outcomes while discussing therapeutic options for localized prostate cancer.

Factors associated with performing a pelvic lymph node dissection during radical prostatectomy

Controversy persists regarding the adequacy of pelvic lymph node dissection (PLND) and cancer control when comparing minimally invasive radical prostatectomy (MIRP) and open radical prostatectomy (RRP). We characterized determinants of performance and extent of PLND during radical prostatectomy in elderly men.[19]

We conducted a population-based study was conducted comprised of 5448 men >65 years undergoing RRP and MIRP during 2004 to 2006 from Surveillance, Epidemiology, and End Results (SEER)–Medicare- linked data. Multivariable logistic regression was used to assess the effect of demographic and tumor characteristics, surgical approach, and surgeon volume on the likelihood of performing PLND.

PLND was performed for 87.6% vs. 38.3% of men undergoing RRP vs. MIRP (P <.001). Among RRP, 82.6% vs. 4.6% underwent extended vs. limited PLND, with a median yield of 4 vs. 3 lymph nodes (P <.001). Median MIRP PLND yield was 3 lymph nodes. In adjusted analyses, men undergoing RRP vs. MIRP (odds ratio [OR] 16.7; 95% confidence interval [CI], 11.1-25.0), those with few vs. multiple comorbidities (OR 1.4, 95% CI 1.02-1.91), intermediate (OR 1.87; 95% CI 1.48-2.37), and high (OR 2.77; 95% CI 2.02-3.78) vs. low-risk features, and men treated by high-volume surgeons (OR 1.008; 95% CI 1.004-1.011) were more likely to undergo PLND. Conversely, Hispanic (OR 0.68, 95% CI 0.49-0.96) vs. white men were less likely to undergo PLND.

Independent of tumor characteristics, men undergoing RRP vs. MIRP were more likely to undergo PLND with greater lymph node yield and racial variation observed.

Patterns of care and outcomes of radiotherapy for lymph node positivity after radical prostatectomy

For men who received PLND and were found to have a positive lymph node for prostate cancer metastases, we used a population-based approach to evaluate the use and outcomes of adjuvant radiation therapy (ART) after radical prostatectomy (RP).[20] We used Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data from 1995 to 2007 to identify 577 men with LN metastases discovered during RP and absence of distant metastases, of which 177 underwent ART <1 year of RP. Propensity score models were used to compare overall mortality and prostate

cancer-specific mortality (PCSM) for men that did and those that did not receive ART.

Men in both groups received adjuvant androgen-deprivation therapy at similar rates after propensity weighting adjustments (33.6% vs. 33.7%, P = 0.977). ART was not associated with differences in overall (5.09 vs. 3.77 events per 100 person-years, P = 0.153) or PCSM (2.89 vs. 1.31, P = 0.090) relative to men who did not receive ART. In conclusion, ART after RP in men with LN-positive prostate cancer was not associated with improved overall or disease-specific survival, in contrast to previous single center studies,[21] prospective randomized studies are needed to assess the effectiveness of ART in this patient population.

Morbidity and costs of salvage vs. primary radical prostatectomy in older men

Salvage radical prostatectomy is performed with curative intent following post-radiotherapy recurrence for prostate cancer. While single-center salvage RP outcomes appear promising, little is known about outcomes in the community setting in elderly men.

We sought to evaluate utilization, outcomes, and costs of salvage RP vs. primary RP in older men using Surveillance, Epidemiology and End Results-Medicare linked data from 1992 to 2007. We identified 18,317 men aged 65 years or older who underwent RP from 2002 to 2007. Propensity score analyses were used to compare outcomes and costs for primary vs. salvage RP.

We found that the use of salvage RP was uncommon, accounting for 0.5% of RP. Men undergoing salvage vs. primary RP were older, white, and less likely to undergo CT, bone scan and prostate biopsy preoperatively (P < 0.05 for all). In adjusted analyses, salvage vs. primary RP was associated with increased 30-day complications (60.1% vs. 22.7%, P _ 0.01), lengths of stay (mean 7 vs. 3 days, P <0.01), and hospital readmissions within 30 days (30.4% vs. 5.7%, P <0.01). The odds of death within 90 days were higher for salvage vs. primary RP (OR 26.7, 95% CI 12.9 –55.1, P <0.01). The median expenditure for salvage RP within 6 months postoperatively was almost twice that for primary RP ($30,881 vs. $12,431, P <0.01).

In conclusion, metastatic workup was performed less frequently before salvage vs. primary RP, and morbidity and mortality for salvage RP was high relative to primary RP. Given the morbidity and high cost of salvage RP, guidelines for patient selection and selective referral may optimize outcomes, especially in older men.

Prostate cancer health care costs

Cost implications of the rapid adoption of new technologies for the treatment of prostate cancer

Intensity-modulated radiation therapy and laparoscopic or robotic minimally invasive radical prostatectomy are costlier alternatives to three-dimensional conformal radiation therapy (3D-CRT) and open radical prostatectomy for treating prostate cancer. We

assessed temporal trends in their utilization and their impact on national health care spending.

We used Surveillance, Epidemiology, and End Results–Medicare linked data, to determine treatment patterns for 45,636 men age > 65 years who received definitive surgery or radiation for localized prostate cancer diagnosed from 2002 to 2005.[22] Costs attributable to prostate cancer care were the difference in Medicare payments in the year after versus the year before diagnosis.

We found that patients received surgery (26%), external RT (38%), or brachytherapy with or without RT (36%). Among surgical patients, MIRP utilization increased substantially (1.5% among 2002 diagnoses *v* 28.7% among 2005 diagnoses, $P < .001$). For RT, IMRT utilization increased substantially (28.7% *v* 81.7%; $P < .001$) and for men receiving brachytherapy, supplemental IMRT increased significantly (8.5% *v* 31.1%; $P < .001$). The mean incremental cost of IMRT versus 3D-CRT was $10,986 (in 2008 dollars); of brachytherapy plus IMRT versus brachytherapy plus 3D-CRT was $10,789; of MIRP versus open RP was $293. Extrapolating these figures to the total US population results in excess spending of $282 million for IMRT, $59 million for brachytherapy plus IMRT, and $4 million for MIRP, compared to less costly alternatives for men diagnosed in 2005.

In conclusion, costlier prostate cancer therapies were rapidly and widely adopted, resulting in additional national spending of more than $350 million among men diagnosed in 2005 and suggesting the need for comparative effectiveness research to weigh their costs against their benefits.

Influence of Surgeon and Hospital Volume on Radical Prostatectomy Costs

While higher radical prostatectomy hospital and surgeon volume are associated with better outcomes, the effect of provider volume on health care costs remains unclear. We performed a population-based study to characterize the effect of surgeon and hospital volume on radical prostatectomy costs, using SEER (Surveillance, Epidemiology and End Results)-Medicare linked data to identify 11,048 men who underwent radical prostatectomy from 2003 to 2009.[23] We categorized hospital and surgeon radical prostatectomy volume into tertiles (low, intermediate, high) and assessed costs from radical prostatectomy until 90 days postoperatively using propensity-adjusted analyses.

We found that higher surgeon volume at intermediate volume hospitals (surgeon volume low $9,915; intermediate $10,068; high $9,451; p = 0.021) and high volume hospitals (surgeon volume low $11,271; intermediate $10,638; high $9,529; p = 0.002) were associated with lower radical prostatectomy costs. Extrapolating nationally, selective referral to high volume radical prostatectomy surgeons at high and intermediate volume hospitals netted more than $28.7 million in cost savings. Conversely, higher hospital volume was associated with greater radical

prostatectomy costs for low volume surgeons (hospital volume low $9,685; intermediate $9,915; high $11,271; p = 0.010) and intermediate volume surgeons (hospital volume low $9,605; intermediate $10,068; high $10,638; p = 0.029). High volume radical prostatectomy surgeon costs were not affected by varying hospital volume, and among low volume hospitals radical prostatectomy costs did not differ by surgeon volume.

Selective referral to high volume radical prostatectomy surgeons operating at intermediate and high volume hospitals nets significant cost savings. However, higher radical prostatectomy hospital volume was associated with greater costs for low and intermediate volume radical prostatectomy surgeons.

Utilization and expense of adjuvant cancer therapies following radical prostatectomy

We sought to identify the costs of adjuvant therapies following radical prostatectomy (RP) and factors associated with their receipt. We used SEER-Medicare data from 2004-2006 to identify 4247 men who underwent RP, of whom 600 subsequently received adjuvant therapies.[24] We used Cox regression to identify factors associated with receipt of adjuvant therapies. Health care expenditures within 12 months of diagnosis were compared for RP alone versus RP with adjuvant therapies. We found that biopsy Gleason score, prostate-specific antigen, risk group, and SEER region were significantly associated with receipt of adjuvant treatments (all P<.001). Higher surgeon volume was associated with lower odds of receiving adjuvant therapies (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.46-0.78 [P<.001]). Factors associated with increased receipt of adjuvant therapies were positive surgical margins (HR, 3.02; 95% CI, 2.55-3.57 [P<.001]), high-risk group versus low-risk group (HR, 7.65; 95% CI, 5.64-10.37 [P<.001]), lymph node–positive disease (HR, 5.36; 95% CI, 3.71-7.75 [P<.001]), and treatment in Iowa (HR, 1.93; 95% CI, 1.12-3.32 [P = .019]) and New Mexico/Georgia/Hawaii (HR, 1.92; 95% CI, 1.09-3.39 [P = .025]) versus San Francisco SEER regions (baseline). Age, race, comorbidities, and surgical approach were not associated with use of adjuvant therapies. The median expenditures attributable to post-prostatectomy hormonal therapy, radiation therapy, and radiation with hormonal therapy versus were $1361, $12,040, and $23,487.

In summary, men treated by high-volume surgeons were less likely to receive adjuvant therapies. Regional variation and high-risk disease characteristics were associated with increased receipt of adjuvant therapies, which increased health care expenditures by 2- to 3-fold when radiotherapy was administered.

CONCLUSION

This Prostate Cancer Physician Training Award resulted multiple publications, highlighted by the 2009 JAMA paper that was the first population-based comparative effectiveness study demonstrating the peri-operative benefits of robotic assisted radical prostatectomy compared to open surgery, including fewer transfusions, anastomotic strictures and shorter lengths of stay, albeit at higher costs. Additionally, we demonstrated the substantial health care costs due to the rapid adoption of IMRT and robotic assisted surgery, published in the Journal of Clinical Oncology. Other publications demonstrated factors associated with the adoption of robotic surgery, such as race, higher income and more education. Our study findings have several important implications. First, we demonstrate potential areas of improvement in our health care system, particularly with regard to the absence of regulation in the adoption of new, unproven but costly technologies. We demonstrate that Certificate of Need programs are largely ineffective in reining in the rampant adoption of IMRT. Our comparative effectiveness study of novel and costly prostate cancer therapies may serve as a paradigm for other disease processes in which there may be rapid adoption of costly technologies. Finally, our extensive work in examining population-based outcomes concerning competing therapies for localized prostate cancer will better inform men diagnosed with prostate cancer in making informed decisions.

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Prostate Cancer

Temporal National Trends of Minimally Invasive and Retropubic Radical Prostatectomy Outcomes from 2003 to 2007: Results from the 100% Medicare Sample

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Abstract

Background: Although the use of minimally invasive radical prostatectomy (MIRP) has increased, there are few comprehensive population-based studies assessing temporal trends and outcomes relative to retropubic radical prostatectomy (RRP).
Objective: Assess temporal trends in the utilization and outcomes of MIRP and RRP among US Medicare beneficiaries from 2003 to 2007.
Design, setting, and participants: A population-based retrospective study of 19 594 MIRP and 58 638 RRP procedures was performed from 2003 to 2007 from the 100% Medicare sample, composed of almost all US men ≥65 yr of age.
Intervention: MIRP and RRP.
Measurements: We measured 30-d outcomes (cardiac, respiratory, vascular, genitourinary, miscellaneous medical, miscellaneous surgical, wound complications, blood transfusions, and death), cystography utilization within 6 wk of surgery, and late complications (anastomotic stricture, ureteral complications, rectourethral fistulae, lymphocele, and corrective incontinence surgery).
Results and limitations: From 2003 to 2007, MIRP increased from 4.9% to 44.5% of radical prostatectomies while RRP decreased from 89.4% to 52.9%. MIRP versus RRP subjects were younger ($p < 0.001$) and had fewer comorbidities ($p < 0.001$). Decreased MIRP genitourinary complications (6.2–4.1%; $p = 0.002$), miscellaneous surgical complications (4.7–3.7%; $p = 0.030$), transfusions (3.5–2.2%; $p = 0.005$), and postoperative cystography utilization (40.3–34.1%; $p < 0.001$) were observed over time. Conversely, overall RRP perioperative complications increased (27.4–32.0%; $p < 0.001$), including an increase in perioperative mortality (0.5–0.8%, $p = 0.009$). Late RRP complications increased, with the exception of fewer anastomotic strictures (10.2–8.8%; $p = 0.002$). In adjusted analyses, RRP versus MIRP was associated with increased 30-d mortality (odds ratio [OR]: 2.67; 95% confidence interval [CI], 1.55–4.59; $p < 0.001$) and more perioperative (OR: 1.60; 95% CI, 1.45–1.76; $p < 0.001$) and late complications (OR: 2.52; 95% CI, 2.20–2.89; $p < 0.001$). Limitations include the inability to distinguish MIRP with versus without robotic assistance and also the lack of pathologic information.
Conclusions: From 2003 to 2007, there were fewer MIRP transfusions, genitourinary complications, and miscellaneous surgical complications, whereas most RRP perioperative and late complications increased. RRP versus MIRP was associated with more postoperative mortality and complications.

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1. Introduction

The use of minimally invasive radical prostatectomy (MIRP) surged in the United States after US Food and Drug Administration approval of the robotic platform in 2000. Initial single-surgeon series at academic centers demonstrated that MIRP was at least as effective as retropubic radical prostatectomy (RRP) [1,2]. However, comparative effectiveness studies of surgical outcomes and complications of MIRP versus RRP remain sparse. Most published MIRP outcomes originate from high-volume referral centers and may not be generalizable to community settings.

Population-based studies comparing MIRP and RRP have shown comparable perioperative outcomes, although MIRP was associated with more erectile dysfunction and incontinence diagnoses [3]. Additionally, another study showed that MIRP was associated with greater risk for salvage therapy and anastomotic stricture, although these risks diminished with increasing surgeon experience [4], mirroring improvement in RRP outcomes during the 1990s [5]. However, previous studies used 5% and 20% samples of Medicare beneficiaries, and some regions within the United States were not characterized [6,7]. Although recent population-based data have noted fewer MIRP inpatient complications from 2001 to 2007, physician and outpatient data were unavailable and RRP outcomes were not characterized and compared [8]. Using data from the 100% Medicare sample from 2003 to 2007, we assessed temporal trends in the utilization and outcomes of MIRP and RRP.

2. Materials and methods

2.1. Study cohort

Our study was approved by the Brigham and Women's Hospital institutional review board; patient data were deidentified, and the requirement for consent was waived. Using the 100% sample of Medicare beneficiaries from the Centers for Medicare and Medicaid Services (CMS), we identified 85 992 men diagnosed with prostate cancer (*International Classification of Disease*, 9th revision [ICD-9] 185.0) who underwent MIRP (n = 21 459) and RRP (n = 64 533) from 2003 to 2007. Medicare is the major health care plan sponsored by the US government covering 97% of US citizens $\geq$65 yr of age [9]. Radical prostatectomy for men $\geq$65 yr of age comprises approximately 32% of all US radical prostatectomies [10].

Surgical approach was determined from the *Current Procedural Terminology* coding system, 4th edition (CPT-4) codes: 55840, 55842, and 55845 for RRP, and 55866 for MIRP. Men not continuously enrolled in Medicare A and B and those simultaneously enrolled in health maintenance organizations were not included for analysis because their claims data may not be accurately captured by CMS. Subjects were required to have Medicare coverage 365 d prior to surgery to capture comorbidities. Men $<$ 65 yr of age were excluded because disability is a requirement for Medicare enrollment at this age, and therefore these men are not representative of the general population. Although 3626 perineal radical prostatectomies (PRPs) were identified, these were not included in outcomes analysis due to relatively low numbers (4% of total). However, trends in PRP outcomes compared with MIRP and RRP were previously addressed in a similar cohort [11]. A unique designation for robotic assistance did not exist during the study period; therefore, we were unable to distinguish pure laparoscopic from robot-assisted surgery, and both were categorized as MIRP. Our final cohort consisted of 19 594 MIRP and 58 638 RRP.

2.2. Dependent variables

We captured outcomes of interest using ICD-9 and CPT-4 diagnosis and procedure codes [12]. Hospital length of stay (LOS) was defined as the interval between hospital admission and discharge. Blood transfusions were characterized during the hospital stay. Perioperative complications were characterized within 30 d of surgery and included potentially life-threatening cardiac, respiratory, or vascular events; genitourinary (GU) complications; bleeding; miscellaneous surgical and medical complications; wound infection; and death. Cystography utilization was identified within 6 wk of surgery. Late complications (anastomotic stricture, ureteral complications [ie, stricture or fistula], rectourethral fistula, lymphocele) were assessed from 31 to 365 d following surgery. Men were excluded from analyses of late complications if they died within 30 d or did not have 365 d of postoperative follow-up. Therefore, surgeries performed in 2007 were excluded from the analysis of late complications.

2.3. Independent variables

Age, comorbidities, and geographic region were obtained from the Medicare file. Comorbidities were characterized with the Hierarchical Condition Category (HCC) risk-adjustment model based on diagnoses from inpatient and outpatient claims [13], with higher scores representing higher cost comorbidities according to CMS.

2.4. Statistical analysis

Using the Mantel-Haenszel test for trend over time [14], we examined change in patient characteristics and outcomes by surgical approach. Proportions were compared with Rao-Scott chi-square tests (adjusting for surgeon clustering), and logistic regression models were constructed to characterize factors associated with mortality and early and late complications. The logistic regression coefficients were estimated via generalized estimating equations to adjust for surgeon clustering. We included covariates a priori that have been shown to be potential confounders for our outcomes of interest: age, comorbidities, geographic region, surgeon volume, surgical approach (MIRP vs RRP), and year of surgery. Surgeon volume was determined using unique physician identification numbers and aggregating the total number of procedures performed by each surgeon over the study period. MIRP and RRP volumes were counted separately. Overall Medicare surgeon volume range over the study period was 1–462 for MIRP and 1–129 for RRP. We did not recalculate surgeon volume each year and instead analyzed surgeon volume in adjusted analysis as a continuous variable over the study period. Year of surgery was included as a variable in adjusted analysis to adjust for learning curve effect. Analyses were performed using SAS v.9.2 (SAS Institute, Cary, NC, USA). The p values were two sided and considered statistically significant at $\leq$0.05.

3. Results

Overall, Medicare radical prostatectomies (including PRP) increased from 17 250 procedures in 2003 to 19 925 in 2007. MIRP use increased from 4.9% in 2003 to 44.5% in 2007; RRP and PRP use decreased from 89.4% to 52.9% and 5.7% to 2.6%, respectively (Fig. 1). Table 1 shows the demographic data for men undergoing MIRP and RRP. Men undergoing MIRP versus RRP were younger and had fewer comorbidities (both

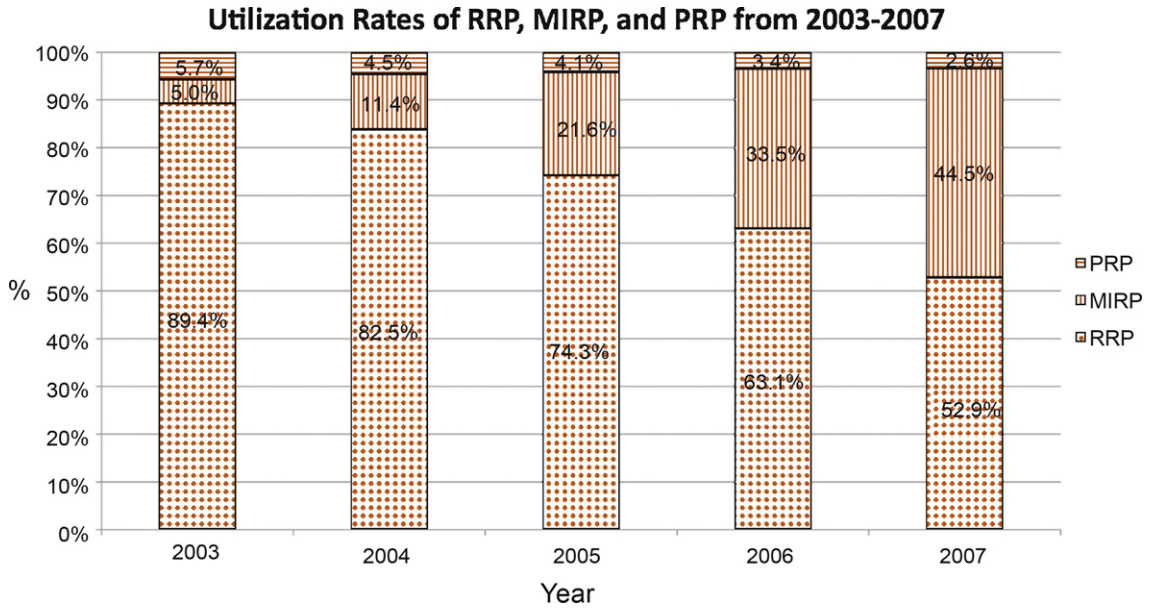

Fig. 1 – Utilization of retropubic radical prostatectomy (RRP), minimally invasive radical prostatectomy (MIRP), and perineal radical prostatectomy (PRP) for Medicare beneficiaries from 2003 to 2007.

$p < 0.001$). There was significant geographic variation, with more MIRP performed in the Northeast and South.

Table 2 summarizes trends of MIRP complications from 2003 to 2007. Although overall MIRP complications did not change, MIRP GU complications, miscellaneous surgical complications, use of blood transfusions, and cystography decreased (all $p < 0.030$). Similarly, the occurrence of rectourethral fistulae decreased ($p = 0.017$).

Conversely, overall RRP complications increased from 27.4% to 32.0% ($p < 0.001$; Table 3), with significant increases in all 30-d perioperative complications, including greater perioperative mortality (0.5–0.8%; $p = 0.009$). Use of cystography also increased ($p < 0.001$). Among late complications, there were more ureteral complications, rectourethral fistulae, and lymphoceles (all $p < 0.026$). However, there was a decrease in anastomotic strictures ($p = 0.002$).

Table 4 compares overall MIRP and RRP outcomes. MIRP versus RRP was associated with fewer perioperative deaths (0.2 vs 0.6%; $p < 0.001$) and fewer overall perioperative complications (19.6 vs 29.8%; $p < 0.001$). MIRP was associated with fewer cardiac (2.2% vs 4.7%), GU (4.8% vs 6.9%), miscellaneous medical (8.8% vs 12.6%), miscellaneous surgical (4.2% vs 6.0%), respiratory (4.1% vs 9.4%), vascular (2.7% vs 4.3%), and wound complications (1.8% vs 3.9%; all $p < 0.001$). Among GU complications, men undergoing RRP were more likely to experience perioperative hydronephrosis (1.4% vs 0.4%) with subsequent stent placement and/or reimplantation as well as increased risk of pyelonephritis (0.36% vs 0%), whereas men undergoing MIRP were more likely to experience ureteral and/or vesical fistula (0.33% vs 0.06%). However, most of the GU complications in both cohorts were recorded as "urinary complications not otherwise specified," a limitation in comparing specific complications. MIRP was also associated with fewer blood transfusions, anastomotic strictures, and lymphoceles compared with RRP (all $p < 0.001$). However, MIRP was associated with a greater use of postoperative cystography ($p < 0.001$). Finally, men undergoing MIRP experienced shorter lengths of stay (2.0 vs 4.2 d; $p < 0.001$).

Table 5 presents adjusted comparative outcomes. RRP was associated with an almost threefold greater odds of perioperative death (OR: 2.67; $p < 0.001$) versus MIRP. Higher comorbidity score (OR: 1.54; $p < 0.001$) and older age ($p < 0.003$) were also associated with greater mortality. RRP (OR: 1.60; $p < 0.001$), increasing comorbidity score (OR: 1.67; $p < 0.001$), and older age ($p < 0.001$) were associated with increased odds for perioperative complications. Only

Table 1 – Demographics of minimally invasive and retropubic radical prostatectomy patient populations

	MIRP $n = 19\,594$	RRP $n = 58\,638$	p value
Age, yr (%)			
65–69	12 399 (63.3)	33 949 (57.9)	<0.001
70–74	5909 (30.2)	17 912 (30.5)	
≥75	1286 (6.6)	6777 (11.6)	
Region, *n* (%)			
Northeast	2840 (14.5)	7372 (12.6)	0.027
Midwest	5449 (27.8)	16 877 (28.8)	
South	7363 (37.6)	21 372 (36.4)	
West	3941 (20.1)	12 687 (21.6)	
Other*	1 (0.0)	330 (0.6)	
HCC comorbidity score, *n* (%)			
1	10 827 (55.3)	29 304 (49.9)	<0.001
2	6296 (32.1)	18 941 (32.3)	
3	1607 (8.2)	5762 (9.8)	
4	517 (2.6)	2239 (3.8)	
5	347 (1.7)	2392 (4.1)	

MIRP = minimally invasive radical prostatectomy; RRP = retropubic radical prostatectomy; HCC = Hierarchical Condition Category.
* Unincorporated US territories: Puerto Rico, Guam, US Virgin Islands, Northern Mariana Islands, and American Samoa.

Table 2 – Trends of minimally invasive radical prostatectomy complications from 2003 to 2007

	2003 *n* = 795	2004 *n* = 1846	2005 *n* = 3503	2006 *n* = 5549	2007 *n* = 7901	*p* value
Length of stay, d, plus or minus standard deviation	2.4 ± 0.2	2.1 ± 0.1	2.0 ± 0.1	2.0 ± 0.1	1.9 ± 0.1	0.402
Perioperative complications, %	21.5	21.3	19.8	19.7	18.8	0.244
Cardiac	2.0	2.4	2.2	2.2	2.2	0.963
Genitourinary	6.2	6.3	5.3	4.6	4.1	0.002
Miscellaneous medical	8.2	9.0	8.6	9.4	8.4	0.571
Miscellaneous surgical	4.7	5.4	4.3	4.3	3.7	0.030
Respiratory	5.2	4.3	4.1	4.3	3.9	0.556
Vascular	2.5	2.2	2.8	3.0	2.4	0.196
Wound	2.6	2.0	1.8	1.8	1.6	0.299
Death	0.0	0.1	0.2	0.2	0.1	0.827
Perioperative blood transfusion, %	3.5	2.7	3.5	2.4	2.2	0.005
Cystography utilization, %	40.3	42.9	39.6	35.7	34.1	<0.001
	2003 *n* = 747	2004 *n* = 1768	2005 *n* = 3309	2006 *n* = 5258		*p* value
Late complications, %						
Anastomotic stricture	4.1	3.6	3.0	2.6		0.066
Ureteral complications	0.3	0.3	0.5	0.6		0.254
Rectourethral fistula	0.7	0.7	0.2	0.2		0.017
Lymphocele	0.9	0.9	1.2	1.5		0.276
Surgical intervention for incontinence	0.0	0.2	0.2	0.4		0.412

Table 3 – Trends of retropubic radical prostatectomy complications from 2003 to 2007

	2003 *n* = 14 131	2004 *n* = 13 093	2005 *n* = 11 761	2006 *n* = 10 255	2007 *n* = 9398	*p* value
Length of stay, d, plus or minus standard deviation	4.1 ± 0.1	4.1 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	0.398
Perioperative complication, %	27.4	28.5	29.8	31.6	32.0	<0.001
Cardiac	4.1	4.8	4.6	5.0	5.3	<0.001
Genitourinary	5.4	5.9	7.2	8.0	9.2	<0.001
Miscellaneous medical	11.3	11.4	12.9	13.7	14.4	<0.001
Miscellaneous surgical	5.1	5.7	6.2	6.5	6.8	<0.001
Respiratory	8.6	8.9	9.5	10.3	10.4	<0.001
Vascular	4.0	4.3	4.1	4.8	4.5	0.002
Wound	3.2	3.7	4.2	4.6	4.3	<0.001
Death	0.5	0.7	0.5	0.7	0.8	0.009
Perioperative blood transfusion, %	16.6	17.4	17.1	17.4	18.3	0.059
Cystography utilization, %	10.6	10.6	10.8	11.6	11.8	0.001
	2003 *n* = 12 835	2004 *n* = 11 999	2005 *n* = 10 671	2006 *n* = 9531		*p* value
Late complications, %						
Anastomotic stricture	10.2	9.1	9.1	8.8		0.002
Ureteral complications	0.9	1.2	1.5	1.7		<0.001
Rectourethral fistula	0.2	0.4	0.3	0.4		0.026
Lymphocele	1.7	2.1	2.2	2.7		<0.001
Surgical intervention for incontinence	0.3	0.2	0.3	0.4		0.278

surgery in the South (OR: 0.78; $p < 0.001$) versus the Northeast was associated with lower odds for perioperative complications. Higher comorbidity score (OR: 1.32; $p < 0.001$), RRP versus MIRP (OR: 2.52; $p < 0.001$), and age ≥75 yr (OR: 1.16; $p = 0.003$) were associated with greater odds for late complications. Conversely, higher surgeon volume (OR: 0.99; $p < 0.001$) was associated with fewer late complications.

4. Discussion

The use of MIRP increased over the past decade with reports of similar oncologic and functional outcomes compared with RRP, combined with decreased blood loss and shorter LOS [15]. MIRP, in particular robot-assisted laparoscopic radical prostatectomy (RALP), was quickly embraced as direct-to-consumer marketing led to patient demand for robotic procedures despite lack of objective evidence demonstrating superiority [2,16]. Studies reporting MIRP outcomes were largely from high-volume academic settings, whereas MIRP perioperative and long-term outcomes in the community are largely unreported. A population-based study design using a 100% sample of Medicare beneficiaries captures temporal trends across health settings without observer and reporting bias that may be present in single-center reports; prior studies of Medicare

Table 4 – Comparison of overall complications of minimally invasive radical prostatectomy and retropubic radical prostatectomy from 2003 to 2007

	MIRP $n = 19\,594$	RRP $n = 58\,638$	p value
Mean length of stay, d, plus or minus standard deviation *n* (%)	2.0 ± 0.1	4.2 ± 0.1	<0.001
Any perioperative complication	3836 (19.6)	17 369 (29.8)	<0.001
Cardiac	431 (2.2)	2756 (4.7)	<0.001
Genitourinary	933 (4.8)	4068 (6.9)	<0.001
Miscellaneous medical	1721 (8.8)	7360 (12.6)	<0.001
Miscellaneous surgical	816 (4.2)	3498 (6.0)	<0.001
Respiratory	808 (4.1)	5535 (9.4)	<0.001
Vascular	520 (2.7)	2529 (4.3)	<0.001
Wound	349 (1.8)	2294 (3.9)	<0.001
Death	30 (0.2)	367 (0.6)	<0.001
Perioperative blood transfusion	502 (2.6)	10 135 (17.3)	<0.001
Cystography utilization	7194 (36.7)	6468 (11.0)	<0.001
	MIRP $n = 11\,108$	RRP $n = 45\,277$	p value
Late complications			
Anastomotic stricture	333 (3.0)	4225 (9.3)	<0.001
Ureteral complications	58 (0.5)	610 (1.3)	<0.001
Rectourethral fistula	39 (0.4)	159 (0.4)	0.999
Lymphocele	146 (1.3)	1003 (2.2)	<0.001
Surgical intervention for incontinence	30 (0.3)	132 (0.3)	0.734

MIRP = minimally invasive radical prostatectomy; RRP = retropubic radical prostatectomy.

Table 5 – Multivariate model for perioperative mortality, perioperative complications, and late complications

	Perioperative mortality		Perioperative complications		Late complications*	
Variable	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Highest quintile HCC score	1.54 (1.38–1.71)	<0.001	1.67 (1.61–1.73)	<0.001	1.32 (1.26–1.39)	<0.001
Surgeon volume	1.00 (0.99–1.01)	0.897	0.99 (0.99–1.00)	0.076	0.99 (0.99–0.99)	0.043
Year (vs 2004)						
2005	0.61 (0.37–1.01)	0.054	1.02 (0.96–1.09)	0.491	1.01 (0.92–1.10)	0.795
2006	0.99 (0.65–1.53)	0.975	1.07 (1.00–1.14)	0.043	1.04 (0.95–1.14)	0.409
2007	0.83 (0.52–1.30)	0.408	1.05 (0.98–1.12)	0.185	–	–
RRP vs MIRP	2.67 (1.55–4.59)	<0.001	1.60 (1.45–1.76)	<0.001	2.52 (2.20–2.89)	<0.001
Region (vs Northeast)						
Midwest	0.86 (0.50–1.46)	0.626	0.88 (0.69–1.00)	0.066	1.01 (0.87–1.18)	0.885
West	0.71 (0.30–1.69)	0.444	0.84 (0.71–1.00)	0.052	0.98 (0.77–1.26)	0.930
South	0.80 (0.48–1.35)	0.408	0.78 (0.68–0.88)	<0.001	1.05 (0.91–1.21)	0.459
Other	1.08 (0.44–2.66)	0.860	1.10 (0.91–1.33)	0.336	1.09 (0.83–1.42)	0.444
Age, yr (vs 65–69)						
70–74	2.04 (1.27–3.27)	0.003	1.15 (1.10–1.20)	<0.001	1.04 (0.97–1.13)	0.284
≥75	7.35 (4.74–11.36)	<0.001	2.47 (2.29–2.66)	<0.001	1.16 (1.04–1.30)	0.008

CI = confidence interval; HCC = Hierarchical Condition Category; RRP = retropubic radical prostatectomy; MIRP = minimally invasive radical prostatectomy.
* Late complications from 31 to 365 d.

radical prostatectomies examined only 5–20% of Medicare beneficiaries' experience.

Our study has several important findings. First, MIRP utilization increased over the study period with a concomitant decrement in utilization of RRP. In 2007, 44.5% of radical prostatectomies among Medicare beneficiaries were performed using a minimally invasive approach. This was likely influenced by the introduction of RALP in 2000. This rapid increase in utilization is similar to laparoscopic cholecystectomy, which comprised 40% of cholecystectomies only 5 yr after introduction, and more rapid than that of laparoscopic nephrectomy, which comprised only 10% of nephrectomies 5 yr after introduction [17]. This is consistent with previous population-based studies that sampled Medicare beneficiaries [4,18].

Second, the demographics of the study population represent a shift in the patterns of care for men with localized prostate cancer. In our study, patients undergoing MIRP versus RRP were younger and had fewer comorbidities. This contrasts previous population-based studies finding that men undergoing MIRP earlier in the learning curve were older and with more comorbidities [4]. This may be due to increased direct-to-consumer marketing targeted toward younger and healthier patients, making

these men more likely to seek MIRP while older men may undergo RRP.

Third, in adjusted analyses, RRP was associated with greater odds of perioperative mortality compared with MIRP. Our 0.6% RRP mortality is higher than population-based studies from Sweden and Canada; Carlsson et al. noted a 0.11% RRP mortality rate [19]; Alibhai et al. noted an overall 0.48% RRP mortality rate without significant differences in mortality when stratified by age [20]. Conversely, MIRP series rarely report mortality; a large series by Patel et al. revealed no deaths [21]. Higher RRP mortality and complications may be secondary to increased blood loss, which has been associated with higher rates of cardiac, respiratory, and renal complications [22,23]. Increased blood loss has been associated with greater mortality with radical cystectomy [24], general and vascular surgeries [25], as well as RRP [26]. Although mortality was rare in both MIRP and RRP cohorts, the reduction in mortality in men undergoing MIRP reveals a potentially significant benefit of the minimally invasive approach.

Fourth, there were fewer MIRP versus RRP complications, regardless of complication type. Most MIRP complications decreased or remained stable over the study period, whereas most of the RRP complications increased. These findings suggest improvement in MIRP outcomes with dissemination of surgical technique and experience. RRP complications were more common even after adjusting for age, comorbidities, and surgeon experience by surgical approach. Therefore, increasing RRP complications over time may be a reflection of patient selection uncharacterizable with our data. For instance, men with high body mass index or prior surgeries may have been more likely to undergo RRP versus MIRP. Alternatively, the rise in RRP complications may be due to better documentation of complications as MIRP has pushed RRP surgeons to better their outcomes [27]. Our RRP findings contrast those of Budäus et al, who noted decreasing RRP complications in Florida from 1999 to 2008 as more men were treated by higher volume surgeons [28]. However, while our findings are limited to elderly Medicare beneficiaries, it is a national rather than statewide study. Our findings are consistent with data from the US Nationwide Inpatient Sample (NIS) that revealed decreasing MIRP complications from 2001 to 2007 [8]. However, our sample draws from a larger cohort of patients and characterizes physician and outpatient experience in addition to hospital outcomes that comprise NIS data.

In adjusted analyses, greater comorbidity and older age were associated with greater mortality and complications consistent with other studies [5,29]. Similarly, higher surgeon volume was associated with fewer late complications, consistent with prior studies [12,29]. Finally, there was significant geographic variation, with MIRP more commonly performed in the South and Northeast. Men undergoing surgery in the South were less likely to experience perioperative complications, and similar geographic variation in complications occurred in the 1990s with greater adoption of RRP [30].

Although our findings were similar to another population-based study by Hu et al. [3] in that MIRP was associated with fewer transfusions, respiratory, and miscellaneous surgical and stricture complications, our study differed in that there was greater RRP mortality but fewer GU complications for MIRP. These differences may be due to additional years of study for the current study, allowing dissemination of surgical technique and greater progress along MIRP learning curves, whereas the study by Hu et al. was limited to men diagnosed with prostate cancer from 2003 to 2005. Our larger sample size resulted in greater statistical power to detect differences between MIRP and RRP outcomes, and it also sampled beyond the Surveillance Epidemiology and End Results database regions. We did not assess erectile dysfunction or urinary incontinence diagnosis because administrative data correlate poorly with patient self-assessment [31].

Our findings must be interpreted in the context of the study design. First, claims are designed to provide billing rather than clinical information, and comorbidity severity may not be captured fully by the HCC model. Second, pathologic data were not available, and therefore we could not adjust for tumor grade or stage. However, previous studies have not demonstrated an association between tumor characteristics and early or late of complications [32]. Nonetheless, higher stage or grade tumors may lead to a higher rate of lymphadenectomy, and therefore higher rates of lymphocele in men undergoing RRP may be due to pathologic differences that we are unable to adjust for. An additional explanation for use of the more RRP lymphocele formation may be due to the more frequent extraperitoneal approach than MIRP. Third, we were unable to determine whether robotic assistance was used during MIRP. However, RALP has become the predominant surgical approach in the United States [33]. Fourth, the large number of subjects in our national study enables greater statistical power; however, readers must discern statistically versus clinically significant differences in MIRP versus RRP outcomes. For instance, although our population-based 30-d mortality for MIRP versus RRP was 0.2% versus 0.6%, 30 versus 367 men died following MIRP versus RRP. This differs from high-volume centers where radical prostatectomy deaths are extremely rare [34], although this may be due to under-reporting and publication bias against presenting suboptimal outcomes. Finally, although we found that RRP complications increased over the study period after controlling for age, comorbidities, surgeon volume, and surgical approach, we are unable to pinpoint the exact cause. This may be related to the shift of surgeons from RRP to MIRP over the study period; however, further study is warranted to confirm our findings.

5. Conclusions

MIRP utilization has greatly increased, comprising 44.5% of Medicare radical prostatectomies in 2007. From 2003 to 2007, men undergoing MIRP versus RRP experienced fewer perioperative and late complications. Although MIRP complications decreased over the study period, RRP complications increased, and RRP was associated with higher mortality.

Author contributions: Jesse M. Levy had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hu, Kowalczyk.
Acquisition of data: Levy, Caplan.
Analysis and interpretation of data: Kowalczyk, Hu, Yu.
Drafting of the manuscript: Kowalczyk, Hu.
Critical revision of the manuscript for important intellectual content: Kowalczyk, Levy, Caplan, Lipsitz, Yu, Hu.
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Hospital Volume, Utilization, Costs and Outcomes of Robot-Assisted Laparoscopic Radical Prostatectomy

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Abbreviations and Acronyms

LOS = length of hospital stay

NIS = Nationwide Inpatient Sample

ORP = open radical prostatectomy

RALP = robot-assisted laparoscopic radical prostatectomy

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For another article on a related topic see page 1861.

Purpose: Although robot-assisted laparoscopic radical prostatectomy has been aggressively marketed and rapidly adopted, there is a paucity of population based utilization, outcome and cost data. High vs low volume hospitals have better outcomes for open and minimally invasive radical prostatectomy (robotic or laparoscopic) but to our knowledge volume outcomes effects for robot-assisted laparoscopic radical prostatectomy alone have not been studied.

Materials and Methods: We characterized robot-assisted laparoscopic radical prostatectomy outcome by hospital volume using the Nationwide Inpatient Sample during the last quarter of 2008. Propensity scoring methods were used to assess outcomes and costs.

Results: At high volume hospitals robot-assisted laparoscopic radical prostatectomy was more likely to be done on men who were white with an income in the highest quartile and age less than 50 years than at low volume hospitals (each $p < 0.01$). Hospitals at above the 50th volume percentile were less likely to show miscellaneous medical and overall complications ($p = 0.01$). Low vs high volume hospitals had longer mean length of stay (1.9 vs 1.6 days) and incurred higher median costs ($12,754 vs $8,623, each $p < 0.01$).

Conclusions: Demographic differences exist in robot-assisted laparoscopic radical prostatectomy patient populations between high and low volume hospitals. Higher volume hospitals showed fewer complications and lower costs than low volume hospitals on a national basis. These findings support referral to high volume centers for robot-assisted laparoscopic radical prostatectomy to decrease complications and costs.

Key Words: prostate, prostatectomy, robotics, hospitals, demography

While published studies provide evidence that RALP provides shorter LOS and decreased blood loss than ORP,[1,2] most are single surgeon/center series. Despite the dearth of population based evidence showing superior outcomes of robotic technology compared to traditional surgical approaches more than 1,400 robotic surgical systems have been installed at American hospitals with up to 5 systems at some and more than 400 international units.[3] Moreover, RALP utilization estimates are provided primarily by the device manufacturer.[3,4]

Direct to consumer advertising has fueled patient demand for RALP[5,6] despite reports that men treated with RALP vs ORP were more often diagnosed with incontinence and erectile dysfunction, and more likely to experience treatment regret.[7,8] Also, this

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technology is more costly than ORP[3] with a capital acquisition cost of $1.7 million and an annual maintenance contract of $150,000. A recent population based study showed that from 2000 to 2009 there was a greater than 25% increase in the number of radical prostatectomies performed with the increase primarily centralized at high volume hospitals.[9] This was associated with a concurrent increase in the number of robotic units, which was most pronounced among high volume hospitals.

Higher hospital and surgeon volumes are associated with better outcomes of ORP and minimally invasive radical prostatectomy, which include but do not distinguish between laparoscopic and robotic approaches.[10,11] However, the RALP learning curve is prolonged and population based studies characterizing the relation between RALP volume and outcome are lacking.

We characterized national RALP utilization rates and patterns of care, and assessed the hospital volume effects of RALP on perioperative outcomes and costs.

MATERIALS AND METHODS

Data Source

Subjects were identified from the Healthcare Cost and Utilization Project NIS, sponsored by the Agency for Healthcare Research and Quality. NIS is a 20% stratified probability sample including a total of approximately 8 million acute hospital stays annually from more than 1,000 hospitals in 42 states. It is the largest, all payer inpatient care observational cohort in the United States, representing approximately 90% of all hospital discharges.

Study Cohort

During the last quarter of 2008 there were 2,093,300 subjects in NIS, representing more than 9.8 million patients using NIS discharge weights. We used ICD-9 code 60.5 to identify radical prostatectomy and the code for robotic assistance (17.4x), initiated on October 1, 2008, to define the RALP cohort.

Covariates

For each procedure we examined hospital and patient level characteristics that may be associated with outcome. Hospital characteristics included United States Census region, urban vs rural location, teaching status and bed size. Hospital RALP procedures were aggregated during the study period to stratify hospital volume into quartiles, in which about 25% of the cases in the sample were done at the hospitals in each quartile. Patient level characteristics included age, number of comorbidities based on the Elixhauser method,[12] race, median income based on hospital ZIP Code[13] and primary payer.

Outcomes

ICD-9 diagnosis and procedure codes were used to identify blood transfusion as well as cardiac, respiratory, genitourinary, vascular, wound, miscellaneous medical and miscellaneous surgical complications.[7,11,14,15] NIS specific outcomes included death, hospital LOS, discharge disposition (routine [home] vs other [rehabilitation, skilled nursing facility, etc]) and total costs. Costs were derived from total charges billed by the hospital using the Healthcare Cost and Utilization Project cost-to-charge ratio, which is a hospital level file that allows the conversion of charges to the amount that hospitals are reimbursed or to actual costs.[16] The all payer inpatient cost-to-charge ratio was used when available, or else group averages were used.

Statistical Analysis

Stratification, clustering and survey weights were used in accordance with the NIS sampling design. Propensity scoring methods were used to adjust for factors that may confound outcomes with the goal of balancing characteristics among groups.[17,18] Due to absent RALP at most rural centers the hospital type variable was dichotomized into rural/urban nonteaching vs urban teaching in the propensity model.

Since there were no small or medium bed size hospitals, or hospitals in the Midwest in the highest volume quartile, bed size and geography could not be included in the propensity model. Patient age, race, comorbidity, primary payer, income and hospital type were included in the final propensity model. Due to few cases in subcategories race was collapsed into white, nonwhite and missing, and primary payer was collapsed into private, Medicare and Medicaid/other to adequately power propensity analysis and minimize $0< n <11$, for which data suppression is required per NIS. All analysis was done with SAS®, version 9.2 with all tests considered statistically significant at $p <0.05$.

RESULTS

Procedure Frequency

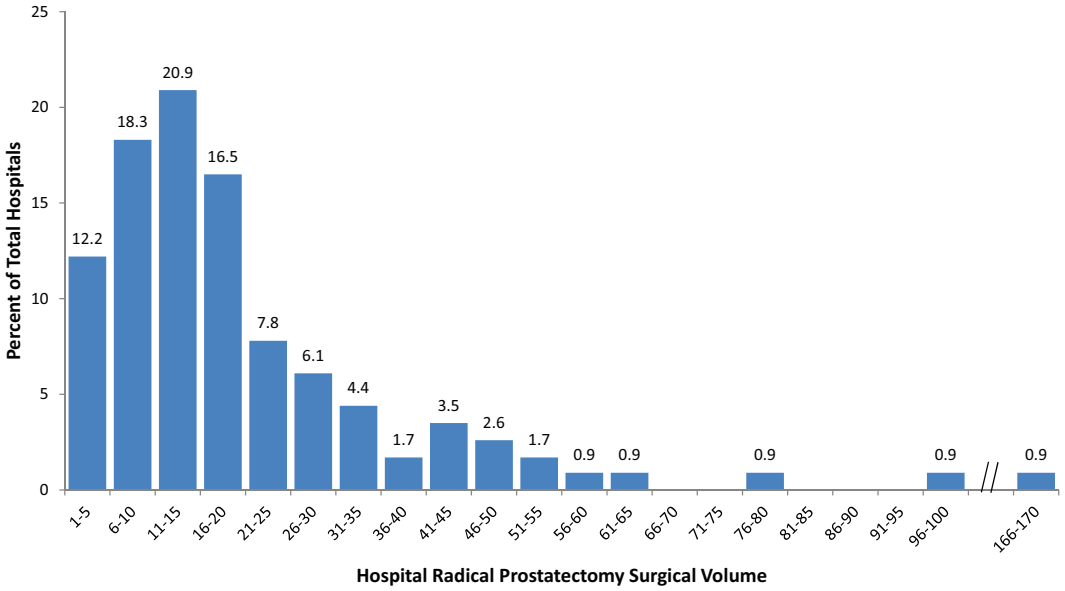
There were 2,348 RALPs in the NIS, representing 11,513 RALPs after incorporating NIS survey weights. Low, medium, high and very high volume quartiles corresponded to 1 to 15, 16 to 29, 30 to 54 and 55 to 166 RALPs, respectively, during the last quarter of 2008. The figure shows the overall hospital RALP volume distribution.

Study Sample Characteristics

Table 1 lists patient and hospital characteristics. At higher volume hospitals RALP was more likely to be done on men younger than 50 years, those who were white or those who earned a higher income (each $p <0.01$). Higher volume hospitals were more likely to be large bed size facilities ($p <0.01$).

Outcomes

Table 2 shows adjusted outcomes since unadjusted and adjusted outcomes were similar. While there were no RALP deaths in hospital, high and very high volume hospitals showed fewer overall and miscellaneous medical complications (each $p \leq 0.01$).



RALP hospital surgical volume for last quarter of 2008

Low volume hospitals had longer mean LOS and fewer routine discharges home (each $p < 0.01$). Finally, higher RALP hospital volume was associated with lower costs ($p < 0.01$). For instance, the median RALP cost at very high volume hospitals was two-thirds that of low volume hospitals ($8,623 vs $12,754). The mean cost for patients with a LOS of fewer than 2 days with vs without complications was $10,267 vs $7,233. Of patients with 2 or more days of LOS the cost for those with vs without complications was $17,245 vs $9,240.

DISCUSSION

Robotic assistance facilitates the learning curve for open surgeons who are transitioning to minimally invasive surgery,[2,19,20] which has the reproducible advantages of smaller incisions, decreased blood loss and postoperative pain, and shorter LOS than open surgery.[1,2] Many patients intuitively perceive that RALP decreases complications and confers the same benefits as laparoscopy and they prefer this technology even at greater cost.[21]

However, rapid adoption combined with the prolonged learning curve and varying accreditation practices to attain privileges for new technology may result in hidden risks. For example, the rapid adoption of laparoscopic cholecystectomy in the 1990s resulted in a spike in biliary tract injuries from 1,500 to 4,000 annually.[22] Results reported from high volume referral centers may not be representative of community practice. Population based comparisons characterize RALP utilization and outcomes across a broad spectrum of practice settings and experience levels.

To our knowledge this is the first population based study to evaluate volume relationships by RALP utilization, patterns of care and outcomes. For instance, prior studies of minimally invasive radical prostatectomy did not distinguish between RALP and pure laparoscopic radical prostatectomy.

Our study has several important findings. 1) Higher hospital volume was associated with fewer medical and overall complications, and shorter LOS while low volume hospitals had a lower likelihood of routine discharge. This parallels the ORP volume outcomes findings of Begg et al.[15]

2) Higher RALP hospital volume was associated with lower costs. Similarly others suggested that cost equivalence to ORP may be achievable with 10 to 14 robotic cases weekly,[23] which would translate to more than 500 cases annually. In our analysis this could only be achieved at very high volume hospitals.

If selective referral of RALP from low to very high volume hospitals were implemented, this would result in an annual cost savings of $10,695,888. More stringent referral of patients from low, medium and high volume hospitals to very high volume hospitals would increase annual cost savings to $18,033,468.

Sensitivity analysis revealed that fewer complications and shorter LOS drove the lower costs at higher vs lower volume hospitals. However, complications were a greater contributor to higher cost than LOS. While our RALP hospital costs excluded surgeon fees and robotic system acquisition/maintenance costs, thus underestimating total RALP costs, these cost estimates are consistent with those of other studies.[3] This is in the context of high volume

Table 1. *NIS weighted unadjusted patient and hospital characteristics*

		Hospital RALP Vol Quartile*				
	Total No. (%)	No. Low (%)	No. Medium (%)	No. High (%)	No. Very High (%)	p Value
Age:						
Less than 50	996 (8.7)	195 (7.1)	240 (8.1)	250 (8.5)	311 (10.9)	
50–59	4,051 (35.2)	1,067 (38.9)	1,003 (33.8)	997 (33.9)	984 (34.4)	
60–69	5,516 (47.9)	1,327 (48.3)	1,371 (46.3)	1,472 (50.0)	1,346 (47.1)	
70 or Greater	950 (8.3)	158 (5.7)	351 (11.8)	226 (7.7)	216 (7.6)	<0.01
Race:						
White	7,948 (69.0)	1,778 (64.7)	2,039 (68.8)	1,833 (62.2)	2,297 (80.4)	
Nonwhite	1,727 (15.0)	523 (19.1)	380 (12.8)	299 (10.1)	525 (18.4)	
Missing	1,838 (16.0)	446 (16.2)	545 (18.4)	813 (27.6)	34 (1.2)	<0.01
Comorbidity:						
None	4,412 (38.3)	1,069 (38.9)	1,024 (34.6)	1,096 (37.2)	1,223 (42.8)	
1	4,448 (38.6)	1,002 (36.5)	1,166 (39.3)	1,186 (40.3)	1,094 (38.3)	
Multiple	2,652 (23.0)	676 (24.6)	774 (26.1)	663 (22.5)	539 (18.9)	0.12
Primary payer:						
Private	7,647 (66.4)	1,795 (65.3)	1,875 (63.2)	2,005 (68.1)	1,973 (69.1)	
Medicare	3,242 (28.2)	759 (27.6)	963 (32.5)	770 (26.1)	750 (26.2)	
Medicaid/other	624 (5.4)	193 (7.0)	126 (4.3)	170 (5.8)	134 (4.7)	0.31
ZIP Code income quartile:						
1st (lowest)	1,575 (13.9)	349 (12.9)	615 (21.1)	296 (10.1)	314 (11.4)	
2nd	2,743 (24.3)	615 (22.7)	897 (30.7)	641 (22.0)	590 (21.5)	
3rd	2,973 (26.3)	849 (31.3)	697 (23.9)	801 (27.4)	627 (22.9)	
4th	4,001 (35.4)	894 (33.0)	710 (24.3)	1,183 (40.4)	1,214 (44.2)	<0.01
Hospital type:						
Rural	229 (2.0)	229 (8.3)	0	0	0	
Urban nonteaching	3,582 (31.1)	1,012 (36.9)	1,330 (44.9)	843 (28.6)	397 (13.9)	
Urban teaching	7,702 (66.9)	1,506 (54.8)	1,635 (55.2)	2,102 (71.4)	2,460 (86.1)	0.17
Hospital bed size:						
Small	851 (7.4)	170 (6.2)	189 (6.4)	492 (16.7)	0	
Medium	1,637 (14.2)	556 (20.2)	618 (20.8)	463 (15.7)	0	
Large	9,025 (78.4)	2,021 (73.6)	2,158 (72.8)	1,990 (67.6)	2,857 (100)	<0.01
Hospital region:						
Northeast	2,352 (20.4)	590 (21.5)	211 (7.1)	715 (24.3)	836 (29.3)	
Midwest	3,266 (28.4)	859 (31.3)	936 (31.6)	1,471 (50.0)	0	
South	3,834 (33.3)	844 (30.7)	1,240 (41.8)	427 (14.5)	1,323 (46.3)	
West	2,061 (17.9)	454 (16.5)	577 (19.5)	332 (11.3)	698 (24.4)	0.97

* Weighted counts using NIS complex survey weights and numbers may not sum to group totals or percents may not total to 100% due to need for rounding.

centers tending to be academic centers that take on patient care regardless of financial risks[24] and have better information technology and documentation to comply with reimbursement guidelines, and since hospitals with significant market shares can negotiate more competitive prices with insurers.[25] All of this would be expected to lead to increased costs at high volume hospitals. Moreover, this suggests that while improved outcomes associated with greater experience offset the costs associated with RALP, this volume effect may underestimate the true cost benefit.

However, there may be indirect costs attributable to differences in time away from work or increased travel distances for treatment at high volume centers, which is associated with the shift of radical prostatectomy volume to these centers and with the adoption of robotic technology.[9] Medicare recently aimed to incentivize hospitals that incur fewer complications and lower costs by using spending per beneficiary as a measure of hospital performance.[26] This brings the cost differentials of costly and high volume treatments such as RALP to the forefront of the American health care debate.

3) White men and men with a higher income were more likely to undergo RALP at high volume hospitals. This may be related to patient preference affected by direct to consumer advertising[27,28] or referral patterns consistent with studies showing variations in patterns of care for nonwhite patients and those in lower socioeconomic groups, including lower utilization of high volume centers.[29] This poses concern that not all patients may benefit from the improved clinical outcomes at more experienced RALP centers.[10]

Our study must be interpreted in the context of the study design. 1) Administrative data are designed for billing purposes and may lack detailed clinical information. We could not characterize disease severity or body mass index, which may affect patient selection and outcomes. For instance, we could not assess differences in tumor characteristics

Table 2. *Propensity adjusted outcomes*

		Hospital RALP Vol Quartile				
	Overall	Low	Medium	High	Very High	p Value
% Complications:						
Cardiac	0.7	0.9	0.7	DS	0.8	0.78
Respiratory	1.2	1.3	1.1	0.9	1.3	0.90
Genitourinary	1.1	1.8	0.7	1.0	0.9	0.20
Wound	0.2		Data suppressed*			0.83
Vascular	0.4		Data suppressed*			0.21
Miscellaneous	5.2	7.5	5.3	3.7	3.4	0.01
Miscellaneous medical	1.9	3.1	1.3	1.6	1.4	0.25
Any surgical	8.6	11.2	7.6	6.7	6.9	<0.01
% Blood transfusion	1.7	2.4	2.3	1.0	0.7	0.06
% Routine discharge home	94.9	93.5	94.5	98.5	94.2	<0.01
Mean ± SD LOS (days)	1.7 ± 3.0	1.9 ± 4.0	1.6 ± 2.3	1.6 ± 2.0	1.6 ± 3.3	<0.01
Median $ costs (IQR)	11,976 (8,315–13,680)	12,754 (10,284–17,356)	10,378 (8,253–12,714)	10,787 (8,543–13,542)	8,623 (7,324–11,538)	<0.01

* Data suppressed according to NIS for 0 to fewer than 11.

by hospital volume that may impact patient selection and outcomes. However, claims data have a high degree of corroboration with chart abstraction and are valid for detecting complications.[27]

2) NIS is limited to the inpatient hospital setting. We could not assess outpatient complications or earlier return to activities of daily living/work.

3) While we attempted to adjust for confounding, 16.0% of patients had missing race data, which were not equally distributed across quartiles. This may reflect differences in actual patient demographics in which nonwhite minority designations may not be specified or may reflect systematic differences in race identification between low and high volume hospitals.

4) While we adjusted for hospital volume, we could not adjust for surgeon volume. However, a review of hospital and surgeon volume effects on outcome showed that while surgeon factors tend to have a significant effect on factors more directly related to surgical skill, such as long-term urinary incontinence, hospital factors tend to affect perioperative care, such as medical complications, consistent with our findings.[30]

5) Using a new administrative code to capture robotic use may have lower sensitivity, which increases with time.

6) This is an observational study. There may be unobserved factors for which we could not adjust.

CONCLUSIONS

Sociodemographic differences exist between patient populations at high vs low volume hospitals. Our findings support the association of higher RALP volume with fewer inpatient complications and lower costs.

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EDITORIAL COMMENTS

These authors used NIS data to address the important relationship between hospital volume and surgical outcomes after RALP. They conclude that patients should be referred to high volume hospitals based on fewer complications, shorter LOS and cost savings at these centers. While regionalization of surgical care to high volume centers has benefits for the patients privileged to be treated at those centers, it may also have potential detriments, including increased patient travel distance (reference 9 in article), and less business and preparedness at low volume hospitals, which could adversely impact access to care for some patients.[1] As the current study suggests, centralization to high volume hospitals may result in unequal RALP use among patients based on sociodemographic differences, including race, income and rural site (reference 29 in article).[2]

In the current era of cost efficiency and optimization of surgical outcomes centralization may be the answer for certain high risk operations.[3,4] Indeed, centralization of care for RALP seems to be occurring as a result of market forces and assessments or perceptions of higher quality of care at high volume centers. Available evidence and common sense support these assessments and perceptions of the volume-quality association but without further evidence of the cost-benefit trade-off for the entire population. With only 1 calendar quarter of administrative data to support the regionalization of RALP it may be premature to encourage further concentration of care for RALP.

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These authors conclude that higher volume hospitals showed fewer complications and lower costs than low volume hospitals. This finding is similar to those of almost all prior studies of the volume-outcome relationship in general[1] and specifically in urology (reference 10 in article). We now know that the volume-outcome relationship also applies to RALP. Perhaps the surprise would be if it did not. Does anyone believe that experience, for which volume is a surrogate, is important in a wide range of surgeries but not for robotic prostatectomy?

The real problem with the study is not so much the platitudinous conclusions as the cookie cutter methodology, that is downloading data from an administrative database, dividing them into quartiles and comparing by quartile. We could ask many interesting questions, such as whether the complication rate continues to decrease with increasing volume in the highest quartile. We will not get answers to these interesting questions if we simply repeat the same questions (and find the same answers) as we did a decade ago (reference 15 in article).[3]

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REPLY BY AUTHORS

We agree with the concerns of Drs. Anderson and Barocas about greater patient travel distance, and less preparedness and business at lower volume hospitals. However, radical prostatectomy is an elective rather than an urgent procedure and there is ample evidence that treatment regret after radical prostatectomy is accentuated by suboptimal outcomes.[1] While NIS data do not characterize these outcomes, there are significant costs of additional cancer therapies, such as radiation and androgen deprivation, and treatment for erectile dysfunction as well as inpatient complications characterized by NIS. To our knowledge there has yet to be a study that characterizes provider volume effects on urinary and sexual function. Why? Such data are difficult to come by since it is hugely time-consuming and expensive to track patients with time, administer questionnaires and manage these data.[2]

While Dr. Vickers accurately points out that the volume-outcome relationships is established for open radical prostatectomy, a prior study failed to show such a relationship within 5 years of the first RALP, likely due to learning curve effects among early adopters.[3] Also, the treatment of prostate cancer has been framed as a litmus test for health care reform, given increasingly costly therapy, such as robot-assisted surgery, with mediocre outcomes (reference 4 in article). Moreover, urologists have been the vanguard for adopting and disseminating robot-assisted surgery relative to other surgical specialties[4] and there is a social responsibility to justify the use of expensive technology in the absence of comparative evidence demonstrating superior outcomes. Thus, our study was formulated a priori to assess potential improvements in RALP outcomes and cost savings at high vs low volume institutions.

The potential for the uninformed to miss the point about proactive prostate cancer health services research is epitomized by the recent United States Preventive Services Task Force unconditional recommendation against prostate specific antigen screening. To assume that a benefit exists without evidence or a demonstration of potential improvement may lead to a not so distant future when health plans refuse to reimburse RALP.

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Comparison of Outpatient Narcotic Prescribing Patterns After Minimally Invasive Versus Retropubic and Perineal Radical Prostatectomy

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Purpose: Studies comparing pain after minimally invasive vs retropubic and perineal radical prostatectomy are conflicting. We characterized population based outpatient narcotic prescribing patterns after minimally invasive, retropubic and perineal radical prostatectomy.

Materials and Methods: We evaluated outpatient prescription data after minimally invasive, retropubic and perineal radical prostatectomy from 2003 to 2006 using MarketScan®. Baseline and postoperative narcotic prescriptions were identified using the National Drug Code. Total prescribed narcotic strength in morphine sulfate equivalents, the number of prescriptions filled and costs were compared. We performed multivariate analysis adjusted for surgical approach, age, comorbidity, baseline narcotic use, health plan and geographic region.

Results: We identified 2,206 minimally invasive, 8,037 retropubic and 463 perineal radical prostatectomies with no differences in baseline narcotic prescription use. Perineal and retropubic operations were associated with greater total morphine sulfate equivalent use than the minimally invasive operation. Perineal prostatectomy was associated with more narcotic refills than minimally invasive and retropubic prostatectomy (42.3% vs 20.2% and 28.9%, respectively, $p < 0.001$). Median narcotic costs were lower for minimally invasive than for perineal and retropubic prostatectomy. On adjusted analysis perineal radical prostatectomy, younger age, baseline narcotic use and preferred provider organization health plan were associated with greater morphine sulfate equivalents and narcotic refills while minimally invasive surgery was associated with fewer refills and lower costs but not with total morphine sulfate equivalents. There was significant geographic variation in narcotic use and costs.

Conclusions: Postoperatively minimally invasive radical prostatectomy required fewer narcotic refills and had lower narcotic costs while perineal radical prostatectomy required the greatest amount of narcotics. However, minimally invasive vs retropubic radical prostatectomy morphine sulfate equivalent requirements did not differ on adjusted analysis. While our findings support the purported advantage of minimally invasive radical prostatectomy of less postoperative pain, confirmatory prospective studies with objective outcomes are needed.

Key Words: prostate; prostatectomy; pain, postoperative; narcotics; robotics

Abbreviations and Acronyms

HMO = health maintenance organization

LRP = laparoscopic RP

MIRP = minimally invasive RP

MSe = morphine sulfate equivalent

POS = point of service

PPO = preferred provider organization

PRP = perineal RP

RALP = robot-assisted RP

RP = radical prostatectomy

RRP = retropubic RP

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MINIMALLY invasive RP use surged in the United States after the demonstration of reproducible technique in 2000 with an estimated 85% of RPs done with robotic assistance in 2008.[1] MIRP offers smaller incisions, decreased blood loss and shorter length of stay than open RRP.[2] Furthermore, single center series show equivalent oncological and functional outcomes for the laparoscopic, robotic and open approaches.[3,4] However, while other minimally invasive urological procedures confer significantly less postoperative pain,[5,6] the promise of decreased pain and shorter convalescence for MIRP has been debated, particularly by open surgeons using lower midline or Pfannenstiel mini-incisions.[7,8]

Theoretically MIRP is associated with less postoperative pain than RRP and PRP due to smaller incisions and decreased traction on the abdominal wall musculature.[9] However, studies are inconsistent in showing significant amelioration of postoperative pain for MIRP[2,10–13] with variations in measuring and reporting postoperative pain. Also, few groups have compared longer term objective outpatient narcotic requirements after RP and extended postoperative pain may be a societal burden since men may require more time away from work.[14] Using a population based approach we compared outpatient narcotic prescription use for MIRP, RRP and PRP.

MATERIALS AND METHODS

Study Population

We identified 31,729 men diagnosed with prostate cancer during 2003 to 2006 from MarketScan using ICD-9 code 185.0. MarketScan incorporates the health services of approximately 3 million employees, dependents and retirees in the United States with primary or Medicare supplemental coverage through privately insured fee for service, POS or capitated health plans.[15] MarketScan is generally representative of the demographic makeup of the United States, although more subjects reside in the South and Midwest than the general population.[16] Men who underwent decreased RP, RRP or MIRP, ie laparoscopic RP with or without robotic assistance, were identified using the CPT-4 codes 55810, 55812 and 55815 for PRP, 55840, 55842 and 55845 for RRP, and 55866 for MIRP.

Many private payers do not contribute outpatient prescription data. Thus, to ensure that we captured narcotic prescription use specific to post-prostatectomy pain we limited the cohort to men who filled a narcotic prescription within 7 days of discharge home. Men were also censored if they changed health plan coverage within 90 days surgery to capture complete followup. After censoring the final cohort consisted of 10,706 men, including 2,206 with MIRP, 8,037 with RRP and 463 with PRP.

Variables

Dependent. We identified outpatient narcotic prescription use up to 90 days before and after RP using Food and Drug Administration designated national drug codes for oral narcotics, including codeine, hydrocodone, hydromorphone, meperidine, morphine, MS Contin®, oxycodone, OxyContin®, pentazocine, propoxyphene and tramadol. To assess the various strengths, types and amount of postoperative narcotic use the cumulative MSe was derived.[5,6] Since distributions were nonnormal, medians were compared by surgical approach.

Independent. Age at diagnosis (less than 55, 55 to 64, 65 to 74 or greater than 75 years), comorbidities using the Charlson index derived from health care encounters the year before prostatectomy,[17] health plan type (comprehensive, HMO, PPO, POS or other) and geographic region classified according to United States Census Bureau regions (Northeast, Midwest, South or West) were obtained from the enrollment files.

Statistical Analysis

Demographic characteristics and narcotic use patterns, including refills, median narcotic strength in MSe and median narcotic costs, were compared with the Pearson chi-square and Kruskal-Wallis tests. Analgesic costs were derived as total primary health plan expenditures for narcotics within 90 days of surgery, excluding insurance deductibles, copayments and other third party payments from supplemental insurance. Multivariate models were constructed to determine the effect of surgical approach, age, comorbidity, geographic region, health plan type and baseline narcotic use on postoperative outpatient MSe use, refills and costs. Statistical significance was considered at 2-sided $p \leq 0.05$. Statistical analysis was done with SAS® 9.1.3.

RESULTS

Table 1 lists study population demographic characteristics. Men undergoing MIRP were younger ($p = 0.002$) while men undergoing RRP had fewer comorbidities ($p = 0.005$). Men with HMO and PPO coverage were less and more likely to undergo MIRP, respectively ($p < 0.001$). MIRP was more commonly done in the Midwest while RRP and PRP were most commonly done in the South ($p < 0.001$). There were no differences in baseline preoperative narcotic use by surgical approach.

On unadjusted analysis MIRP was associated with lower median total narcotic strength consumption than RRP and PRP (6.7 vs 6.9 and 8.3 MSe, respectively, $p < 0.001$, fig. 1). Similarly fewer additional narcotic refills were associated with MIRP than with RRP and PRP (20.2% vs 28.9% and 42.3%, respectively, $p < 0.001$, table 2). Correspondingly lower median narcotic costs were associated with MIRP vs PRP and RRP ($8 vs $10 and $10, respectively, $p < 0.001$, fig. 2).

On adjusted analysis PRP (RR 1.11, 95% CI 1.03–1.21, referent RRP), younger age (less than 55 years RR 1.22, 95% CI 1.04–1.43 and 55 to 64 years RR 1.17, 95% CI 1.00–1.37, referent greater than 75

Table 1. *Baseline patient demographics*

	No. MIRP (%)	No. PRP (%)	No. RRP (%)	p Value
Preop narcotic use	260 (11.8)	70 (15.1)	1,093 (13.6)	0.146
Age:				
Less than 55	547 (24.8)	105 (22.7)	1,807 (22.5)	0.002
55–64	1,213 (55.0)	247 (53.4)	4,272 (53.2)	
65–74	422 (19.1)	109 (23.5)	1,866 (23.2)	
Greater than 75	24 (1.1)	2 (0.4)	92 (1.1)	
Insurance:				
Comprehensive	622 (28.2)	155 (33.5)	2,095 (26.1)	<0.001
HMO	313 (14.2)	66 (14.3)	1,606 (20.0)	
PPO	962 (43.6)	192 (41.5)	3,325 (41.4)	
POS	277 (12.6)	41 (8.9)	896 (11.2)	
Other	12 (0.5)	1 (0.2)	24 (0.3)	
Unknown	20 (0.9)	8 (1.7)	91 (1.1)	
Charlson comorbidity index:				
0	1,661 (75.3)	336 (72.6)	6,317 (78.6)	0.005
1	330 (15.0)	87 (18.8)	1,304 (16.2)	
2	42 (1.9)	13 (2.8)	169 (2.1)	
3+	28 (1.3)	4 (0.9)	50 (0.6)	
Unknown	145 (6.6)	23 (5.0)	197 (2.5)	
Geography:				
Midwest	914 (41.4)	177 (38.2)	2,565 (31.9)	<0.001
Northeast	203 (9.2)	17 (3.7)	650 (8.1)	
South	730 (33.1)	213 (46.0)	2,829 (35.2)	
West	350 (15.9)	51 (11.0)	1,948 (24.2)	
Unknown	9 (0.4)	5 (1.1)	45 (0.6)	

years) and baseline narcotic use (RR 2.70, 95% CI 2.56–2.84) were associated with greater MSe consumption (table 3). Although MIRP was not associated with differences in MSe consumption vs RRP, MIRP was associated with fewer narcotic refills (OR 0.6, 95% CI 0.54–0.69) and lower narcotic prescription costs (RR 0.94, 95% CI 0.90–0.98). Similar to MSe consumption, younger age (less than 55 years OR 2.22, 95% CI 1.38–3.59 and 55 to 64 years OR

Table 2. *Postoperative narcotic prescription refills by surgical approach*

	No. MIRP (%)	No. PRP (%)	No. RRP (%)	Total No (%)
No. refills after initial postop prescription:*	445 (20.2)	196 (42.3)	2,319 (28.9)	2,960 (27.6)
1	265 (12.0)	114 (24.6)	1,498 (18.6)	1,877 (17.5)
2	89 (4.0)	45 (9.7)	354 (4.4)	488 (4.6)
3 or Greater	91 (4.1)	37 (8.0)	467 (5.8)	595 (5.6)

* p <0.001.

1.66, 95% CI 1.04–2.67) and baseline narcotic use (OR 2.85, 95% CI 2.50–3.25) were associated with additional narcotic refills. Paralleling the determinants of MSe use, PRP (RR 1.16, 95% CI 1.08–1.26), younger age (less than 55 years RR 1.48, 95% CI 1.26–1.73 and 55 to 64 years RR 1.34 95% CI 1.15–1.57) and baseline narcotic use (RR 3.00, 95% CI 2.85–3.15) were associated with higher narcotic prescription costs. Significant geographic variation was observed for MSe consumption, narcotic refills and narcotic prescription costs.

DISCUSSION

Direct to consumer advertising suggests that MIRP offers smaller incisions, less postoperative pain and more rapid return to normal activity.[18] However, direct comparisons of pain after MIRP, RRP and PRP remain sparse and inconsistent. For example, Tewari et al reported improved pain using a visual scale in men undergoing RALP vs RRP[2] but Webster et al found that significant differences in RALP vs RRP postoperative pain did not last beyond the postoperative day 1.[10] Wood et al reached a similar conclusion, finding that RALP vs RRP was associated

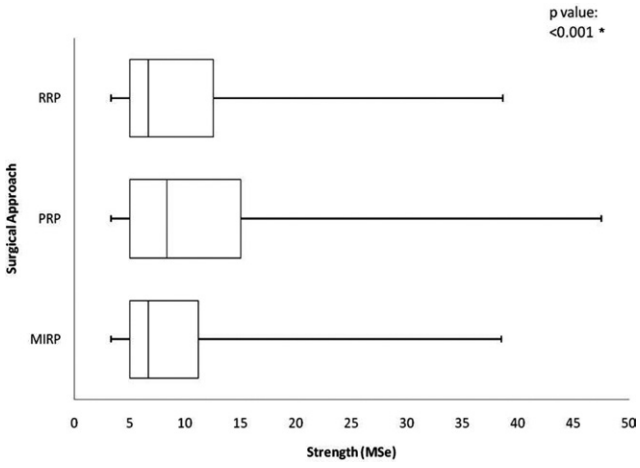

Figure 1. Postoperative narcotic strength in MSe by surgical approach. Asterisk indicates Kruskal-Wallis test.

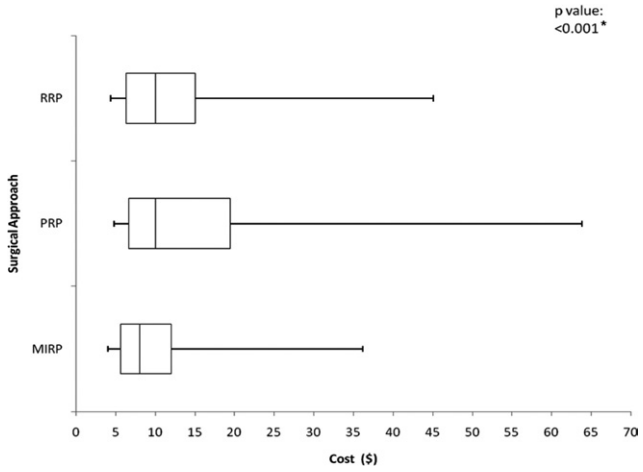

Figure 2. Postoperative narcotic costs by surgical approach. Asterisk indicates Kruskal-Wallis test.

Table 3. *Multivariate model of total postoperative narcotic prescription strength in MSe, narcotic prescription refills needed and total postoperative narcotic cost*

	Total Strength		Additional Refills		Total Cost	
	RR (95% CI)	p Value	OR (95% CI)	p Value	RR (95% CI)	p Value
Surgical approach (vs RRP):						
MIRP	0.97 (0.93–1.01)	0.104	0.61 (0.54–0.69)	<0.001	0.94 (0.90–0.98)	0.003
PRP	1.11 (1.03–1.21)	0.010	1.75 (1.43–2.15)	<0.001	1.16 (1.08–1.26)	<0.001
Age (vs greater than 75):						
Less than 55	1.22 (1.04–1.43)	0.015	2.22 (1.38–3.59)	0.001	1.48 (1.26–1.73)	<0.001
55–64	1.17 (1.01–1.37)	0.045	1.66 (1.04–2.67)	0.035	1.34 (1.15–1.57)	<0.001
65–74	1.13 (0.97–1.32)	0.126	1.27 (0.79–2.05)	0.326	1.17 (1.01–1.37)	0.047
Region (vs West):						
South	1.18 (1.12–1.24)	<0.001	1.07 (0.93–1.22)	0.329	0.91 (0.87–0.95)	<0.001
Midwest	0.84 (0.79–0.91)	<0.001	0.78 (0.64–0.96)	0.016	0.78 (0.73–0.84)	<0.001
Northeast	1.01 (0.96–1.06)	0.674	1.14 (1.00–1.30)	0.050	1.14 (1.09–1.19)	<0.001
Insurance plan (vs HMO):						
Comprehensive	1.02 (0.97–1.08)	0.404	0.94 (0.81–1.10)	0.428	1.01 (0.96–1.07)	0.599
PPO	0.95 (0.91–1.00)	0.045	0.82 (0.72–0.93)	0.002	0.92 (0.88–0.97)	<0.001
POS	0.94 (0.88–1.00)	0.064	0.79 (0.66–0.94)	0.009	1.00 (0.94–1.07)	0.997
Other	0.89 (0.67–1.20)	0.449	0.99 (0.46–2.13)	0.980	0.62 (0.46–0.83)	<0.001
Baseline narcotic use (vs none)	2.70 (2.56–2.84)	<0.001	2.85 (2.50–3.25)	<0.001	3.00 (2.85–3.15)	<0.001
Charlson score (vs 3 or greater):						
0	0.99 (0.82–1.19)	0.904	0.80 (0.49–1.30)	0.370	0.90 (0.75–1.08)	0.246
1	1.18 (0.98–1.42)	0.084	1.06 (0.64–1.75)	0.820	1.09 (0.91–1.31)	0.328
2	1.13 (0.92–1.40)	0.252	0.90 (0.51–1.59)	0.716	0.95 (0.77–1.17)	0.612

with a similar duration of narcotic use.[13] While observational case series are inconsistent, population based comparisons without potential observation biases are lacking. We used a population based approach to determine patterns of postoperative narcotic prescription use among men undergoing MIRP, RRP and PRP.

Our study has several important findings. 1) MIRP was associated with fewer narcotic refills and a lower cost of outpatient narcotics. Similar to our findings, Rassweiler et al found that only 9% of laparoscopic RPs required narcotics on postoperative day 2 vs 55% of RRPs.[4] Also, Bhayani et al found that men undergoing laparoscopic RP postoperatively required fewer narcotics and had shorter time to complete convalescence.[11] More recently Miller et al prospectively compared health related quality of life assessed by a validated questionnaire for RALP vs RRP.[12] RALP was associated with better quality of life 6 weeks after hospital discharge and decreased postoperative pain was a contributing factor. These findings suggest that MIRP confers decreased postoperative pain.

However, despite requiring fewer refills at lower cost MIRP did not differ in MSe requirements compared to RRP on adjusted analysis. While the 8% increment in RRP vs MIRP refills may be statistically significant and contribute to greater narcotic costs since each refill is accompanied by health plan expenses, it did not contribute to significant differences in MSe requirements.

Conversely PRP was associated with more MSe use, narcotic refills and greater costs than MIRP and RRP. This contrasts with the notion that the perineal approach is associated with significantly less postoperative pain. For instance, in a prospective study Namiki et al found less postoperative pain during hospitalization for PRP than for RRP and MIRP.[19] While our findings contrast with those of Namiki et al, the greater PRP outpatient narcotic prescription use may reflect neuropathic pain not captured by inpatient studies. Also, PRP is done with the patient in an exaggerated lithotomy position, which may result in lower extremity neuropraxia in up to 21% of patients.[20]

2) Younger men required more outpatient narcotics at a greater cost. This finding correlates with that of Mattila et al, who noted that age greater than 65 years was a significant predictor of decreased postoperative pain after ambulatory surgery.[21] In a large meta-analysis Ip et al found that younger age was a strong predictor of postoperative pain and analgesia requirement.[22] Suggested influences contributing to lower narcotic requirement in elderly patients may include blunted nociceptive function resulting in increased pain tolerance[23] and an alteration in pharmacokinetics with age that leads to increased narcotic sensitivity.[24,25] Elderly patients are also given fewer narcotic prescriptions due to concern regarding increased postoperative pulmonary and gastrointestinal complications.[26] Finally, younger men may need to return to work and resume daily life activity at a more rapid pace than potentially retired older men, leading to a greater need for narcotics.

3) Health plan type was significantly associated with post-prostatectomy narcotic prescription use. The 4 health care plans examined in our study included the most commonly used health plans for insurance coverage in the United States. Comprehensive care coverage is the least restrictive of the health plan types with few barriers in choice of physicians and medications, although at higher cost. HMO plans are capitated with an assigned primary care physician selected from a list of providers that coordinate all patient care. POS and PPO plans have financial incentives to use specific providers in a physician network with the former requiring an assigned primary care physician to coordinate care.[27] After RP men with PPO and POS plans required fewer narcotic refills while PPO was also associated with lower cost and total narcotic prescription strength. Joyce et al found that prescription costs among employer provided health care plans were lower in plans with tiered copayment systems for patients seeking out of network care and nonpreferred medications.[28] Thus, higher copayments in PPO and POS plans may have dissuaded men in our study from seeking additional narcotic refills postoperatively.

4) There was significant geographic variation in narcotic prescribing patterns. Men in the Midwest required fewer narcotic refills, corresponding to lower total narcotic strength and cost. Similarly Webster et al observed that patients in the South were more likely to receive a greater amount of narcotics for lower back pain due to numerous socioeconomic factors.[29] Using a population based approach Curtis et al noted significant geographic variation in narcotic prescription use among states with notably lower rates of narcotic prescription use in states with prescription monitoring programs that prevent narcotic abuse.[30]

Our findings must be interpreted in the context of our study design. 1) We characterized outpatient narcotic prescribing patterns and refills rather than directly measuring pain with validated instruments. We could not assess inpatient analgesic requirements. 2) We could only capture narcotics filled with a prescription and covered by health plans. Thus, we could not assess the use of nonsteroidal anti-inflammatory drugs and acetaminophen purchased over the counter without a prescription. 3) While our study design assessed whether a prescription had been filled, we could not determine whether all prescribed narcotics were consumed. Since our data reflects narcotic prescriptions provided and not necessarily consumed, this may simply be an over reflection of physician practice patterns rather than of patient narcotic need. However, to our knowledge our population based findings are the first to characterize post-prostatectomy outpatient narcotic use in the United States. Most studies of post-prostatectomy pain have not used objective assessment of long-term pain requirements, focusing primarily on immediate postoperative pain with reliance on subjective, nonvalidated pain scales. 4) Our cost analysis likely underestimates post-prostatectomy outpatient narcotic costs and may underestimate cost differences by surgical approach since we could not assess contributions from copayments, deductibles and supplementary insurance.

CONCLUSIONS

While up to 27.6% of men require narcotic refills after RP, those who underwent MIRP vs RRP and PRP required fewer narcotic refills with lower narcotic costs. However, MIRP and RRP MSe requirements did not differ on adjusted analysis. Conversely men who underwent PRP required the greatest amount of narcotics at the highest cost. Our findings are consistent with those of others revealing less postoperative pain for MIRP than for open surgical approaches to RP. However, prospective studies with objective outcomes are required to confirm this finding.

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EDITORIAL COMMENTS

These authors address the controversy surrounding whether MIRP causes less postoperative pain than RRP and brings to mind some thought provoking issues for future study. On multivariate analysis they found that the MSe between MIRP and RRP was equivalent but patients with RRP required more refills, creating higher overall prescription costs. One wonders why this is the case. Perhaps patients undergoing RRP were given more pills per prescription than their MIRP counterparts due to prescribing physician biases that those with RRP would need more medication. Also, patients who did not fill a narcotic prescription within 7 days of hospital discharge were excluded from analysis. It would be interesting to know whether there were any differences between groups in these patients. Lastly and somewhat surprisingly the patients with the highest MSe requirement were the PRP group, possibly due to postoperative neuropathic pain issues, as the authors propose.

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Comparing pain and convalescence after prostate cancer surgery is challenging when considering single surgeon experiences. In that regard population based data despite some inherent limitations provide information that may be more generalizable to all practitioners. This study allows for several observations. To my surprise PRP appears to be significantly more painful than a minimally invasive or retropubic approach. Also, MIRP may cause less pain than RRP, although the jury is still out. Indeed, adjusted analysis revealed no differences in narcotic prescription strength between the 2 modalities, although patients with RRP required more refills (table 3). The latter observation begs the obvious question of the clinical vs the statistical significance of such differences. Finally, while it is beyond the scope of this data set, one wonders whether a difference in pain may be attributable to postoperative ileus when considering intraperitoneal vs extraperitoneal MIRP. Prospective evaluation at a multicenter study may delineate this further.

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REVIEW

Utilization of Pharmacotherapy for Erectile Dysfunction Following Treatment for Prostate Cancer

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ABSTRACT

Introduction. Pharmacotherapies improve sexual function following treatments for localized prostate cancer; however, patterns of care remain unknown.

Aim. To ascertain post-treatment utilization of pharmacotherapies for erectile dysfunction (ED) using a population-based approach.

Methods. We identified 38,958 men who underwent definitive treatment for localized prostate cancer during 2003–2006 from the MarketScan Medstat data.

Main Outcome Measures. We compared the use of ED pharmacotherapy at baseline (up to 3 months prior) and up to 30 months following radical prostatectomy (RP) or radiotherapy (RT) for localized prostate cancer by utilizing National Drug Classification codes for phosphodiesterase-5 inhibitors (PDE5I), intracavernosal injectable therapies (IT), urethral suppositories and vacuum erection devices (VED). In adjusted analyses, we controlled for the effect of age, comorbidity, type of treatment, health plan and use of adjuvant hormone therapy on the use of pharmacotherapies.

Results. Men undergoing RP vs. RT were younger with less co-morbid conditions. Utilization of PDE5I was up to three times greater for men undergoing RP vs. RT, 25.6% vs. 8.8%, ($P < 0.0001$) in the first post-treatment year, and usage of these agents was greatest for men undergoing minimally-invasive RP procedures. A higher percentage of men also used IT, suppositories and VED after RP vs. RT ($P < 0.001$). However, more men in the RT group received adjuvant hormonal therapy (39.53% vs. 5.25% for RP, $P < 0.01$). In adjusted analyses, men undergoing RP vs. RT were more than two times likely (OR 2.1, 95% CI 1.98, 2.26) to use PDE5I post-treatment while men on adjuvant hormonal therapy were less likely to use PDE5I (OR 0.74, 95% CI 0.70–0.79, $P < 0.0001$).

Conclusion. Men undergoing RP vs. RT, particularly minimally-invasive RP, are more likely to employ IT, suppositories, VED, and PDE5I pharmacotherapy post-treatment. **Prasad MM, Prasad SM, Hevlone ND, Gu X, Weinberg AC, Lipsitz SR, Palapattu GS, and Hu JC. Utilization of pharmacotherapy for erectile dysfunction following treatment for prostate cancer. J Sex Med 2010;7:1062–1073.**

Key Words. Erectile Dysfunction; Prostate Cancer; Pharmacotherapy; PDE5 Inhibitors

Introduction

Definitive therapy for prostate cancer may result in erectile dysfunction (ED). Sexual function diminishes gradually following

Assurances: The data were de-identified and, therefore, the research protocol was exempt from institutional review boards. The authors examined the data and do not have any conflicts of interest or disclosures to report.

radiotherapy, whereas men experience an immediate decline followed potentially by gradual recovery after nerve-sparing radical prostatectomy (RP) [1–3]. Recovery of sexual function has been found to be higher in single-center studies and younger men, while no difference has been noted between single and multiple-surgeon series and surgical approach[4]. Moreover, the prevalence of post-treatment erectile dysfunction varies widely in published reports but may be as high as 80–90%, depending on the type of treatment and pre-operative erectile function [5,6]. While many studies have assessed the benefit of pharmacotherapy for erectile dysfunction after treatment for prostate cancer, few have characterized patterns of utilization [7–13]. Because long-term survival is relatively high following any treatment for localized prostate cancer, maintaining health-related quality of life (HRQOL) is critical. Since the dawn of the prostate specific antigen (PSA) era, localized disease and smaller tumors have been increasingly prevalent in younger men for whom maintaining sexual function is particularly relevant. Furthermore, use of pharmacotherapies for erectile dysfunction improves HRQOL and impacts satisfaction with prostate cancer care [14].

However, the timing of pharmacotherapy to maximize post-treatment sexual function remains debatable. There are few randomized controlled trials (level 1A evidence) demonstrating the effectiveness of these medications in the immediate post-operative period [12,13,15–17]. In addition, the financial burden of pharmacotherapies for ED has been the subject of recent investigation and adds to the indirect costs of treatment of prostate cancer [18].

The goal of our study was to determine patterns of care for the utilization of various types of ED pharmacotherapy following different treatments for localized prostate cancer.

Methods

We identified 38,958 men treated for localized prostate cancer using 2003–2006 Medstat MarketScan® administrative data, a national sample drawn from large self-insured U.S. employers. More than 80 employers contribute data to MarketScan. Claims data are received from all of their medical and pharmaceutical insurers to capture the inpatient, outpatient, and outpatient prescription experience of several million beneficiaries and their dependents covered under a variety of fee-for service and capitated health plans, including preferred provider organizations, point of service plans, indemnity plans, and health maintenance organizations [19].

Men who underwent open (i.e., perineal and retropubic RP), and minimally invasive (i.e., laparoscopic RP with or without robotic assistance) surgery for prostate cancer (N = 18,928) were identified based on the presence of Physicians Current Procedural Terminology Coding System (4th) edition [CPT-4]): codes 55810, 55812, 55815 for perineal radical prostatectomy (PRP); 55840, 55842, 55845 for retropubic radical prostatectomy (RRP); and 55866 for minimally-invasive radical prostatectomy (MIRP). While CPT-4 code 55899 (unlisted procedure male genital system) may sometimes be used along with an ICD-9 code for radical prostatectomy to bill for MIRP, this has poor sensitivity and, we found very few men with this combination of codes; it was therefore excluded. Men who underwent radiation therapy (i.e., external beam radiation [RT] and interstitial brachytherapy [BT]) or a combination of the two (BT + RT) (N = 20,030) were identified on the presence of CPT-4 and Healthcare Common Procedure Coding System (HCPCS) codes as well as an International Classification of Disease, 9th edition primary diagnosis for prostate cancer (ICD-9: 185) (see Appendix). Men undergoing radiotherapy due to metastases were excluded. Use of concurrent adjuvant hormonal therapy (HT) was captured by HCPCS codes (see Appendix). Furthermore, in order to characterize baseline utilization of ED pharmacotherapy, we captured medication use in the 3 months prior to prostate cancer treatment and denoted this as baseline usage prior to therapy. To ensure complete follow-up, subjects were censored if they changed health plan coverage during the 30-month follow-up. Comorbidities were assessed using the Charlson index based on administrative data captured the year prior to treatment [20].

Utilization rates for phosphodiesterase inhibitors (PDE5I), intracavernosal injectable therapies (IT), alprostadil urethral suppositories, and vacuum erection devices (VED) were derived on the basis of National Drug Classification and Health Care Common Procedure Coding System codes (see Appendix). However, we were unable to assess ED pharmacotherapy utilization that did not require a prescription, i.e., cash paying patients, samples, or internet purchases.

Any utilization of these therapies was captured in the following 6-month intervals in addition to the aforementioned baseline period: 0–6, 7–12,

13–18, 19–24, and 25–30 months. Utilization rates of IT, urethral suppositories, and VED were very low and thus excluded from adjusted analyses.

Multivariate models were constructed to determine the effect of treatment approach on utilization of PDE5I while adjusting for age, comorbidity, use of hormone therapy, and health insurance coverage. We compared the four most common types of health plans for insurance coverage in the United States: comprehensive care, health maintenance organization (HMO), point of service (POS), and preferred provider organization (PPO) plans. The pertinent aspects of these plans are reviewed in more detail later. These analyses were performed with a stratification of therapies by surgical approach and radiotherapy technique. The c-statistic was used to estimate overall model predictive values.

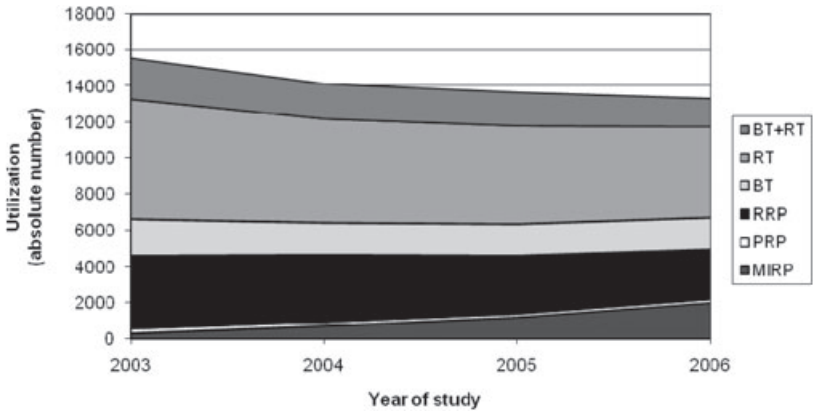
The Pearson Chi-Square coefficient was used to detect differences in demographic characteristics and utilization patterns over time. Generalized estimating equations were used to obtain an overall odds ratio estimate, pooled over time, for the effect of hormone therapy on usage of PDEI. In all analyses, $P < 0.05$ was used to denote significance.

Results

Median follow-up for the study sample was 452 days. Over the four-year study period, overall utilization of RP remained relatively constant while utilization of RT declined overall (Figure 1). Further analysis demonstrated that increased MIRP utilization was offset by a decreased utilization of RRP. Meanwhile, use of RT and BT+RT decreased while use of BT remained relatively constant. The demographic characteristics of our study population are shown in Table 1. Men undergoing RP vs. radiotherapy were younger, had less co-morbid conditions, and differed in health plan status. The median duration of adjuvant hormonal therapy was 271.7 days, and more men used hormone therapy in conjunction with RT vs. RP (39.5% vs. 5.3%, $P < 0.01$).

At baseline, a similar proportion of men undergoing RP and RT used PDE5I (5.4% vs. 5.8%, $P = 0.05$) and urethral suppositories (0.04% vs. 0.1%, $P = 0.97$) (Table 2). Usage of PDE5I was significantly greater for men undergoing RP vs. RT at each six month post-treatment time interval, with a striking difference of two to three times greater utilization during the first post-treatment year (OR 2.4, 95% CI 2.26–2.62). This usage difference attenuated over time but remained significant more than two years post-treatment. The same trend was observed for urethral suppositories.

When sub-stratifying by treatment type, usage of PDE5I was greatest for MIRP followed by RRP and PRP at baseline and in the first postoperative year (Figure 2). Beyond one year, PDE5I usage remained greatest for MIRP, remaining just below 20%, while PRP PDE5I usage equaled and then exceeded RRP utilization during this period ($P < 0.01$). BT PDE5I usage exceeded BT + RT followed by RT usage at baseline and throughout the post-treatment six month period ($P < 0.01$). Moreover, when stratified by age (Figure 3), greater than 30% vs. approximately 20% of men aged less than 60 years used PDE5I following RP vs. RT ($P < 0.001$). While a similar pattern of significantly greater post-treatment utilization of IT and VED emerged in the RP vs. RT cohorts, base-



RT = external beam radiotherapy; BT = interstitial brachytherapy; RRP = radical retropubic prostatectomy; PRP = perineal radical prostatectomy; MIRP = minimally invasive radical prostatectomy

Figure 1 Treatment utilization for localized prostate cancer over the 4-year study period.

Table 1 Patient Demographics, 2003–2006

	Radical prostatectomy		Radiation therapy		
	n	%	n	%	*P* value
Age					
≤55	3,542	18.7	928	4.6	<0.0001
56–60	4,809	25.4	2,082	10.4	
61–65	5,593	29.6	3,766	18.8	
66–70	2,952	15.6	3,272	16.3	
71–75	1,586	8.4	4,749	23.7	
≥76	446	2.3	5,233	26.1	
Insurance status					
Comprehensive	4,593	24.3	8,606	43.0	<0.0001
HMO	3,433	18.1	4,493	22.4	
PPO	8,431	10.1	841	4.2	
POS	1,917	44.5	5,648	28.2	
Other	554	2.9	442	2.2	
Charlson comorbidity index					
0	12,264	73.4	11,616	64.0	<0.0001
1–2	4,087	24.5	5,707	31.5	
≥3	355	2.1	825	4.6	
Use of hormone therapy	994	5.3	7,917	39.5	<0.0001

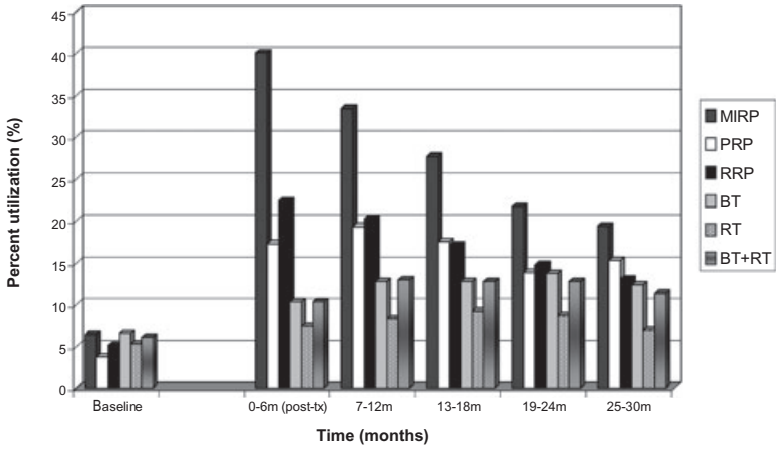
HMO = health maintenance organization; PPO = preferred provider organization; POS = point of service health plan.

line usage differed (Table 2). IT usage was more prevalent prior to radiotherapy vs. surgery while VED use was not observed pre-treatment in either cohort.

In adjusted analyses (Table 3), men undergoing surgery vs. radiotherapy were more than two times more likely (OR 2.1, 95% CI 1.98, 2.26) to use PDE5I post-treatment. Younger age and less co-morbidity were also significant determinants of PDE5I usage. Health plan type was also a significant determinant of post-treatment PDE5I usage, with comprehensive plan enrollees almost three

Table 2 Utilization of pharmacotherapy for erectile dysfunction

	Radical prostatectomy (N = 18,928)		Radiation therapy (N = 20,030)		
Time interval (months)	N	%	N	%	p-value
PDE5-Inhibitors					
Baseline	1,012	*5.4*	1,163	*5.8*	0.0482
0–6 (post-tx)	3,604	*25.6*	1,375	*8.8*	<0.0001
7–12	2,290	*22.3*	1,241	*10.6*	<0.0001
13–18	1,447	*18.7*	972	*11.0*	<0.0001
19–24	839	*15.6*	651	*11.0*	<0.0001
25–30	490	*13.8*	345	*9.4*	<0.0001
Injectable Therapies					
Baseline	13	*0.1*	29	*0.1*	0.0222
0–6 (post-tx)	181	*1.3*	23	*0.1*	<0.0001
7–12	234	*2.3*	36	*0.3*	<0.0001
13–18	179	*2.3*	23	*0.3*	<0.0001
19–24	128	*2.4*	17	*0.3*	<0.0001
25–30	73	*2.1*	11	*0.30*	<0.0001
Urethral Suppositories					
Baseline	8	*0.0*	18	*0.1*	0.069
0–6 (post-tx)	226	*1.6*	23	*0.2*	<0.0001
7–12	206	*2.0*	33	*0.3*	<0.0001
13–18	122	*1.6*	29	*0.3*	<0.0001
19–24	83	*1.5*	11	*0.2*	<0.0001
25–30	43	*1.2*	17	*0.5*	0.0005
Vacuum Erection Device					
Baseline	0	—	0	—	—
0–6 (post-tx)	583	*4.1*	26	*0.2*	<0.0001
7–12	227	*2.2*	25	*0.2*	<0.0001
13–18	82	*1.1*	16	*0.2*	<0.0001
19–24	36	*0.7*	10	*0.2*	<0.0001
25–30	0	—	0	—	—



*Numbers based on the larger cohort of 38,958 men
MIRP = minimally invasive radical prostatectomy; RRP = radical retropubic prostatectomy; PRP = perineal radical prostatectomy; BT = interstitial brachytherapy; RT = external beam radiotherapy

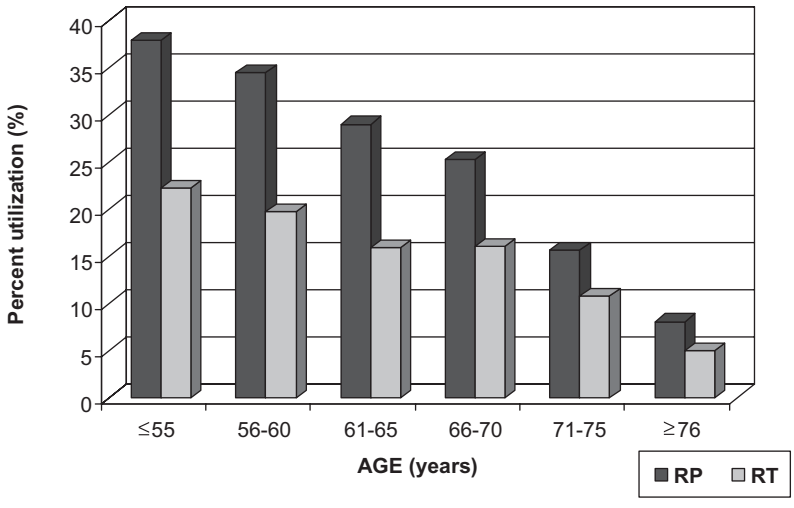
Figure 2 Utilization of phosphodiesterase-5 inhibitors before and after therapies for prostate cancer. Baseline denotes a period up to 3 months prior to treatment.*

times more likely to use PDE5I, followed by greater use for men covered by PPO and POS health plans using HMO plan beneficiaries as the referent group. For the surgical cohort, men who underwent MIRP vs. RRP were 1.8 times more likely (95% CI 1.7, 1.9) to use PDE5I, while men who underwent PRP vs. RRP were 0.8 times (95% CI 0.6, 0.9) as likely to use PDE5I. For recipients of radiotherapy, men who received BT vs. RT were more likely to use PDE5I post-treatment (OR 1.7, 95% CI 1.5, 1.9), while those who underwent BT + RT vs. RT alone were also more likely (OR 1.4, 95% CI 1.3, 1.6) to use PDE5I post-treatment. For the overall population, men using hormonal therapy, regardless of treatment type, were less likely to use PDE5I (OR 0.74, 95% CI 0.70, 0.79).

Discussion

Modern management of prostate cancer seeks to optimize both functional—voiding and erectile dysfunction—and oncologic outcomes. Refinements in radiation delivery and adoption of nerve-sparing techniques during radical prostatectomy have improved post-treatment sexual function without sacrificing oncologic control [21,22]. Despite these advances, many men require pharmacotherapy assistance to achieve adequate sexual function following treatment for prostate cancer [23].

Sun et al. reported that men with ED spend $119 annually for all ED-related services and treatments. This amounts to an annual burden of >$120,000



RP = radical prostatectomy; RT = radiotherapy

Figure 3 Utilization of phosphodiesterase-5 inhibitors before and after therapies for prostate cancer. Baseline denotes a period up to 3 months prior to treatment.

Table 3 Adjusted analyses of phosphodiesterase-5 inhibitor usage in men undergoing treatments for localized prostate cancer

	ALL		Radical Prostatectomy		Radiotherapy	
	OR	95% CI	OR	95% CI	OR	95% CI
Treatment type						
Surgery vs. radiotherapy	2.11	1.98–2.26				
Surgical approach (referent = RRP)						
MIRP			1.77	1.63–1.92		
PRP			0.78	0.64–0.94		
Radiotherapy technique (referent = RT)						
BT					1.64	1.47–1.84
BT + RT					1.58	1.42–1.77
Age (referent = >75 years)						
<55	7.18	6.17–8.35	10.34	7.01–15.24	6.74	5.46–8.32
55–60	5.83	5.05–6.74	8.49	5.78–12.49	5.61	4.70–6.71
60–65	4.13	3.60–4.75	6.18	4.21–9.08	4.00	3.40–4.70
65–70	3.15	2.73–3.62	4.50	3.05–6.64	3.25	2.77–3.81
70–75	1.96	1.70–2.27	2.47	1.65–3.70	2.21	1.90–2.58
Charlson score (referent = 3)						
0	1.60	1.32–1.94	1.36	1.04–1.77	1.99	1.53–2.57
1 or 2	1.29	1.05–1.57	1.09	0.83–1.43	1.55	1.18–2.02
Insurance plan (referent = HMO)						
Comprehensive	3.06	2.78–3.35	2.99	2.65–3.37	2.81	2.44–3.24
PPO	1.62	1.41–1.85	1.73	1.56–1.93	1.57	1.20–2.06
POS	1.81	1.66–1.98	1.51	1.29–1.77	1.77	1.52–2.07
Other	0.52	0.41–0.67	0.42	0.31–0.56	0.66	0.44–0.99
Hormone therapy (referent = No)	0.74	0.70–0.79	0.72	0.58–0.90	0.90	0.84–0.98
c-statistic	0.77		0.70		0.80	

RRP = radical retropubic prostatectomy; MIRP = minimally invasive RP; PRP = perineal RP; RT = external beam radiotherapy; BT = interstitial brachytherapy; HMO = health maintenance organization; PPO = preferred provider organization; POS = point of service.

to a health plan with 100,000 members [18]. IT was the first form of medical therapy for post-prostatectomy ED and was followed by the introduction of PDE5I in 1998 [23,24]. Utilization of these pharmacotherapies has grown and has perhaps been influenced by the direct-to-consumer advertising by the Internet, magazines, and television now prevalent in the United States [25,26]. The United States is one of the few countries that allow direct-to-consumer advertising and this may affect pharmacotherapy utilization. Recently, a survey by the National Prostate Cancer Coalition revealed that the Internet ranked ahead of physicians as the most popular and trusted source of information for men with prostate cancer [27,28].

Population-based ED pharmacotherapy utilization patterns following prostate cancer surgery and radiotherapy treatments have not been previously described. Quantifying utilization is important as interest grows in post-surgical potency rehabilitation protocols [11,16,17,29]. A recent survey of French urologists revealed that 38% routinely recommend ED treatment of some form (PDE5I, IT, or VED) to their patients after RP [10]. Few multi-center, randomized controlled trial results (level 1A evidence) exist to prove the effectiveness of these protocols, although a recent trial did demonstrate improved efficacy with on-demand dosing vs. daily consumption [12,30] While basic science studies have supported beneficial local effects on penile tissue with daily dosing, human studies have not demonstrated significant clinical benefit in the post-prostatectomy patient [31]. Utilization of these therapies—either on-demand or with daily consumption—contributes significantly to indirect treatment costs following RP, both through capital expense and possible side-effects of medication utilization [32]. Furthermore, the discontinuation rate from PDE5I treatment in post-RP patients may not be insignificant if patients are not adequately counseled; a recent prospective study showed that only 51% of sexually active participants chose to initiate any ED therapy despite a professed interest in maintaining potency post-RP [33]. Any successful rehabilitation protocol should incorporate education and

not merely access to pharmacotherapy as early treatment failure does not automatically exclude future success [34].

Our study has several important findings. First, we identified contemporary patterns of care for competing localized prostate cancer treatments and ED therapies before and after these treatments. PDE5I, IT, and VED usage all increased dramatically immediately following surgery and radiotherapy and attenuated gradually over our 30-month follow-up period. In addition, PDE5I was the most popular ED therapy followed by IT and VED. The attenuation of ED medical therapy usage may be due to recovery of sexual function and/or absence of efficacy over the follow-up time interval [14,33,35]. This needs further investigation.

Second, we characterized the utilization rates by overall treatment type and specific surgical approach and radiotherapy technique. PDE5I usage was greater for men who underwent surgery vs. radiotherapy; a difference that persisted after controlling for hormonal therapy usage. Immediately following therapy, the use of PDE5I was more than two fold greater in men undergoing RP vs. RT after adjusting for age and co-morbidities. Among surgical subjects, PDE5I usage was greatest for patients undergoing MIRP followed by RRP and PRP. Similarly, among radiotherapy subjects, PDE5I usage was greatest for BT followed by BT+RT and RT alone. Prior studies have demonstrated a more rapid recovery of baseline sexual function in RT patients when compared to BT and RP alone [14,36]. As expected, men on hormone therapy were less likely to use PDE5I. Since HT is more frequently given in conjunction with RT, this is a potential confounder. We controlled for this factor in adjusted analyses and continued to identify significant differences in PDE5I usage by treatment type.

One explanation for the greater utilization of ED pharmacotherapy after MIRP vs. open approaches may be related to market forces and direct-to-consumer advertising that drives increased MIRP utilization in the United States. This cohort of men may be more likely to seek out and embrace "new" techniques or approaches and, therefore, have greater interest in post-prostatectomy potency rehabilitation programs despite the absence of level 1A evidence. Furthermore, there may be heightened expectations for improved functional outcomes after MIRP, as suggested by a recent study which demonstrated greater regret and dissatisfaction in men following MIRP vs. RRP [37]. Thus, the expectation of a "faster" recovery may contribute to a greater interest in using ED pharmacotherapy early in the post-treatment period. Additionally, the growing literature supporting the safe utilization of testosterone replacement therapy following radical prostatectomy may influence functional outcomes if ED severity improves following concomitant testosterone with ED pharmacotherapy [38,39].

Third, in addition to age and comorbidities, type of health plan was a strong determinant of PDE5I usage while hormone therapy had a negative effect. There are four commonly used health plans for insurance coverage in the United States: comprehensive care, HMO, POS, and PPO. Comprehensive care coverage is the least restrictive of the health plan types. For instance, HMO plans are capitated with an assigned primary-care physician selected from a list of providers. POS and PPO plans have financial incentives to utilize specific providers with the former requiring an assigned PCP. Although no definitive statement can be made about these relationships based on our data, it appears that beneficiaries of less restrictive health plans were more likely to utilize pharmacotherapies for ED.

Our findings must be interpreted in the context of our study design. First, administrative data does not contain a baseline or post-treatment sexual function assessment. Prior studies have demonstrated the importance of understanding the baseline potency rate in men undergoing treatment for radical prostatectomy. Up to one-quarter to one-third may have pre-existing moderate to severe ED which may confound medical decision-making and treatment outcomes [40,41]. Thus, given the lack of pre-existing baseline data, we may have been unable to best characterize the effectiveness of the pharmacotherapy in each group. Second, our use of administrative data does not capture the use of pharmaceuticals that were not filled with a prescription or not covered by the health plan, i.e., samples or medications obtained over the internet or obtained by cash-paying patients. Nor does it ascertain whether a filled prescription was actually consumed. This could potentially act as a confounder if younger men were more likely to undergo MIRP and self-prescribe via the Internet. Moreover, we were unable to assess patient income, as more affluent men may be more likely to employ pharmacotherapies for erectile dysfunction. However, ED pharmacotherapies require physician prescriptions in the United States, which would be cap-

tured by our administrative data. This is an advantage of the database as compared to data from countries where it may be purchased over the counter and difficult to track. Third, we were unable to ascertain the race of our subjects, which has been shown to be a determinant of post-operative sexual function [2]. Finally, we were unable to adjust for tumor characteristics or treatment techniques that affect post-treatment sexual function (i.e., nerve-sparing during surgery, conformal or intensity modulated radiotherapy, or the delivery dose of radiotherapy).

Conclusion

Men undergoing RP or MIRP (versus RT) are more likely to employ pharmacotherapy for ED in the immediate post-operative period. This may be impacted by the rising interest in immediate post-RP potency rehabilitation with pharmacotherapies; however, the efficacy of the early use of pharmacotherapy for ultimate recovery of sexual function remains unclear.

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Conflict of Interest: None.

Statement of Authorship

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Category 3

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Appendix

National Drug Classification (NDC) codes for phosphodiesterase-5 inhibitors

GENERIC (TRADE) NAME	NDC Number	Application Number	DOSAGE
Vardenafil (*Levitra*)	12527-8710	021400	2.5MG
	12527-8720	021400	5.926MG
	12527-8730	021400	10MG
	12527-8740	021400	20MG
	00085-1934	021400	20MG
	00085-1901	021400	10MG
	00085-1945	021400	5MG
	00085-1923	021400	2.5MG
	65243-*334	021400	10MG
	65243-*335	021400	20MG
(Levitra) *Vardenafil*	63629-3372	021400	20MG
	00179-1522	021400	20MG
	49999-*625	021400	20MG
	51129-3586	021400	5MG
	54868-4967	021400	20MG
	67544-*512	021400	10MG
	67544-*507	021400	20MG
	67296-0286	021400	20MG
Sildenafil (*Viagra*)	63629-1792		100MG
(Viagra) *Sildenafil*	54569-4568	20895	25MG
	54569-4570	20895	100MG
	54569-4569	20895	50MG
	66105-*536		100MG
	66105-*535		50MG
	57866-7981	20895	100MG
	55887-*118	20895	100MG
	66267-*406	20895	100MG
	55289-*524	20895	100MG
	00069-4200	20895	25MG
	00069-4210	20895	50MG
	00069-4220	20895	100MG
	65837-*420	20895	25MG
	65837-*421	20895	50MG
	65837-*422	20895	100MG
	65427-*422	20895	100MG
	54868-4784	20895	25MG
	54868-4084		50MG
	68788-4220	20895	100MG
	58864-*862	20895	50MG
	67544-*356	20895	100MG
	21695-*158	20895	100MG
	21695-*157	20895	50MG
	67296-0265	20895	100MG
	58016-*371	20895	100MG
	58016-*355	20895	50MG
	63539-*421	20895	50MG
	63539-*422	20895	100MG
Tadalafil (*Cialis*)	54569-5544	021368	10MG
	12280-*166	021368	20MG
	55887-*117	021368	20MG
	00002-4462	021368	5MG
	00002-4463	021368	10MG
	00002-4464	021368	20MG
	00110-1105	021368	10MG
	00110-1106	021368	20MG
	00110-4464	021368	20MG
	00110-4463	021368	10MG
	00110-4462	021368	5MG
	68071-*606	021368	10MG
	54868-4665	021368	10MG
	21695-*028	021368	10MG
	21695-*029	021368	20MG
	67296-0266	021368	20MG
	58016-*306	021368	5MG

Appendix Continued

National Drug Classification (NDC) codes for injectable therapies

GENERIC (TRADE) NAME	NDC Number	Application Number	DOSAGE
Alprostadil (*Caverject*)	59603-5182	021212	20MG
	59632-5182	021212	20MCG/0.5ML
	59632-5181	021212	10MCG/0.5ML
	59267-5182	021212	20MCG/0.5ML
	59267-5181	021212	10MCG/0.5ML
	00009-5182	021212	20MCG/0.5ML
	00009-5181	021212	10MCG/0.5ML
	00009-5131	020379	5MCG/ML
	00009-7686	020379	40.0MCG
	00009-3701	020379	20MCG
	00009-3701	Other	20MCG
	00009-3778	020379	10MCG
	00009-3778	Other	10MCG
	54868-4890	021212	20;45.4MCG/0.5ML;
Alprostadil (*Muse*)	62541-*120	020700	250MCG
	62541-*110	020700	125MCG
	62541-*140	020700	1000MCG
	62541-*130	020700	500MCG
Alprostadil (*Edex*)	00091-1027	020649	347.55;10.MCG;MCG
	00091-1027	Other	347.55;10.MCG;MCG
	00091-1029	020649	695.2;21.5MCG;MCG
	00091-1029	Other	695.2;21.5MCG;MCG
	00091-1032	020649	40MCG
	00091-1032	Other	40MCG
	00091-1110	020649	10MCG
	00091-1110	Other	10MCG
	00091-1120	Other	20MCG
	00091-1140	020649	40MCG
	00091-1140	Other	40MCG
	00091-1040	020649	40MCG/VIAL
	00091-1020	020649	20MCG/VIAL
	00091-1010	020649	10MCG
	00131-1110	020649	10MCG
	00131-1110	Other	10MCG
	00131-1120	020649	20MCG
	00131-1120	Other	20MCG
	00131-1140	020649	40MCG
	00131-1140	Other	40MCG
	62195-*801	020649	347.55;10.MCG;MCG;%
	62195-*801	Other	347.55;10.MCG;MCG;%
	62195-*802	020649	695.2;21.5MCG;MCG;%
	62195-*802	Other	695.2;21.5MCG;MCG;%
	62195-*803	020649	1390.3;43;MCG;MCG;%
	62195-*803	Other	1390.3;43;MCG;MCG;%
Alprostadil	55390-*503	074815	500MCG/ML
	55390-*506	074815	500MCG/ML
	10130-*506	074815	500MCG/ML
	00703-1501	075196	500MCG/ML
Phentolamine (*Regitine*)	14656-9898	Other	
	17088-6830	008278	5MG
	00083-6830	008278	5MG/VIAL
Phentolamine	55390-*113	040235	5MG/VIAL
	10130-*113	040235	5MG/VIAL

Appendix Continued

GENERIC (TRADE) NAME	NDC Number	Application Number	DOSAGE
Papaverine	54575-*014	Other	30MG/ML
	54575-*015	Other	30MG/ML
	00517-4002	Other	30MG/ML
	00517-4010	Other	30MG/ML
	55390-*107	Other	30MG/ML
	10130-*107	Other	30MG/ML
	36000-*015	Other	60MG/2ML
	55045-1629	Other	150MG
	66758-*015	Other	30MG/ML
	00185-5156	Other	150MG
	60267-*518	Other	30MG/ML
	00179-1773	Other	150MG
	10797-*400	Other	30MG/ML
	10797-*401	Other	30MG/ML
	00904-2180	Other	150MG
	11704-*236	Other	30MG/ML
	11704-*238	Other	30MG/ML
	54868-3663	Other	150MG
	00603-5043	Other	150MG
	11098-*517	Other	30MG/ML

Codes for Defining Treatment

Type of Treatment	Procedure Codes
Brachytherapy (BT)	ICD-9: 9227 CPT-4: 55860, 55865, 55862, 55859, 77326, 77327, 77328, 77331, 77750, 77751, 77752, 77753, 77754, 77755, 77756, 77757, 77758, 77759, 77760, 77761, 77762, 77763, 77764, 77765, 77766, 77767, 77768, 77769, 77770, 77771, 77772, 77773, 77774, 77775, 77776, 77777, 77778, 77779, 77780, 77781, 77782, 77783, 77784, 77785, 77786, 77787, 77788, 77789, 77790, 77791, 77792, 77793, 77794, 77795, 77796, 77797, 77798, 77799 HCPCS: C1715, C1716, C1717, C1718, C1719, C1728, C2632, C2633, C2634, C2635, C2636, Q3001
Radiotherapy (RT)	ICD-9: 9222, 9223, 9224, 9225, 9226, 9229 CPT-4: 77401, 77402, 77403, 77404, 77405, 77406, 77407, 77408, 77409, 77410, 77411, 77412, 77413, 77414, 77415, 77416, 77417, 77418, 77419, 77420, 77421, 77422, 77423, 77424, 77425, 77426, 77427, 77428, 77429, 77430, 77431, 77520, 77521, 77522, 77523, 77524, 77525
Hormone therapy (HT)	ICD-9: 62.41 CPT-4: 54520 HCPCS: C9216, C9430, G0356, J0128, J3315, J9202, J9217, J9218, J9219, S0165, S9560

ICD-9 = International Classification of Disease, 9th edition; CPT-4 = Physicians Current Procedural Terminology Coding System, 4th edition; HCPCS = Healthcare Common Procedure Coding System.

Comparative Effectiveness of Minimally Invasive vs Open Radical Prostatectomy

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Context Minimally invasive radical prostatectomy (MIRP) has diffused rapidly despite limited data on outcomes and greater costs compared with open retropubic radical prostatectomy (RRP).

Objective To determine the comparative effectiveness of MIRP vs RRP.

Design, Setting, and Patients Population-based observational cohort study using US Surveillance, Epidemiology, and End Results Medicare linked data from 2003 through 2007. We identified men with prostate cancer who underwent MIRP (n=1938) vs RRP (n=6899).

Main Outcome Measures We compared postoperative 30-day complications, anastomotic stricture 31 to 365 days postoperatively, long-term incontinence and erectile dysfunction more than 18 months postoperatively, and postoperative use of additional cancer therapies, a surrogate for cancer control.

Results Among men undergoing prostatectomy, use of MIRP increased from 9.2% (95% confidence interval [CI], 8.1%-10.5%) in 2003 to 43.2% (95% CI, 39.6%-46.9%) in 2006-2007. Men undergoing MIRP vs RRP were more likely to be recorded as Asian (6.1% vs 3.2%), less likely to be recorded as black (6.2% vs 7.8%) or Hispanic (5.6% vs 7.9%), and more likely to live in areas with at least 90% high school graduation rates (50.2% vs 41.0%) and with median incomes of at least $60 000 (35.8% vs 21.5%) (all $P<.001$). In propensity score–adjusted analyses, MIRP vs RRP was associated with shorter length of stay (median, 2.0 vs 3.0 days; $P<.001$) and lower rates of blood transfusions (2.7% vs 20.8%; $P<.001$), postoperative respiratory complications (4.3% vs 6.6%; $P=.004$), miscellaneous surgical complications (4.3% vs 5.6%; $P=.03$), and anastomotic stricture (5.8% vs 14.0%; $P<.001$). However, MIRP vs RRP was associated with an increased risk of genitourinary complications (4.7% vs 2.1%; $P=.001$) and diagnoses of incontinence (15.9 vs 12.2 per 100 person-years; $P=.02$) and erectile dysfunction (26.8 vs 19.2 per 100 person-years; $P=.009$). Rates of use of additional cancer therapies did not differ by surgical procedure (8.2 vs 6.9 per 100 person-years; $P=.35$).

Conclusion Men undergoing MIRP vs RRP experienced shorter length of stay, fewer respiratory and miscellaneous surgical complications and strictures, and similar postoperative use of additional cancer therapies but experienced more genitourinary complications, incontinence, and erectile dysfunction.

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FOLLOWING THE DESCRIPTION OF consistently reproducible advantages of minimally invasive radical prostatectomy (MIRP) with and without robotic assistance in 2000-2001,[1,2] use of MIRP has surged.[3,4] In particular, use of robotic-assisted MIRP increased from 1% to 40% of all radical prostatectomies from 2001 to 2006.[5,6] Many patients intuitively perceive minimally invasive approaches to reduce complications compared with conventional open operations and prefer minimally invasive procedures because of smaller incisions requiring less analgesics and shorter hospital stays, even at greater cost.[7]

Moreover, the widespread direct-to-consumer advertising and marketed benefits of robotic-assisted MIRP in the United States may promote publication bias against studies that detail challenges and suboptimal outcomes early in the MIRP learning curve.[8] Until comparative effectiveness of robotic-assisted MIRP can be demonstrated, open retropubic radical prostatectomy (RRP), with a 20-year lead time for dissemination of surgical technique[9] relative to MIRP, remains the gold standard surgical therapy for localized prostate cancer.[10]

For surgeons eager to add robotic-assisted MIRP to their armamentarium, there are few barriers to entry; surgeons must attend a 2-day course before scheduling cases proctored by another surgeon who has performed at least 20 robotic-assisted MIRPs. Requirements may be less rigorous for attaining hospital privileges for MIRP without robotic assistance. Studies estimate the learning curve for either approach to be at least 150 to 250 cases,[11,12] and greater RRP or MIRP sur-

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geon volume is associated with better outcomes.[4,13-15]

In the absence of randomized controlled trials, population-based studies allow comparison of competing therapies across a broad range of health settings. The aim of our study was to assess outcomes following MIRP vs RRP.

METHODS

Data

Our study was approved by the Brigham and Women's Institutional Review Board; patient data were deidentified and the requirement for consent was waived. We used Surveillance, Epidemiology, and End Results (SEER)–Medicare data for analyses,[16] which are composed of a linkage of population-based cancer registry data from 16 SEER areas covering approximately 26% of the US population with Medicare administrative data. The Medicare program provides benefits to most Americans aged 65 years or older.

Study Cohort

We identified 137 217 men aged 65 years or older who were diagnosed as having prostate cancer from 2002 to 2005 and followed up through December 31, 2007. We excluded 10 441 men who were enrolled in a health maintenance organization or who were not enrolled in both Medicare Part A and Part B throughout the duration of the study (because claims are not reliably submitted for such patients). To increase the sensitivity for detection of postoperative radiation therapy, we restricted our analyses to men with prostate cancer diagnosed as their first and only cancer and excluded 8271 men with other cancers. We excluded 452 men who underwent an open perineal radical prostatectomy because this approach was used infrequently (4.9% of radical prostatectomies during our study period) and differs in surgical incision, anatomic approach, and outcomes from RRP and MIRP,[17,18] and we performed a sensitivity analysis that revealed differences in perineal radical prostatectomy vs RRP outcomes.

We then identified the study cohort of 8837 men who underwent radical prostatectomy from January 1, 2003, through December 31, 2007. Radical prostatectomy was identified from Medicare inpatient, outpatient, and carrier component files (formerly Physician/Provider B files) based on the presence of Current Procedural Terminology, Fourth Edition (CPT-4) codes 55840, 55842, and 55845 for RRP (n=6899) and 55866 for MIRP (n=1938).

The CPT-4 code 55899, unspecified male genitourinary procedure, may sometimes be used along with an RRP *International Classification of Diseases, Ninth Revision* code to specify MIRP with robotic assistance for private health plans.[19] Medicare does not recognize this variation in coding, and we identified very few men with this combination of codes; therefore, it was not used to ascertain MIRP.

Outcomes

We examined outcomes consistent with prior studies: mortality/morbidity, length of stay, anastomotic strictures, incontinence, erectile dysfunction, and additional cancer therapy[3,4,13,14,20-22] (eAppendix). Postoperative complications and transfusions were assessed in the 30 days after surgery. Complication categories included cardiac, respiratory, genitourinary, vascular, wound, and miscellaneous events. Postoperative mortality was defined as death within 30 days of radical prostatectomy.

Anastomotic strictures were assessed from 31 to 365 days after surgery.[13] Long-term diagnoses and procedures for incontinence[13] and erectile dysfunction[20,21] were assessed based on administrative data more than 18 months after surgery, the interim required for recovery of postoperative urinary and sexual function to plateau.[23] Therefore, men undergoing MIRP and RRP in the latter half of 2006 and 2007 were excluded from the assessment of postoperative functional outcomes.

We also identified men undergoing additional cancer therapy after prostatectomy consistent with prior studies[3,22] as a surrogate for cancer control. According to guidelines, additional radiation therapy, hormone therapy, or both should be administered after surgery if prostate-specific antigen levels fail to reach undetectable levels or for men with adverse pathologic features or positive surgical margins.[24] We documented overall additional cancer therapy and the individual components of radiation and hormone therapy.

Control Variables

Information on patient age was obtained from the Medicare file, while race/ethnicity (based on medical record review and supplemented with Hispanic surname matching), census tract measures of median household income and proportion of individuals with at least a high school education, SEER region, population density (urban vs rural), and marital status were obtained from SEER registry data. We examined race/ethnicity because we hypothesized that disparities may exist in patient access or self-selection for a novel marketed procedure without proven benefit compared with a gold standard. Because of small numbers, we combined the New Mexico, rural Georgia, and Atlanta SEER registries.

Comorbidity using the Klabunde modification of the Charlson index and preoperative diagnoses of incontinence and erectile dysfunction were captured based on inpatient, outpatient, and carrier claims during the year before surgery.[25] We controlled for baseline incontinence and erectile dysfunction in our adjusted analysis and also conducted a sensitivity analysis in which we excluded men with preexisting incontinence and erectile dysfunction and obtained similar results. Variables were categorized as in TABLE 1.

Because surgeon rather than hospital volume is the more significant determinant of outcomes following RRP,[14] we determined surgeon volume for each type of procedure by aggregating the number of procedures for all men in the cohort performed from 2003 through 2007. For men with more than

Table 1. Demographic and Tumor Characteristics of the Study Population[a]

Characteristics	Before Propensity Weighting			After Propensity Weighting[b]		
	MIRP (n = 1938)	RRP (n = 6899)	*P* Value	MIRP (n = 1938)	RRP (n = 6889)	*P* Value
Year of surgery[c]						
2003	244 (12.6)	2394 (34.7)	<.001	586 (30.2)	2059 (29.9)	>.99
2004	542 (28.0)	2218 (32.2)		600 (30.9)	2150 (31.2)	
2005	843 (43.5)	1881 (27.3)		604 (31.1)	2144 (31.1)	
2006	277 (14.3)	370 (5.4)		139 (7.1)	489 (7.1)	
2007	32 (1.7)	36 (0.5)		14 (0.7)	53 (0.8)	
Age, y						
65-69	1162 (60.0)	4351 (63.1)	.12	1209 (62.2)	4310 (62.5)	.97
70-74	626 (32.3)	2094 (30.4)		599 (30.8)	2119 (30.7)	
≥75	150 (7.7)	454 (6.6)		135 (7)	465 (6.7)	
Charlson comorbidity score						
0	1375 (71.0)	4704 (68.2)	.10	1295 (66.7)	4740 (68.7)	.50
1	430 (22.2)	1706 (24.7)		506 (26)	1667 (24.2)	
≥2	133 (6.9)	489 (7.1)		142 (7.3)	488 (7.1)	
Race/ethnicity						
White	1558 (80.4)	5514 (79.9)	.001	1496 (77)	5520 (80.1)	.60
Black	120 (6.2)	535 (7.8)		204 (10.5)	519 (7.5)	
Hispanic	109 (5.6)	547 (7.9)		143 (7.3)	512 (7.4)	
Asian	119 (6.1)	220 (3.2)		74 (3.8)	255 (3.7)	
Other	32 (1.7)	83 (1.2)		26 (1.3)	89 (1.3)	
Marital status						
Not married	261 (13.5)	1053 (15.3)	<.001	287 (14.8)	1031 (15)	.97
Married	1497 (77.2)	5528 (80.1)		1550 (79.8)	5471 (79.4)	
Unknown	180 (9.3)	318 (4.6)		106 (5.5)	392 (5.7)	
Residents in patient's census tract with at least a high school education, %						
<75	283 (14.6)	1381 (20.0)	<.001	364 (18.8)	1297 (18.8)	.86
75-84.9	354 (18.3)	1380 (20.0)		418 (21.5)	1356 (19.7)	
85-90	328 (16.9)	1309 (19.0)		352 (18.1)	1278 (18.5)	
>90	973 (50.2)	2827 (41.0)		808 (41.6)	2961 (43)	
Median household income in census tract of residence, $						
<35 000	359 (18.5)	2134 (30.9)	<.001	553 (28.5)	1947 (28.2)	.95
35 000-44 499	408 (21.1)	1662 (24.1)		475 (24.4)	1614 (23.4)	
45 000-59 999	477 (24.6)	1616 (23.4)		437 (22.5)	1636 (23.7)	
≥60 000	694 (35.8)	1485 (21.5)		478 (24.6)	1696 (24.6)	
SEER registry						
San Francisco	95 (4.9)	228 (3.3)	.01	82 (4.2)	258 (3.7)	>.99
Detroit	284 (14.7)	385 (5.6)		151 (7.8)	526 (7.6)	
Hawaii	41 (2.1)	63 (0.9)		19 (1)	74 (1.1)	
Iowa	53 (2.7)	461 (6.7)		119 (6.1)	403 (5.8)	
Seattle	101 (5.2)	643 (9.3)		122 (6.3)	575 (8.3)	
Utah	65 (3.4)	435 (6.3)		87 (4.5)	390 (5.7)	
Connecticut	61 (3.2)	267 (3.9)		67 (3.5)	257 (3.7)	
San Jose	50 (2.6)	149 (2.2)		60 (3.1)	160 (2.3)	
Los Angeles	262 (13.5)	719 (10.4)		212 (10.9)	759 (11)	
Greater California	519 (26.8)	1641 (23.8)		475 (24.4)	1679 (24.4)	
Kentucky	111 (5.7)	404 (5.9)		99 (5.1)	403 (5.9)	
Louisiana	84 (4.3)	603 (8.7)		152 (7.8)	536 (7.8)	
New Jersey	177 (9.1)	521 (7.6)		156 (8)	548 (8)	
New Mexico/Atlanta/rural Georgia	35 (1.8)	380 (5.5)		143 (7.4)	325 (4.7)	
Population density						
Metropolitan	1846 (95.3)	6292 (91.2)	.007	1821 (93.8)	6349 (92.1)	.33
Nonmetropolitan	92 (4.8)	607 (8.8)		121 (6.2)	545 (7.9)	

(continued)

Table 1. Demographic and Tumor Characteristics of the Study Population[a] (continued)

Characteristics	Before Propensity Weighting			After Propensity Weighting[b]		
	MIRP (n = 1938)	RRP (n = 6899)	*P* Value	MIRP (n = 1938)	RRP (n = 6889)	*P* Value
Baseline urinary incontinence	118 (6.1)	257 (3.7)	.007	77 (4)	299 (4.3)	.67
Baseline erectile dysfunction	441 (22.8)	773 (11.2)	<.001	261 (13.4)	948 (13.8)	.90
AJCC pathologic stage						
T2 (organ-confined)	1323 (68.3)	4196 (60.8)	<.001	1157 (59.6)	4306 (62.5)	.43
T3 (extracapsular or seminal vesicle invasion)	339 (17.5)	1733 (25.1)		438 (22.6)	1615 (23.4)	
T4 (invading bladder and/or rectum)	22 (1.1)	97 (1.4)		34 (1.7)	93 (1.4)	
Unknown	254 (13.1)	873 (12.7)		313 (16.1)	880 (12.8)	
Tumor grade						
Well-/moderately differentiated	947 (48.9)	3485 (50.5)	.59	962 (49.5)	3460 (50.2)	.95
Poorly/undifferentiated	979 (50.5)	3381 (49.0)		972 (50)	3400 (49.3)	
Unknown	12 (0.6)	33 (0.5)		9 (0.5)	34 (0.5)	

Abbreviations: AJCC, American Joint Committee on Cancer; MIRP, minimally invasive radical prostatectomy; RRP, open retropubic radical prostatectomy; SEER, Surveillance, Epidemiology, and End Results.
[a]Data are presented as No. (%) unless otherwise noted.
[b]Using propensity score weighting to balance all characteristics in the 2 groups based on all characteristics in the table.
[c]The study cohort included men diagnosed as having prostate cancer in 2002-2005 who underwent radical prostatectomy in 2003-2007.

1 surgeon listed, we selected the surgeon who performed the larger volume of radical prostatectomies for analysis.[13] We also adjusted for year of surgery because outcomes may improve over time.[20]

Statistical Analysis

Annual utilization rates for RRP and MIRP were derived, and temporal trends in use were compared using the Mantel-Haenszel χ^2 test for trend, adjusted for surgeon clustering. Because of the relatively smaller number of procedures performed in 2007, we combined procedure data from 2006 and 2007 for the analysis of temporal trends. For dichotomous outcomes occurring within a fixed time interval, such as 30-day outcomes and 31- to 365-day (anastomotic strictures) outcomes, we compared proportions (number of events divided by number of patients) for MIRP vs RRP. For outcome variables without an upper time bound, in which length of follow-up could vary (eg, use of additional cancer therapy, diagnosis or procedures for incontinence and erectile dysfunction), we compared rates (number of events per 100 person-years of follow-up) for MIRP vs RRP. We also compared median length of stay between groups.

Because men undergoing MIRP differed from those undergoing RRP in terms of demographic and tumor characteristics, we used weighted propensity score methods to adjust for these differences.[26,27] Propensity score methods permit control for observed confounding factors that might influence both group assignment and outcome using a single composite measure and attempts to balance patient characteristics between groups.

To conduct the propensity score adjustment, we used a logistic regression model to calculate the propensity (probability) of undergoing MIRP vs RRP based on all covariates described above and then weighted each patient's data based on the inverse propensity of being in 1 of the 2 treatment groups.[28] Covariate balance was checked after adjustment (Table 1). In secondary analyses, we repeated the propensity-adjusted comparisons including surgeon volume in the propensity score models to assess if differences in surgeon volume explained differences in the outcomes studied; however, no differences were observed, suggesting that surgeon volume does not explain the differences observed.

Generalized estimating equations[29] (GEEs) were used to account for surgeon clustering in both unadjusted and adjusted analyses. To compare unadjusted proportions, we fit GEE logistic regressions with surgical approach (MIRP vs RRP) as the only covariate. To compare unadjusted rates, we fit GEE log-linear Poisson regression[30,31] with surgical approach as the only covariate. The *P* value for significance of surgical approach is calculated from the GEE logistic regression and Poisson regression *z* tests. A GEE was used in which length of stay was modeled as log-normal to compare length of stay. The models for the adjusted vs unadjusted GEE analyses were identical except that each patient was weighted by the inverse of the propensity score in the adjusted GEE.

Missing data were infrequent (<5% on any variable). We performed additional analyses using various missing data statistical approaches including multiple imputation and weighted estimating equations.[32,33] The results changed very little, so we present the results analyzing missing data as a separate category. With 8837 men in our cohort and a 5% type I error, we had more than 80% power to detect an odds ratio (OR) of 1.97 for infrequent outcomes such as cardiac complications (using a GEE logistic regression *z* test) and to detect a rate ratio of 1.36 for more frequent outcomes such as erectile dysfunction (using a GEE Poisson regression *z* test). All tests were considered statistically significant at $\alpha = .05$.

All analyses were performed with SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

RESULTS

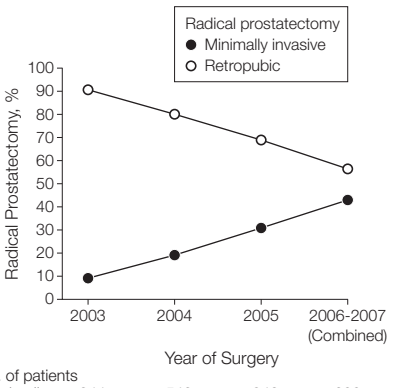
Among the 8837 men undergoing radical prostatectomy, use of MIRP increased almost 5-fold from 9.2% (95% confidence interval [CI], 8.1%-10.5%) in 2003 to 43.2% (95% CI, 39.6%-46.9%) in 2006-2007 (FIGURE). The number of surgeries performed in 2006 and 2007 appears to have decreased because data on new cancer diagnoses were available only through 2005. We observed sociodemographic differences among men undergoing MIRP vs RRP (Table 1). Relatively fewer men recorded as black (6.2% vs 7.8%) and Hispanic (5.6% vs 7.9%) underwent MIRP vs RRP, whereas those recorded as Asian were more likely (6.1% vs 3.2%) to undergo MIRP vs RRP ($P<.001$). In addition, men who underwent MIRP vs RRP were more likely to live in areas with at least 90% high school graduation rates (50.2% vs 41.0%) and median household income of at least $60 000 (35.8% vs 21.5%) (all $P<.001$).

We also observed geographic variation, with relatively greater use of MIRP vs RRP in the Detroit, Michigan (14.7% vs 5.6%), Los Angeles, California (13.5% vs 10.4%), and greater California (26.8% vs 23.8%) tumor registries. Moreover, the Detroit and California tumor registries contributed almost two-thirds of the MIRP vs less than half of the RRP cohort. In addition, men undergoing MIRP vs RRP more often lived in metropolitan vs nonmetropolitan areas (95.3% vs 91.2%; $P=.007$). While pathologic tumor grade was similar, men undergoing MIRP vs RRP were more likely to have organ-confined disease (68.3% vs 60.8%; $P<.001$).

Ten men (0.5%) vs 58 men (0.8%) died within 1 year of MIRP vs RRP surgery ($P=.17$), and the mortality rate did not differ through the remainder of our study (0.8 vs 0.9 per 100 person-years; $P=.72$). Patients were censored from analysis at the time of death, and median follow-up was 2.8 years (range, 1 day to 5 years). Unadjusted associations are presented in TABLE 2. Results are generally consistent with adjusted associations. In the propensity-adjusted analyses (TABLE 3), men undergoing MIRP vs RRP experienced shorter length of stay (median, 2.0 vs 3.0 days; OR, 0.67; 95% CI, 0.58-0.72), were less likely to receive heterologous transfusions (2.7% vs 20.8%; OR, 0.11; 95% CI, 0.06-0.17), and were at lower risk of postoperative respiratory complications (4.3% vs 6.6%; OR, 0.63; 95% CI, 0.46-0.87), miscellaneous surgical complications (4.3% vs 5.6%; OR, 0.75; 95% CI, 0.56-0.99), and anastomotic stricture (5.8% vs 14.0%; OR, 0.38; 95% CI, 0.28-0.52).

However, men undergoing MIRP vs RRP experienced more genitourinary complications (4.7% vs 2.1%; OR, 2.28; 95% CI, 1.61-3.22) and were more often diagnosed as having incontinence (15.9 vs 12.2 per 100 person-years; OR, 1.3; 95% CI, 1.05-1.61) and erectile dysfunction (26.8 vs 19.2 per 100 person-years; OR, 1.4; 95% CI, 1.14-1.72). The

Figure. Use of Minimally Invasive vs Open Retropubic Radical Prostatectomy for Men Diagnosed as Having Prostate Cancer in 2002-2005 and Undergoing Surgery in 2003-2007



No. of patients				
Minimally invasive	244	542	843	309
Retropubic	2394	2218	1881	406

Table 2. Unadjusted Outcomes by Surgical Approach

	MIRP	RRP	*P* Value
Length of stay, median (IQR)	2 (1-2)	3 (2-4)	<.001
Heterologous blood transfusion, No. (%)	49 (2.5)	1383 (20.1)	<.001
30-Day postoperative complications, No. (%)			
Overall	422 (21.9)	1606 (23.4)	.31
Cardiac	39 (2.0)	206 (3.0)	.03
Respiratory	80 (4.2)	465 (6.8)	<.001
Genitourinary	77 (4.0)	150 (2.2)	<.001
Wound	31 (1.6)	129 (1.9)	.41
Vascular	56 (2.9)	265 (3.9)	.08
Miscellaneous medical	181 (9.4)	598 (8.7)	.49
Miscellaneous surgical	91 (4.7)	387 (5.6)	.15
Death	2 (0.1)	12 (0.2)	.46
Anastomotic stricture, No. (%)[a]	99 (5.3)	946 (14.2)	<.001
Incontinence per 100 person-years[b]			
Diagnosis	18.2	11.9	<.001
Procedures	9.5	8.5	.30
Erectile dysfunction per 100 person-years[b]			
Diagnosis	33.8	18.2	<.001
Procedure	2.8	2.1	.04
Additional cancer therapy per 100 person-years			
Overall	6.1	6.9	.18
Radiation	4.3	4.9	.16
Hormone	3.5	3.7	.58
Death during the study period	0.7	0.9	.11

Abbreviations: IQR, interquartile range; MIRP, minimally invasive radical prostatectomy; RRP, open retropubic radical prostatectomy.
[a] Men who underwent surgery in 2007 were excluded because of insufficient follow-up to capture this outcome.
[b] Men who underwent surgery in the latter half of 2006 through the end of 2007 were excluded because of insufficient follow-up to capture this outcome.

need for additional cancer therapies was similar by surgical approach (8.2 vs 6.9 per 100 person-years; OR, 1.19; 95% CI, 0.84-1.69).

COMMENT

For many disease processes, minimally invasive surgery offers distinct, consistently reproducible advantages compared with open approaches, including shorter hospital stays, fewer inpatient procedures, and lower costs. However, RRP is performed through a relatively small incision that is infrequently associated with significant pain and has relatively short lengths of stay, averaging 1 to 3 days at high-volume referral centers.[34-36] Some studies suggest that MIRP vs RRP results in significantly less blood loss, lower transfusion rates, less use of postoperative analgesics, and quicker convalescence.[35,37-40] However, distinguishing perception from reality may be difficult for novel procedures such as MIRP,[39] particularly with assertions in the popular media of lower complication rates, shorter recovery time, better cancer removal, and faster removal of urinary catheter with robotic-assisted MIRP.[6]

Our study has several important findings. First, MIRP has been rapidly adopted since the initial suggestion of potential advantages over RRP.[3,4] Additionally, we observed significant sociodemographic and geographic variation in use of MIRP vs RRP. Black and Hispanic vs white and Asian men were less likely to undergo MIRP vs RRP. In addition, living in areas of higher socioeconomic status based on education and income was associated with greater receipt of MIRP vs RRP. This sociodemographic variation may result from the highly successful robotic-assisted MIRP marketing campaign[10] disseminated via the Internet,[41] radio, and print media channels[5,6] likely to be frequented by men of higher socioeconomic status. Additionally, black men and Hispanic men and men with lower socioeconomic status may not have access to networks or surgeons that offer MIRP.

Second, men undergoing MIRP vs RRP experienced shorter lengths of stay and were less likely to receive blood transfusions or develop postoperative respiratory and miscellaneous surgical complications. However, MIRP vs RRP was associated with an almost 2-fold increase in the odds of postoperative genitourinary complications.

Third, men undergoing MIRP vs RRP were more likely to be diagnosed as having incontinence and erectile dysfunction following surgery, even after adjusting for differences in baseline rates of these conditions. Because these outcomes were based on the presence of diagnosis codes only, it is not clear if men were more likely to have these conditions or were more likely to report them to a clinician. Men opting for MIRP may have heightened expectations for a heavily marketed "innovative" procedure, which may lead to greater dissatisfaction and regret compared with RRP.[42] Alternatively, this difference may be attributable to the lengthy learning curve[12] and relative changes in rates of MIRP vs RRP surgical technique during our study period. Nevertheless, we observed no difference in rates of procedures for incontinence or erectile dysfunction.

Fourth, after adjustment for patient and tumor characteristics, men undergoing MIRP vs RRP had similar rates of additional cancer therapy, a surro-

Table 3. Propensity Model–Adjusted Outcomes by Surgical Approach[a]

Outcomes	MIRP	RRP	MIRP vs RRP, Ratio (95% Confidence Interval)[b]	*P* Value
Length of stay, median (IQR)[c]	2 (1-2)	3 (2-4)	0.67 (0.58-0.72)	<.001
Heterologous blood transfusion, %	2.7	20.8	0.11 (0.06-0.17)	<.001
30-Day complications, %				
Overall	22.2	23.2	0.95 (0.77-1.16)	.58
Cardiac	2.4	2.9	0.81 (0.49-1.33)	.37
Respiratory	4.3	6.6	0.63 (0.46-0.87)	.004
Genitourinary	4.7	2.1	2.28 (1.61-3.22)	.001
Wound	2	1.9	1.05 (0.61-1.82)	.86
Vascular	3.4	3.9	0.86 (0.55-1.35)	.50
Miscellaneous medical	10	8.5	1.19 (0.89-1.6)	.26
Miscellaneous surgical	4.3	5.6	0.75 (0.56-0.99)	.03
Death	0.1	0.2	0.31 (0.07-1.28)	.05
Anastomotic stricture, %[d]	5.8	14.0	0.38 (0.28-0.52)	<.001
Incontinence per 100 person-years[e]				
Diagnosis	15.9	12.2	1.3 (1.05-1.61)	.02
Procedures	7.8	8.9	0.87 (0.69-1.1)	.24
Erectile dysfunction per 100 person-years[e]				
Diagnosis	26.8	19.2	1.40 (1.14-1.72)	.009
Procedure	2.3	2.2	1.05 (0.74-1.51)	.78
Additional cancer therapy per 100 person-years				
Overall	8.2	6.9	1.19 (0.84-1.69)	.35
Radiation	5.1	4.9	1.05 (0.84-1.32)	.67
Hormone	5.3	3.7	1.42 (0.88-2.32)	.21
Death during the study period per 100 person-years	0.8	0.9	0.91 (0.53-1.57)	.72

Abbreviations: IQR, interquartile range; MIRP, minimally invasive radical prostatectomy; RRP, open retropubic radical prostatectomy.

[a] The weighted propensity score adjusted for the following: year of surgery, age, comorbidity, baseline urinary incontinence, baseline erectile dysfunction, race/ethnicity, marital status, education, income, Surveillance, Epidemiology, and End Results region, population density, pathologic grade, and stage.

[b] The MIRP vs RRP ratios are median ratios for length of stay; odds ratios for heterologous transfusion, 30-day complications, and anastomotic stricture; and rate ratios for incontinence, erectile dysfunction, and additional cancer therapy.

[c] Length-of-stay odds ratio determined by the ratio of the medians.

[d] Men who underwent surgery in 2007 were excluded because of insufficient follow-up to capture this outcome, and the propensity score was recalculated for this outcome.

[e] Men who underwent surgery in the latter half of 2006 through the end of 2007 were excluded because of insufficient follow-up to capture this outcome, and the propensity score was recalculated for these outcomes.

gate for cancer control. In contrast with a recently published, population-based study that demonstrated greater risks of anastomotic stricture and worse cancer control with MIRP vs RRP[3], we observed a lower stricture rate and similar cancer control for MIRP vs RRP. Anastomotic strictures require additional surgery to dilate or incise the scar tissue under general anesthesia, which may result in incontinence, requiring placement of an artificial urinary sphincter in severe cases.[40,43] The different results may be related to differences in the study populations. The prior study examined a 5% random sample of Medicare beneficiaries nationwide[3] vs 100% of the Medicare beneficiaries in SEER registry areas in this study. This is particularly relevant because almost two-thirds of MIRPs in our study were performed in Detroit and California, regions containing high-volume MIRP centers,[5,44-46] where outcomes might be better.

Our findings must be interpreted within the context of limitations of our study design. First, claims files are primarily designed to provide billing information, not detailed clinical information. More comprehensive clinical data on severity of illness and comorbidity might have influenced the associations we identified. However, Medicare claims have a high degree of validity for detecting complications of prostatectomy, with 89% of Medicare complications corroborated by medical record abstraction.[47]

Second, short-term prostate cancer survival is high, and lengthier follow-up is needed to assess differences in cancer recurrence.

Third, our finding that men were more likely to be diagnosed as having urinary incontinence and erectile dysfunction following MIRP vs RRP is subject to observer bias. For instance, erectile dysfunction that impairs quality of life but does not necessitate seeking medical attention may not be captured from Medicare claims, and patient self-assessment with validated quality-of-life instruments provides a more precise measure of these outcomes. Moreover, we were unable to adjust for nerve-sparing surgical technique during radical prostatectomy, which improves postoperative sexual function.[48]

Fourth, MIRP included procedures performed with and without robotic assistance because both share a common CPT code. We were therefore unable to distinguish whether the robot was used during laparoscopy; however, the intraoperative strategy is similar and the prostatic anatomy is by definition identical.[49(p546, discussion)] Contemporary estimates of US robotic-assisted MIRP use range from 50% to 70%,[50-52] whereas a recent survey revealed a 25% to 75% decline in radical prostatectomy volume among urologists performing RRP and MIRP without robotic assistance.[53]

Fifth, this is an observational study of practice patterns and outcomes for elderly men undergoing surgery in SEER regions, and despite careful adjustment with propensity score methods, there may be unobserved differences in the groups for which we were unable to adjust. In addition, our findings may not be generalizable to younger men and those undergoing radical prostatectomy outside SEER regions, particularly because there is geographic variation in the use of MIRP and RRP that may result in variation in outcomes.[3,14,20,54]

CONCLUSION

During our study period, the use of MIRP increased, and men undergoing MIRP vs RRP experienced fewer transfusions, respiratory and miscellaneous surgical complications, and anastomotic strictures but more genitourinary complications and a greater likelihood of being diagnosed as having incontinence and erectile dysfunction in the long term. In light of the mixed outcomes associated with MIRP, our finding that men of higher socioeconomic status opted for a high-technology alternative despite insufficient data demonstrating superiority over an established gold standard may be a reflection of a society and health care system enamored with new technology that increased direct and indirect health care costs but had yet to uniformly realize marketed or potential benefits during early adoption.

Author Contributions: Dr Hu had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Hu, Lipsitz, Barry, D'Amico, Keating.
Analysis and interpretation of data: Hu, Gu, Lipsitz, D'Amico, Weinberg, Keating.
Drafting of the manuscript: Hu, Gu, Lipsitz, D'Amico, Weinberg.
Critical revision of the manuscript for important intellectual content: Hu, Gu, Lipsitz, Barry, D'Amico, Keating.
Statistical analysis: Gu, Lipsitz, Keating.
Administrative, technical, or material support: Weinberg.
Study supervision: Hu, Barry, D'Amico, Keating.
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Factors Associated with the Adoption of Minimally Invasive Radical Prostatectomy in the United States

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Purpose: Minimally invasive radical prostatectomy has supplanted radical retropubic prostatectomy in popularity despite the absence of strong comparative effectiveness data demonstrating its superiority. We examined the influence of patient, surgeon and hospital characteristics on the use of minimally invasive radical prostatectomy vs radical retropubic prostatectomy.

Materials and Methods: Using SEER (Surveillance, Epidemiology and End Results)-Medicare linked data we identified 11,732 men who underwent radical prostatectomy from 2003 to 2007. We assessed the contribution of patient, surgeon and hospital characteristics to the likelihood of undergoing minimally invasive radical prostatectomy vs radical retropubic prostatectomy using multilevel logistic regression mixed models.

Results: Patient factors (36.7%) contributed most to the use of minimally invasive radical prostatectomy vs radical retropubic prostatectomy, followed by surgeon (19.1%) and hospital (11.8%) factors. Among patient specific factors Asian race (OR 1.86, 95% CI 1.27–2.72, p = 0.001), clinically organ confined tumors (OR 2.71, 95% CI 1.60–4.57, p <0.001) and obtaining a second opinion from a urologist (OR 3.41, 95% CI 2.67–4.37, p <0.001) were associated with the highest use of minimally invasive radical prostatectomy while lower income was associated with decreased use of minimally invasive radical prostatectomy. Among surgeon and hospital specific factors, higher surgeon volume (OR 1.022, 95% CI 1.015–1.028, p <0.001), surgeon age younger than 50 years (OR 2.68, 95% CI 1.69–4.24, p <0.001) and greater hospital bed size (OR 1.001, 95% CI 1.001–1.002, p <0.001) were associated with increased use of minimally invasive radical prostatectomy, while solo or 2 urologist practices were associated with decreased use of minimally invasive radical prostatectomy (OR 0.48, 95% CI 0.27–0.86, p = 0.013).

Conclusions: The adoption of minimally invasive radical prostatectomy vs radical retropubic prostatectomy is multifactorial, and associated with specific patient, surgeon and hospital related factors. Obtaining a second opinion from another urologist was the strongest factor associated with opting for minimally invasive radical prostatectomy.

Key Words: surgical procedures, minimally invasive; prostatic neoplasms; referral and consultation; choice behavior

Abbreviations and Acronyms

MIRP = minimally invasive radical prostatectomy

NCI = National Cancer Institute

RALP = robotic assisted laparoscopic prostatectomy

RRP = radical retropubic prostatectomy

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In 2011 an estimated 240,890 men were diagnosed with prostate cancer and 33,720 died of the disease.[1] Controversy exists regarding the optimal management of newly diagnosed prostate cancer and, as a result, wide variations exist in practice patterns and treatment recommendations for clinically localized prostate cancer.[2] While radical prostatectomy remains the most common treatment for localized prostate cancer in the United States, men must choose between open radical retropubic prostatectomy and minimally invasive radical prostatectomy despite the lack of definitive data showing superior outcomes for either approach.[3,4] Although MIRP has been associated with less blood loss, shorter inpatient hospitalizations and fewer postoperative complications,[5] long-term comparisons of urinary and sexual function and cancer control remain sparse.

Despite the lack of data demonstrating the clear superiority of MIRP, there has been a 60% increase in the number of MIRPs performed in the United States between 2005 and 2008, largely due to the adoption of RALP.[6] Increased MIRP use, more specifically RALP, is likely multifactorial, and to our knowledge the role of patient, surgeon and hospital characteristics in the rapid adoption of MIRP has not yet been explored. Therefore, we assessed the relative contribution of various patient, surgeon and hospital factors associated with the use of MIRP vs RRP.

METHODS

Data

Our study was approved by the Brigham and Women's Hospital institutional review board. Patient data were de-identified and the requirement for consent was waived. We used linked data from the NCI SEER program and CMS (Centers for Medicare and Medicaid Services). SEER is comprised of population based cancer registry data from 16 registries covering approximately 28% of the United States population with Medicare administrative data from CMS.[7]

Study Cohort

Using ICD-9-CM code 185 we identified a cohort of 13,636 men age 65 years or older diagnosed with prostate cancer from 2002 to 2007 who underwent radical prostatectomy from 2003 to 2009. CPT-4 codes were used to identify men who underwent MIRP with or without robotic assistance (55866) vs RRP (55840, 55842, 55845). We excluded 1,772 men from analysis who were not continuously enrolled in Medicare Part A and B, and we also excluded 132 patients with incomplete demographic information or tumor characteristics. The final cohort consisted of 11,732 men who underwent MIRP or RRP during the study period.

Independent Variables

Age was obtained from the Medicare file. Comorbidity was assessed using inpatient, outpatient and carrier claims during the year before surgery.[8] Race/ethnicity, census measurements of median household income, the proportion of individuals with at least a high school education, U.S. Census region, population density and marital status were obtained from SEER.

Dependent Variables

Individual surgeons were identified using UPINs (Unique Physician Identifier Numbers) from the Medicare carrier file, while surgeon volume was determined by aggregating the total number of surgical procedures performed by each surgeon during the study period. Surgeon age, practice size (solo, small group [2 or fewer urologists] or large group [more than 2 urologists] practice), academic hospital affiliation and government vs nongovernment hospital affiliation were determined by linking physician UPINs to the American Medical Association Masterfile. A subject was deemed to have obtained a second opinion from a urologist if outpatient encounters with more than 1 urologist occurred between prostate cancer diagnosis and radical prostatectomy. Hospital characteristics (bed size, public vs private ownership, NCI Comprehensive Cancer Center designation and teaching status) were obtained by merging the inpatient file with a hospital file created by the NCI. Hospital volume was assessed as the total number of radical prostatectomies (MIRP and RRP) performed during the study period.

Statistical Analysis

Univariable differences between treatment modalities were assessed using chi-square tests. Multivariable logistic regression models to predict the use of MIRP were generated incorporating all study variables. Because of the correlation between MIRP vs RRP use in a particular surgeon practice and hospital, multilevel (hierarchical) logistic regression mixed models (generalized linear mixed models) were used to determine surgeon, hospital and patient level contributions to observed variation in surgical approach.[9] The multilevel model included fixed effects for patient characteristics and random surgeon and hospital effects, as well as fixed surgeon and hospital characteristics that could account for some of the variability in outcomes across surgeons and hospitals. For the multilevel model we identified 1,726 primary surgeons who performed radical prostatectomies during the study period. We excluded cases from low volume surgeons and hospitals that performed less than 5 surgeries during the study period, leaving 551 surgeons, 343 hospitals and 8,442 men for multilevel analysis. To determine the explanatory power of patient, surgeon and hospital level variables, the change in multilevel hierarchical logistic regression pseudo-R^2 was examined.[10] Time since obtaining a medical license was not included in the analysis as this was co-linear with surgeon age. All analyses were performed with SAS® version 9.2.

RESULTS

During the study period 67.9% vs 32.1% of men underwent RRP vs MIRP, respectively. The proportion of men undergoing MIRP increased during each year of the study period ($p < 0.001$). Men undergoing MIRP were more likely to be white and Asian, while

those treated with RRP were more likely to be black and Hispanic ($p < 0.001$). Men undergoing MIRP were also more likely to be married, have higher education and income levels, and live in urban areas ($p < 0.02$ for all). Men undergoing MIRP were more likely to have localized stage cT1 disease, while those undergoing RRP were more likely to have extraprostatic (cT3/T4) disease ($p < 0.001$). However, men undergoing MIRP were more likely to have poor or undifferentiated tumors compared to those treated with RRP ($p < 0.001$).

On unadjusted analysis MIRP was more likely to be performed at teaching hospitals and at NCI designated Comprehensive Cancer Centers ($p < 0.001$, table 1). MIRP was less likely to be performed by surgeons in solo or small group practices and those primarily affiliated with medical schools ($p < 0.001$). MIRP was performed more commonly by younger surgeons and those in practice for less than 10 years ($p < 0.003$ for both).

Table 2 presents multilevel models demonstrating that patient, surgeon and hospital characteristics together accounted for 46.4% of the overall variability in the use of MIRP vs RRP. Patient level characteristics contributed the most variability in the use of MIRP (36.7%), followed by surgeon (19.1%) and hospital level (11.8%) characteristics. Of the individual patient level characteristics that determined variability in the use of MIRP vs RRP, tumor stage (8.6%), demographics (13.9%) and receiving a second opinion from another urologist (24.5%) were the most common. The most common surgeon level characteristics were employment status (5.4%), surgeon age (9.6%) and case volume (11.8%). Finally, the most common hospital level contributors were bed size (3.6%) and teaching hospital status (3.1%).

Multivariable analysis for predictors of MIRP vs RRP was performed. Asian race was associated with increased use of MIRP (vs white race OR 1.86, 95% CI 1.27–2.72, $p = 0.001$). Compared to men with a median income of $60,000 or greater, those with a median income of less than $35,000 (OR 0.62, 95% CI 0.41–0.93, $p = 0.021$) and $35,000 to $44,999 (OR 0.69, 95% CI 0.51–0.95, $p = 0.021$) were less likely to undergo MIRP. Men with cT1 (OR 2.71, 95% CI 1.60–4.57, $p < 0.001$) and cT2 (OR 2.2, 95% CI 1.29–3.75) vs cT3/cT4 disease were more likely to undergo MIRP vs RRP. Obtaining a second opinion from another urologist before treatment was also associated with MIRP (OR 3.41, 95% CI 2.67–4.37, $p < 0.001$). In terms of surgeon characteristics, surgeon volume (OR 1.022 for each surgical procedure performed, 95% CI 1.015–1.028, $p < 0.001$), solo or 2 physician practices (OR 0.48, 95% CI 0.27–0.86, $p = 0.013$) and younger surgeon age (OR 2.68, 95% CI 1.69–4.24, $p < 0.001$) were associated with increased use of MIRP. Finally, among hospital level characteristics only increasing bed size was associated with a greater likelihood of MIRP vs RRP (OR 1.001, 95% CI 1.001–1.002, $p < 0.001$).

Table 1. *Hospital and surgeon characteristics*

	MIRP	RRP	p Value
No. pts	3,774	7,958	
	Hospital		
No. ownership (%):			
Nonprofit	3,120 (83.0)	6,020 (76.6)	0.108
Proprietary	260 (6.9)	787 (10.0)	
Government	377 (10.0)	1,049 (13.4)	
No. teaching (%):			
Yes	2,563 (87.9)	4,227 (67.7)	0.010
No	353 (12.1)	2,015 (32.3)	
No. NCI center (%):			
No	2,726 (72.6)	7,147 (91.0)	<0.001
Clinical	56 (1.5)	88 (1.1)	
Comprehensive	975 (26.0)	621 (7.9)	
	Surgeon		
No. employment (%):			
Solo/2-person practice	219 (7.7)	1,709 (25.0)	<0.001
Group	2,139 (74.9)	4,297 (62.8)	
Medical school	126 (4.4)	435 (6.4)	
Nongovernment	197 (6.9)	80 (1.2)	
Government	176 (6.2)	318 (4.6)	
No. yrs with medical license (%):			
Less than 10	1,499 (45.3)	1,437 (20.0)	0.002
10 or More	1,812 (54.7)	5,744 (80.0)	
No. surgeon age (%):			
Younger than 50	2,318 (70.0)	3,194 (44.5)	<0.001
50 or Older	993 (30.0)	3,987 (55.5)	

All percentages may not add to 100% due to rounding. Ownership status and NCI cancer status were unknown for 178 cases, and teaching hospital status was unknown for 1,162 cases. Employment status of the surgeon was unknown for 1,098 men, and years with license and age were unknown for 808.

Table 2. *Hospital, surgeon and patient contributions to variability in the use of MIRP*

	% Variability in Use of MIRP
Pt:	
Overall characteristics	36.7
Demographics	13.9
Comorbidity	0.4
Tumor characteristics	8.6
Second opinion	24.5
Surgeon:	
Overall characteristics	19.1
Present employment	5.4
Age	9.6
Case vol	11.8
Hospital:	
Overall characteristics	11.8
Ownership	2
Teaching	3.1
NCI	0.3
Bed size	3.6
Radical prostatectomy case vol	0.2
Overall	46.4

DISCUSSION

Our study has generated several important findings. Patient, surgeon and hospital level characteristics all influenced the selection of surgical approach, consistent with speculation that the use of MIRP is driven by patient behavior and demand, surgeon preference and hospital acquisition of robotic systems.[6] Patient related factors such as demographics and tumor characteristics have been shown to influence treatment choice in other specialties. For example, patient age, parity and family history were significant determinants for undergoing breast conserving surgery vs mastectomy for breast cancer.[11] In addition, among patients undergoing anterior cruciate ligament reconstruction, those who conducted significant Internet based research or had higher levels of education were more likely to choose allografts vs autografts.[12] Surgeon level characteristics also contributed to variability in the selection of MIRP vs RRP, although to a lesser extent than patient level characteristics. While not specifically examined in this study, the contribution of surgeons and hospitals may be related to monetary factors. The adoption of RALP over RRP has been shown to increase case volume and profits for the surgeon, while leading to hospital losses if the robotic system is not used frequently.[13] Interestingly hospital radical prostatectomy volume was not a significant contributor to the use of MIRP, which may suggest that during the study period centers with significant radical prostatectomy volume were less likely to acquire and use robotic surgical systems, or that the migration of radical prostatectomy approach from RRP to MIRP also resulted in the clustering of MIRP among the initially limited number of hospitals with robotic systems rather than those with the highest radical prostatectomy volume. Conversely, in a multi-state analysis Makarov et al demonstrated that hospitals that acquired a surgical robot between 2001 and 2005 performed approximately 30 additional radical prostatectomy procedures annually, compared with a mean decrease of 5 prostatectomies annually in those hospitals without robots.[14]

In addition, men receiving a second opinion from another urologist before intervention were more than 3 times more likely to undergo MIRP vs RRP, and this was the biggest contributor to variability in the use of MIRP. This may reflect increased reliance on direct-to-consumer advertising among MIRP surgeons that disrupts traditional word of mouth referral patterns,[15] similar to changes observed with brachytherapy for prostate cancer.[16] Media coverage and marketing of MIRP are more widespread than for RRP,[17] which may influence patients to seek a second opinion with an advertised MIRP surgeon outside of traditional referral patterns. Unfortunately, high expectations due to advertising and self-referral may contribute to postoperative regret in men undergoing MIRP vs RRP.[18] Schroeck et al suggested that MIRP does not decrease the technical challenges associated with obese patients, large prostates, middle lobe size/location or prior surgery, where outcomes continue to be less satisfactory.[18] In addition, the association between obtaining a second opinion from a urologist and MIRP may also be related to exposure to multiple providers, increasing the likelihood of finding a surgeon that performs MIRP.[19] Similarly, obtaining second opinions has altered surgical treatment in breast cancer, as women visiting a second surgeon have been shown to be more likely to undergo breast conserving surgery vs radical mastectomy.[11]

Younger surgeons (younger than 50 years) were 2.5 times more likely to use MIRP. Current urological training exposes younger trainees to more minimally invasive procedures and, therefore, younger surgeons are likely more inclined to offer MIRP vs RRP. Although the surgical learning curve for MIRP may be long,[20] increased exposure to laparoscopy and robotics during residency training likely attenuates the learning curve effect and makes younger surgeons more comfortable with the procedure. This finding echoes those seen in other areas of medicine, where physician age has been associated with differences in the use of colorectal screening,[21] cesarean sections[22] and adjuvant chemotherapy.[23] In addition, given the shift to increasing use of MIRP vs RRP, younger surgeons may have less experience with RRP overall from residency and fellowship training than their older colleagues.[24]

We also identified demographic factors that contribute to the use of MIRP vs RRP. Asian men were more likely to undergo MIRP and men with lower incomes were less likely to undergo MIRP. Further research is needed to explain the greater likelihood of MIRP in the Asian patient population, although Asian men are also more likely to undergo more expensive radiation therapies for prostate cancer treatment.[25] Ethnic differences have previously been associated with variability of treatment with curative intent in early stage disease, as well as the performance of pelvic lymph node dissection during radical prostatectomy for poorly differentiated prostate cancer.[26,27] The difference among income levels may be a function of access to care facilities with minimally invasive technology. It may also reflect a lack of insurance coverage for MIRP for men with lower incomes. Disparities in surgical approach based on insurance status have also been noted in general surgery, where patients with private insurance were more likely to undergo laparoscopic vs open appendectomy.[28]

Finally we found that men with lower stage tumors were nearly 3 times more likely to undergo MIRP while those with advanced tumors were more likely to undergo RRP. This finding may be associated with the belief that locally advanced prostate cancer may be better served with open radical prostatectomy that allows for tactile sensation and palpation of the prostate gland.[29] Tumor characteristics were the fifth most important factor on multilevel analysis explaining the observed variability in the use of MIRP, and may reflect physician preference to perform open surgery for more aggressive tumors.

Our study must be interpreted in the context of the study design as the associations from this cross-sectional study are observational and do not confirm causation. Our analyses were limited only to Medicare beneficiaries older than 65 years and, therefore, these results may not be applicable to younger men choosing between MIRP and RRP. Our study period was also during a time of rapid growth of MIRP and our multilevel model may not reflect the current importance of hospital, surgeon or patient attributes in the likelihood of undergoing a particular surgical approach as availability, use and acceptance of MIRP (especially with robotic assistance) have increased. In addition, we did not examine the potential impact of visits to other providers such as radiation and/or medical oncologists that may influence the selection of surgical options. Although we were able to determine whether consultations with more than 1 urologist took place in the form of second opinions, we were unable to delineate whether second opinions were physician vs self-referred. Also, we cannot capture all clinical variables that may have influenced the choice of surgical approach, such as prior surgeries, body mass index and personal factors that may contribute to selection bias. Finally, this study did not include followup to determine patient satisfaction and adverse events. One recent study showed that the risks of problems with continence and sexual function are high after both procedures.[30]

CONCLUSIONS

The majority of the identifiable variability in the use of MIRP vs RRP appears to be attributable to patient and surgeon level characteristics rather than hospital characteristics. Patient tumor and demographic characteristics as well as surgeon case volume appear to contribute most to increased MIRP use. The most important factor in undergoing MIRP was receiving a second opinion from a urologist. These men are more than 3 times more likely to undergo MIRP vs RRP, and this may reflect doctor shopping secondary to Internet browsing or direct-to-consumer advertising influencing patient treatment decisions.

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Population Based Assessment of Determining Treatments for Prostate Cancer

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ABSTRACT

Context: Overtreatment of indolent prostate cancer is associated with significant detriments of quality of life and increased health care expenditures. Without a better understanding of the mutable agents and predictors of treatment types, diffusion of widespread adoption of active surveillance will be slow.

Objectives: To characterize the determinants and variance of treatments for men diagnosed with prostate cancer.

Design, Setting and Patients: We used Surveillance, Epidemiology, and End Results (SEER)–Medicare linked data to identify 510,031 men diagnosed with prostate cancer from 1991–2007 and were followed until December 31, 2009. The final cohort consisted of 37,621 men

Main Outcome Measure: We used mixed-effects logistic regression analysis to determine the predictors aggressive treatment and utilization of active surveillance for men with prostate cancer.

Results: The most common treatment type is radiation therapy (57.9%), followed by radical prostatectomy (19.1%), and watchful waiting or active surveillance (9.6%). Moreover, patients and providers significantly integrate proxies for life expectancy (age and comorbidities) when determining radical prostatectomy, while regional

variation and referral patterns influence the utility of radiation therapy. Patient demographics and tumor characteristics significantly account for 43% of patients undergoing prostatectomy, 14% of men choosing watchful waiting or active surveillance, and only 3% undergoing radiotherapy.

Conclusion: There is increased utilization of radiotherapy among all risk groups with limited to no correlation with proxies of life expectancy or tumor biology. Active surveillance is underutilized and a significant proportion of the variance is unexplained. Further research into qualitatively describing the contributing factors that drive decision-making recommendations for prostate cancer patients are needed.

INTRODUCTION

Prostate cancer remains the most commonly diagnosed solid organ tumor among U.S. men with an estimated 241,740 new cases and 28,170 deaths in 2012 (1). With recent stage migration (2), the natural history of prostate cancer has shifted toward a more indolent course in a majority of newly diagnosed cases (3). Treatment options for prostate cancer may include radical prostatectomy, external beam radiotherapy and brachytherapy. Active surveillance has been recommended for men diagnosed with low-risk prostate cancer, however, the incidence of overtreatment of low-risk disease is still prevalent (4, 5).

Prostate cancer has been singled out as a litmus test for health care reform with a lack of consensus regarding optimal treatment strategies (6). Despite varying reimbursements for currently available treatment options, survival rates remain equivalent in terms of intermediate and high-risk disease (7). Furthermore, side effects associated with these treatments are substantial both from a clinical and economic standpoint.(8, 9) With more indolent cancers being diagnosed, active surveillance protocols have been established with promising oncologic results and have the greatest quality adjusted life expectancy (10). Moreover, delayed treatment in select patients on active surveillance does not alter survival (11). Prior studies have suggested patient, provider and socioeconomic factors contributing to overtreatment of low-risk disease (12-15). Given the above, patients must often consider the recommendations of their physician, the aggressiveness of their cancer, and whether

active surveillance is preferred over definitive treatment and the pursuant morbidity (mainly urinary, bowel, and sexual dysfunction), health care costs (16, 17). The fact that patients continue to pursue treatment for indolent disease underscores the importance of a physicians' recommendation in this complex decision-making process (16). Additionally, recent studies have suggested increased self-referral and non-tumor biology related factors may contribute significantly to physicians' treatment recommendations (15, 16). The purpose of our population-based study was to identify determinants for use of watchful waiting and active surveillance as well as various treatments in a contemporary cohort of elderly Americans.

MATERIALS AND METHODS

Data Source

We used linked Surveillance, Epidemiology, and End Results (SEER)–Medicare data from the National Cancer Institute, which contains claims records on individuals aged 65 years and older. We restricted our analysis to patients with prostate cancer diagnosed in 1991 through 2007 and followed until December 31, 2009. SEER data are summarized in the Patient Entitlement and Diagnosis Summary File (PEDSF); the database contains information on patient demographics, tumor characteristics, and follow-up information. The PEDSF was linked with 100% of Medicare claims from inpatient, outpatient, and national claims history files, and was restricted to subjects who had Medicare Fee-for-Service coverage, and for whom Medicare Parts A and B claims data were available 12 months prior to and 24 months after diagnosis of prostate cancer (18). Using the Medicare Provider Analysis and Review (MEDPAR), outpatient, and carrier files, we were able to identify and subsequently categorize treatment type into watchful waiting/active surveillance, cryotherapy, radiation therapy, radical prostatectomy, and androgen deprivation therapy.

Study Cohort

We identified 510,031 men from SEER-Medicare linked data diagnosed with prostate cancer between 1991 and 2007 with follow-up of Medicare services through 2009. We excluded 472,410 for the following reasons: diagnosis obtained from death certificate or autopsy; not the first and only malignancy; prostate cancer was not pathologically confirmed; enrolled in Medicare for end stage renal disease or

disability; date of diagnosis in SEER differs from that in Medicare by more than three months; <65 years of age at diagnosis; invalid month of diagnosis; concurrent health maintenance organization coverage and/or not enrolled in Medicare Part A and B throughout the study period; lacking information one year-prior to and two-years after diagnosis; lacking initial diagnostic biopsy for prostate cancer; unknown Gleason Grade, prostate specific antigen (PSA), and clinical stage; and unknown socioeconomic and comorbidity data. The final cohort consisted of 37,621 men (Figure 1).

Study Variables

From the PEDSF, we determined patient age (65–69, 70–74, 75–79, and ≥80), race/ethnicity (White, Black, Hispanic, Asian, and Other), marital status (not married, married, and unknown), Gleason Grade (≤6, 7, and 8–10), PSA (≤4, 4.1–9.9,10–19.9, and ≥20 ng/mL) clinical stage (T1, T2, T3, T4), SEER region (Northeast, South, Midwest, and West), and area of residence (metropolitan and rural). Using Gleason Grade, PSA, and clinical stage, we were able to categorize tumor risk strata into D'Amico risk—low, intermediate and high (7). Low risk was defined as clinical stage ≤T2a, Gleason Grade ≤6, and PSA ≤10 ng/mL; intermediate risk as clinical stage T2b, or Gleason Grade 7, or PSA 10.1–20 ng/mL; and high risk as clinical stage ≥T2c, or Gleason Grade 8–10, or PSA >20 ng/mL. We imputed subject socioeconomic status by using 2000 US Census data to derive quartiles of ZIP code-level median household income and percent of residents that are high-school graduates (19). We used the modification by Klabunde et al of the Charlson

Comorbidity Index to quantify severity of preexisting comorbidities. (20, 21) For each patient, we noted the provider and institution where the initial prostate cancer was diagnosed, using the Unique Physician Identifier Number (UPIN) and the corresponding institution. We limited our cohort to those who survived at least two years to determine varying treatments during the initial two-year period after diagnosis.

Outcomes

The aim of our study was to examine the use of various treatment options and identify patient- and provider-level variables to drive treatment type. Treatment options were categorized into watchful waiting/active surveillance (no definitive treatment within two years of diagnosis), cryotherapy, radiation therapy (brachytherapy, intense modulated radiation therapy, and external beam radiation therapy), radical prostatectomy (radical retropubic prostatectomy and minimally invasive radical prostatectomy), and androgen deprivation therapy. To examine the factors that drive the decision to pursue popular treatment options, we limited our multilevel analysis to those that underwent active surveillance/watchful waiting, radiation therapy or radical prostatectomy. Since the long-term benefits of varying treatment options are attributable to tumor risk and the overall health of the patient, we quantified the proportion of the variance that is attributable to patient demographics, tumor characteristics, region and year, as well as consultation with other specialists.

Statistical Analysis

We first compared patient demographics and tumor characteristics with treatments—watchful waiting/active surveillance, cryotherapy, radiation therapy, radical prostatectomy, and androgen deprivation therapy—using χ^2 analyses and Fisher's exact test. We then examined the association of patient demographics, tumor characteristics, region of diagnosis, and consultation with other specialists with the three most common treatment options for men with prostate cancer—watchful waiting/active surveillance, radiation therapy, and radical prostatectomy. Since receipt of health care services may be clustered on the treating physician, we generated mixed-effects logistic regression models to account for both fixed and random effects associated with treatment type. Each model included patient age, race, marital status, Charlson comorbidity score, education, household income, region, area of residence, clinical stage, Gleason Grade, PSA, D'Amico tumor risk, and consultation with subspecialists as fixed terms, while each unique surgeon identifier (UPIN) was appended to the random effects part of the mixed-effects model. Estimates in the multivariate mixed-effects model are reported as odds ratios with corresponding 95% confidence intervals.

Partitioning of variance was conducted utilizing the following equation: $\frac{\sigma_F^2}{\sigma_F^2+\tau_0^2+\sigma_R^2}$ Where σ_F^2 is defined as the variance of the fixed term (covariate or group of covariates) derived from latent-variable approach; τ_0^2 is defined as the intercept (level-2) variance; and σ_R^2 is defined as the level-one residual variance ($\frac{\pi^2}{3}$ in our logistic model) (22). Groups of patient- and provider-level variables were included as fixed effects for each treatment type. We stratified these groups as the following: 1)

sociodemographic (age, race, marital status, socioeconomic status, comorbidities); 2) tumor risk (clinical stage, PSA, and Gleason Grade); 3) region and year (SEER region, area of residence, and year of diagnosis); and 4) consultation with other specialists (medical oncology and radiation oncology). Provider-attributable residual intraclass correlation coefficient (ICC)—representing unexplained provider-level variance—was estimated from the full model of each outcome measure. Unexplained surgeon factors were derived from the intraclass correlation coefficient of the unconditional or *null* model of each treatment. Unexplained patient factors were derived from the residual variance.

All analyses were performed using SAS (version 9.2; Cary, North Carolina) and STATA software (version 11.1; College Station, Texas). All statistical tests were two-tailed, and the probability of a type I error was set at <0.05. The institutional review board at the University of California, Los Angeles, exempted our study protocol.

RESULTS

The plurality of the cohort was 70–74 years of age, white, married, without any comorbid conditions and diagnosed in a metropolitan environment in the west (Table 1). Most men were stage T1, with PSA of 4.1–9.9 ng/mL, Gleason Grade ≤6, and D'Amico intermediate risk.

We performed a bivariate analysis comparing varying treatment options according to tumor biology as shown in Table 2. While the effect size in differences in outcomes varied, statistical significance was maintained across all metrics. Greater frequency of undergoing radiotherapy was significantly maintained regardless of associated tumor risk categories when compared with other treatment options. The most common treatment type is radiation therapy (57.9%), followed by radical prostatectomy (19.1%), ADT (10.8%), watchful waiting/active surveillance (9.6%), and cryotherapy (2.6%). Treatment with radiation therapy was the most common treatment (48–66%) irrespective of stage, PSA, Gleason Grade, or D'Amico tumor risk. Radical prostatectomy was significantly influenced by PSA: from 24% for those with PSA ≤4.0 ng/mL to 9% for those with values ≥20 ng/mL. Utilization of watchful waiting/active surveillance was guided clinical stage, Gleason Grade, and D'Amico tumor risk strata: from 9% for those with stage T1 to 4% for stage T3/T4; from 15% for Gleason Grade ≤6 to 4% for Gleason Grade 8–10; and 13% for D'Amico low-risk disease to 6% for those with high-grade disease. ADT was significantly influenced by clinical stage, PSA, Gleason Grade, and D'Amico tumor risk: 8% for clinical stage T1 to 19% for stage T3/T4; 6% for PSA ≤4.0 to 22% for ≥20 ng/mL; 7% for Gleason Grade ≤6 to 21% for 8–10; and 4% for D'Amico low-risk to 22% for high-risk disease.

We then examined the association between patient demographics, tumor characteristics, and regional factors with treatment type (Table 3). The utilization of watchful waiting/active surveillance increased with advanced age, demographics (other race, unknown marital status), region (non-Northeast SEER), and a referral to a medical oncologist. Lower use of watchful waiting/active surveillance was associated with demographics (Asians, married men), tumor characteristics (PSA 4.1–19.9 ng/mL, Gleason Grade >6, D'Amico high-risk disease), and those referred to a radiation oncologist. Increased utilization of radical prostatectomy was associated with demographics (married, higher income and education), SEER region (diagnosed in non-Northeast SEER), and tumor characteristics (Gleason Grade 7, as well as D'Amico intermediate and high tumor risk). Lower utilization of radical prostatectomy was associated with advance age, demographics (Black, Hispanic and other race, unknown marital status), more significant comorbidities, tumor characteristics (stage >T1 and PSA >4 ng/mL), and referral to either medical or radiation oncologists. Increased utilization of radiation therapy was found with advancing age, demographics (Black, Hispanic, and Asian race), more significant comorbidities, tumor characteristics (PSA 4.1–19.9 ng/mL), and referral to a radiation oncologist. Lower utilization of radiation therapy was associated with demographics (other race), region (non-Northeast region), and tumor characteristics (D'Amico intermediate risk).

To determine the source in variation of treatment type, we quantified the relative contribution of patient demographics, tumor characteristics, and referral patterns in

our cohort (Figure 2). Unexplained patient and surgeon factors were the largest contributors to patient choosing watchful waiting/active surveillance (71%). Patient demographics and tumor characteristics explained less than 15% of the variation. Referral to other consultants explained 14% of the variance. As to radical prostatectomy, patient demographics was the largest source of variation in treatment (41%). Referral to other consultants accounted for 24% of the variance, while unexplained patient and surgeon factors explained 31%. Referral to other consultants—primarily radiation oncology—accounted for the largest source of variation (44%). Unexplained patient and surgeon factors explained 50% of the variation. Patient demographics and tumor characteristics accounted for less than 5% of the variation.

COMMENT

PSA screening has led to a significant increase in detection of clinically localized prostate cancer (23, 24). While active surveillance is recommended for men diagnosed with low risk prostate cancer, utilization of aggressive treatments has not relented (4). However, a recent nationwide population based study from Sweden have shown the feasibility of limiting overtreatment with almost 70% of men having received active surveillance for low risk disease in their country (15). We sought to provide population-based evidence to further discern determinants for selecting treatments in men with low risk disease.

Our study has several important findings. First, irrespective of prostate cancer risk stratification a vast majority of patients are being treated with radiotherapy. This is striking, given that our study was limited to men aged 65 years and older, who are at greater risk for death due to competing risks. Furthermore, it has been previously demonstrated that aside from age, there is overutilization of treatments in men with low risk disease and significant comorbidities (25). Our finding that increased utilization of radiotherapy across all risk categories portends to a collaborative need for increased dissemination of prostate cancer treatment guidelines among our radiation oncology colleagues. While we were unable to identify tumor biology factors as determinants for patients undergoing radiotherapy, prior studies have suggested self referral patterns may lead to increased utilization and costs of medical care (26, 27). Furthermore, consultation with radiation oncologists and regional variation significantly impact utilization of radiotherapy treatment options (28). The magnitude

of utilization of radiotherapy treatment options is significantly increased with integration of urology and radiation oncology practices into prostate cancer center groups (28). Furthermore, companies that sell turnkey intensity-modulated radiation treatment (IMRT) programs to urology practices market the potential for increased IMRT revenue to replace lost earnings from androgen deprivation therapy (ADT), for which reimbursement decreased sharply as part of the 2003 Medicare Modernization Act (28, 29). Further research into ongoing patient and provider factors determining treatment decisions are needed to limit costs and overtreatment.

Second, we found greater frequency of radical prostatectomy was predominantly due to patient and tumor related factors. These findings corroborate prior findings which surgery is less likely to be offered to patients with increased comorbidities or in the setting of high risk disease (30). However, many of these patients are offered radiotherapy, which may not be most appropriate especially in the setting of low-risk disease and significant comorbidities (30, 31). Jacobs et al. recently identified overall treatment rates for low-risk disease to remain relatively stable, however, utilization of advanced treatment technologies including IMRT and robotic surgery have increased (32). Furthermore, rates of other forms of radiotherapy and open surgery decreased suggesting this newer technology has been rapidly adopted prior to demonstrating superiority to prior treatments (32). Further comparative effectiveness research separating the diagnosis and treatment of prostate cancer are needed in order to limit overtreatment of low risk disease (15, 25).

Finally, although greater frequency of watchful waiting/active surveillance was inversely associated with prostate cancer risk, the differences were not as strikingly different. Unexplained patient and provider factors accounted for greater than 70% of the variance in utilization of watchful waiting/active surveillance. Prior data have shown overtreatment of low-risk disease and undertreatment of high-risk disease are not explained by 'measurable factors' (30). While age, marital status, education level have been associated with selection of active surveillance the current study suggests this accounts for only 11% of the explanation (15). Further comparative effectiveness research is needed help guide evidence based decision-making pathways.

While our findings are policy relevant, they must be interpreted in the context of the study design. First, SEER-Medicare is limited to men aged 65 years or older and our results may not be generalizable to younger men diagnosed with prostate cancer. Second, we were unable to identify patient-based determinants for treatments and further research into factors which drive decision-making processes are needed. Lastly, while we attempted to identify predictors for undergoing active surveillance, there are undetermined patient/provider factors that need to be discerned. Finally, observational studies reflect practice patterns and when compared with results from well-conducted randomized controlled trials they do not appear to overestimate treatment effects nor differ qualitatively (33).

In conclusion, there remains an increased utilization of treatments in men diagnosed with prostate cancer and underutilization of active surveillance in men with low-risk disease. There is an increased utilization of radiotherapy among all risk

groups with limited correlation according to tumor biology and patient health. Further research into identifying determinants that drive decision-making recommendations for patients diagnosed with prostate cancer are needed. These findings must be balanced when considering health care reform initiatives to improve quality of care.

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Variables	N=37,621	%
Age		
65–69	10,728	28.5%
70–74	12,201	32.4%
75–79	8,846	23.5%
≥80	5,846	15.5%
Race/Ethnicity		
White	29,517	78.4%
Black	3,107	8.3%
Hispanic	2,153	5.7%
Asian	1,532	4.1%
Other	1,312	3.5%
Marital Status		
Not Married	7,089	18.8%
Married	26,594	70.7%
Unknown	3,938	10.5%
Charlson Score		
0	25,750	68.4%
1	8,086	21.5%
≥2	3,785	10.1%
Median Annual Household Income		
<$35,000	13,641	36.3%
$35,000–$44,999	8,480	22.5%
$45,000–$59,999	8,141	21.6%

≥$60,000	7,359	19.6%
High School Graduate (? Have to clarify with XM)		
<75.0%	7,833	20.8%
75.0%–84.9%	8,099	21.5%
85.0%–89.9%	7,046	18.8%
≥90.0%	14,643	38.9%
SEER Region		
Northeast	8,100	21.5%
South	6,640	17.7%
Midwest	4,894	13.0%
West	17,987	47.8%
Population		
Metropolitan	33,984	90.3%
Rural	3,637	9.7%
Clinical Stage		
T1	20,695	55.0%
T2	15,756	41.9%
T3	1,003	2.6%
T4	177	0.5%
PSA		
≤4.0	4,743	12.6%
4.1–9.9	21,780	57.9%
10.0–19.9	6,765	18.0%
≥20	4,333	11.5%

Gleason Score		
≤6	16,482	43.8%
7	14,706	39.1%
8–10	6,433	17.1%
D'Amico Tumor Risk		
Low	8,178	21.7%
Intermediate	19,962	53.1%
High	9,481	25.2%

Table 2: Bivariate analysis examining the association of tumor biology and treatment choice

	Watchful Waiting Active Surveillance	Cryotherapy	Brachytherapy IMRT EBRT	RRP MIRP	ADT	p-value
	3,622 (9.6%)	981 (2.6%)	21,785 (57.9%)	7,184 (19.1%)	4,049 (10.8%)	
Clinical Stage						<0.01
T1	1,951 (9.4%)	518 (2.5%)	12,467 (60.3%)	4,017 (19.4%)	1,732 (8.4%)	
T2	1,629 (10.3%)	444 (2.8%)	8,600 (54.6%)	2,990 (19.0%)	2,093 (13.3%)	
T3	33 (3.3%)	17 (1.7%)	634 (63.2%)	170 (16.9%)	149 (14.9%)	
T4	9 (5.1%)	2 (1.1%)	84 (47.5%)	7 (3.9%)	75 (42.4%)	
PSA						<0.01
≤4.0	518 (10.9%)	122 (2.6%)	2,708 (57.1%)	1,120 (23.6%)	275 (5.8%)	
4.1–9.9	2082 (9.6%)	621 (2.9%)	13,073 (60.0%)	4,689 (21.5%)	1,315 (6.0%)	
10.0–19.9	641 (9.4%)	154 (2.3%)	3,902 (57.7%)	987 (14.6%)	1,081 (16.0%)	
≥20	381 (8.8%)	84 (1.9%)	2,102 (48.5%)	388 (9.0%)	1,378 (21.8%)	
Gleason Grade						<0.01
≤6	2,473 (15.0%)	404 (2.4%)	10,083 (61.2%)	2,389 (14.5%)	1,133 (6.9%)	
7	865 (5.9%)	438 (3.0%)	8,086 (55.0%)	3,759 (25.5%)	1,558 (10.6%)	
8–10	284 (4.4%)	139 (2.2%)	3,616 (56.2%)	1,036 (16.1%)	1,358 (21.1%)	
D'Amico Tumor Risk						<0.01
Low	1,087 (13.3%)	183 (2.2%)	5,369 (65.7%)	1,212 (14.8%)	327 (4.0%)	
Intermediate	1,966 (9.8%)	588 (3.0%)	11,194 (56.1%)	4,567 (22.9%)	1,647 (8.2%)	
High	569 (6.0%)	210 (2.2%)	5,222 (55.1%)	1,405 (14.8%)	2,075 (21.9%)	

Table 3: Mixed-effects model examining the association of varying treatments with sociodemographic and tumor characteristics

Variables	WW/AS OR (95% CI)	Prostatectomy OR (95% CI)	Radiotherapy OR (95% CI)
Age (Referent: 65–69)			
70–74	1.82 (1.61–2.06)**	0.32 (0.29–0.35)**	1.88 (1.73–2.04)**
75–79	3.50 (3.08–3.97)**	0.06 (0.05–0.07)**	2.14 (1.96–2.34)**
≥80	5.12 (4.48–5.86)**	0.01 (0.01–0.01)**	0.99 (0.89–1.10)
Race/Ethnicity (Referent: White)			
Black	1.09 (0.91–1.30)	0.56 (0.47–0.67)**	1.24 (1.08–1.42)**
Hispanic	0.86 (0.70–1.06)	0.78 (0.63–0.95)*	1.27 (1.08–1.49)**
Asian	0.77 (0.59–0.99)*	0.96 (0.76–1.20)	1.14 (0.94–1.39)
Other	2.49 (2.10–2.95)**	0.26 (0.19–0.34)**	0.55 (0.45–0.66)**
Marital Status (Referent: Not Married)			
Married	0.69 (0.62–0.77)**	1.69 (1.52–1.89)**	0.94 (0.87–1.03)
Unknown	1.96 (1.70–2.26)**	0.44 (0.36–0.53)**	0.50 (0.44–0.57)**
Charlson Score (Referent:0)			
1	1.09 (0.99–1.21)	0.62 (0.56–0.68)**	1.16 (1.07–1.25)**
≥2	1.10 (0.96–1.26)	0.33 (0.28–0.39)**	1.12 (1.00–1.25)*
Median Annual Household Income (Referent: <$35,000)			
$35,000–$44,999	0.92 (0.81–1.04)	1.15 (1.02–1.31)*	1.05 (0.95–1.16)
$45,000–$59,999	0.90 (0.78–1.05)	1.28 (1.11–1.48)**	1.03 (0.92–1.16)
≥$60,000	1.11 (0.93–1.31)	1.35 (1.14–1.59)**	0.89 (0.78–1.02)
High School Graduate (Referent: <75.0%)			

75.0%–84.9%	1.00 (0.87–1.15)	1.15 (0.99–1.33)	0.99 (0.89–1.11)
85.0%–89.9%	1.13 (0.96–1.32)	1.24 (1.05–1.47)*	0.93 (0.82–1.06)
≥90.0%	1.06 (0.89–1.25)	1.37 (1.16–1.63)**	0.95 (0.83–1.08)
SEER Region (Referent: Northeast)			
South	1.37 (1.12–1.66)**	1.54 (1.23–1.93)**	0.57 (0.47–0.68)**
Midwest	1.20 (0.96–1.49)	2.82 (2.21–3.61)**	0.41 (0.34–0.51)**
West	1.55 (1.32–1.81)**	3.03 (2.53–3.62)**	0.35 (0.30–0.41)**
Population (Referent: Metropolitan)			
Rural	0.89 (0.74–1.06)	1.03 (0.87–1.23)	0.93 (0.80–1.07)
Clinical Stage (Referent: T1)			
T2	1.01 (0.90–1.13)	0.78 (0.71–0.86)**	1.06 (0.98–1.14)
T3	0.75 (0.50–1.13)	0.59 (0.44–0.78)**	1.11 (0.90–1.38)
T4	0.71 (0.33–1.54)	0.14 (0.06–0.35)**	1.15 (0.73–1.80)
PSA (Referent: ≤4.0)			
4.1–9.9	0.88 (0.78–1.00)*	0.82 (0.73–0.92)**	1.16 (1.05–1.29)**
10.0–19.9	0.72 (0.62–0.85)**	0.59 (0.51–0.68)**	1.23 (1.09–1.39)**
≥20	0.95 (0.72–1.25)	0.13 (0.10–0.17)**	0.95 (0.80–1.14)
Gleason Score (Referent: ≤6)			
7	0.26 (0.23–0.29)**	2.78 (2.48–3.11)**	0.91 (0.83–0.99)*
8–10	0.19 (0.15–0.25)**	1.21 (0.92–1.58)	1.01 (0.85–1.21)
D'Amico Tumor Risk (Referent: Low)			
Intermediate	1.06 (0.91–1.23)	1.36 (1.17–1.58)**	0.80 (0.71–0.90)**
High	0.72 (0.52–0.98)*	2.91 (2.13–3.97)**	0.85 (0.69–1.06)
Consultation with Radiation Oncologist (Referent: No)			

Yes	0.19 (0.17–0.21)**	0.05 (0.04–0.05)**	44.46 (41.04–48.17)**
Consultation with Medical Oncologist (Referent: No)			
Yes	1.83 (1.51–2.22)**	0.75 (0.61–0.91)**	1.06 (0.91–1.24)

* denotes $p<0.05$

** denotes $p<0.01$

Figure 1: Flow Diagram

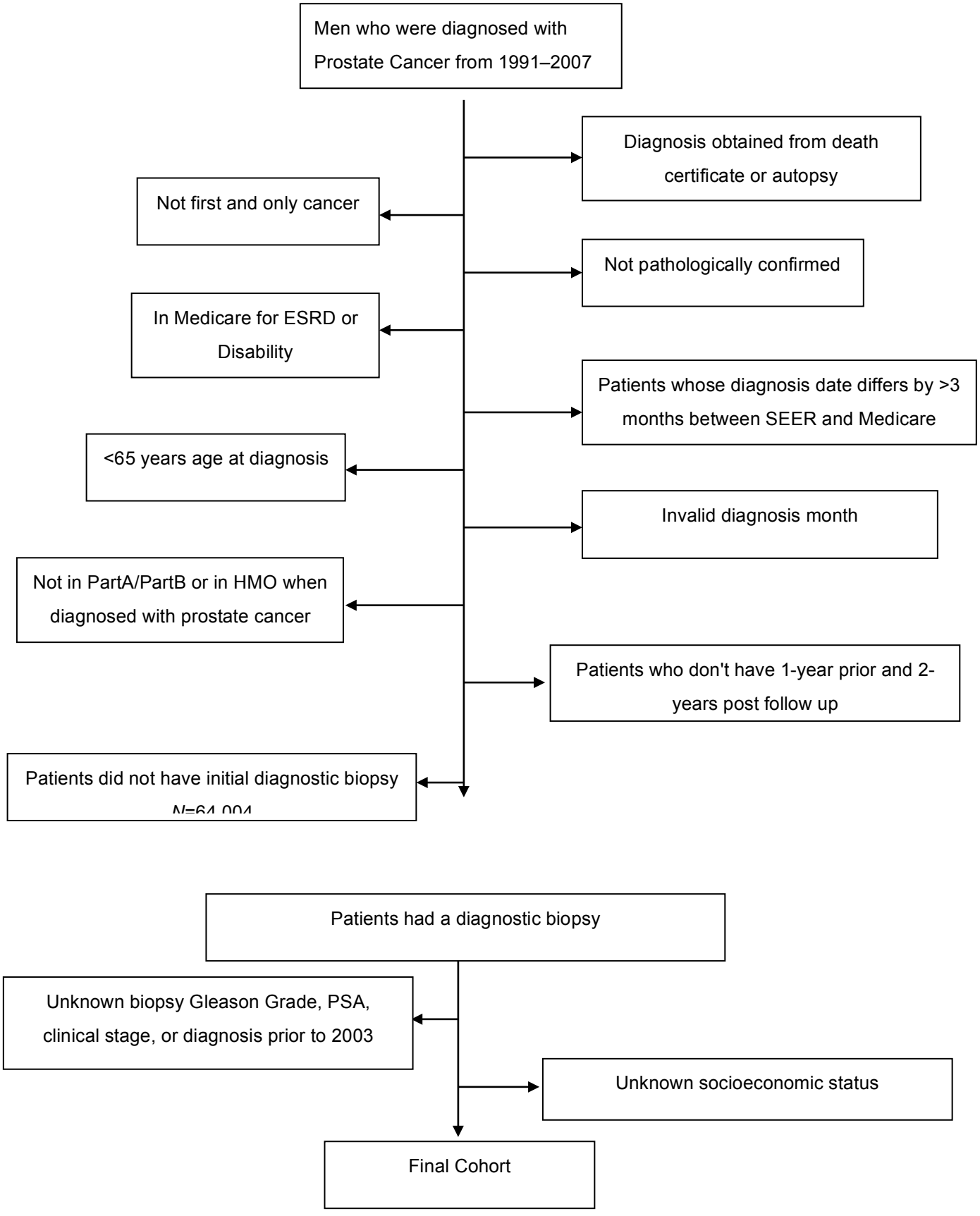
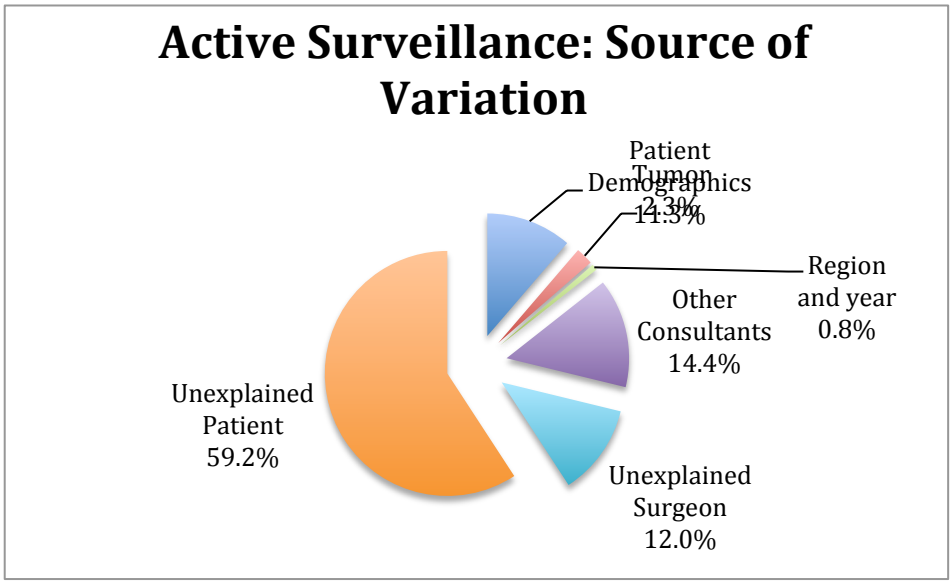
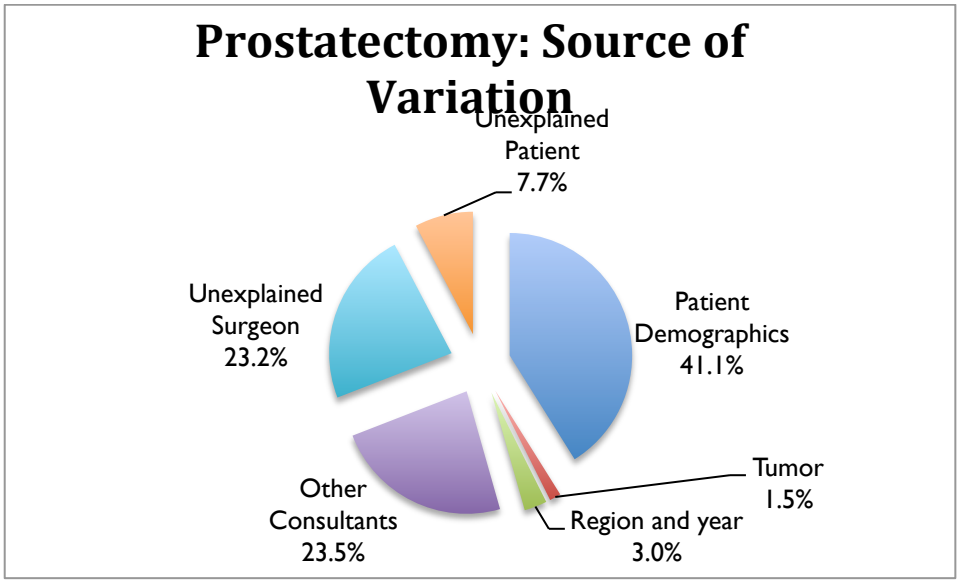
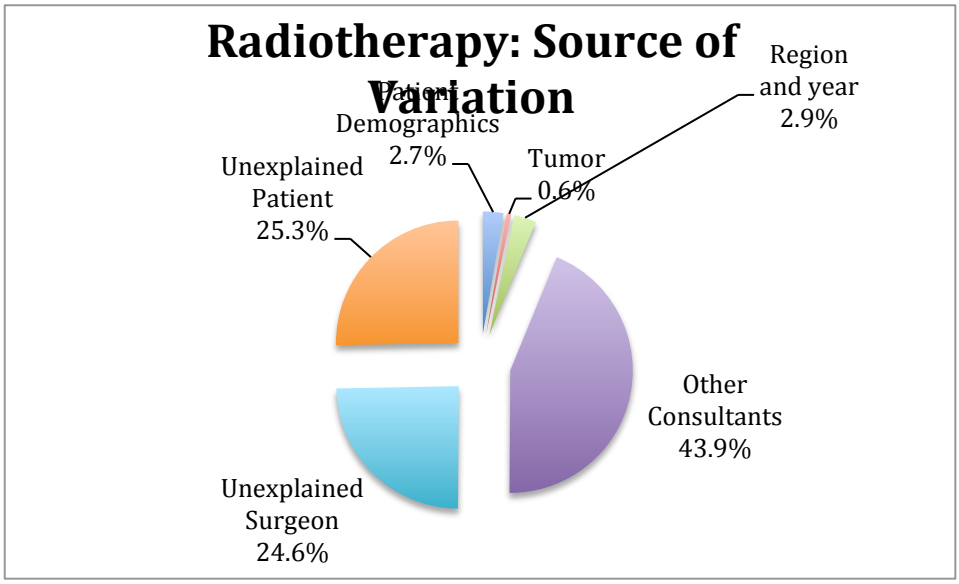


Figure 2: Source of variation for differing treatment options derived from mixed-effects logistic regression analyses






Radiotherapy: Source of Variation
Region and year 2.9%
Patient Demographics 2.7%
Tumor 0.6%
Unexplained Patient 25.3%
Other Consultants 43.9%
Unexplained Surgeon 24.6%

Use of Testosterone Replacement Therapy in the United States and Its Effect on Subsequent Prostate Cancer Outcomes

Alan L. Kaplan and Jim C. Hu

OBJECTIVE To assess utilization trends and determine the effect of testosterone replacement therapy on outcomes in men who subsequently developed prostate cancer.

METHODS We used linked Surveillance, Epidemiology, and End Results—Medicare data to identify 149,354 men diagnosed with prostate cancer from 1992 to 2007. Of those, 2,237 men (1.5%) underwent testosterone replacement therapy before their prostate cancer diagnosis. Propensity scoring methods were used to assess cancer-specific outcomes of testosterone replacement vs no replacement therapy.

RESULTS Testosterone replacement was associated with older age at cancer diagnosis, nonwhite race, and higher comorbidity ($P < .001$). No testosterone vs testosterone before the prostate cancer diagnosis was associated with higher grade (34% vs 30%, $P < .0001$) and more T4 (6.5% vs 4.3%, $P < .0001$) tumors. Mortality was decreased in men with ≥ 2 prostate-specific antigen (PSA) tests in the year before their cancer diagnosis. No significant difference was found between groups in overall survival, cancer-specific survival, or use of salvage androgen-deprivation therapy after initial treatment.

CONCLUSION Through our observational study design, we show that testosterone use was low throughout the study period. Testosterone use was not associated with aggressive prostate cancer and did not affect overall or disease-specific mortality. Although our findings support growing evidence that testosterone replacement is safe with respect to prostate cancer, confirmatory prospective studies are needed. UROLOGY 82: 321—326, 2013. © 2013 Elsevier Inc.

Up to 25% of older men experience hypogonadism. Prevalence is higher in men with comorbid disease and increases with age starting in the fourth decade.[1-3] Hypogonadal men have lower muscle mass, bone mineral density, and hemoglobin, and are in poorer general health.[4] During the past decade, there has been increasing awareness of the health benefits conferred by testosterone replacement therapy (TRT).[5] TRT for hypogonadism increases muscle mass and bone mineral density, decreases fat mass, and improves mood, libido, and sexual performance.[4-6]

Despite these benefits, there is an historical fear that administration of exogenous testosterone may increase the risk of developing prostate cancer or an aggressive form of the disease.[5,7] The seminal report by Huggins et al[8] in 1941 demonstrated that prostate cancer is androgen-dependent, in that testosterone "enhanced the rate of growth" of prostate cancer. Forty years later, Fowler et al[9] found that 87% of men with metastatic prostate cancer who received exogenous testosterone suffered exacerbation, leading to the oft-repeated suggestion that TRT in men with prostate cancer was akin to "pouring gasoline on a fire."

This historical concern that has led to hesitation in TRT administration for men without prostate cancer appears unfounded. Several longitudinal studies have shown no influence of serum testosterone levels on the risk of developing prostate cancer.[6,10] Although many small trials and 1 large specialty-center study demonstrate prostate safety with TRT, population-based data are limited, and practice patterns and outcomes in the community remain unclear.[10,11] Therefore, the objectives of our study were to characterize the use of TRT and its effect on outcomes in men that subsequently developed prostate cancer.

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METHODS

Our study was approved by the University of California Los Angeles Institutional Review Board. Patient-specific data were de-identified, and requirement for consent was waived.

Data Source

We analyzed Surveillance, Epidemiology, and End Results (SEER)—Medicare data, which consisted of a linkage of population-based cancer registries from 20 SEER regions covering approximately 28% of the United States (U.S.) population with Medicare administrative data.[12] Medicare provides health care benefits to most elderly Americans. SEER-Medicare linked data captures approximately 97% of incident cancer cases and collects data on patient demographics, tumor characteristics, and initial treatment course.[13]

Study Cohort

We identified 348,372 men aged 65 years or older with a pathologic diagnosis of prostate cancer from 1991 to 2007. We excluded 113,844 men who were enrolled in a health maintenance organization or who were not enrolled in both Medicare Part A and B throughout the study period to avoid unreliable claims submissions. Complete information, including race, marital status, and clinical stages, was available for 169,414 men. An additional 20,060 men without 1 year of available data before their cancer diagnosis to assess comorbidity were excluded. After complete exclusion criteria were applied, our remaining cohort consisted of 149,354 men with prostate cancer. We divided this cohort into those who received TRT (n = 2237) before their prostate cancer diagnosis and those who did not (n = 147,117). TRT usage was identified by the presence of Physicians Current Procedural Terminology Coding System, 4th edition (CPT-4), for injection-based (J0900, J1060, J1070, J1080, J2320, J3120, J3130, J3140, J3150) and subcutaneous pellet (S0189) testosterone formulations.

Control Variables

Information on patient age (65-69, 70-74, ≥75 years) was obtained from the Medicare denominator file, whereas race (white/non-Hispanic, black/non-Hispanic, Hispanic, Asian/non-Hispanic), SEER region, education level, household income, population density (urban vs rural), and tumor characteristics were obtained from SEER registry data. Because of small numbers, we combined the Hawaii and rural Georgia SEER registries.

Comorbidity was assessed using the Klabunde modification of the Charlson Comorbidity Index based on inpatient, outpatient, and physician services the year before the prostate cancer diagnosis.[14] In addition, access to medical care, particularly Medicare-covered preventative testing (cholesterol screening, influenza vaccination, colonoscopy) and the frequency of prostate-specific antigen (PSA) screening before the prostate cancer diagnosis, may influence tumor stage and grade and survival outcomes, and we captured the use of these services through Medicare. Treatment type was also captured by the associated CPT-4 procedure code.

Outcomes

On the basis of receipt of TRT, we examined prostate cancer—specific outcomes, including tumor grade on biopsy specimen, clinical stage, initial treatment modality, and need for salvage androgen-deprivation therapy (ADT), and disease-specific and overall survival. Use of ADT was identified using techniques previously described.[15]

Statistical Analysis

We used weighted propensity score methods to adjust for differences in demographic and tumor characteristics.[16,17] Propensity score methods permit control for observed confounding factors that may influence group assignment and outcomes by using a single composite measure, attempting to balance patient characteristics between groups as would cohort randomization. Because length of follow-up varied, we compared rates (events per 100 person-years) of overall survival, disease-specific survival, and need for salvage ADT by TRT vs no TRT before the prostate cancer diagnosis. All tests were considered statistically significant at $\alpha = 0.05$. Statistical analyses were performed with SAS 9.1.3 software (SAS Institute Inc, Cary, NC).

RESULTS

Median age of our study sample was 73 years (interquartile range [IQR], 69-78 years). Of the 149,354 men in our cohort, 2,237 (1.50%) used TRT before their prostate cancer diagnosis. Use increased with age: 47.5% on TRT were aged 75 years or older (Table 1). TRT use was greater between 1997 and 2002 (Fig. 1), peaking in 1998, with 2.8% of those diagnosed with prostate cancer using TRT. Median length of TRT use was 93 days (IQR, 30-449 days).

We observed minimal sociodemographic differences between groups. Propensity weighted analysis found no significant demographic factors associated with TRT usage. However, TRT was associated with PSA testing and preventive tests performed in the year before diagnosis ($P < .0001$), although this pattern lost significance with propensity analysis.

Median follow-up after the prostate cancer diagnosis was 5.0 years (IQR, 2.9-7.6 years). In adjusted analyses (Table 2), TRT vs no TRT men were more likely to be diagnosed with moderately differentiated disease (63.5% vs 59.2%, $P < .001$) and less likely to have poorly differentiated disease (29.7% vs 34.2%, $P < .001$). In addition, TRT vs no TRT men were more likely to be diagnosed with clinical stage T3 (4.0% vs 3.1%, $P < .001$) and less likely to have T4 disease (4.3% vs 6.5%, $P < .001$). TRT vs no TRT men were more likely to undergo radical prostatectomy (20.0% vs 18.4%), radiotherapy (53.1% vs. 50.6%), and active surveillance (14.7% vs 14.1%; all $P < .001$). No TRT was associated with greater use of ADT (16.9% vs 12.3%, $P < .0001$). Finally, use of TRT was not associated with differences in overall survival ($P = .288$), disease-specific survival ($P = .259$), or need for salvage ADT ($P = .525$; Table 3).

COMMENT

Men who experience hypogonadism are in poorer general health than eugonadal men.[4] Hypogonadism is associated

Table 1. Characteristics of the study population

Variable	Categories	Before Propensity Weighting			After Propensity Weighting		
		No TRT No. (%)	TRT No. (%)	*P* Value	No TRT No. (%)	TRT No. (%)	*P* Value
Age, y	65-69	37,584 (25.5)	413 (18.5)	<.0001	37,422 (25.4)	591 (26.0)	.1755
	70-74	47,350 (32.2)	762 (34.0)		47,384 (32.3)	773 (34.0)	
	≥75	62,183 (42.3)	1062 (47.5)		62,287 (42.3)	896 (40.0)	
Race	White/non-Hispanic	11,8504 (80.6)	1743 (77.9)	<.0001	118,428 (80.5)	1835 (81.1)	.9430
	Black/non-Hispanic	14,482 (9.8)	294 (13.1)		14,552 (9.9)	211 (9.4)	
	Hispanic	8039 (5.5)	165 (7.4)		8080 (5.5)	125 (5.5)	
	Asian/non-Hispanic	6092 (4.1)	35 (1.6)		6034 (4.1)	90 (4.0)	
Charlson Comorbidity Index score	0	100,758 (68.4)	1352 (60.5)	<.0001	100,565 (68.4)	1551 (68.6)	.7444
	1	30,536 (20.8)	582 (26.0)		30,647 (20.8)	479 (21.2)	
	≥2	15,823 (10.8)	303 (13.5)		15,881 (10.8)	230 (10.2)	
Median household income in census tract of residence, $	<35,000	51,097 (34.7)	829 (37.1)	.048	51,140 (34.8)	759 (33.6)	.3624
	35,000-44,999	34,568 (23.5)	495 (22.1)		34,532 (23.5)	503 (22.3)	
	45,000-59,999	32,438 (22.1)	459 (20.5)		32,399 (22.0)	510 (22.5)	
	≥60,000	29,014 (19.7)	454 (20.3)		29,022 (19.7)	488 (21.6)	
At least a high school education in census tract of residence, %	<75	31,326 (21.3)	507 (22.7)	<.0001	31,351 (21.3)	481 (21.3)	.3186
	75-84.9	34,446 (23.4)	461 (20.6)		34,397 (23.3)	493 (21.8)	
	85-89.9	29,397 (20.0)	404 (18.1)		29,350 (20.0)	432 (19.1)	
	≥90	51,948 (35.3)	865 (38.6)		52,014 (35.4)	854 (37.8)	
Population density	Metropolitan	132,344 (90.0)	2051 (91.7)	.007	13,2361 (90.0)	2025 (89.6)	.6164
	Nonmetropolitan	14,773 (10.0)	186 (8.3)		14,733 (10.0)	236 (10.4)	
PSA tests 1-y before to diagnosis, No.	0	26,477 (18.0)	256 (11.4)	<.0001	26,329 (17.9)	410 (18.1)	.3873
	1	49,353 (33.5)	684 (30.6)		49,279 (33.5)	705 (31.2)	
	2	39,509 (26.9)	671 (30.0)		39,572 (26.9)	622 (27.5)	
	3+	31,778 (21.6)	626 (28.0)		31,914 (21.7)	524 (23.2)	
Preventive tests 1-y before diagnosis, No.	0	31,406 (21.4)	325 (14.5)	<.0001	31,251 (21.2)	478 (21.1)	.6717
	1	52,398 (35.6)	757 (33.9)		52,350 (35.6)	770 (34.1)	
	2	46,667 (31.7)	812 (36.3)		46,761 (31.8)	741 (32.8)	
	3+	16,646 (11.3)	343 (15.3)		16,732 (11.4)	272 (12.0)	

PSA, prostate-specific antigen; TRT, testosterone replacement therapy.

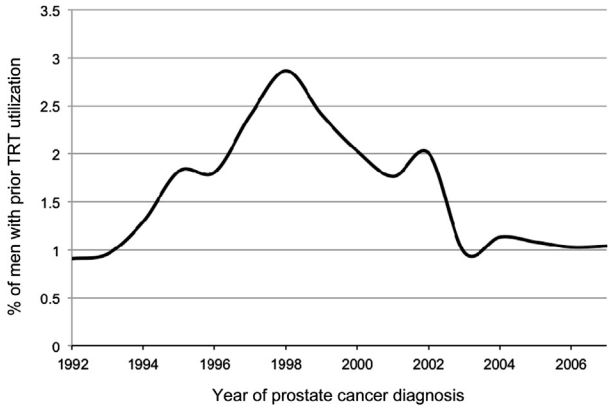

Figure 1. Use of testosterone replacement therapy (TRT) in men diagnosed with prostate cancer in a given year.

with the development of the metabolic syndrome,[18] type 2 diabetes mellitus,[19] and cardiovascular disease.[20] Hypogonadal men incur higher medical costs compared with controls.[21,22] Men treated with TRT demonstrate improved sexual function, mood, and experience improved overall health.[4,6,7,23,24] Prevalence of hypogonadism, as determined by longitudinal and cross-sectional studies, ranges from 2.1%-25%, depending on the strictness of criteria.[1-3,25] Average ages in these cohorts ranged between 47 and 59 years. These studies uniformly show that the prevalence of hypogonadism increases with age, starting in the fourth decade, and increases with medical comorbidity such as the metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease.[1] Men in the Massachusetts Male Aging Study (MMAS) demonstrated a 10% decrease in total testosterone per decade and a 24% decrease in free testosterone per decade.[25]

Our study has many important findings. First, overall use of TRT was low throughout the study period, peaking at 2.8% in 1998. Given the median age in our cohort was 73 years, we expected the prevalence of hypogonadism would be higher than in the aforementioned studies. Despite abundant contrary evidence and expert reviews attempting to dispel the fallacy that TRT increases prostate cancer risk, the myth persists.[6,8] In an international survey study, more than 50% of physicians cited prostate cancer risk as their rationale for withholding TRT in hypogonadal men.[26]

Second, a use of TRT was not associated with more aggressive prostate cancer at diagnosis. Men in the TRT group were no more likely to be diagnosed with poorly differentiated tumors or T4 disease, even after adjusting for the number of preventive and PSA tests before diagnosis. A recently published prospective, observational cohort of 1365 hypogonadal men in the United Kingdom treated with TRT found no significant increase in prostate cancer incidence.[12] Of the 14 incident cancers in that cohort, all tumors were clinically localized and curable. Prostate cancer detection in several TRT trials of approximately 1% is similar to age-matched populations.[6,27,28] Our findings corroborate those of previous studies.

Third, TRT use did not worsen overall or cancer-specific survival. Median follow-up in our study was 5.0 years (IQR, 2.9-7.6 years). Even in high-risk prostate cancer, the likelihood of death in this timeframe is low. However, we also found no significant difference between groups for rates of skeletal-related events or the need for salvage ADT.

Finally, increased frequency of PSA testing in our cohort predicted improved overall and cancer-specific survival. We hypothesized that men treated with TRT would seek more medical care and undergo more preventive testing and cancer screening than controls. In adjusting for this potential confounder, we examined the number of PSA tests in the year before the prostate cancer diagnosis and the number of preventive tests before diagnosis. The improved cancer-specific and overall survival was an important finding in light of the recent U.S. Preventive Services Task Force recommendations against prostate cancer screening.[29] Our findings agree with those of the European Randomized Study of Screening for Prostate Cancer trial, which showed a statistically significant absolute risk reduction in prostate cancer-specific mortality (relative risk, 0.80; 95% confidence interval, 0.65-0.98).[30]

Our findings must be interpreted in the context of the study design. First, claims-based data are designed to provide billing rather than clinical information. More comprehensive clinical data regarding TRT administration, diagnoses of hypogonadism, and prostate cancer outcomes might have influenced the associations we identified. We were not unable to identify users of TRT before age 65 years nor do we have information on serum testosterone levels that prompted therapy. Our study primarily captures TRT encounters in the era before aggressive pharmaceutical company marketing and did not capture testosterone gel or oral formulations. Gel formulations were not approved by the U.S. Food and Drug Administration until the end of our study period, and oral testosterone is rarely used in the U.S.

Second, our analysis only captures TRT usage during Medicare coverage. Limited data exist regarding TRT use in men aged younger than 65 years. Although the prevalence of hypogonadism increases as men age, we were only able to capture those with Medicare eligibility.

Third, 5-year survival after prostate cancer diagnosis is high, and longer follow-up might impact the effect of TRT on cancer-specific outcomes. However, patients in the TRT group were no more likely to have poor tumor grade or stage characteristics nor did they require salvage ADT more frequently, both of which are surrogate markers of poor prostate cancer prognosis.

Table 2. Unadjusted and adjusted prostate cancer-specific outcomes for testosterone replacement therapy before prostate cancer diagnosis vs no testosterone replacement therapy

Variable	Categories	No TRT No. (%)	TRT No. (%)	*P* Value	No-TRT No. (%)	TRT No. (%)	*P* Value
Grade	Well	9722 (6.6)	160 (7.2)	<.0001	6.6	6.8	<.0001
	Moderately	87,084 (59.2)	1444 (64.6)		59.2	63.5	
	Poorly	50,311 (34.2)	633 (28.3)		34.2	29.7	
Clinical stage	T1	58,807 (40.0)	932 (41.7)	<.0001	40.0	41.6	<.0001
	T2	74,210 (50.4)	1152 (51.5)		50.5	50.1	
	T3	4580 (3.1)	73 (3.3)		3.1	4.0	
	T4	9520 (6.5)	80 (3.6)		6.5	4.3	
Initial treatment	ADT	24,878 (16.9)	321 (14.4)	.006	16.9	12.3	<.0001
	RP	27,034 (18.4)	401 (17.9)		18.4	20.0	
	RT	74,391 (50.6)	1181 (52.8)		50.6	53.1	
	WWAS	20,814 (14.2)	334 (14.9)		14.1	14.7	

ADT, androgen-deprivation therapy; RP, radical prostatectomy; RT, radiotherapy; WWAS, watchful waiting with active surveillance; other abbreviation as in Table 1.

Table 3. Adjusted survival and disease severity outcomes in men who did and did not use testosterone replacement therapy

Per 100 person-years	No TRT	TRT	*P* Value
Overall survival	6.87	6.56	.2882
Disease-specific survival	1.56	1.34	.2586
Use of salvage ADT	1.32	1.21	.5250

Abbreviations as in Tables 1 and 2.

CONCLUSION

Despite the high prevalence of hypogonadism in older men and well-established health benefits of TRT, use of TRT is markedly low. The concern of increasing prostate cancer risk or cancer severity by administering TRT has been widely disproved. Using SEER-Medicare linked data, we found no change in prostate cancer-specific outcomes, cancer-specific survival, or overall survival in men treated with TRT before their prostate cancer diagnosis. Our population-based study adds to the growing body of evidence that TRT does not confer worse prostate cancer outcomes.

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Population Based Assessment of Prostate-Specific Antigen Screening for Prostate Cancer

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Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

ABSTRACT

Purpose: The debate of prostate-specific antigen (PSA) screening continues with lack of consensus among various organizations. We performed a population-based analysis to characterize the effect of PSA screening on oncologic outcomes in men diagnosed with prostate cancer.

Materials and Methods: We used Surveillance, Epidemiology, and End Results (SEER)–Medicare linked data to identify 98,883 men diagnosed with prostate cancer from 1996–2007. We stratified frequency of PSA testing as none, 1–2, 3–5, and ≥6 in the 5-years prior to prostate cancer diagnosis. We used propensity scoring methods to assess the effect of frequency of PSA screening on likelihood of: (1) metastases at diagnosis; (2) overall and prostate-cancer specific mortality.

Results: In adjusted analyses, the likelihood of being diagnosed with metastatic prostate cancer decreased with greater frequency of PSA screening (none, 10.6; 1–2, 8.3; 3–5, 3.7; ≥6, 2.5 events per 100 person years, $p<0.001$). Additionally, greater frequency of PSA screening was associated with improved overall and prostate cancer specific survival ($p<0.001$ for both).

Conclusions: Greater frequency of PSA screening in the 5 years prior to prostate cancer diagnosis is associated with lower likelihood of being diagnosed with metastatic prostate cancer, improved overall and prostate cancer-specific survival.

INTRODUCTION

Prostate cancer remains the most commonly diagnosed solid organ tumor among U.S. men with an estimated 241,740 new cases and 28,170 deaths in 2012.[1] Prostate cancer has been singled out as a litmus test for health care reform with a lack of consensus regarding optimal screening or treatment strategies.[2] Prostate specific antigen (PSA) screening has led to a significant increase in detection of clinically localized T1c prostate cancer with concomitant stage migration.[3] It is widely believed that PSA screening adds net costs to the healthcare system without overwhelming support from randomized controlled trials demonstrating improved survival. The randomized controlled trials of PSA screening versus no screening have yielded conflicting results. While the European Randomized Study of Screening for Prostate Cancer (ERSPC) demonstrated that PSA screening in a largely PSA naïve population reduced prostate cancer specific mortality by 20%, [4] the U.S. Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial did not demonstrate a survival benefit of annual PSA screening compared with a control arm in which 52% of subjects had undergone PSA testing before randomization and/or outside of the trial. [5] After a systematic review of the evidence largely weighted by these studies, the U.S. Preventative Services Task Force recommended against PSA screening due to moderate to high certainty the service has no net benefit and the harms outweigh the benefits. [6]

While clinical trials overcome concerns of internal validity, there are often concerns regarding external validity and generalizability— clinical trial enrollees tend to be younger and healthier than most cancer patients and often times represent highly selected patient subgroups. [7-9] Therefore, the purpose of our population-based study was to determine whether use and frequency of PSA-screening in the five years prior to prostate cancer diagnosis affects prostate cancer stage and overall and prostate cancer-specific mortality in a contemporary cohort of elderly Americans.

METHODS

Data

Our study was approved by the University of California, Los Angeles Institutional Review Board; patient data were de-identified and the requirement for consent was waived. We used Surveillance, Epidemiology, and End Results (SEER)–Medicare linked data for analyses, comprised of a linkage of population-based cancer registry data from 16 SEER regions covering approximately 26% of the U.S. population with Medicare administrative data. The Medicare program provides benefits to 97% of Americans aged ≥65 years.[10]

Study Cohort

We identified 267,052 men from SEER-Medicare linked data diagnosed with prostate cancer between 1996 and 2007 with follow-up of Medicare services through 2009. Since we evaluated PSA screening in the five years prior to diagnosis, 182,190 men aged ≥70 years at the time of prostate cancer diagnosis were identified. We excluded 73,134 men who also had health maintenance organization coverage and/or not enrolled to Medicare throughout the study period, as medical services for these men may be incompletely captured. Moreover, we excluded 5,345 men due to missing tumor stage at diagnosis and 4,828 men due to missing demographic or co-morbidity characteristics resulting in a final cohort of 98,883 men.

We identified PSA screening tests prior to prostate cancer diagnosis using Healthcare Common Procedure Coding System (HCPCS) codes 84153, 84154, G0103. Against the backdrop of the U.S. Preventative Services Task Force's recent recommendation against any PSA screening and the inherent differences in patient characteristics of men who never receive any PSA screening from those who obtained at least one PSA test in the 5-years prior to prostate cancer diagnosis, we categorized men who did not have any PSA screening separate from those who had at least one PSA test. These men were categorized into 1–2, 3–5, and ≥6 PSA tests in the 5 years prior to prostate cancer diagnosis. However, in sensitivity analyses, we also combined men with 0 and 1–2 PSA tests and results were similar.

Control Variables

Age was obtained from the Medicare file; tumor characteristics, race, census tract measures of median household income and high school education, region, population density (urban vs. rural), and marital status were obtained from SEER registries. Comorbidity was assessed using the Klabunde modification of the Charlson index during the year before surgery. [11] Use of other Medicare covered preventive procedures for men by Medicare were identified using corresponding HCPCS codes: (1) influenza vaccination 90732, 90724, 90659, 90658, 90669, G0008; (2) cholesterol testing 82465, 83718, 83721, 83719, 80061; (3) colorectal cancer testing 82270, 82272, 82274, 82270, G0328, G0107.

Statistical Analysis

Because men with varying use of PSA screening differed in terms of demographic characteristics and use of other preventative tests covered by Medicare, we used weighted propensity score methods to adjust for these differences. [12, 13] Propensity score methods permit control for observed confounding factors that may influence both group assignment and outcome using a single composite measure and attempts to balance patient characteristics between groups. To conduct the propensity score adjustment, we used a logistic regression model to calculate the propensity (probability) of being in one of the four PSA screening frequency groups based on all covariates described above and then weighted each subject's data based on the inverse propensity of being in 1 of the 4 PSA screening frequency groups. [14] To compare unadjusted proportions across PSA testing groups, we used Pearson's chi-squared test; to compare propensity adjusted proportions across PSA testing groups, we used a Rao-Scott chi-squared test, [14] which accounts for the propensity weighting. To compare unadjusted rates, we fit a Poisson log-linear regression model [15] with PSA testing groups as the only covariate. To compare propensity adjusted rates, we fit a Poisson log-linear regression model [16] with PSA testing groups as the only covariate, but also weighting each subject by the inverse propensity score and using a robust standard error to account for the weighting. [17] We corrected for lead time bias using the approach of Duffy et al. [18] Covariate balance was checked after

adjustment (Table 1). All tests were considered statistically significant at $\alpha=0.05$. All analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

The characteristics of the study population are shown in Table 1 and mean follow-up was 5.4 years following prostate cancer diagnosis. The incidence of foregoing PSA screening was more common among those who are older and have significant comorbidities, Black race, unmarried, lower socioeconomic status, live in rural or in the South, and don't undergo other preventative screenings. After propensity score matching, there was no significant difference of the frequency of PSA screening in terms of the aforementioned variables.

We then examined the effect of frequency of PSA screening on likelihood of metastases at diagnosis, overall and prostate-cancer specific mortality and cost of prostate cancer care (Table 2). While the effect size in differences in outcomes varied between the unadjusted and adjusted variables, statistical significance was maintained in all the core outcome metrics. Greater frequency of PSA screening was associated with a lower likelihood of being diagnosed with metastatic prostate cancer (none, 10.6; 1–2, 8.3; 3–5, 3.7; ≥6, 2.5 events per 100 person years, $p<0.001$). Additionally, greater frequency of PSA screening was associated with lower prostate cancer specific mortality (none, 5.0; 1–2, 6.8; 3–5, 3.2; ≥6, 2.2 events per 100 person years, $p<0.001$) and overall mortality (none, 11.8; 1–2, 17.9; 3–5, 14.2; ≥6, 12.1, $p<0.001$) after

adjustment for lead-time bias. Adjusted Kaplan-Meier survival curves for prostate cancer specific and overall mortality according to year of diagnosis are shown in Figures 1 and 2.

DISCUSSION

PSA screening has led to a significant increase in detection of clinically localized prostate cancer. [3] Since the randomized controlled trials of PSA screening have demonstrated conflicting results, [4, 5] the U.S. Preventative Services Task Force recommended against PSA screening in all men. [6] We sought to provide population-based evidence to further discern the clinical utility and cost effectiveness of PSA based screening.

Our study has two principal findings. First, greater frequency of PSA screening in the five years prior to diagnosis of prostate cancer was associated with lower overall and prostate cancer-specific mortality. This is striking, given that our study was limited to men aged 70 years and older, who are at greater risk for death due to competing risks. Similarly, surgical treatment of prostate cancer versus observation has also been shown to improve overall and prostate cancer specific mortality. [19] Our finding that greater frequency of PSA screening was associated with mortality reduction may be secondary to diagnosing earlier stage, lower-volume disease with fewer metastases. However, while we were unable to adjust for residual confounders such as diet, lifestyle, and body mass index which may affect overall and prostate-cancer specific mortality, [20] a study of baseline PSA drawn from men aged 50 years or less demonstrated that while a higher PSA was associated with a greater risk of subsequent prostate cancer diagnosis, no other anthropometric, lifestyle, biochemical or medical history factors were predictive of a subsequent diagnosis of prostate cancer. [21] Additionally, although the ERSPC demonstrated that PSA screening every 2 to 7 years versus no screening was associated with a 29% reduction in prostate cancer specific mortality, it

demonstrated no difference in overall mortality. [4, 22] Conversely, the PLCO trial demonstrated no difference in prostate-cancer specific mortality for annual PSA screening versus no screening, but it suffered from major limitations including 44% of men obtaining a PSA test prior to enrollment and 52% in the no screening arm receiving a PSA test during the study. [5, 23] Moreover, Crawford et al demonstrated in sub-analyses that men with no or minimal comorbidities who were randomly assigned to screening, were less likely to die of prostate cancer than those who were not. [24]

Second, greater frequency of PSA screening was associated with a lower likelihood of metastases at the time of prostate cancer diagnosis. These findings corroborate the expected stage migration observed with widespread PSA screening. [25] The percentage of men with newly diagnosed metastatic prostate cancer has declined from 25% in 1980 to 4% in 2002 [25] with resultant decrease in prostate cancer-specific mortality by 4.1% annually between 1994 and 2006. [26] It has been previously demonstrated that when compared with younger patients (<75 years old), older patients are more likely to present with metastatic disease and prostate cancer-specific mortality despite increased comorbidities. [27] Our results lend support to investigate screening methods that will identify and treat clinically significant prostate cancers prior to metastases.

While our findings are policy relevant, they must be interpreted in the context of the study design. First, SEER-Medicare is limited to men aged 65 years or older and our results may not be generalizable to younger men undergoing PSA-based screening. Second, our follow-up was relatively modest considering prior studies have demonstrated longer follow-up is needed to see a survival benefit. [22, 28] In terms of treatment benefit, the Scandinavian Prostate Cancer Study has shown with

15-years of follow-up prostate-cancer specific mortality and all-cause mortality are lower in men treated surgically compared with watchful waiting. [19] These results were more pronounced in men younger than 65 years of age. Thus, our results may underestimate the actual survival benefits associated with PSA screening prior to diagnosis and treatment for prostate cancer. Lastly, while we attempted to control for known predictors for prostate cancer-specific mortality the findings are hypothesis generating and it is expected that with longer follow-up from the current randomized controlled trials there will be greater clarification regarding the role of PSA screening. Finally, observational studies reflect practice patterns and when compared with results from well-conducted randomized controlled trials they do not appear to overestimate treatment effects nor differ qualitatively. [29]

CONCLUSIONS

In conclusion, the intensity of PSA-based screening prior to a diagnosis of prostate cancer was associated with lower likelihood of being diagnosed with metastatic prostate cancer, improved overall and prostate cancer-specific survival. These findings must be balanced when considering health care reform initiatives to improve quality of care.

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Table 1. Characteristics of the study population by the frequency of PSA testing in the 5-years prior to prostate cancer diagnosis.

		Before Propensity Weighting					After Propensity Weighting				
		Number of PSA screening tests in the 5-years prior to prostate cancer diagnosis									
		0	1-2	3-5	≥6		0	1-2	3-5	≥6	
n (%)		**n=4,271**	**n=26,301**	**n=33,797**	**n=34,514**	**p-value**					**p-value**
Age at diagnosis (years)	70-74	1471 (3.8)	10183 (26.1)	14064 (36.1)	13297 (34.1)	<0.001	1674 (4.3)	10463 (26.6)	13370 (34.0)	13767 (35.1)	0.959
	≥75	2800 (4.7)	16118 (26.9)	19733 (33.0)	21217 (35.4)		2512 (4.2)	15813 (26.5)	20455 (34.3)	20829 (34.9)	
Charlson Score	0	2589 (4.0)	17458 (27.1)	21801 (33.9)	22472 (35.0)	<0.001	2685 (4.2)	16994 (26.4)	21997 (34.2)	22584 (35.1)	0.420
	1	855 (3.9)	5431 (24.6)	7742 (35.1)	8012 (36.4)		904 (4.1)	5904 (26.8)	7520 (34.1)	7714 (35.0)	
	≥2	827 (6.6)	3412 (27.3)	4254 (34.0)	4030 (32.2)		597 (4.7)	3379 (26.9)	4308 (34.2)	4298 (34.2)	
Race	White	3201 (4.1)	20348 (25.9)	27100 (34.4)	28066 (35.7)	<0.001	3335 (4.2)	20902 (26.6)	26894 (34.2)	27526 (35.0)	0.973
	Black	643 (7.6)	2763 (32.5)	2837 (33.4)	2248 (26.5)		385 (4.5)	2249 (26.4)	2915 (34.3)	2957 (34.8)	
	Hispanic	223 (4.5)	1622 (32.5)	1715 (34.3)	1434 (28.7)		177 (3.6)	1330 (26.8)	1711 (34.5)	1741 (35.1)	
	Asian	151 (4.2)	945 (26.0)	1171 (32.2)	1372 (37.7)		179 (4.8)	968 (26.0)	1263 (33.9)	1317 (35.3)	
	Other	53 (1.7)	623 (20.5)	974 (32.0)	1394 (45.8)		111 (3.6)	827 (27.2)	1042 (34.3)	1055 (34.8)	

		Before Propensity Weighting					After Propensity Weighting				
		Number of PSA screening tests in the 5-years prior to prostate cancer diagnosis									
		0	1-2	3-5	≥6		0	1-2	3-5	≥6	
n (%)		**n=4,271**	**n=26,301**	**n=33,797**	**n=34,514**	**p-value**					**p-value**
Marital status	Not married	1477 (7.0)	6566 (31.1)	6801 (32.2)	6256 (29.7)	<0.001	844 (4.0)	5647 (26.9)	7171 (34.2)	7312 (34.9)	0.331
	Married	2531 (3.9)	16441 (25.1)	22733 (34.8)	23721 (36.3)		2721 (4.2)	17379 (26.5)	22409 (34.2)	22951 (35.1)	
	Unknown	263 (2.1)	3294 (26.7)	4263 (34.5)	4537 (36.7)		621 (5.0)	3249 (26.1)	4245 (34.1)	4333 (34.8)	
High school education	<75	1273 (5.9)	7112 (33.1)	7042 (32.8)	6068 (28.2)	<0.001	897 (4.2)	5753 (26.7)	7384 (34.3)	7515 (34.9)	0.384
	75-84.99	1104 (4.9)	6446 (28.4)	7791 (34.3)	7372 (32.5)		975 (4.2)	6095 (26.5)	7812 (34.0)	8113 (35.3)	
	85-89.99	767 (4.0)	5252 (27.1)	6761 (34.9)	6623 (34.1)		716 (3.7)	5158 (27.0)	6588 (34.4)	6673 (34.9)	
	≥90	1127 (3.2)	7491 (21.2)	12203 (34.6)	14451 (41.0)		1598 (4.5)	9270 (26.3)	12042 (34.2)	12295 (34.9)	
Median household income	<$35,000	2319 (5.7)	13081 (32.1)	13681 (33.5)	11719 (28.7)	<0.001	1807 (4.4)	10926 (26.6)	14030 (34.1)	14366 (34.9)	0.809
	$35-44,999	870 (3.8)	5906 (25.7)	8011 (34.8)	8226 (35.8)		877 (3.8)	6083 (26.6)	7846 (34.3)	8069 (35.3)	
	$45-59,999	639 (3.4)	4366 (23.0)	6634 (35.0)	7327 (38.6)		843 (4.5)	5045 (26.6)	6463 (34.1)	6584 (34.8)	
	≥$60,000	443 (2.8)	2948 (18.3)	5471 (34.0)	7242 (45.0)		659 (4.1)	4221 (26.5)	5487 (34.4)	5577 (35)	
U.S. Census Region	Northeast	780 (3.8)	4722 (23.3)	6605 (32.6)	8183 (40.3)	<0.001	756 (3.8)	5326 (26.6)	6908 (34.5)	7033 (35.1)	0.123
	South	815 (5.2)	5309 (34.1)	5262 (33.8)	4207 (27.0)		721 (4.6)	4087 (26.2)	5367 (34.4)	5423 (34.8)	

		Before Propensity Weighting					After Propensity Weighting				
		Number of PSA screening tests in the 5-years prior to prostate cancer diagnosis									
		0	1-2	3-5	≥6		0	1-2	3-5	≥6	
n (%)		**n=4,271**	**n=26,301**	**n=33,797**	**n=34,514**	**p-value**					**p-value**
	Midwest	914 (4.4)	5836 (27.8)	7732 (36.8)	6548 (31.1)		1004 (4.7)	5612 (26.3)	7218 (33.8)	7533 (35.3)	
	West	1762 (4.2)	10434 (24.9)	14198 (33.8)	15576 (37.1)		1705 (4.1)	11250 (26.9)	14333 (34.2)	14607 (34.9)	
Population density	Metropolitan	3641 (4.1)	22470 (25.4)	30312 (34.3)	31972 (36.2)	<0.001	3682 (4.2)	23434 (26.6)	30177 (34.3)	30660 (34.9)	0.127
	Rural	630 (6.0)	3831 (36.5)	3485 (33.2)	2542 (24.2)		505 (4.6)	2842 (26.0)	3648 (33.4)	3936 (36.0)	
Other preventive tests prior to diagnosis*	None	1663 (26.4)	3541 (56.3)	786 (12.5)	301 (4.8)	<0.001	275 (4.3)	1679 (26.4)	2160 (34.0)	2244 (35.3)	0.999
	1	1319 (8.3)	7487 (47.0)	4539 (28.5)	2603 (16.3)		706 (4.4)	4253 (26.5)	5463 (34.1)	5608 (35.0)	
	2	882 (2.7)	9215 (28.2)	12147 (37.2)	10454 (32.0)		1377 (4.2)	8720 (26.7)	11182 (34.2)	11421 (34.9)	
	All 3	407 (0.9)	6058 (13.8)	16325 (37.2)	21156 (48.1)		1828 (4.2)	11624 (26.5)	15020 (34.3)	15322 (35)	
Year of diagnosis	1996	487 (10.2)	2122 (44.4)	1686 (35.3)	481 (10.1)	<0.001	212 (4.4)	1272 (26.5)	1628 (34.0)	1678 (35.0)	0.999
	1997	377 (7.7)	1749 (35.7)	1766 (36.0)	1014 (20.7)		195 (4.0)	1306 (26.7)	1672 (34.3)	1708 (35.0)	
	1998	312 (6.6)	1416 (30.2)	1701 (36.2)	1268 (27.0)		204 (4.3)	1251 (26.5)	1598 (33.9)	1667 (35.3)	
	1999	255 (5.1)	1495 (29.6)	1698 (33.6)	1606 (31.8)		208 (4.1)	1351 (26.6)	1729 (34.1)	1783 (35.2)	
	2000	502 (4.8)	3597 (34.0)	3231 (30.6)	3246 (30.7)		434 (4.1)	2800 (26.6)	3609 (34.3)	3671 (34.9)	

		Before Propensity Weighting					After Propensity Weighting				
		Number of PSA screening tests in the 5-years prior to prostate cancer diagnosis									
		0	1-2	3-5	≥6		0	1-2	3-5	≥6	
n (%)		**n=4,271**	**n=26,301**	**n=33,797**	**n=34,514**	**p-value**					**p-value**
	2001	509 (4.7)	3113 (28.5)	3748 (34.3)	3571 (32.6)		459 (4.2)	2887 (26.5)	3748 (34.5)	3784 (34.8)	
	2002	390 (3.6)	2836 (26.1)	3782 (34.8)	3848 (35.5)		450 (4.2)	2849 (26.5)	3709 (34.4)	3759 (34.9)	
	2003	339 (3.6)	2322 (24.3)	3374 (35.3)	3520 (36.8)		399 (4.2)	2514 (26.3)	3279 (34.3)	3362 (35.2)	
	2004	309 (3.2)	2155 (22.5)	3269 (34.1)	3862 (40.3)		384 (4.0)	2570 (26.8)	3282 (34.2)	3353 (35.0)	
	2005	293 (3.2)	1945 (21.2)	3072 (33.5)	3854 (42.1)		372 (4.1)	2454 (26.8)	3136 (34.2)	3210 (35.0)	
	2006	252 (2.7)	1831 (19.6)	3184 (34.0)	4098 (43.8)		454 (4.8)	2473 (26.2)	3208 (34.0)	3291 (34.9)	
	2007	246 (2.6)	1720 (18.3)	3286 (35.0)	4146 (44.1)		416 (4.4)	2549 (26.8)	3226 (33.9)	3330 (35.0)	

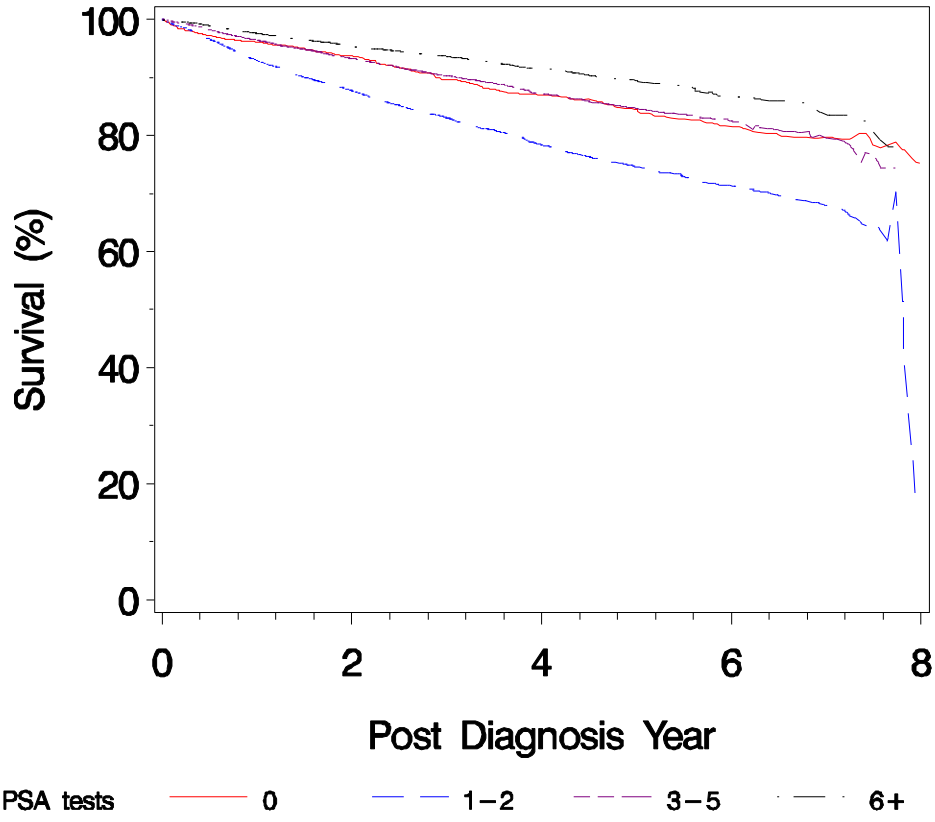
*Includes influenza vaccination and cholesterol and colorectal cancer testing.

Table 2. Overall and Prostate Cancer-Specific Mortality By Clinical Stage

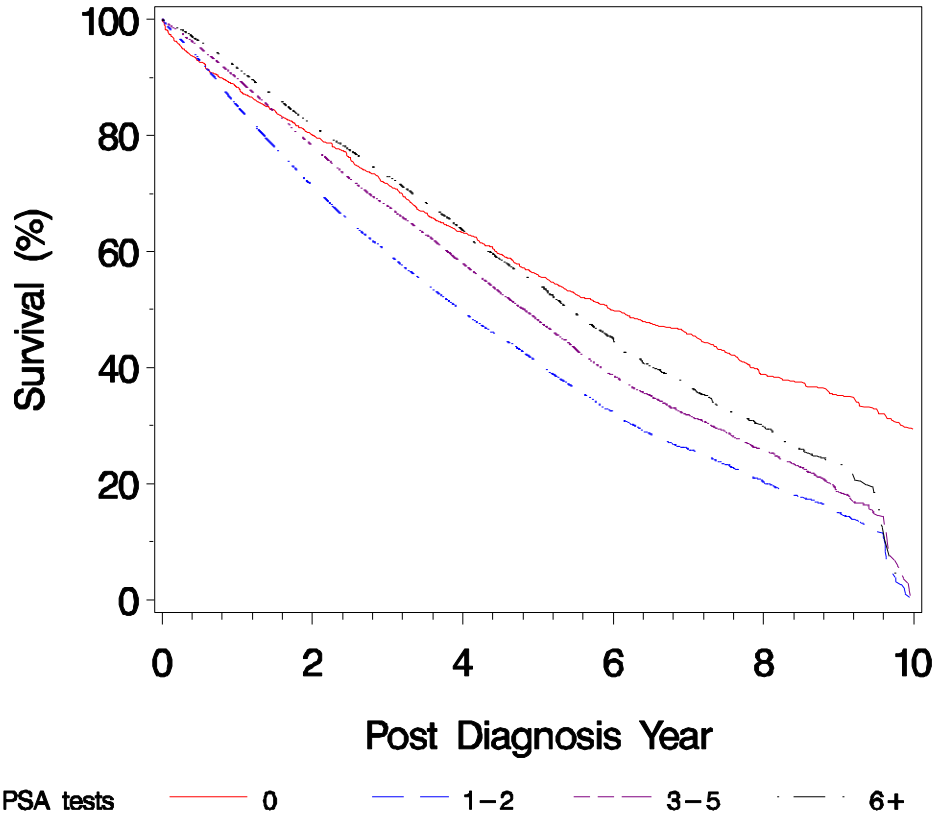
Variable	Before Propensity Weighting					After Pr	
	Number of PSA screening tests in the 5-years prior to prostate car						
	0	1-2	3-5	>=6	p-value	0	1-2
Metastasis at diagnosis*	16.4	9.3	3.5	2.2	<0.001	10.6	8.3
Overall Mortality*	15.1	10.2	7.1	5.6	<0.001	15.1	18.9
Overall Mortality* (adjustment for lead-time bias)	11.8	9.3	7.4	6.3	<0.001	11.8	17.9
Prostate cancer-specific mortality*	5.0	3.0	1.4	0.9	<0.001	5.0	6.8
Prostate cancer-specific mortality* (adjustment for lead-time bias)	3.5	2.7	1.5	1.0	<0.001	3.5	6.3

*events per 100 person years

Prostate Cancer Specific Survival



Overall Survival



Certificate of Need Programs, Intensity Modulated Radiation Therapy Use and the Cost of Prostate Cancer Care

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Purpose: Certificate of need programs are a primary mechanism to regulate the use and cost of health care services at the state level. The effect of certificate of need programs on the use of intensity modulated radiation therapy and the increasing costs of prostate cancer care is unknown. We compared the use of intensity modulated radiation therapy and change in prostate cancer health care costs in regions with vs without active certificate of need programs.

Materials and Methods: This population based, observational study using SEER (Surveillance, Epidemiology, and End Results)-Medicare linked data from 2002 through 2009 was comprised of 13,814 men treated for prostate cancer in 3 regions with active certificate of need programs (CON Yes) vs 44,541 men treated for prostate cancer in 9 regions without active certificate of need programs (CON No). We assessed intensity modulated radiation therapy use relative to other prostate cancer definitive therapies and overall prostate cancer health care costs with respect to certificate of need status.

Results: In propensity score adjusted analyses, intensity modulated radiation therapy use increased from 2.3% to 46.4% of prostate cancer definitive therapies in CON Yes regions vs 11.3% to 41.7% in CON No regions from 2002 to 2009. Furthermore, we observed greater intensity modulated radiation therapy use with time in CON Yes vs No regions ($p < 0.001$). Annual cost growth did not differ between CON Yes vs No regions ($p = 0.396$).

Conclusions: Certificate of need programs were not effective in limiting intensity modulated radiation therapy use or attenuating prostate cancer health care costs. There remains an unmet need to control the rapid adoption of new, more expensive therapies for prostate cancer that have limited cost and comparative effectiveness data.

Key Words: prostatic neoplasms; radiotherapy, intensity-modulated; health care costs; certificate of need

Abbreviations and Acronyms

3D-CRT = 3-dimensional conformal radiotherapy

CON = certificate of need

IMRT = intensity modulated radiation therapy

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See Editorial on page 12.

HEALTH care expenditures continue to skyrocket in the United States and currently account for 17.6% of gross domestic product.[1] Certificate of need programs have long been the primary regulatory mechanism for curbing the rapid expansion of health care services and controlling health care costs at the state level.[2] Mandated by the federal government during the late 1970s and early 1980s, CON programs require state approval before the establishment of new health facilities or the investment in health care

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equipment.[3] Despite an end to the federal mandate for CON programs more than 2 decades ago,[3] a number of states continue to rely on CON programs to contain health care costs.[4]

Several studies have examined the impact of CON programs on coronary artery bypass graft and percutaneous coronary intervention,[5–10] neonatal intensive care,[11] plastic surgery,[12] and gastrointestinal and pulmonary cancer resections.[2] However, few have assessed the effect of CON programs on the adoption of novel technologies with limited comparative effectiveness data that are often associated with significantly greater costs. In addition, the role of CON programs in prostate cancer treatment and cost has not been examined. Prostate cancer is the most common cancer among American men and has been described as a litmus test for evaluating health reform due to its increasing costs with limited prospective outcomes data.[13] In the last decade IMRT has rapidly emerged as the radiation modality of choice for men with prostate cancer,[14] despite its significantly higher costs compared to other forms of therapy.[15] To our knowledge there have been no randomized trials comparing clinical outcomes of IMRT with those of less costly alternatives.[14] The few studies that have examined IMRT outcomes have been retrospective, and have not compared IMRT to other treatment modalities such as radical prostatectomy, which remains the most widely used therapy for prostate cancer.[16–18]

With this in mind, we evaluated the effectiveness of CON regulations in curtailing IMRT use and overall prostate cancer costs. Our objective was to compare use of IMRT and prostate cancer cost growth in regions with and without active CON programs. We hypothesized that greater adoption of IMRT and more rapid growth in the cost of prostate cancer care would be observed in regions without CON programs regulating IMRT.

METHODS

We used SEER-Medicare linked data for analyses. SEER is a cancer registry database comprising 16 geographic areas covering approximately 28% of the United States population.[19] The presence or absence of CON programs, date of initiation and duration were determined from the National Conference of State Legislatures[4] and confirmed by contacting each state's health department. SEER regions in states that required CON approval (Connecticut, Michigan, Iowa) for radiation therapy or linear accelerators were designated CON Yes while regions in states without CON programs (California, New Mexico, Utah) or states with CON programs that did not cover radiation therapy during the study period (Washington, Louisiana, New Jersey) were designated CON No. Three states (Hawaii, Georgia and Kentucky) had specific exemptions from the CON process such as capital expenditure thresholds, population density requirements or clauses regarding the demographics of patients served. These states were excluded from our analyses given their heterogeneity in IMRT CON requirements.

We identified 155,107 men age 65 years or older who were diagnosed with prostate cancer from 2002 to 2007 and followed through Medicare services through December 31, 2009. Of these men 107,340 were enrolled in Medicare Part A and Part B, and were not enrolled in a health maintenance organization during the study period. From this group 69,630 had radiation therapy or radical prostatectomy as definitive therapy. Excluding men in CON indeterminate areas yielded a study population of 61,332 patients. An additional 2,977 men were excluded from study due to incomplete demographic information. This yielded a study population of 58,355 men, including 44,541 in 6 regions that do not have CON programs covering radiation therapy (CON No) and 13,814 in 3 regions with current CON programs regulating radiation therapy (CON Yes).

Men undergoing IMRT, 3D-CRT, brachytherapy and radical prostatectomy were identified using corresponding CPT-4 codes. Use of IMRT relative to other definitive therapies for prostate cancer is presented as a proportion.

Prostate cancer health care costs (inpatient, outpatient and physician services) were assessed in the year after prostate cancer diagnosis. To isolate costs associated with prostate cancer care, we subtracted baseline health care costs in the 12 months before prostate cancer diagnosis, allowing each subject to serve as his own control.[14] Of the 58,355 men who were included in IMRT use analyses, 20,866 were excluded from cost analyses because they did not initiate treatment within 6 months after prostate cancer diagnosis, they were not continuously enrolled in the 12 months before and after diagnosis, they did not have Medicare as their primary health insurance or they had incomplete demographic information. All costs were adjusted to 2010 dollars using the 2007 annual report of the Boards of Trustees of the Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Fund.

Age, race, education, income, geographic region, and clinical tumor grade and stage were derived from the SEER registries. Education was defined as the percentage of residents in a census tract attaining at least a high school education. Comorbidity status using the Klabunde modification of the Charlson comorbidity index was based on inpatient, outpatient and carrier Medicare claims in the year before diagnosis.[20,21]

We compared baseline demographic and tumor characteristics between CON Yes and CON No groups using chi-square tests. A Mantel-Haenszel test was performed to compare IMRT use in CON Yes vs CON No regions over time. The Wilcoxon rank sum test was used to compare median prostate cancer health care costs. We used propensity score methods to adjust for differences in demographic and tumor characteristics in CON Yes vs CON No regions.[22,23] Propensity score methods balanced characteristics between groups using a single composite measure to control for observed confounding factors that may influence group assignment and outcome. The propensity score adjustment was performed using a logistic regression model that calculated the propensity (probability) of

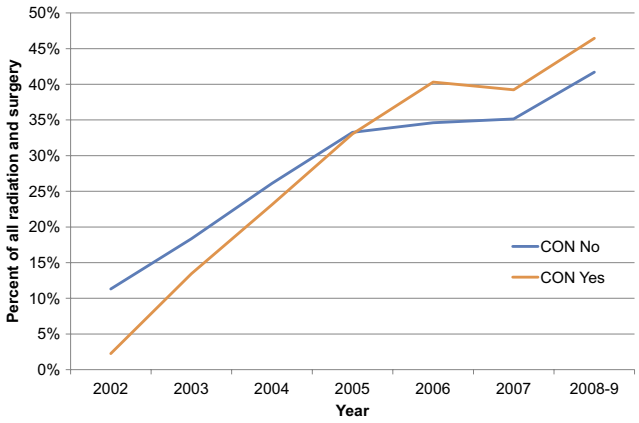
being in a CON Yes vs No region based on all covariates previously described. Data for each subject were weighted based on the inverse propensity of being in 1 of the 2 regions. Covariate balance was assessed after the propensity score adjustment was performed (supplementary table, www.jurology.com). Due to the relatively smaller number of patients treated in 2009, we combined data from 2008 to 2009 in our analyses. The threshold for statistical significance was set at $\alpha = 0.05$. All analyses were performed using SAS® 9.2.

RESULTS

Demographic characteristics of CON Yes and CON No groups can be found in the supplementary table. CON No regions had a greater proportion of men with well differentiated tumors, clinical stage T1 cancer, age 65 to 59 years at diagnosis, and Hispanic and Asian race. More men in CON No regions lived in areas with less than 75% high school education rates, a greater than $60,000 median income and high population density. Propensity score methods adjusted for these differences.

While the use of IMRT as a proportion of all definitive treatments for localized prostate cancer (ie radical prostatectomy, IMRT, 3D-CRT and brachytherapy) increased dramatically during the study period in CON Yes (2.3% of all treatments in 2002, 46.4% in 2008 to 2009) and CON No (11.3% of all treatments in 2002, 41.7% in 2008 to 2009) regions, greater growth of IMRT use was observed in CON Yes (slope 0.403) vs CON No (slope 0.241) regions in adjusted analyses ($p < 0.001$, see figure, table 1).

Prostate cancer health care costs decreased in CON Yes ($23,250 in 2002, $18,511 in 2008 to 2009) and CON No ($23,091 in 2002, $19,815 in 2008 to 2009) regions. In adjusted analyses the median cost decrease per year was similar in CON Yes ($908, 95% CI $1,294–$522) and CON No ($790, 95% CI $958–$623) regions ($p = 0.396$, table 2).



Proportion of IMRT use as fraction of all definitive treatments for clinically localized prostate cancer during study period. Blue line represents regions without active CON programs and orange line represents regions with active CON programs regulating radiation therapy.

Table 1. *Propensity score adjusted Mantel-Haenszel test for IMRT use by CON status*

Yr	% IMRT in CON No	% IMRT in CON Yes
2002	11.32	2.26
2003	18.35	13.45
2004	26.12	23.12
2005	33.27	33.05
2006	34.61	40.31
2007	35.15	39.23
2008–2009	41.7	46.44

IMRT use presented as a proportion of all definitive therapies for prostate cancer.

DISCUSSION

Using a population based approach we observed a rapid expansion in the use of IMRT for prostate cancer, unchecked by CON programs. Furthermore, CON programs did not appear to influence the change in prostate cancer health care costs. This study represents what is to our knowledge the first analysis of the impact of CON programs on IMRT use and prostate cancer care costs.

Contrary to our hypothesis, we found that CON programs were ineffective in limiting the use of IMRT for prostate cancer. Some have suggested that CON programs may help control the increase in urologist owned IMRT centers, an issue that many credit for the steep increase in the use of IMRT for prostate cancer.[13,24,25] Notably, we found that regions with active CON programs regulating IMRT actually experienced greater growth in the use of IMRT. It is possible that the presence of CON regulations selects for areas in which the overuse of health services is already an issue, thus motivating these states to maintain active CON regulations. In this case, there would be an inherent predisposition toward increased IMRT use in states with CON programs. Alternatively in some cases the CON process may be more of a formality than a true barrier

Table 2. *Propensity score adjusted Wilcoxon rank sum test for prostate cancer health care costs by CON status*

Yr	Cost of Care in CON No ($)	Cost of Care in CON Yes ($)	p Value
2002	23,091	23,250	0.628
2003	23,660	25,230	0.054
2004	21,332	22,091	0.191
2005	20,518	20,691	0.783
2006	20,025	20,231	0.792
2007	20,252	20,291	0.958
2008–2009	19,815	18,511	0.379

to entry. For instance, in Michigan between 2002 and 2007, 55 of 71 CON applications for megavoltage radiation therapy (eg linear accelerators, cyberknife, gamma knife, heavy particle accelerator, IMRT) were approved.[26] The remaining 16 were either granted conditional approval pending specific requirements being met, waived for not requiring CON approval or were withdrawn by applicants. None of the 71 applications for megavoltage radiation therapy was denied. Many of these proposals were on a large scale as the total value of such approved projects for the state of Michigan exceeded a quarter billion dollars during the study period. It is important to note that we were unable to accurately estimate the number of projects for which the CON process acted as a deterrent, causing providers to alter their practice strategies or relocate to other regions.

Furthermore, we observed that CON regulations have not had the intended effect in controlling prostate cancer health care expenditures. The cost of IMRT is significantly greater than that of alternative therapies,[27,28] with some estimates that IMRT costs almost twice as much as other radiation modalities for prostate cancer and nearly 6 times as much as radical prostatectomy.[15] To date, to our knowledge, there have been no prospective randomized studies comparing IMRT vs brachytherapy, 3D-CRT or radical prostatectomy for the treatment of clinically localized prostate cancer.[14] Studies examining the cost-effectiveness of IMRT are similarly scarce. A recent study showed that widespread adoption of IMRT had already taken place before even a single study was published examining its cost-effectiveness.[14] Thus, mechanisms to contain the rapid adoption of newer, more expensive therapies and to limit prostate cancer health care costs are increasingly relevant, particularly given the absence of compelling comparative effectiveness data.

Prior studies have demonstrated that CON programs control the supply of certain health services. Lorch et al demonstrated that the absence of CON regulations was associated with more hospitals with neonatal intensive care units and more neonatal intensive care beds.[11] Hellinger suggested that CON programs were associated with modest reductions in the number of hospital beds and slight reductions in health expenditures.[29] In terms of cancer care Short et al illustrated that CON regions had fewer hospitals per cancer incident performing pulmonary lobectomy, rectal resection and colectomy for cancer.[2] With regard to coronary interventions Vaughan Sarrazin[5] and Ross[7] et al showed greater resource use in the absence of CON programs. These and other studies demonstrated the limited expansion of coronary intervention services leading to higher per provider volumes in the presence of CON programs, a desired outcome of the CON program.[6,9,10] While CON has controlled the supply and use of various health services, CON may not be the solution to the rapid and widespread adoption of newer, more expensive therapies for prostate cancer.

Alternative approaches to control the use of costly new technology include innovations in health delivery systems such as accountable care organizations, which may incentivize physicians to balance clinical benefit against cost. In addition, value based insurance design may emphasize the utility of health services and engage patients in cost containment. Reimbursement reform may also reduce physician incentives for the use of costly health services.[30]

Our findings must be interpreted in the context of the study design. Our study of Medicare beneficiaries may not be generalizable to younger men (ie age less than 65 years). Moreover, private insurance typically reimburses at higher levels than Medicare, thereby leading to potential underestimates of our prostate cancer costs. In addition, states without CON programs may have other regulatory mechanisms in place to control health services use and cost that we were unable to identify. Future studies should attempt to gauge the existence and influence of such regulations in states without official CON programs. There was also likely regional variation in the actual cost of providing care within and between groups. To account for this variation we adjusted for population density in all analyses and used change in annual cost rather than actual cost as our main cost variable, in effect controlling for regional cost variation.

Given the prevalence of prostate cancer, current controversy regarding its treatment and present emphasis on health care economics, we believe our study is particularly insightful and timely. Despite the increased cost and limited comparative effectiveness data for IMRT, the proportion of its use among all prostate cancer treatment modalities increased dramatically in all states in our sample. CON programs appear ineffective in attenuating IMRT use and prostate cancer health care costs.

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Overuse of Imaging for Staging Low Risk Prostate Cancer

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Purpose: Routine imaging for staging low risk prostate cancer is not recommended according to current guidelines. We characterized patterns of care and factors associated with imaging overuse.

Materials and Methods: We used SEER-Medicare linked data to identify men diagnosed with low risk prostate cancer from 2004 to 2005, and determined if imaging (computerized tomography, magnetic resonance imaging, bone scan, abdominal ultrasound) was obtained following prostate cancer diagnosis before treatment.

Results: Of the 6,444 men identified with low risk disease 2,330 (36.2%) underwent imaging studies. Of these men 1,512 (23.5%), 1,710 (26.5%) and 118 (1.8%) underwent cross-sectional imaging (computerized tomography or magnetic resonance imaging), bone scan and abdominal ultrasound, respectively. Radiation therapy vs surgery was associated with greater odds of imaging (OR 1.99, 95% CI 1.68–2.35, p <0.01), while active surveillance vs surgery was associated with lower odds of imaging (OR 0.44, 95% CI 0.34–0.56, p <0.01). Associated with increased odds of imaging was median household income greater than $60,000 (OR 1.41, 95% CI 1.11–1.79, p <0.01), and men from New Jersey vs San Francisco (OR 3.11, 95% CI 2.24–4.33, p <0.01) experienced greater odds of imaging. Men living in areas with greater than 90% vs less than 75% high school education experienced lower odds of imaging (OR 0.76, 95% CI 0.6–0.95, p = 0.02).

Conclusions: There is widespread overuse and significant geographic variation in the use of imaging to stage low risk prostate cancer. Moreover treatment associated variation in imaging was noted with the greatest vs lowest imaging use observed for radiation therapy vs active surveillance.

Key Words: diagnostic imaging, health services misuse, prostatic neoplasms, health expenditures

Abbreviations and Acronyms

ACR = American College of Radiologists
CT = computerized tomography
MRI = magnetic resonance imaging
NCCN = National Comprehensive Cancer Network
PSA = prostate specific antigen
SEER = Surveillance, Epidemiology and End Results

PROSTATE cancer remains the most commonly diagnosed solid organ tumor among United States men with approximately 192,280 incident cases in 2009.[1] Due to widespread PSA screening and resultant stage migration, the majority of men are diagnosed with low risk disease as defined by D'Amico et al as clinical stage T1c or T2a, PSA less than 10 ng/ml and Gleason score less than or equal to 6.[2] While the appropriate treatment for men with these indolent tumor characteristics is widely debated, the risk of metastasis is low, obviating the need for imaging for staging purposes. Because there is a less than 1% chance of a positive bone scan or CT when imaging men with low risk prostate cancer,[3–8] the ACR[9] and the

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NCCN[10] advised against routine imaging for men with low risk features.

Despite the recommendations of the ACR and NCCN, Plawker et al found that 28.6% and 52.4% of urologists in 1997 ordered CT and bone scan, respectively, for all men with prostate cancer regardless of risk.[11] Using data from an observational cohort of men with prostate cancer Cooperberg et al reported persistent inappropriate use with 22.7% of men diagnosed with low risk prostate cancer undergoing radiographic staging before treatment.[12]

More recently emerging evidence has shown that the overall use of imaging, especially CT, is increasing, and that there is widespread variation in use and cost without apparent benefit.[13] Against this backdrop we characterized patterns of care and factors associated with the use of imaging in men with low risk prostate cancer using a contemporary, population based, observational cohort.

MATERIALS AND METHODS

Data

Our study was approved by the Brigham and Women's institutional review board. Patient data were de-identified and the requirement for consent was waived. We used SEER-Medicare[14] data for analysis, which is comprised of a linkage of population based cancer registry data from 16 SEER areas with Medicare administrative data, and covers approximately 26% of the United States population. The Medicare program provides benefits to 97% of Americans 65 years old or older.[15]

Study Cohort

We identified 49,364 men 65 years old or older diagnosed with prostate cancer during 2004 to 2005 with at least 1 year of followup after diagnosis to ascertain whether imaging was obtained and the type of treatment rendered. We excluded from study 5,404 men who were enrolled in a health maintenance organization or who were not enrolled in Medicare Part A and Part B because claims are not reliably submitted for these men. To increase sensitivity for detection of imaging we restricted our analyses to men with prostate cancer as their first and only cancer, and excluded 3,378 men with other cancers including nonmelanoma skin cancers. We also excluded 8,249 men diagnosed with metastatic prostate cancer. Finally, we excluded men with intermediate (14,884), high (7,388) and unknown (3,617) risk disease, which provided our cohort with 6,444 men with low risk prostate cancer.[2] Demographic and tumor characteristics were obtained from SEER registry data while patient age was obtained from the Medicare file. Comorbidity was assessed using the Klabunde modification of the Charlson index based on claims submitted during the year before surgery.[16] The Klabunde modification uses comorbid conditions identified by the Charlson comorbidity index, and incorporates the diagnostic and procedure data contained in Medicare physician (Part B) claims.

Outcomes

We examined the use of pretreatment imaging after prostate cancer diagnosis for low risk prostate cancer. These imaging modalities included cross-sectional imaging (CT, MRI, endorectal coil MRI), bone scan and abdominal ultrasound. Cross-sectional imaging for radiation treatment planning was excluded from analysis because this is billed with unique CPT-4 codes. We included only imaging studies designated with a corresponding primary ICD-9 diagnosis code 185.0 for prostate cancer.

Treatments

Treatment choice was determined by the corresponding CPT-4 and ICD-9 codes from Medicare inpatient, outpatient and carrier component files (formerly Physician/Provider B files). Surgical therapy included open radical prostatectomy, open perineal prostatectomy and minimally invasive radical prostatectomy. Radiation therapy included brachytherapy, brachytherapy combined with 3-dimensional conformal external beam radiation therapy or intensity modulated radiation therapy, external beam radiation therapy alone, intensity modulated radiation therapy alone, and proton beam therapy. Men undergoing hormone ablation were identified based on the presence of the Healthcare Common Procedure Coding System codes used for gonadotropin-releasing hormone agonists without a designation for definitive therapy. Men avoiding definitive therapy for 12 or more months after diagnosis were categorized as on active surveillance.

Statistical Analysis

Characteristics associated with over-imaging for low risk disease were compared with the Pearson chi-square statistic and the Fisher exact test. Univariable and multivariable logistic regression analyses were performed to identify clinical covariates significantly associated with an increased likelihood of having imaging.[17] A multivariate logistic regression model was constructed with year of diagnosis, age, Charlson comorbidity index, race, marital status, education level, income, SEER region, population density (urban vs rural) and treatment type as covariates. All tests were considered statistically significant at $\alpha = 0.05$. Analyses were performed with SAS® version 9.2.

RESULTS

The demographics of our study population are summarized elsewhere. We observed an increased use of imaging among men treated with radiation followed by surgery and active surveillance (45.5%, 26.1% and 12.8%, $p < 0.01$). Moreover while age, race, marital status, year of diagnosis and comorbidity were not associated with imaging use, there was significant geographic variation in the use of imaging with New Jersey vs Seattle having the highest and lowest use rates (61.6% vs 18.0%, $p < 0.01$). Men with median household incomes greater than $60,000 vs less than $35,000 were more likely to undergo imaging (39.6% vs 35.6%, $p = 0.03$), while men living in areas with 90% or greater vs less than 75% high school

education were less likely to undergo imaging (33.7% vs 37.4%, p = 0.01).

Results from adjusted analysis were consistent with these results. Median household incomes greater than $60,000 vs less than $35,000 experienced greater odds of imaging (OR 1.41, 95% CI 1.11–1.79, p <0.01), while men living in areas with greater than 90% vs less than 75% high school education experienced lower odds of imaging (OR 0.76, 95% CI 0.6–0.95, p = 0.02). Men living in New Jersey (OR 3.11, 95% CI 2.24–4.33, p <0.01), Hawaii (OR 1.84, 95% CI 1.22–2.79, p <0.01) and Los Angeles (OR 1.68, 95% CI 1.18 – 2.41, p <0.01) experienced greater odds of imaging compared to San Francisco, while men living in Seattle experienced lower odds of imaging (OR 0.6, 95% CI 0.40–0.91, p = 0.02). Finally, men undergoing radiation (OR 1.99, 95% CI 1.68–2.35, p <0.01) vs surgery experienced greater odds of imaging, while those undergoing active surveillance (OR 0.44, 95% CI 0.34–0.56, p <0.01) vs surgery experienced lower odds of imaging. Finally, the use of imaging did not differ significantly for cryotherapy and hormone therapy compared to surgery.

The type of imaging obtained by treatment type is shown in the table. Overall 36.2% of men underwent at least 1 imaging study before treatment. Cross-sectional imaging was performed in 23.5% of men while 26.5% underwent a bone scan. Additionally, 1.8% of men underwent abdominal ultrasound. Moreover 3,340 imaging studies were performed in 2,330 men, and men undergoing imaging received 1.4 studies on average. Men undergoing radiation therapy vs surgery were more likely to receive cross-sectional imaging (31.5% vs 15.9%, p <0.01) and bone scans (32.9% vs 21.4%, p <0.01). Of note, CT comprised more than 97% of all cross-sectional imaging studies obtained.

DISCUSSION

With the widespread use of PSA screening there has been greater detection of low risk prostate cancer.[2] Prior studies have demonstrated the rarity of positive radiographic findings when imaging men with low risk features[3–8] and current guidelines do not recommend imaging for low risk disease.[9,10] Hunchrarek and Muscat estimated that eliminating unnecessary CTs alone may net a cost savings of $20 to $50 million a year in direct prostate cancer expenditures.[18] Although the exact cost burden (direct and indirect) of the overuse of imaging remains unknown, it is likely high given the large number of men exposed. Assuming 232,090 men were diagnosed with prostate cancer in 2005[19] and half were diagnosed with low risk disease, extrapolating from our findings suggests that at least 41,000 men were exposed to 58,800 studies that year.

Our study has several important findings. There is widespread overuse of imaging for low risk prostate cancer. We found that more than a third of men with low risk disease underwent imaging before treatment. We limited our analysis to those men with low risk disease because there is clear consensus that these men should not undergo imaging. Oesterling studied 2,064 consecutive men with prostate cancer and a PSA less than 20 ng/ml, and found 7 (0.3%) had a positive bone scan with only 1 positive finding with a PSA less than 10 ng/ml.[4] In a study of 861 men with prostate cancer Levran et al found that 13 (1.5%) had nodal disease on CT confirmed by biopsy and that all of these men had a PSA greater than 20 ng/ml.[6] In addition, no positive bone scans were found in men with PSA less than 20 ng/ml. Similarly Lee et al studied 588 men with low risk prostate cancer and did not identify a positive CT among them.[7] In a recent review of MRI and functional MRI techniques used in prostate cancer Seitz et al found functional MRI more reliable than conventional MRI in detecting and staging prostate cancer.[20] However, there are currently no guidelines available to suggest which technique is optimal in a specific clinical scenario. Interestingly there is improved accuracy when combining the Kattan nomogram variables with MRI/magnetic resonance spectroscopy.[21] However, MRI detection of extracapsular extension varies widely, ranging from 54% to 83%, with improved accuracy when MRI is combined with functional MRI.[20] These studies led the NCCN and

Type of imaging ordered and treatment rendered

	Watchful Waiting	Hormone Ablation Only	Surgery	Cryotherapy	Radiation	Totals
No. men treated	1,096	273	1,026	116	3,933	6,444
No. men with imaging (%)	140 (12.8)	95 (34.8)	268 (26.1)	37 (31.9)	1,790 (45.5)	2,330 (36.2)
No. cross-sectional (%)*	44 (4.0)	47 (17.2)	163 (15.9)	23 (19.8)	1,235 (31.5)	1,512 (23.5)
No. bone scan (%)	91 (8.3)	84 (30.8)	220 (21.4)	23 (19.8)	1,292 (32.9)	1,710 (26.5)
No. abdominal ultrasound (%)	Less than 11 (less than 1)†	Less than 11 (less than 4)†	22 (2.1)	Less than 11 (less than 9)†	83 (2.1)	118 (1.8)

All values p < 0.01.

* Includes CT and MRI.

† Values less than 11 censored for confidentiality.

the ACR to advise against the routine use of pretreatment imaging for low risk disease.[9,10] Recently Briganti et al validated the existing guidelines for bone scan use, finding them to be highly accurate.[22] Furthermore, the use of bone scans in men with low risk prostate cancer is a negative quality indicator in the Physician Performance Measurement Set for Prostate Cancer, which was proposed for implementation in the 2008 Physician Quality Reporting Initiative.[23] The Physician Quality Reporting Initiative is a Centers for Medicare and Medicaid Services initiative linking physician reimbursement to quality. While the use of abdominal ultrasound in our series for staging purposes is uncommon, it is unwarranted for staging purposes.

In addition, we found significant variation in treatment rendered and in demographics in the use of pretreatment imaging. In adjusted analyses while the likelihood of imaging for men undergoing surgery vs hormone ablation vs cryotherapy was similar, the likelihood of imaging for men undergoing radiation vs surgery was 2-fold greater. These results are similar to those of other studies that adjusted for age and comorbidities, and demonstrated that men were more likely to undergo radiographic staging before radiation therapy vs surgery.[24] Differences in practice patterns across specialties and access to imaging modalities may contribute to this finding. Additionally, men on active surveillance vs those treated with surgery were less likely to undergo radiographic imaging.

We also found significant geographic variation in use. For instance, men in New Jersey were 5 times more likely to undergo imaging than those in Seattle. These results are consistent with previous reports showing significant geographic variability. In 2000 Albertsen et al showed that rates of CT in pretreatment imaging for all risks of prostate cancer varied from 83% in Connecticut to 58% in Seattle.[25] Similarly in 2002 Cooperberg et al showed that men living in the East had a higher chance of undergoing imaging (75.4%) vs those living in the West (52.1%).[26] While other studies have shown that insurance type was predictive of test use in men with prostate cancer,[11,26] we observed a striking geographic variation in our study of Medicare beneficiaries.

Finally, men living in areas of greater income were more likely to undergo imaging for low risk disease. This may be a result of increased patient demand and better access to imaging modalities. Men living in areas of greater income may be more likely to expect imaging for staging purposes,[27] may possess generous supplemental insurance, and may be more likely to afford copayments and, therefore, more likely to access imaging. However, men residing in areas of greater education were less likely to receive over-imaging. We performed a subanalysis demonstrating that only 43% of men living in areas with greater than 90% high school education lived in areas where the median income was greater than $60,000, allowing for the duality of these findings. Ultimately men living in areas or physicians treating men living in areas with more than a 90% high school education rate may better understand the low yield and extraneous cost of pretreatment imaging for low risk prostate cancer.

Variation in prostate cancer health delivery is not limited to radiographic staging. The Dartmouth Atlas of Healthcare Project found that radical prostatectomy was characterized by the greatest local variation of all the procedures studied. The absolute rate of radical prostatectomy, adjusted for prostate cancer prevalence, varied by almost 10-fold from region to region.[28] Moreover Fisher et al demonstrated wide geographic variation in total Medicare costs, in part driven by the use of diagnostic tests, but no difference in access to or quality of care.[29]

Our study must be interpreted in the context of the study design. Administrative data are primarily designed to provide billing information, not detailed clinical information. The SEER-Medicare data linkage was initiated to examine population based patterns of care.[14] Our findings may not be generalizable to men younger than 65 years. However, previous studies have shown that age does not predict test use before treatment in men with prostate cancer.[26] Finally, our measures of use may overestimate radiographic staging for low risk disease. However, we excluded men with other malignancies from our cohort and only included imaging studies performed with a primary diagnosis of prostate cancer. Furthermore, approximately 70% of our study population had no comorbidities while approximately 20% had a Charlson comorbidity index of 1, reducing the likelihood of nonprostate cancer imaging studies. Moreover the number and severity of comorbidities were not significantly associated with the use of pretreatment imaging.

In summary, treatment type, geographic variation, and patient income and education contributed to 36% of men with low risk prostate cancer undergoing unnecessary pretreatment imaging for staging purposes despite existing expert guidelines. Dunnick et al surmised that inappropriate use of imaging studies was a result of physician ignorance, patient expectations, defensive medicine and economic gain from self-referral.[27] This is particularly relevant for men with low risk disease because prostate cancer has been called a litmus test for health care reform with costly treatments and mediocre results.[30]

CONCLUSIONS

There is significant geographic variation and overuse of imaging for low risk prostate cancer, particularly for men of greater income, living in areas of lesser education, and for those undergoing radiation therapy.

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Original Article

Inappropriate Utilization of Radiographic Imaging in Men With Newly Diagnosed Prostate Cancer in the United States

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BACKGROUND: The use of radiographic imaging (bone scan and computerized tomography) is only recommended for men diagnosed with high-risk prostate cancer characteristics. The authors sought to characterize utilization patterns of imaging in men with newly diagnosed prostate cancer. **METHODS:** The authors performed a population-based observational cohort study using the US Surveillance, Epidemiology, and End Results-Medicare linked data to identify 30,183 men diagnosed with prostate cancer during 2004 to 2005. **RESULTS:** Thirty-four percent of men with low-risk and 48% with intermediate-risk prostate cancer underwent imaging, whereas only 60% of men with high-risk disease received imaging before treatment. Radiographic imaging utilization was greater for men who were older than 75 years (odds ratio [OR], 1.28; 95% confidence interval [CI], 1.20-1.37; $P < .001$), were black (OR, 1.11; 95% CI, 1.01-1.21; $P = .030$), resided in wealthier areas (OR, 1.19; 95% CI, 1.08-1.32 for median income >$60,000 vs <$35,000; $P < .001$), lived in rural regions (OR, 1.23; 95% CI, 1.12-1.36; $P < .001$), or underwent standard radiation therapies (OR, 1.71; 95% CI, 1.60-1.84; $P < .001$). Imaging utilization was less for men living in areas with greater high school education (OR, 0.83; 95% CI, 0.75-0.91 between highest and lowest graduation rates; $P < .001$) or opting for active surveillance (OR, 0.17; 95% CI, 0.15-0.19 vs radical prostatectomy; $P < .001$). The estimated cost of unnecessary imaging over this 2-year period exceeded $3.6 million. **CONCLUSIONS:** In the United States, there is widespread overutilization of imaging for low-risk and intermediate-risk prostate cancer, whereas a worrisome number of men with high-risk disease did not receive appropriate imaging studies to exclude metastases before therapy. ***Cancer*** **2012;118:1260–7.**

KEYWORDS: imaging, cost, prostate cancer, utilization, staging.

INTRODUCTION

Prostate cancer is the most common noncutaneous cancer diagnosis and second most common cause of death among men in the United States. In 2010, an estimated 217,730 men were diagnosed with prostate cancer compared with approximately 99,000 cases diagnosed in 1988,[1] attributable to the advent of prostate-specific antigen (PSA) screening. Consequently, there has been stage migration with earlier stage at diagnosis. Presently, 92% of incident prostate cancers are locoregional versus metastatic.[2,3] Accurate staging before treatment is desirable given the relatively high number of men who must be treated to prevent 1 prostate cancer-specific death.[4] Currently, radionuclide bone scan and computerized tomography (CT) are the most common modalities used to stage newly diagnosed prostate cancer and to determine the appropriateness of therapy.

The American Urological Association issued a Best Practice Statement in 2000 recommending pretreatment staging of prostate cancer only in the setting of high-risk disease.[4] This expert consensus used PSA, Gleason grade at biopsy, and clinical stage to predict the yield of imaging studies.[5] Other professional societies involved in the management of prostate cancer (eg, American Society of Clinical Oncology, American Society for Therapeutic Radiology and Oncology, and American Cancer Society) do not have specific recommendations for utilization of postdiagnosis radiographic screening.

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The goals of this study were to: 1) characterize utilization patterns for diagnostic imaging relative to established guidelines in a large, population-based cohort stratified by risk group; and 2) estimate the cost of imaging overutilization.

MATERIALS AND METHODS

Data

Our study was approved by the Brigham and Women's Hospital Institutional Review Board; subject data were deidentified, and the requirement for consent was waived. We identified 51,619 men aged 65 years or older who were diagnosed with prostate cancer from 2004 to 2005 and followed through December 31, 2007 using Surveillance, Epidemiology, and End Results (SEER)-Medicare data. These data comprise demographic and cancer characteristics abstracted by the National Cancer Institute's cancer registry program linked to Medicare administrative data.[6] SEER-Medicare encompasses approximately 26% of Medicare beneficiaries nationwide.

International Classification of Diseases, 9th Edition (ICD-9) codes were used to identify disease categories, whereas Current Procedural Terminology, 4th Edition (CPT-4) and Healthcare Common Procedure Coding System code sets were used to identify medical, surgical, and diagnostic services. To increase specificity, only imaging studies designated with a corresponding ICD-9 code for prostate cancer were included. Subject age was obtained from the Medicare file, whereas the SEER registry provided data on race/ethnicity, population density, marital status, and census measurements of median household income and proportion of individuals with at least a high school education. Comorbidity using the Klabunde modification of the Charlson index was based on inpatient, outpatient, and carrier claims during the year before diagnosis.[7]

Study Population

We excluded 14,074 men who were not Medicare Part A and Part B eligible or were enrolled in a health maintenance organization at the time of diagnosis, as claims are not reliably submitted for these men. To increase the specificity for detection of postdiagnosis imaging and avoid confounding, we restricted our analyses to men with prostate cancer diagnosed as their only cancer, and excluded 2066 men with other cancers. Finally, we excluded 2866 men either with metastatic disease at the time of diagnosis, who died within 6 months of diagnosis, or who became ineligible for Medicare during the follow-up period. PSA data was available for 27,232 men. However, if a man had a Gleason score $\geq$8 or stage T3/T4 disease, he was categorized as high risk even if PSA data were missing. The final study cohort of 30,183 men was stratified into National Comprehensive Cancer Network risk groups according to available clinical TNM stage, preoperative PSA level, and Gleason score.[8] Low-risk characteristics include clinical stage T1-T2a, a PSA level $\leq$10 ng/mL, and Gleason scores of 6 or less; intermediate-risk characteristics include clinical stage T2b-T2c disease, PSA level of 10.1 to 20 ng/mL, or Gleason score of 7; and high-risk characteristics include clinical stage T3 or greater, PSA level >20 ng/mL, or Gleason score of 8 to 10. Per SEER convention, surgical staging and grading were used for men who underwent radical prostatectomy, and clinical staging and grading were used for all other men.

Outcomes

The primary outcome was utilization of radiographic staging studies (CT or bone scan) before the start of treatment. Intensity-modulated or conformal external beam radiation therapy and interstitial brachytherapy were considered jointly as standard radiation therapies, whereas proton beam therapy was considered separately. Pretreatment imaging for radiation planning was identified by corresponding CPT-4 codes and excluded from analysis. Men who did not undergo definitive therapy >1 year after diagnosis were categorized as active surveillance.

Expenditures

To best attribute the cost associated with radiology services, we assessed Medicare payments from outpatient claims. The estimated cost per additional study was estimated as the sum of the median expenditure per claim from the outpatient and carrier files. All costs were adjusted to 2008 dollars using the 2007 Annual Report of the Boards of Trustees of the Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Funds.[9]

Statistical Analysis

Demographic and clinical characteristics associated with utilization of staging imaging were assessed with the Pearson chi-square statistic and Fisher exact tests. Ordinal variables such as risk group and age were assessed with the Mantel-Haenszel chi-square test for trend. After

Table 1. Demographics of Study Population

Characteristic	Patients in Risk Category, %				*P*
	All Patients, n=30,183	Low, n=9640	Intermediate, n=12,966	High, n=7577	
Year					
2004	15,784	53	52	52	.30
2005	14,399	47	48	48	
Age					
65-69 years	9635	38	32	24	<.001
70-74 years	8810	32	29	25	
≥75 years	11,738	30	38	51	
Charlson score					
0	20,246	69	68	64	<.001
1	5940	20	19	20	
2+	2887	8	9	12	
Race[a]					
White	22,796	77	76	73	<.001
Black	3043	9	10	11	
Hispanic	1951	6	6	7	
Asian	1270	3	5	5	
Marital status[b]					
Not married	5978	18	19	23	<.001
Married	20,547	69	69	64	
% with high school education					
<75	6970	22	23	25	<.001
75-84.9	6585	21	22	23	
85-89.9	5617	18	19	18	
≥90	10,991	38	37	33	
Household income					
<$35,000	11,454	35	38	42	<.001
$35,000-$44,999	6927	23	23	23	
$45,000-$59,999	6426	23	21	19	
≥$60,000	5356	19	18	15	
Population density					
Urban	27,422	92	91	90	<.001
Rural	2761	8	9	10	
Treatment					
Radical prostatectomy	5699	17	23	14	<.001
ADT only	4441	7	13	27	
Cryotherapy	670	2	3	2	
Proton beam therapy	271	1	1	1	
Standard radiation therapy	15,060	54	49	47	
Active surveillance	4042	19	12	9	
Pretreatment imaging	14,105	34	48	60	<.001

Abbreviation: ADT, androgen deprivation therapy.
All percentages may not add to 100% due to rounding.
[a] Race was unknown/other in 1123 men.
[b] Marital status was unknown in 3658 men.

univariate analysis, we used a multivariate logistic regression model to calculate the probability of undergoing CT or bone scan based on all covariates described. All tests were considered statistically significant at $\alpha = .05$. Statistical analyses were performed with SAS version 9.1.3 (SAS Institute, Cary, NC).

RESULTS

In 2004 and 2005, 9640 (32%) men were diagnosed with low-risk prostate cancer, whereas 12,966 (43%) and 7577 (25%) men had intermediate-risk and high-risk disease, respectively (Table 1). Thirty-four percent, 48%, and 60% of low-risk, medium-risk, and high-risk subjects,

respectively, underwent radiographic imaging during the interim between diagnosis and treatment initiation. Bone scan was the most common test used in all 3 risk strata, and greater utilization of both modalities was observed with increasing risk (Fig. 1).

Men with low-risk prostate cancer were more likely to be younger, white, reside in urban areas, and have fewer comorbidities than men with intermediate-risk and high-risk disease ($P < .001$ for all). Men with high-risk disease were more likely to be unmarried and had lower education levels and household incomes compared with men with lower-risk prostate cancer ($P < .001$ for all). Men with intermediate-risk disease were more likely to undergo radical prostatectomy compared with men with either low-risk or high-risk disease, whereas men with low-risk disease were most likely to opt for active surveillance ($P < .001$). Treatment with androgen deprivation therapy (ADT) alone was most likely among men with high-risk disease, whereas standard radiation therapies were less likely with more aggressive tumor characteristics ($P < .001$). In the high-risk cohort, 58% versus 77% of men underwent imaging before radical prostatectomy versus standard radiation therapies ($P < .001$).

In adjusted analyses (Table 2), men aged ≥70 years were more likely to undergo imaging compared with men aged 65 to 69 years (age 70-74 years: OR, 1.12; 95% CI, 1.05-1.19; $P < .001$; age ≥75 years: OR, 1.28; 95% CI, 1.2-1.37; $P < .001$). Black men were more likely (OR, 1.11; 95% CI, 1.01-1.21; $P = .030$) to undergo imaging than white men. Men residing in areas with higher education levels were less likely (≥90% with high school education vs <75%: OR, 0.83; 95% CI, 0.75-0.91; $P < .001$) to undergo imaging. Compared with men living in areas with median household income <$35,000, men with median household incomes of $35,000 to $44,999 (OR, 1.12; 95% CI, 1.04-1.20; $P = .003$), $45,000 to $59,999 (OR, 1.1; 95% CI, 1.01-1.2; $P = .026$), or ≥$60,000 (OR, 1.19; 95% CI, 1.08-1.32; $P < .001$) were more likely to undergo prostate cancer imaging. Moreover, men residing in rural versus urban areas were more likely (OR, 1.23; 95% CI, 1.11-1.34; $P < .001$) to undergo imaging studies. Men undergoing ADT alone (OR, 0.85; 95% CI, 0.77-0.93; $P < .001$) or active surveillance (OR, 0.17; 95% CI, 0.15-0.19; $P < .001$) versus radical prostatectomy were less likely to undergo imaging (Fig. 2). However, men treated with cryotherapy (OR, 1.25; 95% CI, 1.06-1.46; $P = .008$), proton beam therapy (OR, 1.37; 95% CI, 1.07-1.76; $P = .012$), or standard radiation therapies (OR, 1.71; 95% CI, 1.6-1.84; $P < .001$) versus radical prostatectomy were more likely to undergo imaging studies.

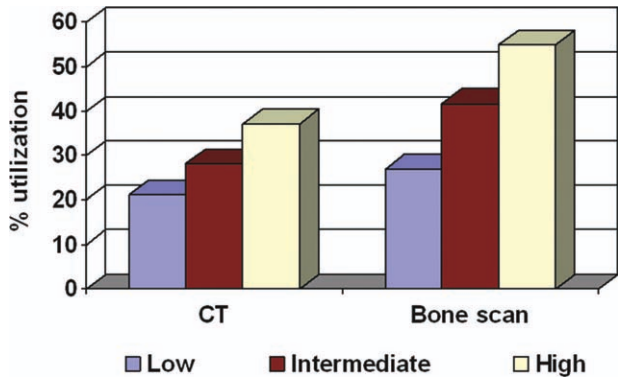

Figure 1. Test utilization is shown by modality and risk strata ($P < .001$ in all groups between risk strata). CT, computed tomography.

Low-Risk Characteristics

Men aged ≥75 years (OR, 1.16; 95% CI, 1.03-1.32; $P = .016$) were more likely to undergo imaging compared with men aged 65 to 69 years. Men living in areas with ≥90% versus <75% high school education were less likely to undergo imaging (OR, 0.76; 95% CI, 0.63-0.92; $P = .004$), whereas men living in areas with median annual household income ≥$60,000 had a higher likelihood of having an imaging study compared with those living in areas with median income <$35,000 (OR, 1.32; 95% CI, 1.08-1.60; $P = .006$). Compared with men undergoing radical prostatectomy, men undergoing cryotherapy (OR, 1.48; 95% CI, 1.08-2.03; $P = .014$) or standard radiation therapies (OR, 1.77; 95% CI, 1.54-2.02; $P < .001$) had greater odds of radiographic imaging, whereas men managed with active surveillance had lower odds of imaging (OR, 0.28; 95% CI, 0.22-0.35; $P < .001$).

Intermediate-Risk Characteristics

Men aged ≥70 years were more likely to undergo imaging compared with men aged 65 to 69 years (vs age 70-74 years: OR, 1.13; 95% CI, 1.03-1.25; $P = .013$; vs age ≥75 years: OR, 1.17; 95% CI, 1.05-1.29; $P = .004$). Black men were more likely to undergo imaging (OR, 1.16; 95% CI, 1.01-1.33; $P = .042$) compared with white men. Compared with intermediate-risk men living in areas with median household income <$35,000, men with median household incomes of $35,000 to $44,999 (OR, 1.2; 95% CI, 1.07-1.35; $P = .002$), $45,000 to $59,999 (OR, 1.22; 95% CI, 1.07-1.4; $P = .003$), or ≥$60,000 (OR, 1.29; 95% CI, 1.1-1.51; $P = .002$) were

Table 2. Multivariate Analysis of Demographic and Clinical Factors Predictive of Test Utilization by Risk Category

Characteristic	Low Risk, n=9640		Intermediate Risk, n=12,966		High Risk, n=7577		All Patients, n=30,183	
	% Use	OR	% Use	OR	% Use	OR	% Use	OR
Age								
65-69 years	33	Ref	45	Ref	62	Ref	43	Ref
70-74 years	35	1.02	51	1.13[a]	65	1.01	48	1.12[a]
≥75 years	35	1.16[a]	48	1.17[a]	57	0.98	46	1.28[a]
Charlson score								
≥2	37	Ref	50	Ref	58	Ref	46	Ref
1	37	1.04	51	1.01	63	1.00	48	1.02
0	35	0.95	49	0.96	62	0.98	46	0.97
Race								
White	34	Ref	48	Ref	61	Ref	45	Ref
Black	36	1.01	50	1.16[a]	55	1.00	47	1.11[a]
Hispanic	36	1.09	46	0.95	57	0.98	45	1.00
Asian	35	0.90	47	0.93	63	0.85	48	0.94
Marital status								
Not married	35	Ref	47	Ref	59	Ref	46	Ref
Married	34	0.97	48	1.02	62	0.95	46	0.96
% with high school education								
<75	36	Ref	49	Ref	56	Ref	46	Ref
75-84.9	37	0.95	50	0.95	60	0.99	48	0.96
85-89.9	35	0.90	49	0.88	62	0.97	46	0.92
≥90	31	0.76[a]	46	0.80[a]	62	0.88	44	0.83[a]
Household income								
<$35,000	34	Ref	47	Ref	56	Ref	45	Ref
$35,000-$44,999	34	1.06	49	1.20[a]	63	1.18	46	1.12[a]
$45,000-$59,999	33	1.08	48	1.22[a]	63	1.26	45	1.10[a]
≥$60,000	36	1.32[a]	49	1.29[a]	65	1.32[a]	47	1.19[a]
Population density								
Urban	34	Ref	48	Ref	60	Ref	45	Ref
Rural	37	1.28[a]	52	1.29[a]	57	1.12	47	1.23[a]
Treatment								
Radical prostatectomy	27	Ref	40	Ref	58	Ref	39	Ref
ADT only	31	1.00	41	0.88	44	0.61[a]	40	0.85[a]
Cryotherapy	37	1.48[a]	53	1.30[a]	73	1.60[a]	50	1.25[a]
Proton beam therapy	27	1.12	53	1.64[a]	75	1.62	49	1.37[a]
Standard radiation therapy	45	1.77[a]	61	1.83[a]	77	2.11[a]	59	1.71[a]
Active surveillance	13	0.28[a]	18	0.23[a]	20	0.16[a]	14	0.17[a]

Abbreviations: ADT, androgen deprivation therapy; OR, odds ratio; Ref, reference value.
[a] Denotes significance at $P < .05$ in multivariate logistic regression.

more likely to undergo prostate cancer imaging. Men living in the most educated areas (≥90% high school education) were less likely than those living in the least educated areas (<75% high school education) to undergo imaging (OR, 0.8; 95% CI, 0.69-0.93; $P = .005$). Men who chose active surveillance were less likely (OR, 0.23; 95% CI, 0.18-0.28; $P < .001$) to have an imaging test than those treated with radical prostatectomy. Men treated with cryotherapy (OR, 1.3; 95% CI, 1.03-1.66; $P = .031$), proton beam therapy (OR, 1.64; 95% CI, 1.13-2.39; $P = .010$), or standard radiation therapies (OR, 1.83; 95% CI, 1.65-2.03; $P < .001$) were more likely to undergo imaging tests than men who had radical prostatectomy.

High-Risk Characteristics

Compared with men living in areas with median household income <$35,000, high-risk men with median household incomes of $35,000 to $44,999 (OR, 1.18; 95% CI, 1-1.38; $P = .044$), $45,000 to $59,999 (OR, 1.26; 95% CI, 1.04-1.52; $P = .018$), or ≥$60,000 (OR,

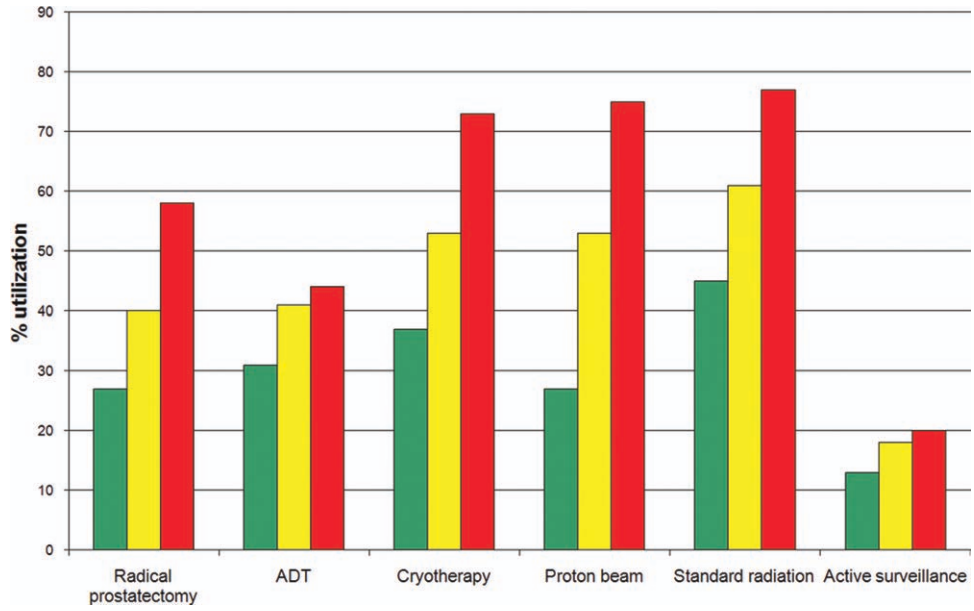

Figure 2. Test utilization is shown by treatment type and risk group ($P < .05$ in all groups between risk strata). ADT, androgen deprivation therapy.

1.32; 95% CI, 1.05-1.65; $P = .019$) were more likely to undergo CT or bone scan. Compared with men undergoing radical prostatectomy, men undergoing ADT alone (OR, 0.61; 95% CI, 0.51-0.74; $P < .001$) or active surveillance (OR, 0.16; 95% CI, 0.12-0.21; $P < .001$) were less likely to undergo imaging, whereas men treated with cryotherapy (OR, 1.6; 95% CI, 1.04-2.48; $P = .034$) or standard radiation therapies (OR, 2.11; 95% CI, 1.79-2.49; $P < .001$) were more likely to have pretreatment imaging.

Expenditures

The median Medicare payment for bone scan and CT was $226 and $407, respectively. The total Medicare payment for imaging in men with low-risk and intermediate-risk prostate cancer in the study population was $3,568,543.

DISCUSSION

The goals of clinical guidelines are to standardize care, diminish practice variation, and improve health outcomes while striking a balance between risk-benefit and cost-effectiveness outcomes.[10] Single-institution studies have identified deviation from established recommendations, overutilization of imaging, and low yield for radiographic staging studies in men with newly diagnosed prostate cancer.[11,12] Increasing use of diagnostic imaging in incident prostate cancer during this period has been demonstrated in a national sample of Medicare beneficiaries,[13] but it is unknown whether this increase was appropriate, as clinical data were unavailable for these men. Therefore, little is known about the impact of and adherence to clinical guidelines on prostate cancer staging nationally.[14]

Our study demonstrates that practice patterns do not align with published guidelines regarding utilization of diagnostic imaging for staging prostate cancer. Possible factors leading to discrepancy between guidelines and clinical practice include lack of awareness or confidence in the scientific foundation of best practice statements, financial incentives, regional variation, and variability of physician practice patterns.[15-17] Identification of these factors may have major public health and policy implications given the focus of the Centers for Medicare and Medicaid Services (CMS) on quality indicators linking reimbursement to performance.[18] This process has already encompassed prostate cancer, as the use of bone scan in low-risk patients is a negative quality indicator in the Physician Quality Reporting Initiative from CMS.[19] In addition, anticipated upgrading and upstaging of prostate needle biopsy specimens may have led some providers to incorporate imaging even for men who did not meet criteria. Whereas upstaging and upgrading are noted in 25% to 30% of prostatectomy specimens, only 5% of patients in 2 large analyses from Johns Hopkins and the Lahey Clinic had upgrading of Gleason score that would have led them to be recategorized as high risk.[20,21]

Our study has several significant findings. First, there is significant disparity in the use of imaging at the national level relative to published consensus guidelines. Although imaging is not recommended for low-risk and intermediate-risk characteristics, 34% and 48% of men, respectively, underwent unnecessary imaging before treatment. These results are consistent with findings from a community-based cohort that 1/4 of men with low-risk disease and more than half of men with intermediate-risk disease undergo imaging inconsistent with guidelines.[22] Even excluding the additional cost derived from coinsurance or deductible payments,[23] the Medicare expenditure for these unnecessary studies was almost $2 million annually. In addition to excess financial cost, these men are also subject to unnecessary radiation exposure secondary to CT scans.[24,25] Our study also demonstrated that underuse of appropriate imaging was also prevalent. When imaging was recommended to rule out metastatic disease for high-risk characteristics, only 60% of men received any radiographic staging before treatment. This may result in men with high-risk prostate cancer with undetected metastases receiving local therapy without benefit.

Second, there was significant geographic variation in imaging utilization. Across risk groups, we found that men living in rural versus urban areas were more likely to undergo imaging. These findings are in line with studies demonstrating significant regional variations in diagnostic imaging practices and may reflect decreased awareness or compliance with imaging guidelines.[15,22] However, in a national study of Medicare beneficiaries, geographic variation in Medicare spending did not lead to significant differences in quality of care or access to medical care.[26] Nonconformity with prostate cancer imaging guidelines significantly increases Medicare expenditure without improving quality of care rendered for men with newly diagnosed prostate cancer.

Third, we identified important demographic and socioeconomic factors associated with imaging. Independent of risk stratum, imaging utilization remained high in men aged $\geq$75 years, a group unlikely to benefit from an extensive workup and treatment plan. Strict adherence to guidelines in older men without accounting for existing comorbidities may lead to overly aggressive interventions that diminish quality of care, although no specific guidelines exist regarding the metastatic workup in older men to guide providers.[27] Black men, especially in the intermediate-risk cohort, were more likely to undergo imaging. We also found that men living in areas of greater income were more likely to undergo imaging across risk groups, perhaps related to variability in patient demand or access to imaging facilities.[28,29] Interestingly, men residing in areas of greater education had decreased rates of imaging, especially in low-risk and intermediate-risk cohorts.

Finally, there was a strong association between type of treatment and radiographic imaging across risk categories even after excluding imaging studies performed for radiation planning. We found that 44% of men with low-risk and intermediate-risk characteristics undergoing standard radiation therapies also underwent a bone scan, which provides no value for radiation planning. Men undergoing medical therapies (ADT and active surveillance) were the least likely to undergo imaging but also the most likely to forgo recommended staging studies in the high-risk group. These data suggest that the treatment decision itself may precede and impact the decision to complete a metastatic workup and may reflect variation in practice patterns among urologists, medical oncologists, and radiation oncologists. Alternatively, the increased use of imaging may reflect defensive medicine practices that exist in the current medicolegal environment of the United States healthcare system.[30]

Our study must be interpreted in the context of the study design. First, analyses were restricted to Medicare beneficiaries older than 65 years who resided in SEER regions. Thus, these results may not be applicable to younger men; however, a previous study has demonstrated the independence of age and pretreatment imaging in men with prostate cancer.[22] Within our study, "younger" men refers to subjects older than 65 years. Second, we analyzed incident prostate cancers from 2004 and 2005 only, as detailed clinical and pathologic data needed to appropriately risk-stratify subjects was not available in SEER before these years. Because of missing PSA values, we may underestimate the number of men with intermediate-risk and high-risk disease by using stage and grade. However, because PSA was missing for only 10% of our cohort, the effect is likely small. Third, the method of assessing test utilization may overestimate imaging specifically for prostate cancer staging, as studies may have been ordered for other reasons. To minimize error, we included only those studies with a prostate-cancer specific diagnosis code and excluded radiation planning imaging studies and men with other malignancies. In addition, we found no association between comorbidity and imaging, and 70% of our study cohort had no comorbidities, reducing the likelihood that we included imaging studies for concomitant disease. We also considered compliance with contemporary guidelines for pretreatment staging in our

analyses, but note that more recent guidelines may allow for a small proportion of intermediate-risk patients with >20% likelihood of lymph node involvement to undergo imaging.[8] Fourth, we excluded evaluation of other modalities such as abdominal ultrasound or ProstaScint fusion imaging, as they are not currently recommended for staging and are limited in clinical use. Fifth, we also excluded magnetic resonance imaging (MRI), as this study may be obtained for surgical planning rather than metastatic workup; an MRI was obtained in <4% of men, and its exclusion is unlikely to alter the overall findings. Finally, we note that the effect size for several of the demographic variables reach statistical significance because of the large study cohort but have relatively small clinical significance. The difference between clinical and statistical significance is important to consider when examining these data.

In conclusion, we identified broad patterns of misuse of imaging for the staging of prostate cancer after diagnosis. Overuse was most common in men who were older, black, and wealthier and resided in rural areas, whereas adherence to recommended guidelines was more common in men residing in areas of greater education. Despite existing guidelines, costly and unnecessary imaging studies continue to be performed in men with low-risk and intermediate-risk prostate cancer, whereas a significant number of men with high-risk disease do not receive adequate staging before treatment.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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Comparative Effectiveness of Perineal Versus Retropubic and Minimally Invasive Radical Prostatectomy

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Purpose: While perineal radical prostatectomy has been largely supplanted by retropubic and minimally invasive radical prostatectomy, it was the predominant surgical approach for prostate cancer for many years. In our population based study we compared the use and outcomes of perineal radical prostatectomy vs retropubic and minimally invasive radical prostatectomy.

Materials and Methods: We identified men diagnosed with prostate cancer from 2003 to 2005 who underwent perineal (452), minimally invasive (1,938) and retropubic (6,899) radical prostatectomy using Surveillance, Epidemiology and End Results-Medicare linked data through 2007. We compared postoperative 30-day and anastomotic stricture complications, incontinence and erectile dysfunction, and cancer therapy (hormonal therapy and/or radiotherapy).

Results: Perineal radical prostatectomy comprised 4.9% of radical prostatectomies during our study period and use decreased with time. On propensity score adjusted analysis men who underwent perineal vs retropubic radical prostatectomy had shorter hospitalization (median 2 vs 3 days, $p < 0.001$), received fewer heterologous transfusions (7.2% vs 20.8%, $p < 0.001$) and required less additional cancer therapy (4.9% vs 6.9%, $p = 0.020$). When comparing perineal vs minimally invasive radical prostatectomy men who underwent the former required more heterologous transfusions (7.2% vs 2.7%, $p = 0.018$) but experienced fewer miscellaneous medical complications (5.3% vs 10.0%, $p = 0.045$) and erectile dysfunction procedures (1.4 vs 2.3/100 person-years, $p = 0.008$). The mean and median expenditure for perineal radical prostatectomy in the first 6 months postoperatively was $1,500 less than for retropubic or minimally invasive radical prostatectomy ($p < 0.001$).

Conclusions: Men who undergo perineal vs retropubic and minimally invasive radical prostatectomy experienced favorable outcomes associated with lower expenditure. Urologists may be abandoning an underused but cost-effective surgical approach that compares favorably with its successors.

Key Words: prostate, prostatic neoplasms, prostatectomy, perineum, complications

Abbreviations and Acronyms

ED = erectile dysfunction

MIRP = minimally invasive RP

PLND = pelvic lymph node dissection

PRP = perineal RP

RP = radical prostatectomy

RRP = retropubic RP

SEER = Surveillance, Epidemiology and End Results

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After the first reported series of RP via a perineal approach in 1905, PRP became the standard prostate cancer surgical treatment for much of the 20th century.[1] Perineal incision proximity to the prostate, decreased blood loss, minimal pain, and ease of the approach in obese men and in those with prior abdominal surgery contributed to PRP being the predominant approach. PRP use decreased after the popularity of external beam radiation therapy in the 1970s and the description of nerve sparing RRP by

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Walsh et al in the 1980s, which obviated the need for a second incision for PLND.[2] However, after the advent of prostate specific antigen screening, resultant stage migration and increasing adoption of MIRP, the PLND rate during RP decreased.[3] Also, the indication for and benefit of PLND has been debated for low risk disease.[4] Given that PRP is associated with less postoperative pain and a shorter hospital stay than RRP, it was suggested that PRP may be underused in cases in which concurrent PLND is unnecessary.[5,6]

In the absence of randomized, controlled trials, population based studies of comparative effectiveness allow the evaluation of competing therapies across a broad range of providers in various health settings. We determined contemporary PRP use and outcomes compared to those of MIRP and RRP.

MATERIALS AND METHODS

Data

Our study was approved by the institutional review board. Participants were de-identified and the consent process was waived. We identified 137,217 men 65 years old or older who were diagnosed with prostate cancer from 2002 to 2005 and followed through December 31, 2007 using SEER-Medicare linked data.[7]

Study Exclusions

Excluded from analysis were 10,441 men enrolled in a health maintenance organization and/or those not enrolled in Medicare Parts A and B throughout the study duration since claims are not reliably submitted in these men. To increase sensitivity to detect postoperative radiation therapy we restricted analysis to men with prostate cancer diagnosed as the only cancer and excluded 4,628 with other cancers. This yielded a study cohort of 9,289 men who underwent RP during 2003 to 2007 based on CPT-4 codes, including 55840, 55842 and 55845 for RRP, 55866 for MIRP, and 55810, 55812 and 55815 for PRP. Other groups have used CPT-4 code 55899 (unspecified male genitourinary procedure) with a RRP CPT-4 code to ascertain MIRP but Medicare does not recognize this coding variant and it was excluded from analysis.

Outcomes

We examined mortality/morbidity, length of stay, anastomotic stricture, incontinence and ED diagnoses and procedures, and additional cancer therapy. Postoperative complications by category and transfusions were assessed within 30 days of surgery. Postoperative mortality was defined as death within 30 days of RP. We assessed anastomotic strictures 31 to 365 days after surgery. Incontinence and ED diagnoses and procedures were evaluated more than 18 months after surgery, which is the time required for urinary and sexual function recovery to plateau.[8] Finally, we identified men who underwent additional cancer therapy (radiation and/or hormonal treatment) after prostatectomy as a surrogate for cancer control.[9]

Expenditures

To best attribute the costs associated with competing surgical approaches we assessed Medicare payments for 6 months including and after RP as 1) total Medicare reimbursements and 2) prostate cancer related Medicare reimbursements for claims submitted with a prostate cancer diagnosis code (ICD-9 185.0).

Control Variables

Patient age was obtained from the Medicare file. The SEER registry provided data on race/ethnicity, census measurements of median household income and the proportion of individuals with at least a high school education, SEER region, population density and marital status. Due to small numbers we combined the New Mexico, rural Georgia and Atlanta SEER registries. Comorbidity using the Klabunde modification of the Charlson index, and preoperative diagnoses of incontinence and ED were based on inpatient, outpatient and carrier claims during the year before surgery.[10] Finally, we adjusted for year of surgery since outcomes may have improved with time.

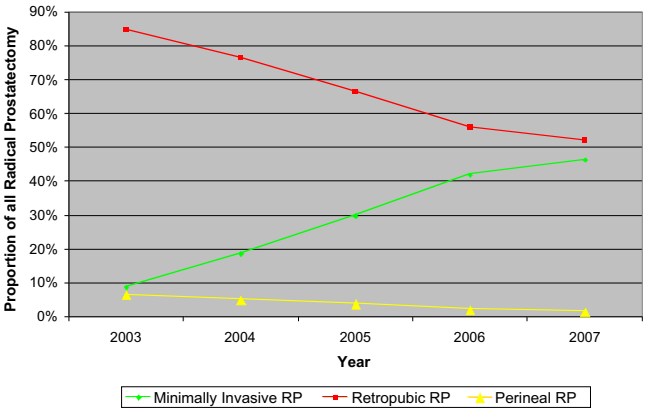
Statistical Analysis

PRP, RRP and MIRP annual use rates were derived and temporal trends in use were compared with the Mantel-Haenszel chi-square test for trend, adjusted for surgeon clustering. For dichotomous outcomes occurring within a fixed interval, such as 30 and 31 to 365-day (anastomotic stricture) outcomes, we compared proportions (the number of events divided by the number of patients) for PRP vs MIRP and RRP. We compared rates for outcome variables without an upper time bound for which followup could vary.[11] We also compared median length of stay among the groups.

Since men who underwent PRP differed from those who underwent MIRP and RRP in terms of demographic characteristics, we used weighted propensity score methods to adjust for these differences.[12,13] Propensity score methods control for all observed confounding factors that may influence group assignment and outcome using a single composite measure. They also balance patient characteristics between groups, as would occur in a randomized experiment.

To perform propensity score adjustment we used a logistic regression model to calculate the probability of undergoing PRP vs MIRP and RRP based on all covariates described, and then weighted data on each patient based on the inverse propensity of being in 1 of the 2 treatment groups.[14] Covariate balance was assessed after adjustment. We used generalized estimating equations to account for surgeon clustering on weighted propensity adjusted analysis. To compare proportions we fit generalized estimating equation logistic regressions with surgical approach (PRP vs MIRP and RRP) as the only covariate, weighted by the inverse propensity score. All tests were considered statistically significant at $\alpha = 0.05$. All analysis was done with SAS®, version 9.1.3.

Due to confidentiality, values less than 11 may not be reported directly or in a derivable way for any SEER-Medicare data obtained from the National Cancer Institute. Therefore, for any patient group with fewer than 11 patients, data are shown as less than 2.4% in the PRP



RP rate by approach during study period

group, less than 0.6% in the MIRP group and less than 0.2% in the RRP group.

RESULTS

From 2003 to 2007 in the study cohort 6,899 men underwent RRP, 1,938 underwent MIRP and 452 underwent PRP. During the study period we found increased use of MIRP with a corresponding decrease in the rate of RRP and PRP (see figure). PRP use decreased more than 3-fold during the study period. Less than 2% of RPs were done via a perineal approach in 2007 vs 6.5% in 2003.

We noted multiple demographic differences in PRP vs MIRP and RRP. Men undergoing PRP vs MIRP were more likely to have comorbidities ($p = 0.008$). Men with lower education and median income were more likely to undergo PRP than MIRP ($p = 0.028$ and <0.001, respectively). Men undergoing PRP vs MIRP were more likely to reside in a nonmetropolitan area ($p < 0.001$). PRP was more commonly done in the South and Midwest compared to MIRP and RRP ($p = 0.014$ and 0.004, respectively). Baseline incontinence was lower for PRP vs MIRP and RRP ($p < 0.001$ and 0.040, respectively). While baseline ED was lower for PRP vs MIRP ($p < 0.001$), there were no differences compared to RRP. We also noted no differences in age, race, marital status, or tumor grade or stage by surgical approach.

When comparing unadjusted outcomes, men undergoing PRP vs RRP had shorter length of stay (2 vs 3 days, $p < 0.001$), and were less likely to undergo blood transfusion (7.1% vs 20.1%, $p < 0.001$) and have anastomotic stricture (8.2% vs 14.2%, $p = 0.002$). The overall 30-day complication rate was lower in men undergoing PRP vs RRP (16.7% vs 23.4%, $p = 0.002$). However, additional cancer therapy did not differ for PRP vs RRP (5.8% vs 6.9%, $p = 0.147$). When we compared unadjusted outcomes in the PRP and MIRP cohorts, men undergoing PRP vs MIRP were more likely to undergo blood transfusion (7.1% vs 2.5%, $p < 0.001$). However, the 30-day complication rate was higher in the MIRP group (16.7% vs 21.9%, $p = 0.016$) while anastomotic stricture rate was higher in the PRP cohort (8.2% vs 5.3%, $p = 0.048$). Finally, PRP had the lowest mean and median Medicare expenditures, followed by RRP and MIRP (see table).

On propensity score adjusted analysis PRP vs RRP was associated with fewer blood transfusions (7.2% vs 20.8%, $p < 0.001$) and shorter length of stay (median 2 vs 3 days, $p < 0.001$). The additional cancer therapy incidence (radiation and hormonal) was higher in the RRP group (4.9% vs 6.9%, $p = 0.020$). There were no differences in PRP vs RRP 30-day complications, mortality, postoperative stricture, or ED or incontinence diagnosis and treatment. When comparing outcomes between PRP and MIRP, PRP was associated with more blood transfusions (7.2% vs 2.7%, $p = 0.018$), fewer miscellaneous medical complications (5.3% vs 10.0%, $p = 0.045$) and fewer procedures for ED (1.4 vs 2.3/100 person-years, $p = 0.008$). MIRP and PRP did not differ in length of stay, overall 30-day complications, mortality, incontinence diagnosis or procedures and additional cancer therapy.

DISCUSSION

RP gained popularity through the mid 1900s with a demonstrated survival benefit for prostate cancer.[15] In the 1970s an evolution from the perineal to the retropubic approach occurred due to the loss of familiarity with perineal surgical anatomy as simple open perineal prostatectomy was abandoned, familiarity with retropubic anatomy as simple retropubic open prostatectomy and radical cystectomy became more common, and increased interest in PLND and the lack of the need for a second incision to perform lymphadenectomy (P. Walsh, personal communication, November 16, 2009). However, with the subse-

Medicare payments within 6 months of RP by surgical approach

	No. Pts	Mean/Median Payment* ($)
Overall:		
PRP	381	11,953/11,019
MIRP	1,548	14,939/13,335
RRP	5,565	14,301/12,767
Prostate Ca (ICD-9 185.0):		
PRP	381	9,957/9,339
MIRP	1,548	12,289/11,324
RRP	5,565	11,884/10,853

* $p < 0.001$.

quent use of prostate specific antigen for prostate cancer screening in the 1990s and corresponding stage migration, the incidence of positive lymph nodes at RP has decreased to less than 3%.[16] Given the low rate of lymph node involvement, the need for concurrent PLND during RP remains debatable. Also, prior groups noted that PRP has shorter operative time and decreased intraoperative operative cost than MIRP or RRP,[17] although the increased surgical expense may be offset by significantly lower nonoperative hospital costs. This was the finding in a retrospective review of 452 patients treated for clinically localized prostate cancer in which total hospital cost differences were less for minimally invasive approaches (robot assisted MIRP and cryosurgical ablation of the prostate) than in the open (PRP or RRP) surgery groups.[18] However, these studies did not account for delayed costs, such as treatment for ED or urinary incontinence, salvage therapy and associated time lost at work. Additional analysis is needed to completely capture these associated costs.

We performed a population based analysis comparing PRP vs RRP and MIRP outcomes with several important findings. 1) We found a significant increase in the rate of MIRP use with concomitant cannibalization of RRP and PRP. During the study period PRP decreased from 6.5% to less than 2% of all RPs done in this cohort. As the scientific literature balances reports of costs and mixed outcomes of MIRP,[17–20] competing approaches to RP may come under greater scrutiny by payors, patients and physicians. This decreased use limits PRP training and exposure of this approach to the next generation of urologists. A survey of recent urology residents revealed that only 13% of those not exposed to PRP used the procedure in practice.[20]

2) Men undergoing MIRP vs PRP were more likely to come from areas of higher socioeconomic status and from metropolitan areas. This difference may be due to the successful marketing approach of robot-assisted MIRP through print media and the Internet as well as early adoption of the robot at wealthier centers.[11]

3) When we compared men undergoing PRP vs RRP, PRP was associated with shorter length of stay and fewer heterologous blood transfusions. While there was no difference in the postoperative stricture rate between PRP and RRP, PRP was associated with less adjuvant therapy use. While this may reflect improved cancer control after PRP, it may also reflect differences in lymph node sampling since adjuvant therapy may be initiated with node positive disease that remains undiagnosed by PRP alone. PRP was associated with lower cost due to decreased median hospital stay, blood transfusion and adjuvant therapy use, consistent with a single institution comparison.[18] Also, total Medicare payments within 6 months of surgery were lower for PRP than for RRP or MIRP with a mean and median PRP expenditure greater than $1,500 less than that for RRP or MIRP. While this may not capture all payments associated with long-term complications beyond 6 months postoperatively, it captures the associated expense of rehospitalizations, emergency department visits and additional radiological or surgical procedures.

4) Comparison between men undergoing PRP vs MIRP revealed no difference in length of stay, although PRP was associated with a 3-fold increase in the likelihood of heterologous blood transfusion. However, this increased PRP blood transfusion rate was not offset by any MIRP advantages in short-term or intermediate term outcomes. MIRP was associated with an almost 2-fold higher rate of medical complications within 30 days of surgery compared with PRP. Cancer control and stricture rates did not differ significantly for PRP vs MIRP.

5) PRP vs MIRP was associated with fewer procedures for ED but we did not account for surgeon skill and experience. For instance, PRP surgeons who have not changed to newer approaches may be comfortable with their PRP ability due to greater experience and proficiency, resulting in better outcomes.

Our findings must be interpreted in the context of the study design. 1) Our study was restricted to Medicare beneficiaries older than 65 years who resided in SEER regions. Thus, these results may not be applicable to younger men or those undergoing surgery outside SEER regions due to geographic variation in RP use and outcomes.[21] 2) We could not distinguish between MIRP with and without robotic assistance since the 2 procedures share a common CPT-4 code. However, robotic assisted MIRP use surged from 1% of RPs in 2001 to 40% in 2006,[22,23] with a current estimate of 50% to 70%.[24] Concurrently MIRP without robotic assistance is disappearing in the United States, consistent with a recent survey of urologists showing a 25% to 75% decrease in surgical volume among those using a nonrobotic approach to RP.[25,26] 3) Observer bias may have a role in the diagnosis of ED and urinary continence, as captured by Medicare claims data. Men diagnosed with these conditions were sufficiently bothered to bring it to the attention of physicians who entered the diagnosis. Patient self-report using validated quality of life instruments remains the gold standard to assess these outcomes. 4) As in any adjusted analysis, propensity score methods cannot control for unmeasured confounders and have other limitations.[27]

CONCLUSIONS

Despite decreased use, PRP has outcomes that are equivalent or improved compared to those of RRP and MIRP with lower cost within the first 6 months postoperatively. Since there is increased attention on comparative effectiveness analysis due to increasing health care costs, our findings contribute to other studies showing that PRP is a favorable and perhaps prematurely abandoned alternative to RP.

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Population-Based Determinants of Radical Prostatectomy Operative Time

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Table: 2

INTRODUCTION:

Operative time as a performance metric has been described on several levels. The length of an operation impacts its adoption by the surgical community. For example, laparoscopic radical prostatectomy was introduced in the early 1990's as a novel minimally invasive approach, yet there was little uptake in the U.S. due in part to excessive operative times of over 9 hours.[1] Once the operative time shortened to a more acceptable length of approximately 3 hours, the technique gained acceptance.[2] Similarly, operative time is commonly used to assess surgeon learning curves. As surgeons become more adept and skilled, the procedural duration decreases accordingly.[3] Operative time additionally has important implications for controlling costs and is used as an indicator of efficiency and as a focus for quality improvement initiatives.[4,5] One minute of operating room time is estimated to cost in excess of $15.[6] While it has been demonstrated that robotic-assisted radical prostatectomy (RARP) is a significantly more costly than retropubic radical prostatectomy (RRP) largely due to fixed overhead costs, it has been shown that as the duration of RARP operative time decreases, so do overall costs.[4] Furthermore, operative time has been utilized to evaluate quality of care, as longer operations have demonstrated an increased risk of post-operative complications for both non-prostate surgery and robotic-assisted urologic surgery.[7,8] Identifying factors that affect length of operative time for RARP and RRP has important implications for surgical training, cost, and quality of care.

While radical prostatectomy operative time has been reported in single-surgeon and single-institution series, evaluation beyond these settings is lacking, and little is known about radical prostatectomy operative times in the community. The purpose of our population-based study is to characterize factors that affect radical prostatectomy operative times.[9]

SUBJECTS/PATIENTS AND METHODS

Data

Our study was exempted by the University of California, Los Angeles Institutional Review Board. Patient data were de-identified and the requirement for consent was waived. We used Surveillance, Epidemiology, and End Results (SEER)- Medicare data for analysis, which are composed of a linkage of population-based cancer registry data from 16 SEER areas covering approximately 28% of the U.S. population with Medicare administrative data.[10]

Study Cohort

We identified 19,914 men diagnosed with localized prostate cancer between 2003-2007 who underwent RRP or RARP through 2009, based on the presence of Current Procedural Terminology, Fourth Edition (CPT-4) codes 55866 for RARP and 55840, 55842, and 55845 for RRP consistent with prior methods.[11] We excluded 2,203 men who were not continuously enrolled in Medicare Part A and B or who were enrolled in health maintenance organizations (HMO) during the study period. We excluded 3,449 men with missing data from their Medicare anesthesia physician claims and 3,811 men missing tumor registry information, resulting in a study cohort of 10,451 men who underwent RARP (n=3,458) and RRP (n=6,993).

Independent Variables

Information on patient age and year of operation was obtained from Medicare file. Comorbidity as measured by Klabunde modification of the Charlson score was derived from inpatient, outpatient, and carrier claims during the year before surgery.[12] Race/ethnicity, census measures of median household income and education, population density (non-metropolitan vs. metropolitan), U.S. Census region, marital status, and NCI designation were obtained from SEER. Obesity was identified by International Classification of Diseases, 9th Edition (ICD-9) diagnosis codes V854, 278.00 and 278.01. We determined surgeon and hospital volume by aggregating the total number of radical prostatectomies performed during the study period and categorizing into quartiles. Surgeon age, practice type (government employment vs. nongovernment solo, nongovernment two person practice, and nongovernment group [more than two urologists] practice), and academic and government hospital affiliation were determined by linking unique physician identifier numbers (UPIN) to the American Medical Association Masterfile.

Operative time was derived from a validated method using anesthesia claims data,[9] Additional anesthesia procedures were identified using the following CPT-4 codes: placement of epidural 62318, 62319, 62310, 62311, 62350; arterial line 36620; central venous catheter (CVC) 93593. Pelvic lymph node dissections (LND) were identified using CPT codes 55842 and 55845 for open RRP and 38571 for robotic LND.

Estimation of Cost Savings

We obtained the number of RPs performed during the year 2007 within each quartile of surgeon volumes from low to very high. We summed the product of surgeon volume parameter estimates and the number of radical prostatectomies performed by low, intermediate, and high volume surgeons to calculate the minutes of operative time that may be avoided by referral to very high volume surgeons. This was multiplied by $15, the estimated cost of operative time per minute.[6] We then extrapolated to the general population by divided by .28, because SEER represents approximately 28% of the U.S. population,[13] and then divided by .32, because approximately 32% of men undergoing RP are older than 65 years.[14] Finally, we initially identified 19,914 men who underwent radical prostatectomy during the study period, however excluded almost half due to missing data and ineligibility based on HMO or Medicare enrollment. To apply these cost savings to this initial cohort, we divided the cost savings by the percentage excluded, or 0.52.

Statistical Analysis

Because the main outcome of interest operative time was heavily right skewed, we report median rather than mean operative times. The non-parametric Wilcoxon Rank-sum (two sample) test adjusting for clustering at the surgeon level was used for bivariable analyses.[15] Median regression was used to determine the effect of patient, surgeon, and hospital characteristics on radical prostatectomy operative time.[16] All analysis was completed using SAS 9.2 (SAS Institute, Cary, NC).

RESULTS

During our study period, the median operative time for RARP decreased from 315 minutes in 2003 to 247 minutes in 2008-2009 ($p<0.001$) while median RRP operative time remained

relatively constant at 195 to 199 minutes (Figure 1). White men experienced shorter RARP operative times (p=0.023), while married men experienced shorter RARP (p=0.012) and RRP (p=0.020) operative times, respectively. Obesity was associated with longer RARP and RRP operative times by fourteen and seven minutes, respectively (p<0.001 for both). Although moderately differentiated tumors were associated with shorter RRP operative times (p<0.001), LND did not significantly lengthen RARP and RRP operative times. Additional anesthesia procedures such as placement of an arterial line, CVC, or other anesthesia procedures lengthened RRP (p<0.001), however only placement of CVC lengthened RARP (p<0.001). There was significant geographic variation in RRP operative times (p<0.001) but not in RARP operative times.

Higher surgeon volumes were associated with shorter RARP and RRP (p<0.001 for both). Likewise, higher hospital volumes were associated with shorter RARP and RRP (p<0.001 and p=0.006, respectively). Additionally, surgeons in a group practice experienced shorter RARP and RRP operative times (p<0.001 for both) than those in other practice types. Moreover, RARP duration in teaching hospitals was 54 minutes longer (p<0.001) than that in non-teaching hospitals. In terms of NCI designation, RARP were shortest when performed in NCI designated Comprehensive Cancer Centers (235 min, p<0.001); however, RRP were shortest when performed in centers without NCI designation (190 minutes, p<0.001). (Table 1)

In adjusted analyses, RARP operative times were longer than RRP (parameter estimate [PE] 70.9, 95% confidence interval [CI] 57.64,84.15, p<0.001). Additionally, obese men experienced longer operative times (PE 15.23; 95% CI 7.03, 23.43; p<0.001), and any additional anesthesia

procedure added a median of 22.4 minutes (PE 22.4; 95% CI 15.93, 28.86, p<0.001). There continued to be significant geographic variation, with shorter operative times in the South (PE -21.68, 95% CI -32.84, -10.52, p<0.001) and Midwest (PE-16.34, 95% CI -25.62, -7.07, p<0.001) vs. the West. Very high, high, and intermediate vs. low surgeon volume were associated with shorter operative times (PE -42.43; 95% CI -53.3, -31.55; p<0.001, PE -26.04; 95% CI -35.4, -16.68; p<0.001, and PE -10.6; 95% CI -18.66, -2.53; p=0.010, respectively), and group practices and non-government vs. government employment were associated with shorter operative times (PE -22.76, 95% CI -38.03, -7.49; p=0.004, and PE -35.59, 95% CI -68.15, -3.03; p=0.032). Non-profit ownership was associated with shorter operative times, compared with government ownership (PE -21.85, 95% CI -32.28, -11.42; p<0.001). Finally, teaching status did not affect radical prostatectomy operative times (PE 3.19, 95% CI -8.52, 14.9, p=0.593). (Table 2)

Finally, if all RPs were performed by very high volume surgeons in 2007, 46,574.6 minutes would be potentially avoided in our SEER-Medicare study, leading a cost savings of $698,619. Extrapolating nationally to radical prostatectomy regardless of age, savings of $14,994,398.17 may be achieved annually by selective referral or improved efficiency to the level of very high volume surgeons.

COMMENT

Since attaining Food and Drug Administration approval in 2001, RARP has become the most popular approach to radical prostatectomy (RP), comprising more than 50% of RP in 2008, edging out the gold standard RRP.[17] As new surgical technologies are disseminated, the ability to identify factors that influence the length of the operation has important implications for

understanding surgeon learning curves, determining quality of care, and estimating the financial impact of these new technologies. For instance, single center series have reported learning curves regarding adoption of the robotic technique.[18] Moreover, a multi-center study demonstrated that RARP was associated with less variance and range in operative time compared to RRP.[19] However, outcomes beyond published high volume centers are sparse.[17]

Our study has several important findings. First, by utilizing a validated method of determining actual OR times by using anesthesia claims data,[10] we found that median RARP vs. RRP operative time was 71 minutes longer. While expert RARP surgeons have reported operative times shorter than RRP,[20] the flattening out of individual surgeon's learning curve in terms of RARP operative times may take more than 700 cases.[21] Our population-based finding that the robotic approach takes over an hour longer suggests that there may be opportunities for shortening RARP. Notably, during the study period from 2003-2009, operative times for RARP decreased annually, while operative time for RRP remained constant. This likely reflects advances along the learning curve for RARP on a community level as this mirrors the national increase in utilization of the robotic technique. This implies that as surgeons gain more experience with this technology, the median operative times progressively decrease. In contrast, RRP has not undergone any recent significant changes in technique, and median operative times remained constant throughout our study period. Improving the surgical efficiency of a new operation such as RARP may be achieved with greater dissemination of sound surgical technique and experience to lower volume surgeons. By providing collaborative feedback to lower volume surgeons, they may have the opportunity progress faster along their learning curve so that their efficiency approaches that of very high volume surgeons. Alternatively, selective referral to very

high volume centers may encourage a shift of RARPs to centers with greater experience and shorter operative times.

Importantly, it has been suggested that as operative times decrease, so do overall costs. Scales et al demonstrated that at high volume hospitals where greater than ten RARPs were being performed weekly, RARP is cost equivalent to RRP and becomes even less expensive if the case volume exceeds fourteen RARP per week.[4] Thus, if RARP operative times shorten to allow more daily procedures, the cost of the robotic operation may be more competitive with its open counterpart.

Second, higher surgeon volume was associated with shorter RARP and RRP operative times. Similarly, higher surgeon volume is associated with fewer complications and shorter lengths of stay.[22] Cost savings for RP has also been demonstrated for high volume surgeons,[23] and extrapolation of our findings demonstrate that almost $15 million annually may be saved by shorter operative times achieved from selective referral to very high volume RP surgeons. Alternatively, these cost savings may also be attained if lower volume surgeons improve efficiency to match that of very high volume surgeons. Moreover, this figure does not factor in additional cost savings derived from the excess operating room capacity to perform additional procedures. To put this figure into context, the NCI allocated $19 million for prostate cancer research in 2011.[24]

Third, we identified obesity as an independent predictor of longer operative times, consistent with a study that showed patient preparation, control of the dorsal vascular complex, and

performing nerve-sparing and the vesico-urethral anastomosis were longer in obese vs. non-obese men.[25] The impact of obesity on operative time is particularly relevant given the rising incidence of obesity in the United States and its impact on exacerbating health care costs.[26] Additionally, obesity has been shown to adversely affect outcomes after radical prostatectomy, as it is associated with a greater risk of biochemical recurrence and castration-resistant disease following RP.[27]

Fourth, we found that the type and location of a surgeon's practice influence operative time for radical prostatectomy. Surgeons in group or nongovernment practices have significantly shorter operating times than those employed by the government. Moreover, hospitals owned by the government have longer operative times than those that are owned by non-government entities. Interestingly, we also found that teaching hospital status did not have an impact on operative time. Additionally, there was significant geographic variation in radical prostatectomy operative times, consistent with prior studies that demonstrate significant geographical variation in radical prostatectomy use and outcomes.[28]

The performance of LND during radical prostatectomy interestingly did not affect the length of the operation. Prior investigation revealed that significant variation exists between the number of lymph nodes resected (extended vs. limited),[29] and this may have a dampening effect on the added LND operative time.

Our study must be interpreted within the context of the study design. Our Medicare study includes only elderly men in which nerve-sparing may be performed with less frequency

compared to younger men, and nerve-sparing technique, which we were unable to adjust for, may lengthen the operation. Additionally, the estimation of operative time was derived from anesthesia claims data, which includes induction time. However, this methodology has been validated as a close approximation of procedure length.[9] Finally, recent findings from the National Surgical Quality Improvement Program show that RARP and RRP "set-up time" are similar, and cancel out when estimating and comparing operative times.[30]

CONCLUSIONS

Operative times for RARP decreased over our contemporary study, while remaining stable for RRP; however, RARP was 71 minutes longer compared to RRP. Moreover, there was significant variation in radical prostatectomy operative times by geography, practice type and hospital ownership. Finally, higher radical prostatectomy surgeon volume was associated with shorter operative times and selective referral to efficient, high volume surgeons nets significant cost savings due to shorter operative times alone.

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CONFLICTS OF INTEREST

Ya-Chen Shih reports paid consultancy work for MRI Advisory Board sponsored by Bayer and received institution funding from AHRQ; R01 (R01HS018535, R01 HS020263), and NCI; R21 (CA165092), outside the submitted work. No other authors declare any conflicts of interest.

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Table 1: Median operative time (minutes) by surgical approach [Robotic assisted Radical Prostatectomy (RARP) vs. Retropubic Radical Prostatectomy (RRP)] based on patient, tumor, hospital, and surgeon characteristics

Variable		RARP	p Value	RRP	p Value
No. pts		3,458		6,993	
		Patient			
Year	2003	315	<0.001	195	0.907
	2004	276		194	
	2005	264		196	
	2006	259		195	
	2007	259		199	
	2008	247		197	
Age at diagnosis	65-69	264	0.636	196	0.766
	70-74	260		195	
	75+	260		192	
Race	White	259	0.023	195	0.234
	Black	286		195	
	Hispanic	278		202	
	Asian	261		210	
	Other	250		195	
Marital status	Not married	274	0.012	202	0.019
	Married	260		195	
	Unknown	267		199	
Education level (% achieving high school degree)	<75	279	0.061	193	0.580
	75-84.99	263		196	
	85-89.99	265		198	
	90+	258		195	
	Unknown	290		161	
Median Income	<$35,000	267	0.375	194	0.231
	$35-44,999	270		194	
	$45-59,999	257		195	

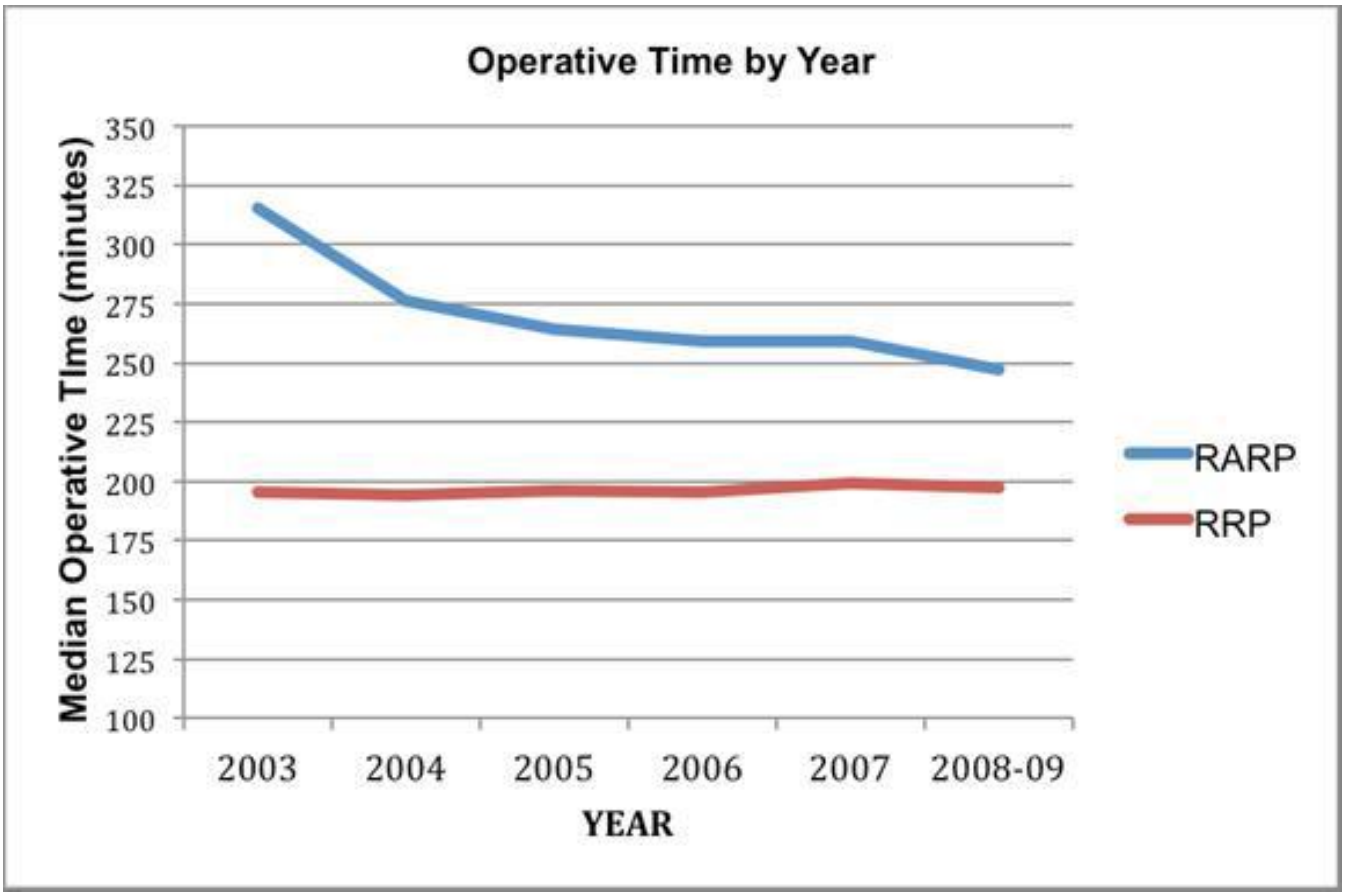
	>=$60,000	259		202	
	Unknown	290		161	
Charlson score	0	261	0.521	195	0.499
	1	269		195	
	2+	258		200	
	Unknown	272		198	
Obesity	No	261	<0.001	195	<0.001
	Yes	286		211	
		Tumor			
Clinical stage	T1	257	0.029	196	0.047
	T2	270		194	
	T3/T4	282		213	
	Unknown	294		189	
Grade	Well	239	0.485	207	<0.001
	Moderately	266		192	
	Poorly/Undiff	261		199	
	Unknown	260		215	
		Hospital			
Geographic regions	Northeast	279	0.630	213	<0.001
	South	249		181	
	Midwest	259		193	
	West	263		198	
Population density	Non-metro	250	0.387	190	0.297
	Metropolitan	264		196	
NCI	No	274	<0.001	190	<0.001
	Clinical	375		265	
	Comprehensive	235		231	
Ownership	Non-profit	257	0.0644	194	0.111
	Proprietary	273		193	
	Government	301		209	

Teaching	No	225	<0.001	195	0.112
	Yes	279		201	
Hospital volume	Low	295	<0.001	206	0.006
	Intermediate	280		197	
	High	275		193	
	Very high	220		189	
		Surgeon			
Surgeon volume	Low	310	<0.001	217	<0.001
	Intermediate	292		202	
	High	253		193	
	Very high	221		177	
Surgeon's age	<50	273	0.219	196	1.000
	50+	250		195	
Group	Solo/2-person practice	290	<0.001	196	<0.001
	Group	259		187	
	Medical school	329		229	
	Non-government	212		238	
	Government	276		226	
	Undefined	274		205	
		Other			
LND	No LND	268	0.216	196	0.473
	Limited	258		207	
	Open	N/A		195	
Epidural	No	262	0.439	195	0.069
	Yes	330		201	
A_line	No	268	0.416	189	<0.001
	Yes	251		235	
CVC	No	262	<0.001	194	<0.001
	Yes	356		235	
Any extra	No	267	0.398	187	<0.001
	Yes	252		216	

Table 2. Overall cohort on adjusted analysis

Variable	Category	Parameter	Low_CL	Upper_ CL	P_value
Surgeon's age		0.37	-0.03	0.76	0.068
Age at diagnosis		-1.10	-4.04	1.85	0.465
Surgeon volume (Ref=low)	Intermediate	-10.60	-18.66	-2.53	0.010
	High	-26.04	-35.40	-16.68	<0.001
	Very high	-42.43	-53.30	-31.55	<0.001
Hospital volume (Ref=low)	Intermediate	-2.03	-10.67	6.61	0.646
	High	1.84	-9.93	13.61	0.760
	Very high	-8.93	-23.10	5.25	0.217
Year of RP (ref=2008)	2003	15.77	4.67	26.88	0.005
	2004	13.97	3.85	24.09	0.007
	2005	13.44	3.18	23.69	0.010
	2006	13.81	4.93	22.70	0.002
	2007	8.60	-0.43	17.64	0.062
Geography regions (ref=west)	1=Northeast	0.32	-12.65	13.28	0.962
	2=South	-21.68	-32.84	-10.52	<0.001
	3=Midwest	-16.34	-25.62	-7.07	<0.001
Clinical stage (ref= T3/T4)	T1	-2.52	-14.96	9.92	0.691
	T2	-2.93	-15.33	9.47	0.644
Grade(ref=Poorly differentiated)	1= moderately	-3.50	-7.93	0.92	0.121
NCI (Ref=No)	Clinical	50.94	29.37	72.51	<0.001
	Comprehensive	-10.75	-27.43	5.92	0.206
Group (ref=Government)	Solo/2 person practice	-11.40	-29.55	6.75	0.218
	Group	-22.76	-38.03	-7.49	0.004
	Medical school	20.09	-0.04	40.22	0.051
	Non-government	-35.59	-68.15	-3.03	0.032
Ownership (ref=Government)	Non-profit	-21.85	-32.28	-11.42	<0.001
	Proprietary	-13.05	-28.00	1.90	0.087
Teaching (ref= No)	Yes	3.19	-8.52	14.90	0.593
Obesity (ref= No)	Yes	15.23	7.03	23.43	<0.001

Any extra anesthesia PX (Ref=No)	Yes	22.40	15.93	28.86	<0.001
LND (Ref=Open)	No	3.04	-6.23	12.31	0.521
	Limited	0.70	-12.44	13.83	0.917
Surgical approach (ref=RRP)	RARP	70.90	57.64	84.15	<0.001



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Original article

The effect of minimally invasive and open radical prostatectomy surgeon volume

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Abstract

Objective: To determine the effect of minimally invasive radical prostatectomy (MIRP) surgeon volume on outcomes, and correlate with those of open radical prostatectomy retropubic (ORP).

Methods and materials: Observational population-based study of 8,831 men undergoing MIRP and ORP by 1,457 low, medium, and high volume surgeons from SEER-Medicare linked data from 2003 to 2007. After stratifying by surgeon ORP and MIRP volume, the following outcomes were studied: length of stay, transfusions, post-operative 30-day and anastomotic stricture complications, and use of additional cancer therapies.

Results: Men undergoing MIRP with high and medium vs. low volume surgeons were less likely to require additional cancer therapies (4.5% and 4.7% vs. 7%, $P = 0.020$). Similarly, men undergoing ORP with high vs. medium and low volume surgeons were less likely to require additional cancer therapies (5.7% vs. 6.8% and 7.1%, $P = 0.044$). Men undergoing ORP with high vs. medium and low volume surgeons experienced shorter lengths of stay (2.9 vs. 3.3 and 3.6 days, $P < 0.001$), and fewer transfusions (15.4% vs. 21.3% and 22.7%, $P = 0.017$), 30-day complications (18.4% vs. 25.6% and 25.7%, $P < 0.001$), and anastomotic strictures (10.1% vs. 15.6% and 16.3%, $P = 0.003$). However, MIRP surgeon volume did not affect these outcomes.

Conclusions: Men undergoing MIRP or ORP with high volume surgeons were less likely to require additional cancer therapies. Additionally, patients of high volume ORP surgeons were more likely to experience shorter hospital stays, fewer transfusions, 30-day complications, and anastomotic strictures, while MIRP surgeon volume did not affect these peri-operative outcomes.

Keywords: Surgeon volume; Surgical outcomes; Radical prostatectomy; Robotic surgery

1. Introduction

Volume-outcome effects, the association between higher volume and better outcomes, have been established for many surgical procedures [1], providing the rationale for using volume as a proxy for quality. Defining quality indicators is a prerequisite for the implementation of pay-for-performance programs, an essential pillar of current U.S. healthcare reform initiatives. Radical prostatectomy is the most common oncologic operation performed by urologists with more than 60,000 procedures performed annually in the U.S. [2]. Several studies have demonstrated an association between higher open radical retropubic prostatectomy (ORP) surgeon volume and better outcomes [3,4], and surgeon volume is a prostate cancer quality indicator [5]. Further, to increase transparency and improve quality-of-care,

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Table 1
Demographic and tumor characteristics by MIRP and ORP surgeon volume

Variable	Categories	Before propensity weighting				After propensity weighting			
		MIRP surgeon volume				MIRP surgeon volume			
		Low $n = 211$	Medium $n = 34$	High $n = 11$	P value	Low $n = 211$	Medium $n = 34$	High $n = 11$	P value
Age (years)	65–69	374 (61.0%)	394 (64.1%)	386 (56.2%)	<0.001	373 (61.5%)	370 (60.3%)	439 (63.2%)	0.940
	70–74	201 (32.8%)	188 (30.6%)	229 (33.3%)		192 (31.7%)	197 (32.2%)	208 (29.9%)	
	75+	38 (6.2%)	33 (5.4%)	72 (10.5%)		41 (6.8%)	46 (7.5%)	48 (6.8%)	
Charlson score	0	427 (69.7%)	442 (71.9%)	497 (72.3%)	0.676	429 (70.7%)	437 (71.3%)	510 (73.5%)	0.842
	1	142 (23.2%)	141 (22.9%)	145 (21.1%)		140 (23.1%)	134 (21.8%)	144 (20.7%)	
	2+	44 (7.2%)	32 (5.2%)	45 (6.6%)		37 (6.1%)	42 (6.9%)	40 (5.8%)	
Race	White	492 (80.3%)	508 (82.6%)	551 (80.2%)	0.852	493 (81.4%)	491 (80.1%)	553 (79.6%)	0.999
	Black	38 (6.2%)	35 (5.7%)	42 (6.1%)		38 (6.3%)	37 (6.1%)	41 (5.9%)	
	Hispanic	43 (7.0%)	26 (4.2%)	37 (5.4%)		31 (5.1%)	36 (5.9%)	39 (5.6%)	
	Asian	29 (4.7%)	36 (5.9%)	52 (7.6%)		35 (5.7%)	39 (6.4%)	52 (7.5%)	
Marital status	Not married	91 (14.9%)	70 (11.4%)	96 (14.0%)	0.170	82 (13.5%)	83 (13.5%)	87 (12.5%)	0.738
	Married	467 (76.2%)	466 (75.8%)	551 (80.2%)		471 (77.6%)	474 (77.3%)	516 (74.3%)	
	Unknown	55 (9.0%)	79 (12.9%)	40 (5.8%)		53 (8.8%)	56 (9.1%)	92 (13.2%)	
% with at least a high school education in census tract of residence	<75	124 (20.3%)	76 (12.4%)	77 (11.2%)	<0.001	91 (15.1%)	93 (15.1%)	109 (15.8%)	0.999
	75–84.9	120 (19.6%)	119 (19.4%)	111 (16.2%)		109 (18%)	112 (18.2%)	120 (17.3%)	
	85–89.9	127 (20.8%)	103 (16.8%)	93 (13.5%)		100 (16.5%)	103 (16.7%)	110 (15.9%)	
	90+	241 (39.4%)	317 (51.5%)	406 (59.1%)		306 (50.5%)	306 (49.9%)	354 (51.1%)	
Median household income ($) in census tract of residence	<35,000	163 (26.6%)	107 (17.4%)	84 (12.2%)	<0.001	112 (18.5%)	117 (19.1%)	138 (19.9%)	0.999
	35–44,999	146 (23.9%)	141 (22.9%)	111 (16.2%)		128 (21.1%)	124 (20.2%)	139 (20%)	
	45–59,999	137 (22.4%)	152 (24.7%)	183 (26.6%)		144 (23.8%)	155 (25.3%)	167 (24%)	
	≥60,000	166 (27.1%)	215 (35.0%)	309 (45.0%)		222 (36.6%)	217 (35.4%)	251 (36.1%)	
Population density	Metropolitan	559 (91.2%)	580 (94.3%)	684 (99.6%)	<0.001	577 (95.2%)	582 (94.9%)	653 (94%)	0.919
AJCC pathologic stage	T2	409 (66.7%)	420 (68.3%)	479 (69.7%)	0.396	420 (69.3%)	416 (67.8%)	462 (66.5%)	0.975
	≥T3	111 (18.1%)	120 (19.5%)	128 (18.6%)		108 (17.8%)	113 (18.4%)	124 (17.7%)	
	Other	93 (15.2%)	75 (12.2%)	80 (11.6%)		78 (12.9%)	84 (13.7%)	109 (15.7%)	
Tumor grade	Well/moderately differentiated	283 (46.2%)	300 (48.8%)	355 (51.7%)	0.425	302 (49.8%)	302 (49.3%)	355 (51.2%)	0.989
	Poorly/undifferentiated	323 (52.7%)	309 (50.2%)	330 (48.0%)		300 (49.5%)	306 (49.9%)	335 (48.2%)	

Table 1
Continued

Variable	Categories	Before propensity weighting				After propensity weighting			
		ORP surgeon volume				ORP surgeon volume			
		Low $n = 879$	Medium $n = 236$	High $n = 86$	P value	Low $n = 879$	Medium $n = 236$	High $n = 86$	P value
Age (years)	65–69	1604 (67.4%)	1453 (61.6%)	1293 (59.4%)	<0.001	1497 (63%)	1481 (62.8%)	1374 (63.1%)	0.999
	70–74	671 (28.2%)	749 (31.8%)	680 (31.2%)		724 (30.5%)	717 (30.4%)	656 (30.1%)	
	75+	105 (4.4%)	156 (6.6%)	204 (9.4%)		156 (6.6%)	160 (6.8%)	147 (6.8%)	
Charlson score	0	1598 (67.1%)	1628 (69.0%)	1527 (70.1%)	0.317	1626 (68.4%)	1617 (68.6%)	1493 (68.5%)	0.999
	1	622 (26.1%)	567 (24.1%)	522 (24.0%)		594 (25%)	586 (24.9%)	544 (25%)	
	2+	160 (6.7%)	163 (6.9%)	128 (5.9%)		157 (6.6%)	155 (6.6%)	141 (6.5%)	
Race	White	1861 (78.2%)	1867 (79.2%)	1810 (83.1%)	0.482	1893 (79.6%)	1886 (80%)	1730 (79.5%)	0.999
	Black	194 (8.2%)	197 (8.4%)	138 (6.3%)		190 (8%)	180 (7.6%)	178 (8.2%)	
	Hispanic	202 (8.5%)	195 (8.3%)	150 (6.9%)		191 (8%)	189 (8%)	175 (8.1%)	
	Asian	85 (3.6%)	75 (3.2%)	59 (2.7%)		76 (3.2%)	75 (3.2%)	69 (3.2%)	
Marital status	Not married	384 (16.1%)	352 (14.9%)	321 (14.8%)	0.005	369 (15.5%)	362 (15.3%)	342 (15.7%)	0.999
	Married	1840 (77.3%)	1915 (81.2%)	1778 (81.7%)		1898 (79.8%)	1885 (79.9%)	1736 (79.7%)	
	Unknown	156 (6.6%)	91 (3.9%)	78 (3.6%)		110 (4.6%)	111 (4.7%)	100 (4.6%)	
% with at least a high school education in census tract of residence	<75	548 (23.1%)	472 (20.0%)	348 (16.0%)	<0.001	479 (20.2%)	467 (19.8%)	443 (20.4%)	0.999
	75–84.9	516 (21.7%)	498 (21.1%)	365 (16.8%)		472 (19.9%)	469 (19.9%)	426 (19.6%)	
	85–90	444 (18.7%)	467 (19.8%)	405 (18.6%)		444 (18.7%)	448 (19%)	409 (18.8%)	
	>90	867 (36.5%)	920 (39.0%)	1057 (48.6%)		981 (41.3%)	972 (41.2%)	897 (41.2%)	
Median household income ($) in census tract of residence	<35,000	762 (32.1%)	776 (32.9%)	580 (26.7%)	0.151	740 (31.1%)	725 (30.8%)	670 (30.8%)	0.999
	35–44,999	546 (23.0%)	557 (23.6%)	556 (25.6%)		559 (23.5%)	563 (23.9%)	525 (24.1%)	
	45–59,000	586 (24.75)	532 (22.6%)	508 (23.4%)		564 (23.7%)	556 (23.6%)	511 (23.5%)	
	≥60,000	481 (20.3%)	492 (20.9%)	531 (24.4%)		513 (21.6%)	513 (21.8%)	470 (21.6%)	
Population density	Metropolitan	2138 (89.8%)	2134 (90.5%)	2041 (93.8%)	0.087	2171 (91.3%)	2153 (91.3%)	1987 (91.2%)	0.999
AJCC pathologic stage	T2	1414 (59.4%)	1426 (60.5%)	1322 (60.7%)	<0.001	1430 (60.2%)	1420 (60.2%)	1305 (59.9%)	0.999
	≥T3	576 (24.2%)	632 (26.1%)	610 (28.0%)		625 (26.3%)	620 (26.3%)	579 (26.5%)	
	Other	390 (16.4%)	300 (12.7%)	245 (11.3%)		322 (13.5%)	318 (13.5%)	294 (13.5%)	
Tumor grade	Well/moderately differentiated	1226 (51.5%)	1170 (49.6%)	1115 (51.2%)	0.147	1213 (51%)	1194 (50.6%)	1112 (51.1%)	0.997
	Poorly/undifferentiated	1132 (47.6%)	1177 (49.9%)	1055 (48.5%)		1151 (48.4%)	1152 (48.8%)	1052 (48.3%)	

state governments have publicized radical prostatectomy surgeon volumes [6]. However, in 2005, 80% of U.S. urologists performed fewer than 10 radical prostatectomies per year, and 25% performed just 1 [7].

Minimally invasive radical prostatectomy (MIRP)—that is, laparoscopic radical prostatectomy with or without robotic assistance—has experienced rapid and widespread diffusion [8,9]. To perform robotic-assisted MIRP, there are few barriers to entry: urologists must attend a 2-day course before scheduling cases supervised by proctors who have performed at least 20 robotic-assisted MIRP. Requirements may be less rigorous for attaining hospital privileges for MIRP without robotic assistance. For these reasons, concern has been raised that outcomes may be sacrificed during the initiation of a MIRP program [10]. While previous studies directly compared MIRP vs. ORP outcomes [11], not much is known about how MIRP volume affects outcomes, and if this differs from the way ORP volume affects outcomes. The purpose of our population-based study is 2-fold: (1) to delineate surgeon volume-outcome effects for MIRP and ORP, and (2) to compare the volume-outcome effects for MIRP vs. ORP.

2. Materials and methods

Our study was approved by the Brigham and Women's Institutional Review Board. Patient data were de-identified and the requirement for consent was waived. We used Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data for analyses. Medicare provides benefits to 97% of Americans aged ≥65 years, and SEER provides cancer-specific registry data to 93% of Medicare beneficiaries. Together, SEER-Medicare comprises approximately 26% of the U.S. population [12].

We identified men aged ≥65 years with complete Medicare coverage who were diagnosed with nonmetastatic prostate cancer from 2002 to 2005 as their only cancer. Men who underwent ORP and MIRP from 2003 to 2006 (n = 8,831) were identified based on the presence of Current Procedural Terminology 4th Edition (CPT-4) codes 55840, 55842, 55845 for ORP, and 55866 for MIRP. Demographic and tumor characteristics were obtained from SEER registry data, while patient age was obtained from the Medicare file. Comorbidity was assessed using the Klabunde modification of the Charlson index based on claims submitted during the year prior to surgery [13].

We examined mortality/morbidity, length of stay, use of cystography, anastomotic strictures, and use of additional cancer therapy (Appendix A), [3,4,8,9]. Postoperative mortality, complications, heterologous transfusions, and use of cystography were captured up to 30 days after surgery. Complication categories included cardiac, respiratory, genitourinary, vascular, wound, and miscellaneous medical and surgical. Anastomotic strictures were assessed from 31 to 365 days after surgery [4]. Long term incontinence [4] and erectile dysfunction [14] were captured on the basis of symptoms leading to a diagnosis or procedures to treat these conditions more than 18 months after surgery, the interim required for recovery of postoperative urinary and sexual function to plateau [15]. We identified men undergoing additional post-prostatectomy cancer therapy (radiation, hormonal therapy) [8], a measure of cancer control.

Because surgeon rather than hospital volume mediates ORP outcomes [3], we determined surgeon volume for each type of procedure by aggregating the number of prostatectomies performed from 2003 to 2006. While we originally stratified surgeon volume into quartiles [4], this resulted in potential confidentiality issues, and we consequently stratified surgeon volume into tertiles (low, medium, high). For men with more than 1 surgeon listed, we selected the surgeon who performed the larger volume of radical prostatectomies for analysis [4].

Unadjusted univariate analysis was performed to compare patient characteristics by surgical approach using the Pearson χ^2 statistic. For dichotomous outcomes such as complications, we compared unadjusted proportions of interest among men undergoing MIRP and ORP, using the Pearson χ^2 statistic. For dichotomous outcome variables in which patients had varying length of follow-up, we compared rates (number of events per 100 person-years follow-up). Generalized estimating equations (GEE) [16] were used to account for surgeon clustering in unadjusted and adjusted analyses. To compare unadjusted proportions and rates, we fit GEE logistic regressions and GEE log-linear Poisson regression, respectively, with surgeon volume as the only covariate.

In adjusted analyses, we used weighted propensity score methods to adjust for possible confounders when examining the effect of surgeon volume on outcomes [17]. Propensity score methods permit control for all observed confounding factors that might influence group assignment and outcome using a single composite measure. In addition, it attempts to balance patient characteristics between groups, as would occur in a randomized experiment. Covariate balance was checked after adjustment (Table 1, weighted values). All tests were considered statistically significant at $\alpha = 0.05$. Analyses were performed with SAS ver. 9.1.3 (SAS Institute, Cary, NC).

3. Results

The demographics of our study population are shown in Table 1. A total of 6,915 men underwent ORP by 1,201 surgeons, and 1,915 men underwent MIRP by 256 surgeons. The MIRP volume tertiles correspond to 1–17 (low), 18–52 (medium), 53–424 (high), patients per surgeon, while the ORP volume categories correspond to 1–11 (low), 12–25 (medium), 26–94 (high) patients per surgeon during the study period. Assuming that 42% of patients undergoing prostatectomy are aged ≥65 years [18], we project that these ranges correspond to total annual volumes of 1–10,

Table 2
Unadjusted association of MIRP and RRP surgeon volume and outcomes

Variable	MIRP surgeon volume tertile				ORP surgeon volume tertile			
	Low $n = 211$	Medium $n = 34$	High $n = 11$	P value	Low $n = 879$	Medium $n = 236$	High $n = 86$	P value
Transfusion	3.3%	2.0%	1.6%	0.274	22.7%	21.3%	15.6%	0.014
Overall complication	21.7%	21.1%	22.4%	0.921	25.5%	25.8%	18.7%	<0.001
Cardiac	2.3%	2.3%	1.9%	0.835	3.5%	2.9%	3.2%	0.554
Respiratory	5.4%	3.7%	3.6%	0.252	8.4%	6.8%	4.9%	<0.001
Genitourinary	2.6%	1.5%	3.1%	0.157	1.6%	1.2%	1.1%	0.274
Wound	<1.9%*	<1.9%*	2.2%	0.021	1.9%	2.1%	1.0%	0.014
Vascular	2.3%	4.1%	2.0%	0.060	4.4%	3.9%	3.4%	0.223
Miscellaneous medical	9.8%	10.1%	7.4%	0.319	9.7%	9.3%	6.9%	0.012
Miscellaneous surgical	4.7%	4.9%	4.5%	0.961	5.8%	6.8%	3.7%	<0.001
Length of stay†	2.3	1.9	1.8	0.016	3.6	3.3	2.8	<0.001
Stricture	6.4%	4.6%	5.4%	0.523	16.4%	15.7%	9.7%	<0.001
Additional cancer therapy‡	7.2	4.6	4.8	0.012	7	7	5.8	0.067
Cystography	25.6%	22.1%	44.8%	0.019	9.4%	7.1%	13.8%	0.065

* The exact percentage is not reported due to potential confidentiality issues.
† Mean ratios.
‡ Rate per 100 person years, follow-up until 12/31/2006.

11–31, and 32–252 procedures per surgeon for MIRP, and 1–6, 7–15, and 16–56 for ORP.

High volume MIRP surgeons were more likely to operate on older men ($P < 0.001$) in metropolitan ($P < 0.001$) census tracts with higher education ($P < 0.001$) and income ($P < 0.001$). Similarly, high volume ORP surgeons were more likely to operate on older men ($P < 0.001$), married men ($P = 0.005$), and those of higher education ($P < 0.001$). High volume ORP surgeons were more likely to operate on men with at least pathologic T3 disease ($P < 0.001$).

The unadjusted comparison of outcomes by surgeon volume and surgical approach is shown in Table 2. There were only 13 peri-operative deaths (0.15%), too few to stratify by surgeon volume. In unadjusted analyses, patients of high volume MIRP surgeons were more likely to undergo cystograms ($P = 0.019$), experience shorter lengths of stay ($P = 0.016$), have fewer wound complications ($P = 0.021$), and are less likely to receive additional cancer therapy ($P = 0.012$). In adjusted analyses (Table 3), men of high volume MIRP surgeons were less likely to require additional cancer therapy only ($P = 0.020$).

In contrast to MIRP, unadjusted analyses revealed that overall 30-day, respiratory, wound, miscellaneous medical and surgical, transfusion, and anastomotic stricture complications were lowest for high volume ORP surgeons ($P < 0.05$, respectively). In addition, patients of high volume ORP surgeons experienced shorter lengths of stay ($P < 0.001$). In adjusted analyses of ORP surgeon volume-outcome effects, all of the associations above remained signif-

Table 3
Adjusted association of MIRP and RRP surgeon volume and outcomes

Variable	MIRP surgeon volume tertile				RRP surgeon volume tertile			
	Low $n = 211$	Medium $n = 34$	High $n = 11$	P value	Low $n = 879$	Medium $n = 236$	High $n = 86$	P value
Transfusion	3.1%	2%	1.4%	0.199	22.7%	21.3%	15.4%	0.017
Overall complication	22%	21.7%	21.7%	0.996	25.7%	25.6%	18.4%	<0.001
Cardiac	1.9%	2.3%	1.8%	0.805	3.5%	2.9%	3.2%	0.493
Respiratory	5.3%	4%	3.3%	0.336	8.2%	6.7%	4.9%	<0.001
Genitourinary	2.7%	1.6%	2.6%	0.339	1.6%	1.1%	1.1%	0.337
Wound	1.2%	<1%	2%	0.169	1.8%	2.1%	0.9%	0.004
Vascular	2.2%	4%	2.1%	0.255	4.4%	3.9%	3.2%	0.111
Miscellaneous medical	10%	10.6%	8%	0.610	10%	9.1%	6.9%	0.011
Miscellaneous surgical	4.5%	5.1%	3.9%	0.611	5.9%	6.8%	3.4%	<0.001
Length of stay†	2.2	2	1.8	0.061	3.6	3.3	2.9	<0.001
Stricture	6.1%	4.8%	5%	0.730	16.3%	15.6%	10.1%	0.003
Additional cancer therapy‡	7	4.7	4.5	0.020	7.1	6.8	5.7	0.044
Cystography	23.7%	22.2%	46.1%	0.146	9.2%	6.9%	13.9%	0.130

† Mean ratios.
‡ Rate per 100 person years, follow-up until 12/31/2006.

icant. Further, patients of high volume ORP surgeons were less likely to require additional cancer therapy ($P = 0.044$).

4. Discussion

Recently, a rapid shift in utilization from ORP to MIRP has occurred with more than 75% of radical prostatectomies being performed via robotic-assisted MIRP today [19]. While significant ORP surgeon volume-outcome effects have been shown [4,20], little is known about how MIRP surgeon volume affects outcomes outside of single institution studies, which have demonstrated prolonged learning curves for MIRP beyond 500 cases [21,22]. Furthermore, less is known if and how the volume outcomes effects for MIRP and ORP differ.

Our study has several important findings. First, men undergoing MIRP and ORP with high volume surgeons were less likely to receive additional cancer therapies, indicating better cancer control. Our population-based findings confirm previous work from single and multi-institution centers of excellence. Vickers found the predicted probability of recurrence at 5 years was 17.9% and 10.7% for men treated by ORP surgeons with 10 and 250 prior operations, respectively [20]. Vickers performed a similar analysis for non-robotic MIRP and demonstrated that prostate cancer recurrence decreased from 17% to 16% to 9% after surgeons had performed 10, 250, and 750 prior procedures, respectively [22]. Additional, a previous study using a different population-based cohort found that higher MIRP surgeon volume was associated with less need for additional cancer therapies [8]. The confirmation of these centers-of-excellence results with those from population-based studies allows for the confident generalization of findings.

Second, we observed significant ORP surgeon volume effects for certain peri-operative outcomes. Patients of higher volume ORP surgeons were more likely to experience shorter hospital stay, and fewer transfusions, 30-day complications and anastomotic strictures. These results recapitulate those from multiple previous studies from the urologic and general surgery literature [3,4]. Higher volume surgeons may possess a better understanding of the complex dorsal venous anatomy, and ability to limit excessive bleeding. Estimated blood loss (EBL) in ORP series range widely from 385 to 1,550 mL per case, resulting in a 4% to 55.7% ORP transfusion rate [23]. Studies have implicated EBL as a significant mediator of blood transfusions, hospital length of stay, and postoperative complications [24]. In addition, higher EBL has been associated with a higher risk of anastomotic stricture, presumably due to poor direct visualization because of bleeding or hematoma formation resulting in urinary leak and subsequent stricture [25]. Differences in EBL between high and low volume surgeons may be the main driver of differences in risk of transfusion, extended hospital stay, 30-day complications, and anastomotic stricture.

Third, we failed to identify MIRP surgeon volume-outcome effects for the peri-operative outcomes observed with ORP, suggesting that MIRP surgical technique affords some advantages that allow low vs. high volume MIRP surgeons to achieve similar peri-operative outcomes. One well-established benefit of MIRP is less variation in estimated blood loss (EBL) due to the tamponade effects of pneumoperitoneum [26]. EBL in recent MIRP series range from 50 to 380 mL [26], and the lower MIRP EBL may contribute to the absence of volume-outcome effects for these outcomes. In addition, during ORP anastomosis, it may be difficult to directly visualize posterior mucosal apposition, and securing the anastomosis is done mostly by feel, which requires significant experience. During MIRP, however, direct visualization of the anastomosis is afforded by the camera, which, in addition to the lower EBL, may explain the absence of a MIRP volume-outcome effect for anastomotic strictures in our population-based study. Furthermore, during intraperitoneal MIRP, mobilization of the bladder may further decrease tension, facilitating the anastomosis.

Our study must be interpreted in the context of the study design. First, administrative data are primarily designed to provide billing information, not detailed clinical information. However, Medicare administrative data have a high degree of validity for detecting in-hospital surgical complications [27]. Second, short-term prostate cancer survival is high, and lengthier follow-up is needed to assess differences in cancer control. There may be regional differences in utilization of adjuvant radiation for pT3 or margin-positive disease that may confound our findings. Third, our findings may not be generalizable to men $\leq$ 65 years, or those undergoing surgery outside of SEER regions. Finally, we were unable to differentiate MIRP with vs. without robotic-assistance, as both share a common CPT-4 code; however, the advent of robotic-assisted MIRP has led to a near disappearance of pure laparoscopic MIRP in the U.S. during our study period, especially in the community setting [28]. Therefore, the robotic-assisted approach likely accounted for the majority of MIRP in our study.

5. Conclusion

Men undergoing MIRP or ORP with high volume vs. low volume surgeons were less likely to require additional cancer therapies. Additionally, men of high volume ORP surgeons were more likely to avoid blood transfusions, experience shorter hospital stays, fewer 30-day complications, and less anastomotic strictures, while MIRP surgeon volume did not affect these peri-operative outcomes.

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Appendix

Type of outcome	Time after surgery	Category	Diagnosis codes	Procedure codes
Postoperative outcomes	0–30 days	Cardiac complication	ICD9: 410.xx, 402.01, 402.11, 402.91, 428.xx, 427.5, 997.1	
		Respiratory complication	ICD9: 518.0, 514, 518.4, 466.xx, 480.xx, 481, 482.xx, 483.xx, 485, 486, 518.5, 518.81, 518.82, 799.1, 997.3	
		Genitourinary complication	ICD9: 595.89, 590.1x, 590.2, 590.8x, 590.9, 591, 596.6, 593.3, 593.4, 593.5, 593.81, 593.82, 997.5, 596.1, 596.2	ICD9: 55.02, 55.03, 55.12, 55.93, 55.94, 59.93, 97.61, 97.62, 56.1, 56.41, 56.74, 56.75, 56.81, 56.84, 56.86, 56.89, 56.91 CPT: 50040, 50120, 50125, 50395, 50398, 50605, 52290, 52332, 52334, 50600, 50700, 50715, 50760, 50770, 50780, 50782, 50783, 50785, 50800, 50810, 50815, 50820, 50825, 50840, 50900, 50940
		Wound complication	ICD9: 567.xx, 998.3, 998.5x, 998.6	ICD9: 54.61, 54.1x, 54.91, 54.0, 59.19 CPT: 26990, 45020, 49060, 51080
		Vascular complication	ICD9: 415.1, 451.1x, 451.2, 451.81, 451.9, 453.8, 453.9, 997.2, 999.2, 444.22, 444.81, 433.xx, 434.xx, 436, 437.xx	
		Miscellaneous medical complication	ICD9: 584.xx, 586, 785.5x, 995.0, 995.4, 998.0, 999.4, 999.5, 999.6, 999.7, 999.8, 457.8, 560.1, 560.8x, 560.9, 997.4, 353.0, 354.2, 723.4, 955.1, 955.3, 955.7, 955.8, 955.9, 593.4, 531.xx, 532.xx, 533.xx, 782.4, 573.8	
		Miscellaneous surgical complication	ICD9: 599.1, 596.1, 596.6, 565.1, 569.3, 569.83, 569.4x, 998.1x, 998.83, 998.9, 998.2, 998.4, 998.7, 604.0, E870.0, E870.4, E870.7, E870.8, E870.9, E871.0, E873.0, E876.0, 956.0, 956.1, 956.4, 956.5, 956.8, 956.9, 902.50, 902.51, 902.52, 902.53, 902.54, 902.59	ICD9: 46.03, 46.04, 46.10, 46.11, 46.14, 48.4x, 48.5, 48.6x, 48.7x, 48.9x
		Blood transfusion		ICD9: 99.0x CPT: 86930, 86965, 86999 HCPCS: P9010, P9011, P9017, P9021, P9022, P9038, P9039, P9040
Anastomotic stricture	31–365 days		ICD9: 596.0, 598.9, 598.2	ICD9: 57.85, 57.92, 57.91, 58.1, 58.5, 58.6, 58.3x CPT: 51800, 53640, 52275, 52276, 52281, 52282, 52283, 52510, 53400, 53405, 53410, 53415, 53420, 53425, 53600, 53601, 53605, 53620, 53621
Long-term incontinence diagnosis	Greater than 18 months		ICD9: 788.3x	
Long-term incontinence repair	Greater than 18 months			ICD9: 58.93, 59.72, 89.21, 89.22, 89.23,89.24, 89.25 CPT: 51715, 53440, 53442, 53443, 53444, 51736, 53445, 51725, 51726, 51772, 51784, 51785, 51792, 51795, 51797, 51798, 51741
Long-term erectile dysfunction diagnosis	Greater than 18 months		ICD9: 607.84	
Long-term erectile dysfunction procedure	Greater than 18 months			ICD9: 64.94, 64.95, 64.96, 64.97 CPT: 54231, 54235, 54400, 54401, 54402, 54405, 54406, 54407, 54408, 54409, 54410, 54411, 54415, 54416, 54417 HCPCS: C1007, C1813, C2622, C3500, C8514, C8516, C8534, J0270, J0275, J2440, J2760, L7900
Additional cancer therapy	Anytime after surgery	Hormonal therapy		ICD9: 62.41 CPT: 54520 HCPCS: C9216, C9430, G0356, J0128, J3315, J9202, J9217, J9218, J9219, S0165, S9560
		Radiation therapy		ICD9: 92.2x CPT: 76965, 77301, 77305, 77310, 77315, 77331, 77371, 77372, 77373, 77399, 77401, 77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416, 77418, 77421, 77422, 77423, 77427, 77431, 77440, 77499, 77520, 77522, 77523, 77525, 79300, 79440, 79999, 4201F, 4210F, 4165F, 79200 HCPCS: G0174, G0242, G0243

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Population-based determinants of radical prostatectomy surgical margin positivity

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Study Type – Prognosis (cohort)
Level of Evidence 2b

What's known on the subject? and What does the study add?
Prior population and single-centre studies have assessed incidence of positive surgical margins. The current study derived population-based positive surgical margin cut-offs in order to help identify underperforming surgeons who may benefit from further courses and/or self study to improve outcomes.

OBJECTIVE

- To characterize factors associated with positive surgical margins (PSMs) and derive population-based PSM cutoffs to evaluate surgeon performance in radical prostatectomy (RP).

PATIENTS AND METHODS

- SEER-Medicare data were used to identify 4247 men diagnosed with prostate cancer during 2004–2005 who underwent RP up to 2006.
- We performed logistic regression to assess the impact of tumour characteristics, surgeon volume and surgical approach on the likelihood of PSMs for pT2 and PT3a disease.
- Moreover, we derived 25th and 10th percentile cutoffs from binomial distribution equations.

RESULTS

- Overall, 19.4% of men experienced PSMs with a pT2 vs pT3a PSM rate of 14.9% vs 42% ($P < 0.001$). Extrapolating from our population-based results, a surgeon incurring more than three PSMs in 10 cases of pT2 disease performed below the 25th percentile.
- There was a trend for fewer PSMs with minimally invasive vs open RP (17.4% vs 20.1%, $P = 0.086$), and the PSM rate also decreased over the study period from 21.3% in 2004 to 16.6% in 2006 ($P = 0.028$) with significant geographic variation ($P < 0.001$).
- In adjusted analyses, temporal and geographic variation in PSM persisted, and men with high (odds ratio 3.68, 95% CI 2.82–4.81) and intermediate (odds ratio 2.52, 95% CI 2.03–3.13) vs low-risk disease were at greater odds to experience PSMs. Notably, neither surgical approach nor surgeon volume was significantly associated with PSMs.

CONCLUSION

- Our population-based PSM benchmarks allow identification of under-performing outliers who may seek courses or video self-study to improve outcomes. There was significant temporal and geographic variation in PSMs but neither surgeon volume nor surgical approach was associated with PSMs.

KEYWORDS

positive margins, prostatectomy, minimally invasive, surgeon volume, outcomes

INTRODUCTION

Positive surgical margin status is a significant predictor of biochemical recurrence after radical prostatectomy [1]. Although positive surgical margins and greater PSA velocity, tumour grade and stage are associated with an increased risk of prostate cancer recurrence, only surgical margin status is influenced by surgical technique. In addition, positive surgical margins for organ-confined prostate cancer may serve as a quality indicator, and recent level 1 evidence shows a survival advantage when adjuvant radiotherapy is administered to counter this undesirable outcome [2,3]. Consequently, positive surgical margins increase the cost of treating prostate cancer secondary to the use of adjuvant radiotherapy and treatment of cancer recurrence.

Minimally invasive radical prostatectomy with and without robotic assistance has been rapidly adopted [4] but there are few comparisons of surgical margin status in minimally invasive surgery with that in open retropubic radical prostatectomy aside from single-centre studies [5]. Furthermore, some contend that the sense of palpation during retropubic radical prostatectomy, which is lacking with the minimally invasive approach, allows better assessment of the extent of tumour [6], potentially resulting in fewer positive margins and better cancer control. Our study objectives were: to characterize determinants of positive surgical margins and to derive population-based positive surgical margin benchmarks for surgeon self-assessment.

PATIENTS AND METHODS

Surveillance, Epidemiology, and End Results (SEER)–Medicare data were used for analyses, which comprise a linkage of population-based cancer registry data from 16 SEER areas covering approximately 26% of the US population with Medicare administrative

TABLE 1 Demographics of the study population

Characteristic	Categories	Total	Positive margin, *n* (%)	*P*-value
Year of surgery	2004	1779	378 (21.3)	0.028
	2005	2058	376 (18.3)	
	2006	410	68 (16.6)	
Age (years)	65–69	2620	485 (18.5)	0.203
	70–74	1332	270 (20.3)	
	≥75	295	67 (22.7)	
Charlson comorbidity index	0	2956	554 (18.7)	0.080
	1	1018	202 (19.8)	
	≥2	273	66 (24.2)	
Race	White	3366	661 (19.6)	0.932
	Black	307	57 (18.6)	
	Hispanic	356	64 (18.0)	
	Asian	186	34 (18.3)	
	Other	32	6 (18.8)	
Marital status	Unmarried	605	102 (16.9)	0.031
	Married	3469	694 (20.0)	
	Unknown	173	26 (15.0)	
Education: % of census tract with at least a high school degree	<75	785	142 (18.1)	0.108
	75–84.99	785	131 (16.7)	
	85–89.99	791	159 (20.1)	
	≥90	1885	389 (20.6)	
Median income in census tract of residence	<$35 000	1106	203 (18.35)	0.321
	$35 000–44 000	975	188 (19.28)	
	$45 000–59 000	1072	227 (21.18)	
	≥$60 000	1093	203 (18.57)	
SEER region	San Francisco	171	31 (18.13)	<0.001
	Detroit	303	59 (19.47)	
	Iowa	195	46 (23.6)	
	Seattle	352	85 (24.15)	
	Utah	284	78 (27.5)	
	Connecticut	127	27 (21.26)	
	San Jose	103	21 (20.39)	
	Los Angele	569	137 (24.08)	
	Greater Ca	1171	232 (19.81)	
	Kentucky	215	31 (14.42)	
	Louisiana	316	43 (13.61)	
	New Jersey	265	13 (4.9)	
	New Mexico/Georgia/Hawaii	176	19 (10.80)	
Population density	Metropolitan	3989	773 (19.38)	0.891
	Rural	258	49 (18.99)	
Clinical stage	T1c	2218	408 (18.39)	0.452
	T2	737	148 (20.08)	
	T3	39	9 (23.08)	
	Unknown	1253	257 (20.51)	
Gleason grade	≤ 6	1687	190 (11.26)	<0.001
	7	2073	487 (23.49)	
	≥8	469	144 (30.70)	
	Unknown	18	1 (5.56)	
PSA	<10	3141	568 (18.08)	0.0001
	10–20	495	123 (24.85)	
	>20	170	47 (27.65)	
	Unknown	441	84 (19.05)	
D'Amico risk	Low	1242	130 (10.47)	<0.001
	Intermediate	2265	502 (22.16)	
	High	637	177 (27.79)	
	Unknown	103	13 (12.62)	

PSA, prostate-specific antigen; SEER, surveillance, epidemiology, and end results.

data. The Medicare programme provides benefits to most Americans aged ≥65 years.

We identified 6153 men aged ≥65 years enrolled in Medicare Parts A and B, not enrolled in the Medicare health maintenance organization (because their claims were not reliably submitted), diagnosed with prostate cancer in 2004 and 2005 who underwent open and minimally invasive radical prostatectomy from 2004 to 2006. We stratified the surgical approach on the basis of the Physicians Current Procedural Terminology Coding System 4th edition, (CPT-4): 55840, 55842, 55845 for open retropubic radical prostatectomy; and 55866 for minimally invasive radical prostatectomy [4,7]. Because SEER only captures positive margin characteristics for the American Joint Commission on Cancer pathological T2 and T3a disease, we excluded 293 men with pathological stage T3b, 63 men with pathological T4 and 1132 men with missing pathological information. We also excluded 318 men who underwent radical prostatectomy outside SEER regions to avoid misclassification of surgeon volume.

The control variables were obtained as follows. Patient age was obtained from the Medicare file; race, census tract measures of median household income and high school education, Census region, population density (urban vs rural), and marital status were obtained from SEER registry data. Comorbidity was assessed using the Klabunde modification of the Charlson index during the year before surgery [8]. Variables were categorized as in Table 1. Additionally, we used PSA, Gleason Grade and stage to stratify men to low-risk, intermediate-risk and high-risk disease [9]. However, clinical tumour stage was missing/unknown for almost one-third of our subjects. Moreover, there was a lower than expected percentage of men (18%) in the low-risk group compared with a community cohort [10]. We hypothesized that biopsy findings, rather than indication for biopsy, may have to be used for clinical staging, contrary to American Joint Committee on Cancer guidelines. We therefore used a modified D'Amico risk stratification that omitted clinical stage, resulting in a low-risk designation for 29% of our cohort.

Because surgeon rather than hospital volume is the more significant determinant of outcomes after retropubic radical prostatectomy [11], we determined surgeon

TABLE 2 Surgical margin status by surgeon volume, surgical approach and pathological stage

Independent variable	Category	Total	Positive margin *n* (%)	*P*-value
Surgical approach	MIRP	1121	195 (17.4)	0.086
	RRP	3119	627 (20.1)	
Surgeon volume in quartiles (no. of surgeons by approach)	Low (MIRP 85; RRP 396)	1027	179 (17.43)	0.329
	Intermediate (MIRP 21; RRP 169)	1130	217 (19.20)	
	High (MIRP 12; RRP 91)	1159	228 (19.67)	
	Very high (MIRP < 11*; RRP 37)	931	198 (21.27)	
Pathological stage	T2	3544	528 (14.9)	<0.001
	T3a	700	294 (42.0)	

MIRP, minimally invasive radical prostatectomy; RRP, radical retropubic prostatectomy.
**Actual number of MIRP surgeons not presented because the National Cancer Institute precludes the reporting of table cells of* n < *11.*

volume by aggregating the number of procedures performed from 2004 to 2006. We assessed surgeon volume a priori as both a continuous and a categorical variable. Categorically, surgeon volume for the study period was divided into quartiles, consistent with a previous study [12], corresponding to 1–7 radical prostatectomies for low, 8–15 for intermediate, 16–29 for high, and 30–91 for very high for open radical prostatectomy surgeons. On the other hand, the minimally invasive radical prostatectomy surgeon volume quartile distribution over the study period was 1–14 radical prostatectomies for low, 15–36 for intermediate, 37–89 for high, and 90–218 for very high volume surgeons.

In sub-analyses, we analysed the effect of surgeon volume on minimally invasive and open radical prostatectomy surgical margin positivity, respectively, and did not find a significant relationship. Finally, we stratified surgical approach into minimally invasive vs open radical prostatectomy.

Bivariate analyses were performed to compare patient characteristics and positive surgical margin status by surgeon volume using the Rao-Scott–Pearson chi-squared statistic, which accounts for clustering by surgeon [13]. A Rao-Scott–Pearson chi-squared test was also used to compare the overall positive margin by surgical approach. Logistic regression was performed to determine the effect of surgeon volume as a continuous and categorical variable; logistic regression was also used to assess the effect of age, race, SEER region, surgical approach, D'Amico risk stratification, and year of surgery on positive surgical margins. For the logistic regressions, generalized estimating equations were used to account for clustering of patients by surgeon [14]. All tests were considered statistically significant at $\alpha = 0.05$. All analyses were performed with SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

To derive the 25th and 10th percentile positive surgical margin thresholds for a given urologist, using results from generalized linear mixed models (given a random urologist effect) [15], the number of operations with positive margins out of the N operations performed by a surgeon follows a binomial distribution. Because most practicing urologists perform fewer than 12 major operations a year including radical prostatectomy [16], we present postivie surgical margin performance thresholds for surgeon volumes of 5 to 12 radical prostatectomies. Moreover, given that 42% [17] of US radical prostatectomies are performed in men aged 65 years and older, we determined that 57.6% and 67.7% of minimally invasive radical prostatectomy surgeons performed fewer than 12 radical prostatectomies in 2004 and 2005 whereas 67.6% and 70.5% of open radical prostatectomy surgeons performed fewer than 12 radical prostatectomies in 2004 and 2005, respectively. Assuming that the probability of a positive margin equals the mean positive margin rate from our study population, the 25th and 10th percentiles for surgeon-specific positive margin rates out of N operations performed can be derived using the binomial distribution formula [18], with π as the mean population-based positive margin rate, and N as the number of operations performed. The exact percentiles can be obtained from the SAS 'quantile' function. A normal-based approximation to the percentiles can be obtained with the formulae [19]:

$$25\text{th percentile} = \pi + 1.5/N + 0.675\sqrt{\pi(1-\pi)/N}$$

$$10\text{th percentile} = \pi + 1.5/N + 1.28\sqrt{\pi(1-\pi)/N}$$

RESULTS

The demographics of our study population are presented in Table 1. The positive surgical margin rate decreased during the 3-year study period from 21.3% to 16.6% from 2004 to 2006. Although there were no significant associations between age, comorbidity and race and positive surgical margins, married men were more likely than unmarried men to experience positive surgical margins (20.0% vs 16.9%, $P = 0.031$). Moreover, there was significant geographic variation in positive surgical margin rates, ranging from 4.9% to 27.5% ($P < 0.001$). Finally, higher PSA level ($P < 0.001$) and Gleason grade ($P < 0.001$), and consequently higher risk disease ($P < 0.001$), were associated with higher positive surgical margin rates.

The relationships between surgical approach, surgeon volume and pathological stage with positive surgical margins are presented in Table 2. There was a trend for fewer positive surgical margins with minimally invasive vs retropubic radical prostatectomy (20.1% vs 17.4%, $P = 0.086$) but there was no association between overall surgeon volume with positive surgical margins. In addition, sub-analyses of minimally invasive and retropubic radical prostatectomy surgeon volume, respectively, did not reveal an association with positive surgical margins. However, the positive surgical margin rate

TABLE 3 Adjusted model for predictors of surgical margin positivity

Covariate (referent)	Categories	OR (95% CI)	*P*-value
Age (≥75 years)	65–69	1.01 (0.69–1.46)	0.978
	70–74	1.03 (0.71–1.48)	0.877
Race (White)	Black	1.19 (0.84–1.69)	0.333
	Hispanic	0.91 (0.68–1.23)	0.547
	Asian	0.88 (0.58–1.34)	0.556
D'Amico risk (Low)	Intermediate	2.52 (2.03–3.13)	<0.001
	High	3.68 (2.82–4.81)	<0.001
Surgical approach (RRP)	MIRP	0.93 (0.77–1.13)	0.464
Surgeon volume (Low)	Intermediate	1.0 (0.77–1.3)	0.989
	High	0.94 (0.74–1.18)	0.583
	Very high	1.02 (0.8–1.31)	0.845
SEER Region (San Francisco)	Detroit	1.16 (0.72–1.86)	0.534
	Iowa	1.41 (0.82–2.4)	0.213
	Seattle	1.43 (0.9–2.28)	0.125
	Utah	1.94 (1.17–3.22)	0.011
	Connecticut	1.23 (0.72–2.11)	0.451
	San Jose	1.24 (0.7–2.19)	0.460
	Los Angeles	1.56 (1.01–2.42)	0.047
	Greater California	1.17 (0.78–1.77)	0.440
	Kentucky	0.73 (0.42–1.26)	0.254
	Louisiana	0.68 (0.39–1.17)	0.160
	New Jersey	0.23 (0.12–0.43)	<0.001
	New Mexico/Georgia/Hawaii	0.54 (0.28–1.05)	0.071
Year (2004)	2005	0.83 (0.7–0.98)	0.033
	2006	0.75 (0.55–1.01)	0.057

95% CI, 95% confidence interval; MIRP, minimally invasive radical prostatectomy; OR, odds ratio; RRP, radical retropubic prostatectomy.

TABLE 4 Positive surgical margin percentile thresholds for surgeon volume of 5 to 12 radical prostatectomies based on binomial distribution and population means for pT2 and pT3a disease

Surgeon volume	Organ-confined disease, $\pi = 0.0149$ *n* cases with positive margins (%)		Extracapsular extension, $\pi = 0.420$ *n* cases with positive margins (%)	
N	25th percentile	10th percentile	25th percentile	10th percentile
5	2 (40)	3 (60)	4 (80)	5 (100)
6	2 (33)	3 (50)	4 (67)	5 (83)
7	3 (43)	3 (43)	5 (71)	6 (86)
8	3 (38)	4 (50)	5 (63)	6 (75)
9	3 (33)	4 (44)	6 (67)	7 (78)
10	3 (30)	4 (40)	6 (60)	7 (70)
11	3 (27)	4 (36)	7 (64)	8 (73)
12	4 (33)	5 (41)	7 (58)	8 (67)

Because of the discreteness of the binomial distribution, the cutoff rates are not identical for different surgeon volumes. Using the n values in this table, the 25th and 10th percentiles are actually (n – 1)/N, but to reduce confusion, because correction action may be undertaken if surgeon-specific positive margin rates exceed the 25th percentiles, this table includes the minimum thresholds for the above percentiles.

was higher for pT3a vs pT2 disease (42.0% vs 14.9%, $P < 0.001$).

The adjusted analyses are presented in Table 3. Men undergoing radical prostatectomy in 2005 vs 2004 experienced lower odds for positive surgical margins (odds ratio 0.83, 95% CI 0.7–0.98), and there was a trend for lower odds of positive surgical margins in 2006 vs 2004 (OR 0.75, 95% CI 0.55–1.01). Significant geographic variation in positive surgical margin rates persisted in adjusted analysis. Whereas men undergoing radical prostatectomy in New Jersey experienced lower odds of positive surgical margins (OR 0.23, 95% CI 0.12–0.43), those in Utah (OR 1.94, 95% CI 1.17–3.22) and Los Angeles (OR 1.56, 95% CI 1.01–2.42) experienced greater odds of positive surgical margins vs San Francisco (referent). Moreover, men with high-risk (OR 3.68 95% CI 2.82–4.81) and intermediate-risk (OR 2.52, 95% CI 2.03–3.13) vs low-risk features experienced greater odds of positive surgical margins. Notably, there was no association between surgeon volume stratified in quartiles and assessed as a continuous variable (Appendix) and likelihood of positive surgical margins.

Table 4 displays the 25th and 10th percentile positive margin rate thresholds for organ-confined disease based on the population-based pT2 positive margin rate of 14.9%. This is derived from the exact binomial for $\pi = 0.149$ and varying surgeon volumes (*N*). For example, a surgeon experiencing positive margins in 3 of 10 men with organ-confined disease would perform at the 25th percentile.

DISCUSSION

Population-based studies have shown that higher radical prostatectomy surgeon volume is associated with fewer in-hospital and late urinary complications, shorter lengths of stay, and less use of additional cancer therapy [4,11,12]. In addition, multicentre studies have characterized a learning curve for cancer control, as greater surgeon experience in open and minimally invasive radical prostatectomies portends fewer biochemical recurrences [20,21]. A recent population-based study showed significantly greater use of additional cancer treatments, i.e. radiation and/or hormonal therapy, within 6 months of minimally invasive vs open radical prostatectomy but potential confounders

such as surgical margin status and pathological stage and grade were unavailable [4]. Additionally, there is an absence of population-based studies that explore the potential influence of surgical approach and surgeon volume on positive margin status. Positive surgical margins increase patient distress and fear of cancer recurrence [22], and add to healthcare costs when adjuvant radiotherapy is added to improve cancer control [2,3].

Our paper has several important findings. First, we present population-based radical prostatectomy positive surgical margin rates of 14.9% for organ-confined disease and 42% for extracapsular extension. In addition, we derived positive surgical margin performance thresholds that may serve as benchmarks for surgeon self-assessment, rather than comparison with published positive margin rates from high-volume single surgeon series. Surgeons experiencing positive margin rates in excess of population-based benchmarks might review intraoperative video of themselves [23] or others and seek courses to improve their surgical technique and lower their positive margin rates. Although we present 25th and 10th percentile population-based positive margin thresholds, others may use the binomial distribution to individualize 'acceptable' performance levels.

Second, we observed lower positive surgical margin rates when comparing radical prostatectomies performed in 2005 vs 2004. There was a trend for lower positive surgical margin rates for 2006 than 2004 but the study might have been underpowered to detect significance because our study cohort comprised men diagnosed with prostate cancer through 2005 who had surgery in 2006, rather than including all men undergoing radical prostatectomy in 2006. Although a temporal trend for fewer positive surgical margins is consistent with the gradual diffusion of surgical technique and improved outcomes that follow [24,25], subsequent years of data, when available, must be analysed to determine if margin rates continue to decrease.

Third, we observed significant geographic variation in positive surgical margin rates. This parallels variations in positive surgical margin rates from single centre reports. Moreover, our regional differences in positive surgical margins parallel other population-based studies showing geographic variation in radical prostatectomy outcomes [11,24,26]. These findings underscore the heterogeneity in radical prostatectomy technique and outcomes. Moreover, we observed that married vs unmarried men experienced high surgical margin positivity; however, the inability to determine use of nerve-sparing technique from SEER-Medicare data prevents us from exploring this further.

Fourth, while there are purported advantages of tumour palpation and intraoperative decision-making on improved cancer control during open compared with minimally invasive radical prostatectomy [6], most US men with prostate cancer increasingly present with raised PSA levels and low-volume disease rather than with disease that is palpable on digital rectal examinations [10,27], and our population-based analyses show similar positive surgical margin rates between minimally invasive and open radical prostatectomy. Moreover, early cancer control was also similar for minimally invasive and open radical prostatectomy from a study of SEER-Medicare linked data [7]. Our findings contrast with those contending that men undergoing minimally invasive vs open radical prostatectomy experience inferior cancer control [4,28].

Finally, we did not observe a relationship between surgeon volume and positive surgical margin status. This contrasts two multicentre studies showing that higher surgeon volume was associated with lower positive margin rates [29,30]. However, individual surgeon characteristics and heterogeneity also affect surgical margin status; surgeon volume was no longer a predictor of surgical margin status after excluding the highest volume surgeon from one study [30] but positive margin rates for open radical prostatectomy surgeons at high volume, academic referral centres varied widely from 11% to 48% in the other study [29]. In addition, a recent multicentre study showed significant heterogeneity in cancer recurrence after adjusting for surgeon experience and tumour characteristics [31].

Our findings must be interpreted in the context of the study design. First, SEER-Medicare does not contain detailed clinical information regarding whether nerve-sparing technique was used, which increases the likelihood of positive surgical margins [32]. Second, Medicare is limited to men aged 65 years and older, and nerve-sparing may be performed more frequently in younger, potent men [32]. This, along with the absence of margin status for pathological T3b and T4 disease, may lead to underestimation of the overall prevalence of positive margins in all men undergoing radical prostatectomy, regardless of age. However, the number of men omitted with pathological T3b and T4 disease was relatively small, and positive margins in organ-confined vs extraprostatic disease may serve as a better litmus test for the quality of surgical technique. Third, heterogeneous pathological processing and interpretation may lead to variation in positive surgical margin status [2,3]. Fourth, we were unable to differentiate between minimally invasive radical prostatectomy performed with and without robotic assistance because both share a common CPT code; however, a recent survey showed a 75% reduction in volume among surgeons performing minimally invasive radical prostatectomy without robotic assistance [33], and the robot-assisted approach likely accounted for most of the minimally invasive radical prostatectomies. Finally, many cases and several years may transpire before low-volume surgeons can accurately characterize their positive margin rates stratified by tumour characteristics, and this may be a potential limitation of our margin positivity thresholds for surgical margin positivity because real-time feedback is unavailable.

Our population-based, organ confined (pT2) positive surgical margin rate of 14.9% and 25th and 10th percentile cutoffs may serve as a benchmark for radical prostatectomy surgeon self-assessment. Although we observed temporal improvement and significant geographic variation in positive surgical margin rates, we did not find a surgeon volume–outcomes effect with positive surgical margins, probably because of heterogeneity in the surgical technique. Finally, positive surgical margin rates were similar for minimally invasive and open radical prostatectomy.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **OR**, odds ratio; **SEER**, surveillance, epidemiology, and end results.

APPENDIX ADJUSTED MODEL OF PREDICTORS OF SURGICAL MARGIN POSITIVITY WITH SURGEON VOLUME AS A CONTINUOUS VARIABLE

Covariate (referent)	Categories	OR (95% CI)	*P*-value
Age (≥75 years)	65–69	1.01 (0.69–1.47)	0.975
	70–74	1.03 (0.71–1.49)	0.874
Race (White)	Black	1.19 (0.84–1.69)	0.335
	Hispanic	0.92 (0.68–1.24)	0.569
	Asian	0.89 (0.59–1.34)	0.567
D'Amico risk (Low)	Intermediate	2.5 (2.03–3.13)	<0.001
	High	3.7 (2.81–4.80)	<0.001
Surgical approach (RRP)	MIRP	0.91 (0.72–1.14)	0.404
Surgeon volume (continuous)	Per 10 surgeries	1.01 (0.99–1.02)	0.512
SEER region	Detroit	1.14 (0.72–1.82)	0.570
	Iowa	1.4 (0.82–2.38)	0.217
	Seattle	1.43 (0.91–2.25)	0.119
	Utah	1.91 (1.15–3.17)	0.012
	Connecticut	1.24 (0.73–2.12)	0.421
	San Jose	1.23 (0.7–2.19)	0.469
	Los Angeles	1.55 (1–2.4)	0.051
	Greater California	1.17 (0.78–1.75)	0.445
	Kentucky	0.73 (0.42–1.25)	0.251
	Louisiana	0.68 (0.4–1.15)	0.152
	New Jersey	0.23 (0.12–0.43)	<0.001
	New Mexico/Georgia/Hawaii	0.55 (0.28–1.06)	0.074
Year (2004)	2005	0.83 (0.7–0.98)	0.033
	2006	0.75 (0.56–1.01)	0.059

95% CI, 95% confidence interval; MIRP, minimally invasive radical prostatectomy; OR, odds ratio; RRP, radical retropubic prostatectomy.

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Comparative effectiveness of cryotherapy vs brachytherapy for localised prostate cancer

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Study Type – Therapy (prospective cohort)
Level of Evidence 2a

What's known on the subject? and What does the study add?
Despite the increased popularity of emerging therapies for localised prostate cancer, such as cryotherapy and brachytherapy, outcomes data remains sparse beyond single-centre comparative studies.

The present study identified that although less costly, cryotherapy was associated with more urinary and ED complications and a greater need for salvage ADT. Conversely, cryotherapy was associated with fewer bowel complications. Patients and providers alike should consider these population-based outcomes when discussing therapeutic options for localised prostate cancer.

OBJECTIVE

- To compare prostate cryotherapy vs brachytherapy outcomes and costs, as despite the greater popularity of these emerging therapies for localised prostate cancer, outcomes data remains sparse beyond single-centre comparative studies.

PATIENTS AND METHODS

- Observational study of 10 928 men who underwent primary cryotherapy (943 patients) or brachytherapy (9985) with ≥2 years of follow-up using USA Surveillance, Epidemiology, and End Results (SEER-) Medicare linked data.
- Weighted propensity score methods were used.

RESULTS

- Use of cryotherapy increased four-fold whereas brachytherapy utilization remained the same from 2001 to 2005 ($P < 0.001$). Men who underwent cryotherapy vs brachytherapy were older ($P < 0.001$), more likely to be Black ($P < 0.001$), less likely to live in areas of higher education ($P < 0.001$), less likely to live in areas with greater income ($P < 0.001$), and were more likely to live in urban vs rural areas ($P = 0.007$).
- In propensity score-weighted analyses, cryotherapy was associated with more urinary (41.4% vs 22.2%, $P < 0.001$) and erectile dysfunction (ED) complications (34.7% vs 21.0%, $P < 0.001$) while brachytherapy was associated with more bowel complications (19.0% vs 12.1%, $P < 0.001$).
- Cryotherapy was associated with greater use of salvage androgen deprivation therapy (ADT; 1.4 vs 0.5 per 100 person-years, $P < 0.001$), suggesting worse cancer control.
- Finally costs were significantly greater for brachytherapy vs cryotherapy ($16 887 vs $12 629 USA dollars, $P < 0.001$).

CONCLUSIONS

- Although less costly, cryotherapy was associated with more urinary and ED complications and greater need for salvage ADT.
- Conversely, cryotherapy was associated with fewer bowel complications. Patients and providers alike should consider these population-based outcomes when discussing therapeutic options for localised prostate cancer.

KEYWORDS

prostate cancer, complications, Surveillance, Epidemiology, and End Results (SEER), cryotherapy, brachytherapy

INTRODUCTION

Prostate cancer remains the most commonly diagnosed non-cutaneous malignancy in USA men with an incidence of ≈192 000 in 2009 [1]. While the use of radical prostatectomy, external-beam radiotherapy and brachytherapy for localised disease remain widespread, cryotherapy has increased in popularity due to potential advantages such as a minimally invasive outpatient approach, reasonable costs, relatively expedient recovery, and preservation of health-related quality of life (HRQL) [2–5]. In terms of technique, cryotherapy is similar to brachytherapy in that both require image guidance with noted technological improvements in both methods. Comparative single-centre studies report equivalent oncological outcomes [6–9]. Moreover, both approaches have a favourable side-effect profile when compared with radical prostatectomy, the most popular therapy for localised prostate

cancer [10]. Malcolm *et al.* [11] reported both brachytherapy and cryotherapy were associated with better urinary and sexual function and less urinary and sexual bother. However, single-centre studies may have patient selection and reporting biases.

There have been few comparative studies of cryotherapy vs brachytherapy [9,11], and there remains an absence of population-based data which characterises outcomes across a broad range of health settings [12]. Moreover, patterns of care and utilization of cryotherapy for localized prostate cancer remain poorly characterised. The aim of our study was to compare prostate cryotherapy vs brachytherapy outcomes and costs.

PATIENTS AND METHODS

We analysed the Surveillance, Epidemiology, and End Results (SEER)-Medicare data, a linkage of population-based cancer registry data from 16 SEER regions covering ≈26% of the USA population with Medicare administrative data. The Medicare programme provides benefits to 97% of Americans aged ≥65 years. The present study was approved by the Brigham and Women's Institutional Review Board: patient data were de-identified and the requirement for consent was waived.

We identified 143 613 men aged ≥65 years who were diagnosed with prostate cancer from 1 January 2001 to 31 December 2005. To increase the specificity for detection of cancer therapy, we restricted our analyses to men diagnosed with prostate cancer as their only cancer, excluding 11 817 men with other cancers. We excluded 39 910 men who were enrolled in a health maintenance organization or who were not enrolled in both Medicare Part A and B at diagnosis (because claims are not reliably submitted for such patients). We identified 13 857 men who underwent primary cryotherapy and brachytherapy from Medicare inpatient, outpatient, and carrier component files (formerly Physician/Provider B files) using Current Procedural Terminology, Fourth Edition (CPT-4) codes and International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) codes as previously described [13]. Men undergoing combined therapies, e.g. brachytherapy with external beam radiation boost, were excluded. Furthermore, 176 men who underwent salvage cryotherapy were excluded. Additionally, 1915 men with clinical stage T4 disease, distant metastasis or insufficient 2-year follow-up were excluded, and 1014 men treated >9 months after diagnosis were excluded resulting in a final cohort of 943 vs 9985 men undergoing cryotherapy vs brachytherapy, respectively.

We examined outcomes consistent with previous studies: urinary morbidity (cystitis, retention, urethral stricture, incontinence, and urethral fistula), bowel morbidity (proctitis/haemorrhage and rectal injury/ulcer), erectile dysfunction (ED) and corresponding invasive procedures [13–15]. All complications were assessed ≤2 years of therapy except for urinary retention, which was assessed ≤30 days of therapy [9]. We also compared salvage androgen-deprivation therapy (ADT), use of ADT >2 years after primary treatment with cryotherapy vs brachytherapy.

Age was obtained from the Medicare file. Race/ethnicity (based on medical record review and supplemented with Hispanic surname matching), census tract measures of median household income and proportion of individuals with at least a high school education, marital status, population density (urban vs rural), geographic region and clinical stage, biopsy tumour grade (well, moderate, and poorly differentiated) and PSA level (normal vs elevated) were obtained from SEER registry data. Comorbidity was captured using the Klabunde modification of the Charlson index using inpatient and outpatient Medicare claims the year before diagnosis [16]. Similarly, we used Medicare diagnoses codes before therapy to characterise baseline incontinence, ED and conditions that may contribute to post-ablation morbidity, e.g. history of TURP [13,17–20].

Use of ADT was captured with corresponding administrative codes [19] and was considered adjuvant if it was initiated during 6 months before until 2 years after therapy. ADT given >2 years post-therapy was considered salvage ADT.

We compared baseline healthcare expenditures in the 6 months before prostate cancer diagnosis for men who underwent cryotherapy vs brachytherapy. To determine the total expense of cryotherapy vs brachytherapy, we summed the total healthcare expenditures for inpatient, outpatient, and physician services within 6 months of prostate cancer diagnosis. We then subtracted baseline healthcare expenditures, allowing subjects to serve as their own controls. Healthcare expenditures included therapies, consultations, imaging and laboratory tests. All costs were adjusted to 2008 USA dollars using the 2007 Annual Report of the Boards of Trustees of the Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Fund [21].

Because men undergoing cryotherapy differed from those undergoing brachytherapy in terms of demographic and tumour characteristics, we used weighted propensity-score methods to adjust for these differences [19,22]. Propensity score methods control for observed differences that might influence both group assignment and outcomes using a single composite measure and attempts to balance patient characteristics between groups [19].

To conduct the propensity score adjustment, we used a logistic regression model to calculate the propensity (probability) of undergoing cryotherapy vs brachytherapy based on all covariates described above and then weighted each subject's data based on the inverse propensity of being in one of the two treatment groups [23]. Covariate balance was checked after adjustment (Table 1). All tests were considered statistically significant at $\alpha = 0.05$.

RESULTS

Use of cryotherapy increased four-fold whereas brachytherapy utilization remained constant during 2001 to 2005 ($P < 0.001$). There were socio-demographic differences among men undergoing cryotherapy vs brachytherapy (Table 1). Men who underwent cryotherapy vs brachytherapy were more likely to be aged >75 years (41.3% vs 31.1%, $P < 0.001$), be Black (12.0% vs 6.3%, $P < 0.001$), less likely to live in areas with at least 90% high school graduates (31.6% vs 39.9%, $P < 0.001$), less likely to have median household income of at least $60 000 (12.8% vs 20.8%, $P < 0.001$), and were more likely to live in urban vs rural areas (11.1% vs 8.9%, $P = 0.020$). Moreover, men undergoing cryotherapy vs brachytherapy were more likely to have

TABLE 1 Demographic and tumour characteristics of the study population

	Before propensity weighting			After propensity weighting		
Variable, *n* (%)	Brachytherapy (*n* = 9985)	Cryotherapy (*n* = 943)	*P*	Brachytherapy	Cryotherapy	*P*
Year of procedure:						
2001	2154 (21.6)	74 (7.9)		2059 (20.6)	166 (17.5)	
2002	2112 (21.2)	148 (15.7)		2040 (20.4)	202 (21.3)	
2003	2056 (20.6)	166 (17.6)	<0.001	2043 (20.5)	205 (21.7)	0.370
2004	1871 (18.7)	266 (28.2)		1914 (19.2)	209 (22.1)	
2005	1792 (18.0)	289 (30.7)		1927 (19.3)	164 (17.3)	
Age, years:						
65–69	3233 (32.38)	218 (23.1)		3154 (31.6)	299 (31.6)	
70–74	3643 (36.48)	336 (35.6)	<0.001	3637 (36.4)	352 (37.2)	0.934
≥75	3109 (31.14)	389 (41.3)		3191 (32)	295 (31.2)	
Charlson comorbidity score:						
0	7534 (75.5)	666 (70.6)		7485 (75)	701 (74.1)	
1	1732 (17.4)	201 (21.3)	0.004	1769 (17.7)	182 (19.2)	0.831
≥2	563 (5.6)	65 (6.9)		575 (5.8)	50 (5.3)	
Unknown	156 (1.6)	11 (1.2)		153 (1.5)	14 (1.5)	
Race:						
White	8496 (85.1)	722 (76.6)		8420 (84.4)	790 (83.5)	
Black	624 (6.3)	113 (12.0)		672 (6.7)	55 (5.9)	
Hispanic	374 (3.8)	47 (5.0)	<0.001	386 (3.9)	44 (4.7)	0.665
Asian	302 (3.0)	31 (3.3)		303 (3)	34 (3.6)	
Other/unknown	189 (1.9)	30 (3.2)		202 (2)	22 (2.3)	
% with high school education:						
<75	1844 (18.5)	232 (24.6)		1897 (19)	181 (19.1)	
75–84.99	2174 (21.8)	248 (26.3)	<0.001	2213 (22.2)	178 (18.8)	0.394
85–89.99	1980 (19.8)	165 (17.5)		1961 (19.6)	192 (20.3)	
≥90	3987 (39.9)	298 (31.6)		3911 (39.2)	396 (41.8)	
Median income, USA $:						
<35 000	3134 (31.4)	396 (42.0)		3223 (32.3)	287 (30.4)	
35 000–44 999	2389 (23.9)	250 (26.5)	<0.001	2412 (24.2)	223 (23.6)	0.796
45 000–59 999	2383 (23.9)	176 (18.7)		2338 (23.4)	229 (24.2)	
≥60 000	2079 (20.8)	121 (12.8)		2009 (20.1)	206 (21.8)	
USA geographic region:						
Northeast	2853 (28.57)	122 (12.94)		2718 (27.2)	255 (26.9)	
South	1928 (19.31)	319 (33.83)	<0.001	2050 (20.5)	172 (18.2)	0.453
Midwest	1085 (10.87)	90 (9.54)		1074 (10.8)	124 (13.1)	
West	4119 (41.25)	412 (43.69)		4141 (41.5)	396 (41.8)	
Population density:						
Urban	9100 (91.1)	838 (88.9)	0.020	9077 (90.9)	879 (92.9)	0.052
Rural	885 (8.9)	105 (11.1)		905 (9.1)	67 (7.1)	
Clinical stage:						
T1	4956 (49.6)	369 (39.1)		4869 (48.8)	467 (49.4)	
T2	4811 (48.2)	530 (56.2)	<0.001	4875 (48.8)	459 (48.5)	0.870
T3/Unknown	218 (2.2%)	44 (4.7)		237 (2.4%)	20 (2.1)	
Tumour grade:						
Well/moderately differentiated	8433 (84.5)	571 (60.6)		8226 (82.4)	780 (82.4)	
Poorly differentiated	1291 (12.9)	338 (35.8)	<0.001	1488 (14.9)	142 (15)	0.970
Unknown/missing	261 (2.6)	34 (3.6)		269 (2.7)	24 (2.6)	
PSA level:						
Elevated	7051 (70.6)	641 (68.0)		7027 (70.4)	676 (71.4)	
Normal	817 (8.2)	65 (6.9)	0.012	805 (8.1)	71 (7.5)	0.890
Unknown	2117 (21.2)	237 (25.1)		2151 (21.5)	199 (21)	
ADT:						
No	5720 (57.3)	537 (57.0)	0.840	5710 (57.2)	519 (54.9)	0.376
Yes	4265 (42.7)	406 (43.1)		4272 (42.8)	427 (45.1)	
Incontinence diagnosis:						
No	9772 (97.9)	909 (96.4)	0.004	9759 (97.8)	924 (97.7)	0.892
Yes	213 (2.1)	34 (3.6)		223 (2.2)	22 (2.3)	
ED diagnosis:						
No	9018 (90.3)	840 (89.1)	0.221	9006 (90.2)	854 (90.3)	0.964
Yes	967 (9.7)	103 (10.9)		976 (9.8)	92 (9.7)	
Prior TURP:						
No	9777 (97.9)	894 (94.8)	<0.001	9739 (97.6)	921 (97.4)	0.716
Yes	208 (2.1)	49 (5.2)		243 (2.4)	25 (2.6)	

TABLE 2 Incidence of complication diagnoses and invasive procedures

	Complication diagnosis			Invasive procedures for complications			Either complication diagnosis or invasive procedure		
Complications, *n* (%)	Cryotherapy (*n* = 943)	Brachytherapy (*n* = 9985)	*P*	Cryotherapy (*n* = 943)	Brachytherapy (*n* = 9985)	*P*	Cryotherapy (*n* = 943)	Brachytherapy (*n* = 9985)	*P*
Overall	613 (65.0)	4871 (48.8)	<0.001	188 (19.9)	1343 (13.5)	<0.001	623 (66.1)	5175 (51.8)	<0.001
Urinary:	370 (39.2)	2197 (22.0)	<0.001	134 (14.2)	1120 (11.2)	0.006	392 (41.6)	2614 (26.2)	<0.001
Cystitis*	<11	237 (2.4)	0.001	<11	<11	N/A	<11	242 (2.4)	0.001
Retention	198 (21.0)	831 (8.3)	<0.001	64 (6.8)	302 (3.0)	<0.001	212 (22.5)	958 (9.6)	<0.001
Urethral stricture	49 (5.2)	371 (3.7)	0.024	58 (6.2)	609 (6.1)	0.950	72 (7.6)	695 (7.0)	0.438
Incontinence	182 (19.3)	1116 (11.2)	<0.001	39 (4.1)	306 (3.1)	0.072	197 (20.9)	1268 (12.7)	<0.001
Urethral fistula*	<11	27 (0.3)	0.003	<11	<11	0.037	<11	27 (0.3)	0.003
Bowel	116 (12.3)	1910 (19.1)	<0.001	<11	148 (1.5)	0.300	121 (12.8)	1974 (19.8)	<0.001
Proctitis/haemorrhage*	111 (11.8)	1867 (18.7)	<0.001	<11	23 (0.2)	0.436	111 (11.8)	1880 (18.8)	<0.001
Rectal injury/ulcer	12 (1.3)	200 (2.0)	0.120	<11	130 (1.3)	0.363	21 (2.2)	309 (3.1)	0.137
ED	331 (35.1)	2102 (21.1)	<0.001	55 (5.8)	116 (1.2)	<0.001	332 (35.2)	2114 (21.2)	<0.001

**Actual numbers not presented because the National Cancer Institute precludes the reporting of table cells of n < 11.*

TABLE 3 Propensity-weighted incidence of complication diagnoses and invasive procedures (calculations expressed as percentages)

	Diagnosis			Invasive procedures for complications			Either complication diagnosis or invasive procedure		
Characteristic, %	Cryotherapy (*n* = 943)	Brachytherapy (*n* = 9985)	*P*	Cryotherapy (*n* = 943)	Brachytherapy (*n* = 9985)	*P*	Cryotherapy (*n* = 943)	Brachytherapy (*n* = 9985)	*P*
Overall	63.6	48.8	<0.001	18.9	13.5	0.005	64.3	51.9	<0.001
Urinary:	41.4	22.2	<0.001	13.6	11.3	0.161	43.3	26.4	<0.001
Cystitis	0.5	2.4	<0.001	Not available due to the small number			0.5	2.5	0.500
Retention	24.5	8.4	<0.001	7.1	3.1	0.002	25.6	9.7	<0.001
Urethral stricture	5.4	3.7	0.190	6.0	6.1	0.941	7.6	6.9	0.630
Incontinence	18.2	11.3	<0.001	3.2	3.1	0.829	19.5	12.8	0.001
Urethral fistula	0.9	0.3	0.1445	0.1	0.0	0.354	0.9	0.3	0.145
Bowel	12.1	19.0	<0.001	1.0	1.5	0.329	12.6	19.7	<0.001
Proctitis/haemorrhage	11.7	18.6	<0.001	0.1	0.2	0.011	11.7	18.7	<0.001
Rectal injury/ulcer	0.8	2.0	<0.001	1.0	1.3	0.486	1.8	3.0	0.027
ED	34.7	21.0	<0.001	5.4	1.2	<0.001	34.8	21.1	<0.001
Additional hormonal therapy (per 100 person-years)	1.4	0.5	<0.001						

higher grade (35.8% vs 12.9%, $P < 0.001$) and clinical stage T3/unknown disease (4.7% vs 2.2%, $P < 0.001$). There was significant geographical variation in utilization, with greater utilization of cryotherapy and brachytherapy in the West (43.7% vs 41.3%, $P < 0.001$).

Unadjusted complication outcomes are presented in Table 2. Men undergoing cryotherapy vs brachytherapy had more overall complications (65.0% vs 48.8%, $P < 0.001$) and corrective invasive procedures (19.9% vs 13.5%, $P < 0.001$). Overall rates of urinary, bowel and ED complications were 39.2%, 12.3% and 35.1% for cryotherapy vs 22.0%, 19.1% and 21.1% for brachytherapy (all $P < 0.001$). Men undergoing cryotherapy vs brachytherapy were more likely to experience urinary retention (21.0% vs 8.3%, $P < 0.001$) and urinary incontinence (19.3% vs 11.2%, $P < 0.001$). Moreover, men undergoing cryotherapy were more likely to undergo procedures for postoperative urinary retention (6.8% vs 3.0%, $P < 0.001$) and ED (5.8% vs 1.2%, $P < 0.001$).

Propensity adjusted analyses are presented in Table 3. Men undergoing cryotherapy vs brachytherapy were more likely to experience complications (64.6% vs 48.8%, $P < 0.001$), undergo corrective procedures (18.9% vs 13.5%, $P = 0.005$) and have either complication diagnosis or invasive procedure (64.3% vs 51.9%, $P < 0.001$). While cryotherapy was associated with more

TABLE 4 Medicare costs of cryotherapy vs brachytherapy

	Cryotherapy	Brachytherapy	*P*
Median (interquartile range):			
Baseline healthcare expenditures 12 months prior to prostate cancer diagnosis, $	1 941 (852–4 718)	1 799 (736–4 123)	<0.001
12 Months post-diagnosis healthcare expenditures*	15 146 (11 718–21 031)	19 398 (14 336–26 431)	<0.001
Difference between post and prior	12 629 (9 163–17 663)	16 887 (11 913–23 474)	<0.001

**We excluded men who underwent cryotherapy or brachytherapy >3 months after prostate cancer diagnosis to ensure that we fully captured the expense associated with treatments.*

urinary complication diagnoses (41.4% vs 22.2%, $P < 0.001$), brachytherapy was associated with more bowel complications (19.0% vs 12.1%, $P < 0.001$). Additionally, cryotherapy was associated with more ED complication diagnoses (34.7% vs 21.0%, $P < 0.001$) and invasive corrective procedures (5.4% vs 1.2%, $P = 0.001$). In adjusted analysis, cryotherapy was associated with greater use of salvage ADT (1.4 vs. 0.5 per 100 person-years, $P < 0.001$).

While median baseline healthcare expenditures (USA dollars) in the 6 months before prostate cancer diagnosis were significantly higher for cryotherapy vs brachytherapy ($1941 vs $1799, $P < 0.001$), median healthcare costs 6 months after prostate cancer diagnosis were higher for brachytherapy ($15 146 vs $19 398, $P < 0.001$) (Table 4). Therefore the costs attributable to cryotherapy vs brachytherapy were ($12 629 vs $16 887, $P < 0.001$).

DISCUSSION

The optimal treatment for prostate cancer should balance both cancer control and minimise morbidity [24]. As a minimally invasive approach, cryotherapy was developed to preserve HRQL as well as provide comparable cancer control relative to competing therapies. Prior studies of cryotherapy complications have largely been single-institutional experiences [2,8,25] that lacked standard definitions of complications, and variable follow-up. Moreover, few studies have directly compared cryotherapy vs other treatment outcomes [11]. As population-based outcomes for cryotherapy remain largely unknown, both the European Association of Urology and the AUA prostate cancer guidelines designate cryotherapy as investigational [9,12].

SEER-Medicare data has many advantages for population-based clinical research; previous studies show this data to have high quality and be representative of the USA population [26]. Medicare claims have a high degree of validity for detecting complications with 89% of Medicare complications corroborated by medical record abstraction, and have been used by previous studies to measure complications after surgery and radiation therapy for prostate cancer [13,19,27].

The present study has several important findings. First, cryotherapy was associated with more urinary complications than brachytherapy. Because the freezing process originates in the prostate and extends to the urethra, cryotherapy urinary complication rates were higher, especially during early introduction [9]. With technical refinement such as improved ultrasonographic localisation and the routine use of urethral warmers, outcomes have improved [9]. Hubosky *et al.* [28] examined HRQL measures in men undergoing third-generation cryotherapy vs brachytherapy and found less irritative and obstructive symptoms with cryotherapy. However, urinary complications remained more likely after cryotherapy during the present study period.

Second, cryotherapy vs brachytherapy was more likely to result in more post-procedure ED diagnoses. Similarly a previous study found brachytherapy vs cryotherapy to be associated with better sexual function and lower sexual bother [11]. During cryotherapy, the neurovascular bundles may become damaged when the prostate apex and the periprostatic tissues are affected by the ice ball [29]. Similarly, Hubosky *et al.* [28] reported brachytherapy vs cryotherapy ED rates of 20% vs 56%.

Third, men undergoing cryotherapy vs brachytherapy were less likely to experience bowel complications, consistent with reported rates of <0.5% [15]. Prostate brachytherapy may lead to chronic radiation proctitis because the rectum, fixed in position and close to the prostate, may receive a large radiation dose during brachytherapy. Additionally, the incidence of chronic radiation proctitis has increased over the past few years paralleling increased utilization of prostate cancer radiation therapy [30].

Fourth, cryotherapy vs brachytherapy was associated with more use of salvage ADT, indicating inferior cancer control. Because the definition for biochemical recurrence after cryotherapy remains imprecise [9], ADT use after therapy serves as an indicator of treatment failure. Causes for local failure after cryotherapy and brachytherapy may be attributed to inappropriate patient selection and difficulty in achieving a geometrically appropriate distribution of temperature or dose within the prostate gland [31,32]. While Stone *et al.* [33] reported 7.7% of men with brachytherapy had a positive biopsy within 2–11 years after implantation, Cohen *et al.* [34] reported a 23%, 10-year positive biopsy rate after primary cryotherapy.

Finally, healthcare expenditures were ≈$4000 greater for brachytherapy vs cryotherapy. To our knowledge, there has not been a direct cost comparison of these two treatment methods. Hummel *et al.* [35] analysed cost effectiveness for localised treatments for prostate cancer taking into account HRQL and found cryotherapy to be inferior to other treatments due to a greater likelihood of ED.

The present findings must be interpreted within the context of the study design. First,

Medicare claims are designed to provide billing information, not detailed clinical information. The diagnosis and invasive procedure codes we used for urinary, bowel and ED may not be as sensitive or specific as the use of patient self-assessment with validated instruments [36]. Complications that affect HRQL but do not necessitate seeking medical attention may not be captured from Medicare claims. Second, our Medicare treatment costs are probably lower than expenditures by private health plans. However, given the greater likelihood of urinary and ED complications and greater use of salvage ADT associated with cryotherapy, it was not a cost-effective treatment option relative to brachytherapy. Furthermore, we captured adjuvant ADT costs, but did not capture salvage ADT costs and costs associated with treatment failure in the discussion. Finally, this is an observational study of outcomes for men aged ≥65 years undergoing cryotherapy and brachytherapy in SEER regions. The present findings may not be generalizable to younger men and those undergoing treatment outside SEER regions.

In conclusion, while the popularity of cryotherapy increased during our study period, men undergoing cryotherapy vs brachytherapy were more likely to experience urinary and ED complications and require salvage ADT, but less likely to experience bowel-related complications. However, cryotherapy was ≈$4000 cheaper than brachytherapy. Patients and providers alike should consider these population-based outcomes when discussing therapeutic options for localised prostate cancer.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **HRQL**, health-related quality of life; **SEER**, Surveillance, Epidemiology, and End Results; **ED**, erectile dysfunction; **ADT**, androgen-deprivation therapy.

Determinants of Performing Radical Prostatectomy Pelvic Lymph Node Dissection and the Number of Lymph Nodes Removed in Elderly Men

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OBJECTIVE Controversy persists regarding the adequacy of pelvic lymph node dissection (PLND) and cancer control when comparing minimally invasive radical prostatectomy (MIRP) and open radical prostatectomy (RRP). We characterized determinants of performance and extent of PLND during radical prostatectomy in elderly men.

METHODS A population-based study was conducted comprised of 5448 men ≥65 years undergoing RRP and MIRP during 2004 to 2006 from Surveillance, Epidemiology, and End Results (SEER)–Medicare-linked data. Multivariable logistic regression was used to assess the effect of demographic and tumor characteristics, surgical approach, and surgeon volume on the likelihood of performing PLND.

RESULTS PLND was performed for 87.6% vs. 38.3% of men undergoing RRP vs. MIRP ($P < .001$). Among RRP, 82.6% vs. 4.6% underwent extended vs. limited PLND, with a median yield of 4 vs. 3 lymph nodes ($P < .001$). Median MIRP PLND yield was 3 lymph nodes. In adjusted analyses, men undergoing RRP vs. MIRP (odds ratio [OR] 16.7; 95% confidence interval [CI], 11.1-25.0), those with few vs. multiple comorbidities (OR 1.4, 95% CI 1.02-1.91), intermediate (OR 1.87; 95% CI 1.48-2.37), and high (OR 2.77; 95% CI 2.02-3.78) vs. low-risk features, and men treated by high-volume surgeons (OR 1.008; 95% CI 1.004-1.011) were more likely to undergo PLND. Conversely, Hispanic (OR 0.68, 95% CI 0.49-0.96) vs. white men were less likely to undergo PLND.

CONCLUSIONS Independent of tumor characteristics, men undergoing RRP vs. MIRP were more likely to undergo PLND with greater lymph node yield and racial variation observed. Further studies are needed to determine the appropriate use of PLND. UROLOGY 77: 402–406, 2011. © 2011 Elsevier Inc.

As surgical evolution unfolds with a shift from open radical prostatectomy (RRP) to minimally invasive radical prostatectomy (MIRP), debates persist regarding the adequacy of pelvic lymph node dissection (PLND) and cancer control. The promise of imaging techniques for accurate staging remains unfulfilled, and PLND remains the most accurate and reliable staging method for detecting occult prostate cancer metastases.[1] Moreover, with greater enthusiasm for extended versus limited PLND, unanswered questions linger concerning the adequacy of PLND during MIRP vs. RRP.

The incidence of lymph node metastases has plummeted from the 40% to 20% range[2,3] before prostate-specific antigen (PSA) screening and resultant stage migration to current levels of 1.2%, with limited and 3.3% to 6.5% with extended PLND at high-volume referral centers.[4,5] Moreover, there is considerable guideline variation concerning indications and anatomic extent of PLND: (1) PLND, extent unspecified, for high risk disease[6]; (2) extended PLND for those with ≥7% predicted risk of involvement[7]; or (3) extended PLND for intermediate- and high-risk disease features.[8] In addition, there is considerable practice pattern variation by surgical approach, because a recent nationwide study demonstrated significant disparity in the use of PLND in 83% of RRP vs. only 17% of MIRP,[9] although the study design precluded assessment of the influence of tumor characteristics on PLND used. Finally, extended PLND has been

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associated with an increased risk of complications[5] and longer hospital stays, and therefore carry the potential of increased morbidity and costs.[10]

The purpose of our population-based study was to: (1) determine clinical and pathologic characteristics associated with performing PLND during RP; and (2) assess the variation in yield and morbidity of PLND by surgical approach, surgeon volume, and extent of dissection.

SUBJECTS AND METHODS

Data

We used Surveillance, Epidemiology, and End Results (SEER)–Medicare data, which is a collaborative effort[11] between the U.S. National Cancer Institute (NCI), which collects population-based cancer registry data from 16 SEER areas covering approximately 26% of the U.S. population with Medicare administrative data from the Center for Medicare and Medicaid Services (CMS). Medicare serves as the primary payer of health insurance for elderly Americans, and surgeons must use *Current Procedural Terminology Coding System*, 4th edition (CPT-4) codes to designate medical procedures to be reimbursed.

Study Cohort

We identified men aged ≥65 years diagnosed with prostate cancer from 2004 to 2005 undergoing radical prostatectomy from 2004 to 2006 (n = 5448) using CPT-4 55840, 55842, and 55845 for RRP without, with limited, and with extended PLND; 55866 for MIRP alone; and 55866 and 38571 for MIRP with PLND. The dependent variable of our analysis was concurrent PLND with radical prostatectomy. Although CPT-4 code 38770 may be used to capture open PLND, it failed to yield additional subjects who underwent PLND at the time of prostatectomy. Moreover, we excluded perineal radical prostatectomy, because it accounted for <5% of all radical prostatectomies performed during our study period. Finally, CPT-4 code 55899 (unspecified male genitourinary procedure) may be used to specify MIRP with robotic assistance for private health plans,[12] but Medicare does not recognize this coding schema and it was therefore excluded. Finally, we excluded men not fully enrolled in Medicare or simultaneously enrolled in health maintenance organizations (because their claims are not reliably submitted).

Study Variables

Age was obtained from the Medicare file; race, census-tracked measures of median household income and proportion of individuals with at least a high school education, SEER region, population density (urban vs. rural), marital status, and tumor characteristics were obtained from the SEER registry data (Table 1). Comorbidity was assessed using the Klabunde modification of the Charlson index during the year before surgery.[13] SEER regions were grouped as Northeast, Midwest, South, and West, consistent with the U.S. Census. In addition, PSA, Gleason grade, and clinical stage were used to stratify men according to the D'Amico risk criteria.[14]

We determined surgeon volume for each type of procedure by aggregating the number of procedures performed from 2004 to 2006. Although assessing surgeon volume as a categorical variable allows for more intuitive clinical interpretability and comparisons, surgeon experience is acquired one case at a time. Therefore, we assessed surgeon volume both categorically and continuously. Initially, we analyzed MIRP and RRP surgeon volume categorically as quartiles. However, this classification resulted in <10 MIRP surgeons in the highest-volume category and the NCI precludes the reporting of small cell sizes because of confidentiality concerns. We therefore re-stratified into tertiles, resulting in 11 MIRP and 81 RRP surgeons in the high-volume groups. Classifying surgeon volume into tertiles vs. quartiles did not alter the direction or significance of our findings.

Statistical Analysis

Unadjusted analysis was performed to compare demographic and tumor characteristics and surgeon volume using the Pearson χ^2 statistic, adjusting for clustering by surgeon. Adjusted analysis with logistic regression was performed to determine the likelihood of performing PLND while controlling for the potential confounder of surgeon volume as a continuous variable, surgical approach, risk stratification, age, comorbidities, race, and region. All tests were considered statistically significant at $\alpha = 0.05$. All analyses were performed with SAS version 9.1.3 (SAS Institute, Cary, NC).

RESULTS

The demographics of our study population are shown in Table 1. Wealthier men (P = .023) and those living in urban vs. rural areas (P = .032) were less likely to undergo PLND. There was a trend for men with fewer comorbidities to be more likely to undergo PLND (P = .056). Men with higher PSA, Gleason grade, and clinical stage were more likely to undergo PLND (P <.001, respectively). Accordingly, 998 (65.6%) of men with low-, 1761 (75.8%) of men with intermediate-, and 1064 (82.1%) of men with high-risk disease underwent PLND (P <.001).

When stratified by surgical approach (Table 2), PLND was performed more frequently with RRP vs. MIRP (87.6% vs. 38.3%, P <.001). Moreover, PLND was performed more frequently by high-volume MIRP and RRP surgeons (P <.001). Although there was less variation in using PLND between high- vs. low-volume RRP surgeons (88.4% vs. 84.9%), high- vs. low-volume MIRP surgeons were almost twice more likely to perform PLND (55.0% vs. 23.2%). In addition, one more lymph node was removed with RRP vs. MIRP (median 4 vs. 3, P <.001), with a trend toward a higher positive lymph node rate (2.5% vs. <1.5%, P = .057).

Among men undergoing RRP, 82.6% vs. 4.6% underwent an extended vs. limited PLND with a median of 4 vs. 3 lymph nodes removed (P = .032). We also examined complications attributable to PLND, such as lymphoceles, obturator nerve injury, and ureteral injury; however, these were uncommon events (<1%, respectively) and did not differ by surgical approach or by extent of PLND (limited vs. extended) during RRP. Furthermore, length of stay was 2 days for RRP and 3 days for MIRP and did not vary based on extent and performance of PLND.

Table 1. Demographic and tumor characteristics stratified by use of PLND

Variable	No PLND (n = 1415)		PLND (n = 4033)		*P* Value*
	n	%	n	%	
Year of surgery					
2004	455	32.2	1716	42.6	<.001
2005	759	53.6	1903	47.2	
2006	201	14.2	414	10.3	
Age (years)					
65-69	881	62.3	2498	61.9	.230
70-74	449	31.7	1237	30.7	
75+	85	6.0	298	7.4	
Charlson index					
0	999	70.6	2762	68.5	.056
1	315	22.3	1021	25.3	
2+	101	7.1	250	6.2	
Race					
White	1122	79.3	3220	79.8	.99
Black	100	7.1	293	7.3	
Hispanic	114	8.1	307	7.6	
Asian	60	4.2	164	4.1	
Marital status					
Not married	208	14.7	587	14.6	.179
Married	1105	78.1	3233	80.2	
Unknown	102	7.2	213	5.3	
% Of men with at least a high school education					
<75	256	18.1	751	18.6	.191
75-84.99	255	18.0	774	19.2	
85-89.99	246	17.4	802	19.9	
90+	657	46.5	1706	42.3	
Median income (USD)					
<35,000	335	23.7	1151	28.5	.023
35,000-44,999	313	22.1	935	23.2	
45,000-59,999	376	26.6	987	24.5	
≥60,000	390	27.6	960	23.8	
Region					
Northeast	180	12.7	433	10.7	.510
South	177	12.5	611	15.2	
Midwest	221	15.6	506	12.6	
West	837	59.2	2483	61.6	
Location					
Urban	1334	94.3	3694	91.6	.032
Rural	81	5.7	339	8.4	
PSA					
≤4	208	14.7	515	12.8	<.001
4.1-10	887	62.7	2294	56.9	
10.1-20	106	7.5	534	13.2	
>20	37	2.6	230	5.7	
Unknown	177	12.5	460	11.4	
Gleason score					
≤6	671	47.4	1407	34.9	<.001
7	616	43.5	1991	49.4	
8	73	5.2	348	8.6	
9/10†	34	2.4	251	6.2	
Clinical stage					
T1	791	55.9	1982	49.1	.006
T2	215	15.2	738	18.3	
T3+T4	16	1.1	83	2.1	
Unknown	393	27.8	1230	30.5	
D'Amico risk					
Low	524	37.0	998	24.8	<.001
Intermediate	563	39.8	1761	43.7	
High	232	16.4	1064	26.4	
Unknown	96	6.8	210	5.2	

* *P* values adjusted for clustering.
† Gleason 9 and 10 scores combined in compliance with NCI confidentiality policy.

Table 2. Use and yield of pelvic lymph node dissection by surgical approach and surgeon volume

	MIRP		RRP		
	n	%	n	%	*P* Value
PLND performed	573	38.3	3460	87.6	<.001
Surgeon volume					
Low	118	23.2	1133	84.9	<.001
Medium	174	36.4	1238	89.5	
High	281	55.0	1089	88.4	
Number of LN removed					
1-3	211	36.8	1030	29.8	.005
4-7	182	31.7	915	26.5	
≥7	68	11.9	836	24.2	
Unknown	112	19.5	679	19.5	
Median LN removed	3		4		<.001

LN = lymph node.

Table 3. Logistic regression model for use of pelvic lymph node dissection

Variable	OR	95% CI	*P* Value
Age (referent = 75+)			
65-69	0.92	0.68-1.24	.569
70-74	0.88	0.64-1.22	.446
Charlson Index (referent = 2+)			
0	1.3	0.99-1.7	.061
1	1.4	1.02-1.91	.038
Race (referent = White)			
Black	0.8	0.47-1.34	.393
Hispanic	0.68	0.49-0.96	.026
Asian	1.38	0.77-2.46	.275
D'Amico risk (referent = low)			
intermediate	1.83	1.44-2.32	<.001
High	2.57	1.94-3.4	<.001
Region (referent = West)			
Northeast	1.18	0.77-1.82	.438
South	1.23	0.69-2.22	.483
Midwest	1.12	0.58-2.16	.743
Surgical approach (referent = MIRP)			
RRP	16.7	11.1-25.0	<.001
Surgeon volume (continuous)	1.008	1.004-1.011	<.001

In adjusted analysis (Table 3), men undergoing RRP vs. MIRP had 16 times greater odds of undergoing PLND (odds ratio [OR] 16.7, 95% confidence interval [CI] 11.1-25.0). Greater surgeon volume was associated with performing PLND (OR 1.008, 95% CI 1.004-1.011). In addition, intermediate- (OR 1.9, 95% CI 1.48-2.37) and high- (OR 2.77, 95% CI 2.02-3.78) vs. low-risk features increased the odds of performing PLND by almost 2- and 3-fold. Moreover, men with few (OR 1.40, 95% CI 1.02-1.91) vs. multiple comorbidities were more likely to undergo PLND. Finally, Hispanic vs. white men were less likely to undergo PLND (OR 0.68, 95% CI 0.49-0.96).

DISCUSSION

Indication and appropriate extent of PLND during radical prostatectomy remains controversial. Although PLND improves staging, prostate cancer metastasizes unpredictably, and PSA criteria are used to define recurrence and initiate adjuvant therapies in contrast to other malignancies that require surveillance imaging and lack a tumor marker. Allaf *et al.* suggested that extended vs. limited PLND leads to better cancer control.[4] Although extended vs. limited PLND were designated during 83.2% vs. 4.9% of RRP, it yielded only 1 additional lymph node on average (mean yield of 5.9 vs. 4.6 lymph nodes) in contrast to referral center yields of 11.6 vs. 8.9 nodes for extended vs. limited PLND.[4] Medicare reimbursed an additional $292 and $92, respectively, for extended and limited PLND vs. RRP alone,[15] and our population-based findings suggest that financial incentives may be driving practice patterns. Although less than a quarter of men presented with high-risk disease, almost three quarters underwent PLND, and positive lymph nodes were identified in <2% of the study population.

Our study has additional important findings. First, use of PLND was significantly greater during RRP vs. MIRP. This difference likely reflects greater surgeon inexperience with MIRP, because of the more recent dissemination, vs. RRP. Although MIRP PLND was used for 25% vs. 43% of men with low- vs. intermediate-risk disease, RRP PLND was used for 83% vs. 89% of men with low- vs. intermediate-risk disease. This suggests that PLND was overused for low- and intermediate-risk disease compared with certain guidelines.[6,7] However, men with high- and intermediate- vs. low-risk disease had greater odds of undergoing PLND. Although some have reported similar lymph node yields for RRP and MIRP,[16] others report higher lymph node yield with RRP vs. MIRP,[17] consistent with our population-based findings of 1 more lymph node removed with RRP vs. MIRP PLND.

Second, greater surgeon volume was associated with greater likelihood for performing PLND independent of surgical approach and tumor characteristics. This finding likely reflects inexperienced surgeons either forgoing PLND, because of increased risk of complications or prolonged operative times. Moreover, men with few vs. multiple comorbidities were more likely to undergo PLND, likely because of lower surgeon-perceived risk for complications in healthier men.[9]

Third, the risk of PLND-associated complications, such as obturator nerve and ureteral injury and lymphoceles, did not vary by surgical approach or extent of PLND during RRP. In contrast, others have reported higher complications and longer hospitalizations with extended vs. limited PLND.[5,10] However, there were greater differences in lymph node yields for extended vs. limited RRP PLND, indicating more aggressive extended PLND templates at these referral centers compared with our population-based difference of 1 lymph node between

extended vs. limited RRP PLND. Therefore, similar yields from limited vs. extended RRP PLND in our study likely resulted from similar dissection templates and resultant complications, despite differences in billing designation and Medicare reimbursement. Moreover, despite descriptions of lymph node dissection templates,[4,18] there is tremendous heterogeneity of radical prostatectomy surgical technique, and our population-based findings accentuate the need to reconcile PLND operative yield with billing designation.

Finally, Hispanic vs. white men were less likely to undergo PLND; however, disparity in PLND use was not observed for other races. Similarly, Hispanic vs. white and black men are less likely to undergo definitive therapy for prostate,[19] and the lower use of PLND among Hispanics may stem from patient rather than physician preferences. Conversely, racial differences in access to procedures, such as percutaneous transluminal coronary angioplasty and coronary artery bypass grafting have been observed for Hispanics.[20] However, our observational study does not allow us to determine whether PLND disparity for Hispanics stems from patient preference vs. limited access imposed by providers.

Our findings must be interpreted in the context of our study design. First, our study was limited to Medicare beneficiaries aged ≥65 years in SEER regions. Therefore, our results may not be generalizable to younger men or those undergoing surgery outside SEER regions. Second, we were unable to differentiate MIRP with vs. without robotic assistance because both share a common CPT-4 code. However, a recent survey revealed a 25% to 75% decline in surgeon volume among urologists using MIRP without robotic assistance.[21] Third, although SEER tumor registry provided tumor characteristics, the number of lymph nodes removed was not recorded for 19.5% of our study cohort. Finally, variation in specimen submission and pathologic interpretation may influence our findings. However, this also limits comparisons and generalizations between single-center studies.

CONCLUSIONS

Independent of tumor characteristics, elderly men undergoing RRP vs. MIRP were more likely to undergo PLND, with greater lymph node yield and racial variation observed. Further studies are needed to determine the appropriate use of PLND for elderly men with prostate cancer.

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Patterns of care and outcomes of radiotherapy for lymph node positivity after radical prostatectomy

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Objective

- To evaluate the use and outcomes of adjuvant radiation therapy (ART) for men with lymph node (LN)-positive disease after radical prostatectomy (RP) using a population-based approach.

Patients and Methods

- Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data from 1995 to 2007 was used to identify 577 men with LN metastases discovered during RP and absence of distant metastases, of which 177 underwent ART ≤1 year of RP.
- Propensity score models were used to compare overall mortality and prostate cancer-specific mortality (PCSM) for men that did and those that did not receive ART.

Results

- Men in both groups received adjuvant androgen-deprivation therapy at similar rates after propensity weighting adjustments (33.6% vs 33.7%, P = 0.977).
- ART was not associated with differences in overall (5.09 vs 3.77 events per 100 person-years, P = 0.153) or PCSM (2.89 vs 1.31, P = 0.090) relative to men who did not receive ART.

Conclusions

- ART after RP in men with LN-positive prostate cancer was not associated with improved overall or disease-specific survival, in contrast to previous single-centre studies.
- Prospective randomised studies are needed to assess the effectiveness of ART in this patient population.

Keywords

prostate cancer, radical prostatectomy, radiation therapy, outcomes

Introduction

Lymph node (LN) metastases are discovered in as many as 8–10% of men with presumed clinically localised prostate cancer at the time of radical prostatectomy (RP) and LN dissection [1,2]. These men can develop symptomatic local progression within a median of 18–24 months after RP [3]. Adjuvant radiation therapy (ART) has been shown to improve biochemical-free survival and metastasis-free survival in men with locally advanced (pT3N0) prostate cancer without LN metastasis [4–6], but optimal treatment after RP for men with LN metastases discovered at the time of RP remains unclear. In a seminal randomised controlled trial, Messing et al. [7] showed that androgen-deprivation therapy (ADT) confers a survival advantage in these patients. The study was limited by a small sample of 98 patients.

For radiation use in this patient population, Johnstone et al. [8] conducted a Surveillance, Epidemiology, and End Results (SEER) database analysis comparing RP alone to RP plus ART for patients with LN-positive disease and found no survival benefit for ART. In contrast, observational data presented by Da Pozzo et al. [9] suggested that the use of ART in these men is associated with improved biochemical recurrence-free survival as well as cancer-specific survival, while Briganti et al. [10] showed that ART combined with ADT vs ADT alone was associated with both overall and

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cancer-specific survival benefits. However, these studies were performed at centres of excellence and community wide practice patterns and outcomes remain unclear. In addition, subjects enrolled in clinical trials may differ from the general population, and results generated from these populations may not be applicable to the population as a whole [11]. Based on these considerations, we compared outcomes for ART vs no ART after RP for men with LN metastases in a population-based sample of 577.

Patients and Methods

The Brigham and Women's Institutional Review Board approved our study. Patient data was de-identified and the consent requirement was waived. Data were obtained from the SEER-Medicare database, comprised of a linkage of population-based cancer registries from 20 SEER areas covering ≈28% of the USA population with Medicare administrative data [12]. Medicare provides healthcare benefits to most Americans aged ≥65 years. SEER-Medicare captures ≈97% of incident cancer cases and collects data such as patient demographics, tumour characteristics, and initial course of treatment [13].

Study Cohort

We identified 32 419 men aged ≥65 years diagnosed with prostate cancer as their only malignancy and treated with RP from 1995 to 2007, and we identified men undergoing RPs using Current Procedural Terminology, 4th edition (CPT-4) [14]. Men were excluded if they were diagnosed at autopsy or had Medicare entitlement due to end-stage renal disease. Men not continually enrolled in Medicare A and B were excluded as their claims data may be incomplete (354 men). We further limited our cohort to those with metastatic LN(s) staged during RP (577 men) not receiving palliative RT (46 excluded). We then identified men receiving ART (177 men) ≤1 year of RP, consistent with prior methods [15].

Independent Variables

Age (65–69, 70–75, >75 years) data were extracted from the Medicare denominator file. Demographic information including race (White/non-Hispanic, Black/non-Hispanic, Hispanic, Asian/non-Hispanic), marital status, education level, median income, geographic region, population density (metropolitan vs non-metropolitan) was obtained from SEER. The Klabunde modification of the Charlson index was used to characterise comorbid conditions based on inpatient, outpatient, and physician services in the year before RP.

Dependent Variables

Grade was defined as well/moderately differentiated (Gleason ≤7) vs poorly differentiated (Gleason 8–10). Pathological stage was defined as T2, T3a, T3b, T4, or unknown. The preoperative PSA was categorised within SEER as elevated, normal, or unknown. The median number of LNs examined and median number of positive LNs were recorded by SEER and used to calculate LN density. Finally, use of adjuvant ADT ≤1 year after RP was recorded.

Outcomes

Primary outcomes measured from time of RP were provided be SEER and included overall mortality and prostate cancer-specific mortality (PCSM).

Statistical Analysis

Univariate differences between cohorts were compared using chi-squared tests. Propensity score models were used to control for potential confounding factors that can affect group assignment and outcomes while attempting to balance variation of patient characteristics between groups. Logistic regression models were used to calculate the probability (propensity) of receiving ART vs not receiving ART considering all covariates described above, weighted against each patient's likelihood of being in one of the two groups [16,17]. As the primary outcomes analysed (overall mortality and PCSM) do not have an upper time limit and duration of follow-up varied, we compared the number of events per 100 person-years of follow-up between groups. P values were two-sided and $P \leq 0.05$ was considered to indicate statistical significance.

Results

Baseline demographics and tumour characteristics before and after propensity weighting are presented in Table 1. The median income, geography, education, marital status, and population density were similar between groups. ART was used more frequently in the late study period. Additionally, ART was used more frequently in the South and less in the Northeast, while rates in the West and Midwest were similar. Before propensity weighting, men undergoing ART were more likely to have an elevated preoperative PSA level (74.1% vs 66.0%, $P = 0.008$) and poorly differentiated tumours (81.4% vs 71.7%, $P = 0.014$), but after propensity weighting this difference was not observed. After propensity weighting, men undergoing ART received adjuvant ADT at similar rates as those men not undergoing ART ($P = 0.977$). There was no difference in preoperative ADT use or LN density in ART vs non-ART men.

Table 2 compares mortality after RP in the ART vs non-ART cohorts. There were no differences in overall

Table 1 Baseline patient demographics, tumour characteristics and LN pathology.

Variable	Before propensity weighting			After propensity weighting		
	No RT (%)	ART (%)	*P*	No RT (%)	ART (%)	*P*
Year of diagnosis:			0.011			0.616
1995–1999	111 (27.8)	29 (16.4)		99 (24.8)	52 (29.3)	
2000–2003	142 (35.5)	68 (38.4)		143 (35.7)	58 (32.6)	
2004–2007	147 (36.7)	80 (45.2)		158 (39.5)	67 (38.1)	
Age at diagnosis, years:			0.375			0.888
60–69	218 (54.5)	104 (58.7)		222 (55.5)	98 (55.5)	
70–74	141 (35.2)	52 (29.4)		135 (33.8)	57 (32.1)	
≥75	41 (10.3)	21 (11.9)		43 (10.7)	22 (12.4)	
Charlson-12:			0.378			0.956
0	306 (76.5)	142 (80.2)		310 (77.5)	136 (77.6)	
1+*	94 (23.5)	35 (19.8)		90 (22.5)	41 (23.4)	
Race:			0.600			0.738
White/non-Hispanic	313 (78.3)	145 (81.9)		316 (79.0)	136 (76.8)	
Black/non-Hispanic	29 (7.2)	11 (6.2)		28 (7.0)	12 (6.6)	
Other	58 (14.5)	21 (11.9)		57 (14.0)	29 (16.6)	
Marital status:			0.245			0.843
Married	305 (76.2)	146 (82.5)		312 (78.0)	136 (76.8)	
Unknown	†	†		†	†	
Education level*:			0.165			0.882
<75	79 (19.7)	34 (19.2)		79 (19.7)	36 (20.4)	
75–84.9	72 (18.0)	43 (24.3)		81 (20.2)	41 (23.2)	
85–89.9	87 (21.8)	27 (15.3)		79 (19.7)	33 (18.8)	
≥90	162 (40.5)	73 (41.2)		161 (40.4)	67 (37.6)	
Median income, $:			0.692			0.976
<35 000	125 (31.3)	50 (28.2)		121 (30.3)	56 (32.0)	
35 000–44 999	100 (25.0)	52 (29.4)		104 (26.0)	47 (26.5)	
45 000–59 999	84 (21.0)	34 (19.2)		82 (20.7)	36 (20.3)	
≥59 999	91 (22.7)	41 (23.2)		91 (23.0)	38 (21.2)	
Geography:			0.031			0.977
South	32 (8.0)	27 (15.3)		41 (10.3)	18 (10.0)	
NE/Midwest‡	103 (25.7)	37 (20.9)		99 (24.7)	45 (25.6)	
West	265 (66.3)	113 (63.8)		260 (65.0)	114 (64.4)	
Population density:			0.615			0.841
Metropolitan	44 (11.0)	17 (9.6)		43 (10.8)	20 (11.5)	
Non-metropolitan	356 (89.0)	160 (90.4)		357 (89.2)	157 (88.5)	
Gleason grade:			0.014			0.444
8–10	287 (71.7)	144 (81.4)		297 (74.2)	125 (70.5)	
<8	113 (28.3)	33 (18.6)		103 (25.8)	52 (29.5)	
Pathology status:			0.221			0.818
Other	69 (17.2)	22 (12.4)		63 (15.7)	33 (18.8)	
T2	64 (16.0)	20 (11.3)		59 (14.6)	24 (13.6)	
T3a	117 (29.3)	59 (33.3)		122 (30.6)	51 (28.9)	
T3b/T4§	150 (37.5)	76 (43.0)		156 (39.1)	69 (38.7)	
PSA level:			0.008			0.283
Elevated	264 (66.0)	131 (74.1)		275 (68.7)	114 (64.2)	
Unknown	136 (34.0)	46 (25.9)		125 (31.3)	63 (35.8)	
LNs examined, n:						
1–3	58 (14.5)	29 (16.4)	0.487	61 (15.2)	26 (14.3)	0.995
4–10	177 (44.3)	71 (40.1)		172 (43.2)	77 (43.7)	
>10	141 (35.2)	61 (34.5)		139 (34.7)	62 (35.0)	
Unknown	24 (6.0)	16 (9.0)		26 (6.9)	12 (7.0)	
Mean/median	10.0/8.0	10.1/8.0	0.930	9.8/8.0	10.0/9.0	0.673
Positive LNs, n:						
1	257 (64.3)	120 (67.8)	0.274	261 (65.1)	113 (63.8)	0.916
2	67 (16.7)	33 (18.6)		70 (17.6)	30 (17.2)	
>2	76 (19.0)	24 (13.6)		69 (17.3)	34 (19.0)	
Mean/median	1.9/1.0	1.7/1.0	0.435	1.9/1.0	1.8/1.0	0.766
Adjuvant ADT:			0.020			0.977
Yes	146 (36.5)	47 (26.6)		134 (33.6)	60 (33.7)	
No	254 (63.5)	130 (73.4)		266 (66.4)	117 (66.3)	

**Charlson scores of 1 and 2+ have been combined as there are <11 subjects within a category and the National Cancer Institute restricts individual cell values to >10. †Unknown marital status is not shown as there are <11 subjects within a category. ‡Geographic regions have been combined as there are <11 subjects within a category. §T3b and T4 have been combined as there are <11 subjects within a category.*

Table 2 Outcomes of ART vs no RT.

	Before propensity weighting			After propensity weighting		
	No RT (*N* = 400)	ART (*N* = 177)	*P*	No RT (*N* = 400)	ART (*N* = 177)	*P*
Overall mortality:						
Deaths	94	47		95	49	
Person-years follow-up	2520	964		2520	964	
Deaths per 100 person-years	3.73	4.87	0.132	3.77	5.09	0.153
PCSM:						
Deaths	24	17		25	21	
Person-years follow-up	1908	726		1908	726	
Deaths per 100 person-years	1.26	2.34	0.071	1.31	2.89	0.090
	No RT	**ART ≤12 months**	***P***	**No RT**	**ART ≤12 months**	***P***
Overall mortality per 100 person-years	3.73	3.66	0.932	3.77	4.01	0.891
PCSM per 100 person-years	1.26	1.16	0.865	1.31	1.42	0.913
	No RT	**ART ≤24 months**	***P***	**No RT**	**ART ≤24 months**	***P***
Overall mortality per 100 person-years	3.73	4.57	0.329	3.77	5.35	0.193
PCSM per 100 person-years	1.26	1.43	0.770	1.30	2.39	0.354

mortality and PCSM between cohorts irrespective of timing of ART.

Discussion

ART after RP for locally advanced, non-metastatic prostate cancer has been shown to reduce the risk of biochemical progression [5], as well as provide a survival benefit when compared with men who do not receive ART [6]. However, little is known about the benefits of ART in men with LN metastasis aside from limited retrospective data suggesting improved biochemical recurrence-free survival, disease-specific survival, and overall survival, findings that conflict with the sole population-based study to date showing no benefit [8–10]. The current standard of care for men with LN metastasis after RP consists of postoperative ADT monotherapy, and relies on the evidence of a small randomised trial by Messing et al. [7]. However, several observational studies have shown an association between ADT and both cardiovascular and peripheral vascular disease, albeit in the setting of non-metastatic disease, thus highlighting the need to assess effectiveness of ADT compared with other treatment options in the context of these potential complications [18,19]. While the benefits of ADT in the setting of LN-positive disease likely outweigh these potential detriments [20], alternative adjuvant therapies with low risk–benefit profiles are appealing. Using a population-based approach, we sought to analyse outcomes of ART after RP in men with LN-positive prostate cancer.

The present study has several important findings. We found no differences in PCSM or overall mortality in men receiving ART vs no ART, similar to a finding by Johnstone et al. [8] in a SEER-only study. This lack of benefit was seen despite equivalent use of adjuvant ADT in the ART group after propensity weighting, which is a finding that could not be quantified in the prior SEER-only study. Given that ADT has been shown to improve survival in patients with LN-positive disease, similar rates of ADT treatment across groups supports a lack of ART benefit. These findings are in contradiction with those from the Da Pozzo et al. [9] and Briganti et al. [10] studies, which were conducted at centres of excellence and showed a disease-specific survival benefit for the use of ART in men with LN-positive prostate cancer [9,10]. It should also be noted that in the Da Pozzo et al. [9] study, the mean number of LNs removed was 16, while only 35% of the present cohort had >10 LNs removed. One possibility for Da Pozzo et al. [9] showing a benefit in contrast to the present study is that after lymphadenectomy, there is precise identification of which LN regions harbour metastatic disease allowing for improved targeting of the LNs at risk. Alternatively, men with a few positive LNs after an extensive LN dissection may have lower disease burden than men with the same number of positive LNs after limited dissection, and thus may have improved outcomes after ART.

The present findings contrast with multiple studies showing a strong positive association between the extent of LN involvement and the likelihood of disease progression after RP combined with ART and/or ADT [6,21,22]. A possible explanation for this difference is reflected in subsequent research suggesting that disease progression in the setting of LN-positive disease is likely multifactorial. Consequently, the extent of LN involvement alone may be an inadequate predictor of patient response to localised ART. For example, factors such as tumour ploidy and

pathological Gleason score may also play a significant role in disease progression and subsequent disease-specific and overall survival. Boorjian et al. [23] retrospectively assessed the impact of clinicopathological factors on outcomes in 507 men with LN-positive disease who underwent RP and showed that pathological Gleason score 8–10, positive surgical margins, tumour ploidy and the extent of LN involvement were all adverse predictors of cancer-specific survival. The investigators also reported that postoperative ADT decreased the risk of biochemical and local recurrence, but was not associated with cancer-specific survival. Leibovici et al. [24] similarly showed that high Gleason grade, advanced disease stage, and high pretreatment PSA levels (>10 ng/mL) may all signal disease progression, even in the presence of undetectable PSA levels after treatment. Indeed, men with LN-positive disease are more likely to have many of the aforementioned adverse pathological factors; therefore localised treatment with ART may offer little therapeutic benefit for this subpopulation of patients.

The results of the present study reflect the need for prospective trials to clarify the role of ART in men after RP with LN-positive disease. In addition, the present results suggest that men with LN-positive disease may already harbour micrometastases that cannot be cured with pelvic RT, but the specific underlying pathophysiology of disease recurrence and progression has not been elucidated. The addition of unnecessary ART in this group may lead to unwarranted patient morbidity as well as cost. The mean incremental cost per patient for ART vs observation after RP has been reported as $6023 (American dollars) [25]. Furthermore, ART is known to interfere with recovery after RP and has been associated with worse urinary and bowel symptom outcomes [26]. Thompson et al. [27] reported urethral stricture rates as high as 17.8% with early addition of ART after RP in patients with locally advanced disease vs 9.5% for patients initially treated with observation. ART use more than doubled the rate of total urinary incontinence (6.5% for early ART, 2.8% for initial observation).

The present results must be considered in the context of the study design. First, as with any population-based study, we could not control for unmeasured confounders. This point is particularly noteworthy given our finding that men undergoing ART were more likely to have an elevated preoperative PSA level and poorly differentiated tumours, both of which confer significant disease-specific mortality risk in the setting of radio-recurrent disease [28,29]. Haukaas et al. [30] found that preoperative serum PSA level was inversely associated with the likelihood of biochemical failure-free survival, whereas histological grade was found to be an independent predictor of clinical recurrence. Similarly, surgical margin status and postoperative PSA values were not available in the SEER-Medicare database; these, too, have been shown to effect cancer-specific survival [22]. While propensity weighting attempts to account for tumour and demographic differences, it is conceivable that ART's previously reported survival benefit is obscured by more advanced, unaccounted-for, baseline characteristics in our ART cohort. Second, SEER registries may under-report RT use, but we used Medicare-linked administrative data, which is highly sensitive for defining RT use [31]. By using Medicare-linked data we hope to avoid potential underreporting of ART use, which may have affected the Johnstone et al. [8] SEER-only analysis. Third, data concerning ART field and dosing was not available in the database, and there is evidence suggesting that the size of the pelvic field is associated with outcomes in high-risk disease [32]. Also, modern-era RT doses are higher than what was being used in the 1990s due to improved conformality of intensity-modulated RT allowing for reduced rectal scatter in addition to retrospective evidence of salvage dose escalation beyond 60 Gy improving postoperative outcomes [33,34]. Finally, we were unable to determine whether ART was given in a true adjuvant vs salvage setting. However, these limitations also exist in previous studies examining the role of ART after RP in men with LN-positive prostate cancer.

In conclusion, using a population-based model, we found that ART in men with LN-positive prostate cancer after RP was not associated with improved overall or disease-specific survival. While the present study comprises a valuable addition to the current literature on the use of ART in this subset of patients, prospective randomised, controlled trials are needed to clarify the need for ART in this patient population.

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Conflict of Interest

None declared.

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Abbreviations: ADT, androgen-deprivation therapy; LN, lymph node; PCSM, prostate cancer-specific mortality; (A)RT, (adjuvant) radiation therapy; RP, radical prostatectomy; SEER, Surveillance, Epidemiology, and End Results.

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Original article

Morbidity and costs of salvage vs. primary radical prostatectomy in older men☆

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Abstract

Objectives: Salvage radical prostatectomy (RP) is performed with curative intent following post-radiotherapy recurrence for prostate cancer. While single-center salvage RP outcomes appear promising, little is known about outcomes in the community setting in elderly men. We sought to evaluate utilization, outcomes, and costs of salvage RP vs. primary RP in older men.

Materials and methods: Surveillance, Epidemiology and End Results-Medicare linked data from 1992 to 2007 was used to identify 18,317 men aged 65 years or older who underwent RP from 2002 to 2007. Propensity score analyses were used to compare outcomes and costs for primary vs. salvage RP.

Results: Salvage RP was rare, accounting for 0.5% of RP. Men undergoing salvage vs. primary RP were older, white, and less likely to undergo CT, bone scan and prostate biopsy preoperatively ($P < 0.05$ for all). In adjusted analyses, salvage vs. primary RP was associated with increased 30-day complications (60.1% vs. 22.7%, $P < 0.01$), lengths of stay (mean 7 vs. 3 days, $P < 0.01$), and hospital readmissions within 30 days (30.4% vs. 5.7%, $P < 0.01$). The odds of death within 90 days were higher for salvage vs. primary RP (OR 26.7, 95% CI 12.9–55.1, $P < 0.01$). The median expenditure for salvage RP within 6 months postoperatively was almost twice that for primary RP (US$30,881 vs. US$12,431, $P < 0.01$).

Conclusions: Metastatic workup was performed less frequently before salvage vs. primary RP, and morbidity and mortality for salvage RP was high relative to primary RP. Given the morbidity and high cost of salvage RP, guidelines for patient selection and selective referral may optimize outcomes, especially in older men.

Keywords: Salvage prostatectomy; Utilization; Outcomes; Radiotherapy

1. Introduction

Prostate cancer (CaP) is the most prevalent solid organ tumor and the second most common cause of death among men in the USA. In 2012, an estimated 241,740 men will be diagnosed with CaP [1]. Over the past 3 decades, stage migration in CaP has resulted in 92% of incident CaPs presenting as locoregional vs. metastatic [2,3]. While treatments for clinically localized CaP vary, the 2 most common are radical prostatectomy (RP) and traditional radiation therapies (external-beam and brachytherapy) [4]. While radiotherapy is a popular treatment option, 63% of men will experience biochemical recurrence (BCR) within 10 years of radiotherapy [5].

Management of the patient with BCR following radiation therapy in most cases includes androgen deprivation therapy (ADT). Approximately 92% of men with post-radiotherapy BCR will undergo ADT that is noncurative and increases the risk for diabetes, cardiovascular disease, and thromboembolic complications [6,7]. Only

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2% of men with post-radiotherapy BCR will undergo salvage RP [8], perhaps because of ineffective cancer control and greater risk for complications [9,10]. While more recent salvage prostatectomy series suggest improved morbidity and 5-year progression-free survival approaching 55% in all patients (and 86% for men with PSA <4 before salvage RP) [11], these data represent single-institution or multi-institutional cohorts from high-volume oncologic centers [12]. At a population level, the outcomes and costs of salvage RP remain unknown, especially in older men who may not benefit from surgical intervention because of limited life expectancy. The purpose of our population-based study is to evaluate utilization, outcomes, and costs of salvage radical prostatectomy in older men relative to radical prostatectomy as primary therapy as a benchmark.

2. Materials and methods

2.1. Data

Our study was approved by the Brigham and Women's Institutional Review Board; patient data were de-identified and the requirement for consent was waived. We used Surveillance, Epidemiology, and End Results (SEER)-Medicare data for analysis, which is currently comprised of a linkage of population-based cancer registry data from 20 SEER areas with Medicare administrative data and covers approximately 28% of the US population. The Medicare program provides benefits to 97% of Americans aged >65 years [13].

2.2. Study cohort

We identified men aged >65 years initially diagnosed with CaP from 1992 to 2007 who underwent open radical prostatectomy between 2002 and 2007 based on *Physicians' Current Procedural Terminology Coding System, 4th edition* (CPT-4) codes (55,840, 55,842, 55,845 for open radical prostatectomy). Subjects were then grouped into primary or salvage prostatectomy cohorts, with salvage RP defined as surgery 12 months or greater following primary radiotherapy (external beam radiotherapy, brachytherapy, and/or intensity-modulated radiotherapy). We excluded perineal and minimally invasive radical prostatectomy as these were uncommon in the salvage setting, totaling 25 procedures. We excluded men not enrolled in both Medicare Part A and B or who were enrolled in a Medicare health maintenance organization because their claims are not reliably submitted. We restricted our cohort to men with CaP diagnosed as their only cancer. Mean follow-up (±standard deviation) for salvage vs. primary RP was 2.0 (±1.9) vs. 4.3 (±2.0) years.

2.3. Outcomes

We examined the utilization of salvage prostatectomy after primary radiotherapy and associated Medicare expenditures in the perioperative and postoperative period.

2.4. Control variables

Age was obtained from the Medicare file; race, census tract measures of median household income and high school education, region, population density (urban vs. rural), and marital status were obtained from SEER registry data. Comorbidity was assessed using the Klabunde et al. modification of the Charlson index during the year before surgery [14]. International Classification of Diseases, 9th Revision (ICD-9) codes were used to identify disease categories, while CPT-4 and Healthcare Common Procedure Coding System code sets were used to identify medical, surgical, and diagnostic services. As CPT-4 codes were utilized to identify complications, data cannot be reported using the Clavien Classification of Surgical Complications but, instead, are presented in a well-established framework by organ system [15]. To increase specificity, only imaging studies designated with a corresponding ICD-9 code for CaP were included.

2.5. Expenditures

To best attribute the costs associated with each surgical setting, we assessed Medicare payments 3 days before the date of surgical admission and 90 days after the date of discharge from all inpatient, outpatient, and carrier claims.

2.6. Statistical analysis

Unadjusted analysis using the Pearson χ^2 statistic was performed to compare demographic and biopsy tumor characteristics for men receiving salvage prostatectomy vs. observation alone, adjusting for clustering by surgeon [16]. In addition, a Pearson χ^2 test was also utilized to compare the use of salvage prostatectomy by clinical and pathologic features.

As men who received salvage RP may differ from those who underwent primary RP in terms of demographic characteristics, we used weighted propensity score methods to adjust for observed differences [17,18]. Propensity score methods control for all observed confounding factors that may influence cohort assignment and outcome using a single composite measure, balancing patient characteristics as would occur in a randomized experiment. Propensity score adjustment was performed using a logistic regression model to calculate the probability of undergoing primary vs. salvage RP based on described covariates and then weighting the data based on the inverse propensity of being in either of the treatment groups [19]. After adjustment, covariate balance was assessed.

Table 1
Demographics of study population

	Initial RP (n = 18,218)		Salvage RP (n = 99)		P value
	n	%	n	%	
Year of initial CaP diagnosis					
1992–1996	18	0.1	11	11.1	<0.01
1997–2001	609	3.3	45	45.5	
2002–2007	17,591	96.6	43	43.4	
Age at initial CaP diagnosis					
65–69	11,435	62.8	40	40.4	<0.01
70–74	5421	29.8	40	40.4	
≥75	1362	7.5	19	19.2	
Race					
White	14,643	80.4	*	*	<0.01
Nonwhite	3575	19.6	*	*	
Median income (US$)					
<35,000	5323	29.2	26	26.3	0.74
35,000–44,999	4122	22.6	20	20.2	
45,000–59,999	4306	23.7	25	25.3	
≥60,000	4454	24.5	28	28.3	
Education					
<75	3457	19.0	*	*	0.03
75–84.9	3604	19.8	*	*	
85–89.9	3340	18.4	*	*	
≥90	7804	42.9	*	*	
Population density					
Urban	16,722	91.8	*	*	0.50
Rural	1496	8.2	*	*	
Region					
Northeast	2497	13.7	21	21.2	<0.01
South	2884	15.8	16	16.2	
Midwest	2344	12.9	23	23.2	
West	10,493	57.6	39	39.4	
Marital status					
Not married	2715	15.8	16	17.4	0.67
Married	14,526	84.3	76	82.6	
Charlson score					
0	14,227	79.4	73	76.0	0.43
≥1	3703	20.7	23	24.0	
Pathologic stage					
T1	9300	51.8	53	55.2	0.50
T2/T3/T4	8670	48.3	43	44.8	
Grade					
Well/moderately differentiated	9201	50.8	29	29.9	0.09
Poorly undifferentiated	8910	49.2	68	70.1	

CaP = prostate cancer; RP = radial prostatectomy.
* Race, education and population density for salvage patients are not shown as there are fewer than 11 subjects within a group.

All tests were considered statistically significant at α = 0.05. All analyses were performed with SAS ver. 9.1.3 (SAS Institute, Cary, NC). Due to confidentiality, values less than 11 may not be reported directly or in a derivable way for any SEER-Medicare data obtained from the National Cancer Institute. Therefore, for any group with fewer than 11 subjects, data are not shown in tables.

3. Results

The demographic and tumor characteristics of our study population are demonstrated in Table 1. Men undergoing salvage RP vs. primary RP were older ($P < 0.01$), more likely to be white ($P < 0.01$), and reside in areas of higher education ($P = 0.02$) and the Northeast and Midwest ($P < 0.01$). There was no difference between groups regarding median income, marital status, urban vs. rural residence, or Charlson score. There were no differences between the 2 groups in terms of pathologic stage or grade. The median time from initial radiation therapy to salvage RP was 55.8 months [interquartile range (IQR): 29.6–87.4 months].

Table 2 shows utilization of prostate needle biopsy and imaging for metastatic work-up in the 6 months before surgery. On adjusted analyses, CT (9.4% vs. 24%, P = 0.04), bone scan (16.3% vs. 39.7%, $P < 0.01$), and prostate

Table 2
Utilization of CT scan, bone scan, and prostate needle biopsy for preoperative metastatic workup

	Primary RP	Salvage RP	*P* value
Unadjusted, *n* (%)			
CT within 6 months	4136 (24.0)	16 (17.0)	0.11
Bone scan within 6 months	6835 (39.7)	15 (16.0)	<0.01
Biopsy within 6 months	14,978 (87.0)	16 (17.0)	<0.01
Adjusted, %			
CT within 6 months	24.0	9.4	0.04
Bone scan within 6 months	39.7	16.3	<0.01
Biopsy within 6 months	86.9	18.0	<0.01

needle biopsy (18% vs. 86.9%, $P < 0.01$) were performed less commonly for salvage vs. primary radical prostatectomy.

Adjusted Medicare expenditures and adjusted outcomes for primary and salvage RP are shown in Table 3. Adjusted Medicare expenditures were more than 2-fold higher for salvage vs. primary RP ($30,881 vs. $12,431, $P < 0.01$). Inpatient, outpatient, and physician costs were all greater for patients undergoing salvage vs. primary RP ($P < 0.01$ for all). The results of unadjusted and adjusted outcomes were similar and, therefore, only adjusted outcomes are presented below. Salvage vs. primary RP was associated with longer lengths of stay (mean 7 vs. 3 days, $P < 0.01$), more overall complications (60.1% vs. 22.7%, $P < 0.01$), and hospital readmissions (30.4% vs. 5.7%, $P < 0.01$) within the first 30 days following surgery. Salvage vs. primary RP complications were more common for all complication categories, including cardiac, respiratory, vascular, genitourinary, wound, and miscellaneous medical. Beyond 30 days postoperatively, salvage RP had a greater risk for anastomotic strictures within 1 year of RP (55.4% vs. 11.7%, $P < 0.01$). Bone metastases were more common following salvage vs. primary RP (13.3% vs. 3.2%, $P < 0.01$). Men undergoing salvage vs. primary RP experienced significantly greater odds of death within 90 days of surgery (OR 26.7, 95% CI 12.9–55.1, $P < 0.01$). Forty-seven percent of men were alive at 5 years after salvage RP compared with 92.4% of men after primary RP ($P < 0.01$). CaP-specific survival was also lower for men at 5 years following salvage RP compared with men who underwent primary RP (86.3% vs. 99.3%, $P < 0.01$).

4. Discussion

Management of CaP following radiation therapy remains challenging, especially for younger men or those with life expectancy >10 years. Treatment options include brachytherapy, cryotherapy, androgen deprivation therapy, and radical prostatectomy. While radical prostatectomy in the salvage setting may offer cure, its use has been limited because of greater perioperative morbidity, including rectal injury, rectourethral fistula, lymphedema, urinary incontinence, and anastomotic stricture reported in single-center case series [20–22]. However, more recent studies have reported lower morbidity that may be secondary to improved and focused delivery of radiotherapy and consequently reduced periprostatic fibrosis [23]. However, most salvage RP series come from academic medical centers and typically include younger patients, and little is known regarding salvage RP in older men and outside traditional referral centers. We sought to characterize contemporary practice patterns and outcomes of salvage RP in a population-based cohort of men older than 65 years of age.

Our paper has several important findings. First, use of diagnostic and radiographic studies was infrequent before salvage RP, with only 18% of men undergoing a prostate needle biopsy within 6 months before salvage RP compared with almost 90% of men undergoing primary RP. Historically, the importance of a positive biopsy following radiotherapy was questioned, but in most salvage RP series, biopsy is performed to confirm local recurrence before salvage prostatectomy [22,24,25]. Despite the greater risk of disease progression, upgrading, and metastatic disease at the

Table 3
Expenditures and adjusted outcomes of initial and salvage RP

	Primary RP (n = 18,218)	Salvage RP (n = 99)	*P* value
Total Medicare expenditures (US$)	$12,431	$30,881	<0.01
Inpatient	$8,848	$24,334	<0.01
Outpatient	$174	$565	<0.01
Physician	$3,248	$5,672	<0.01
Adjusted outcomes			
Mean length of stay (days)	3	7	<0.01
Perioperative complications	%	%	
Transfusion	14.4	17.5	0.60
Readmission within 30 days	5.7	30.4	<0.01
30-day postoperative complications			
Overall	22.7	60.1	<0.01
Cardiac	3.3	11.1	<0.01
Respiratory	6.1	30.3	<0.01
Vascular	3.8	15.4	<0.01
Genitourinary	2.5	19.8	<0.01
Wound	2.0	8.3	0.03
Miscellaneous medical	8.9	32.0	<0.01
Miscellaneous surgical	5.7	13.2	0.08
Long-term outcomes			
Anastomotic stricture within 1 year of RP	11.7	55.4	<0.01
Bone metastases	3.2	13.3	<0.01
Death within 90 days	0.4	6.2	<0.01
Survival			
Overall 5-year survival	92.4	47.0	<0.01
Disease-specific survival 5 years after RP	99.3	86.3	<0.01

time of salvage RP, bone scan or CT was used in <20% of men 6 months before surgery, and 17% of men developed bone metastases relatively soon following salvage radical prostatectomy. The lack of preoperative biopsy and radiographic imaging for staging in the salvage setting may in part explain the high rates of metastatic disease found in the cohort. The relatively infrequent use of biopsy and radiographic staging are particularly worrisome in light of the significant morbidity associated with salvage RP, and we would advocate, in compliance with European Association of Urology and National Comprehensive Cancer Network guidelines, that all patients considered for salvage RP must have life expectancy long enough to benefit from surgery, negative metastatic staging studies, and documentation of recurrent or residual cancer with prostate needle biopsy before surgery [12,26,27]. Prior research from our group demonstrated similar underuse of imaging for metastatic staging for men with high-risk CaP in the primary setting [28].

Second, salvage RP is associated with significantly higher perioperative morbidity and mortality rates than previously reported in single-center or multi-institutional series [29]. Overall complications were more than 2-fold higher with salvage vs. primary RP, with striking differences in genitourinary, respiratory, wound, and miscellaneous medical and vascular complications. Interestingly, the rate of transfusion was not significantly different between the 2 groups. Overall, more than 70% of men experienced a postoperative complication in the salvage RP cohort—a 3-fold increase over the comparative cohort undergoing primary RP. Mean length of stay was twice as long and the likelihood of hospital readmission within 1 month of surgery was almost 6 times greater for salvage vs. primary RP. Mortality differences were also striking, with greater than 25-fold odds of death within 3 months of surgery. The mortality at 5 years is significantly higher than in other series, although this may reflect the older age of men in our analysis. In the largest multi-institutional cohort analysis of 404 men who underwent salvage RP, the 10-year BCR-free survival, metastasis-free survival, and cancer-specific survival probabilities were 37%, 77%, and 83%, respectively [29]. The men in this multi-institutional study had a mean age of 65 years and a third had presalvage RP biopsy Gleason score ≤7 and PSA ≤4 ng/ml. This select group had the highest probability of cure, and no men in this cohort died of CaP. The 47% overall survival rate following salvage RP in this study is comparable or superior to outcomes in other men with BCR following radiotherapy who undergo cryotherapy, brachytherapy, and hormonal therapy [30,31]. Comparative analysis is limited by the lack of pathologic data and PSA kinetics, but a significant increase in overall and disease-specific survival were not observed in our cohort.

Third, in addition to the striking differences in postoperative complications, the rate of bladder neck contracture was higher following salvage vs. primary RP. These findings differ from 2 recent salvage prostatectomy series from expert centers, which demonstrate continence rates approaching 80%—a significant improvement over historical series [32,33]. We believe that we captured most bladder neck contracture diagnoses as the mean follow-up exceeded 2 years in the salvage RP group, beyond the interim during which anastomotic strictures present [15]. The increased rate of bladder neck contracture in our series compared with single-institution reports may reflect population-level outcomes outside of centers of excellence.

Finally, this is the first study reporting costs of salvage RP relative to primary RP in the literature. Medicare payment for salvage vs. primary RP was more than 2-fold higher, with a difference of almost US$19,000. While this figure may not capture all payments associated with longer-term complications beyond 3 months, such as postoperative nursing home care or rehabilitation services, it does include costs of emergency room visits, readmission, and additional surgical or radiologic procedures. However, selective referral to experienced salvage RP surgeons may reduce the significant morbidity and costs observed in our study. While salvage RP was found to be more expensive than primary RP, use of surgery in the salvage setting remains comparable to adjuvant or salvage radiation therapies.

Our findings must be interpreted in the context of the study design. First, analyses were restricted to Medicare beneficiaries older than 65 years residing in SEER regions, and our findings may not be applicable to younger men who may comprise a significant proportion of all patients undergoing salvage RP. We also used claims files to capture complications and procedures, and it is possible that some events were not captured. However, Medicare claims have a high degree of validity for complications, with 89% of Medicare complications corroborated by medical record review [34]. Moreover, recurrence prostate-specific antigen values were unavailable before salvage radical prostatectomy. Additionally, without using validated quality of life instruments, we were unable to compare functional outcomes following salvage vs. primary RP. We also excluded those men undergoing minimally invasive radical prostatectomy, and results for these men may differ from those undergoing open RP. While our study period incorporated CaP diagnoses over a 17-year span during which outcomes may change over time, all surgeries were performed between 2002 and 2007, well within the modern era (after 1993) defined by Stephenson et al., where complication rates were similar [33]. To avoid misallocation bias, we included only those men who had a new diagnosis of CaP after age 65. Finally, as with any adjusted analysis, propensity score methods do not control for unmeasured confounders and possess other limitations [35].

In summary, despite reports of improved perioperative outcomes, salvage RP in the elderly remains a morbid and costly procedure. Salvage surgery should be offered judiciously in those patients who have the greatest chance of achieving cure.

Acknowledgments

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ORIGINAL REPORT

Cost Implications of the Rapid Adoption of Newer Technologies for Treating Prostate Cancer

Paul L. Nguyen, Xiangmei Gu, Stuart R. Lipsitz, Toni K. Choueiri, Wesley W. Choi, Yin Lei, Karen E. Hoffman, and Jim C. Hu

See accompanying editorial on page 1503

A B S T R A C T

Purpose
Intensity-modulated radiation therapy (IMRT) and laparoscopic or robotic minimally invasive radical prostatectomy (MIRP) are costlier alternatives to three-dimensional conformal radiation therapy (3D-CRT) and open radical prostatectomy for treating prostate cancer. We assessed temporal trends in their utilization and their impact on national health care spending.

Methods
Using Surveillance, Epidemiology, and End Results–Medicare linked data, we determined treatment patterns for 45,636 men age ≥ 65 years who received definitive surgery or radiation for localized prostate cancer diagnosed from 2002 to 2005. Costs attributable to prostate cancer care were the difference in Medicare payments in the year after versus the year before diagnosis.

Results
Patients received surgery (26%), external RT (38%), or brachytherapy with or without RT (36%). Among surgical patients, MIRP utilization increased substantially (1.5% among 2002 diagnoses *v* 28.7% among 2005 diagnoses, $P < .001$). For RT, IMRT utilization increased substantially (28.7% *v* 81.7%; $P < .001$) and for men receiving brachytherapy, supplemental IMRT increased significantly (8.5% *v* 31.1%; $P < .001$). The mean incremental cost of IMRT versus 3D-CRT was $10,986 (in 2008 dollars); of brachytherapy plus IMRT versus brachytherapy plus 3D-CRT was $10,789; of MIRP versus open RP was $293. Extrapolating these figures to the total US population results in excess spending of $282 million for IMRT, $59 million for brachytherapy plus IMRT, and $4 million for MIRP, compared to less costly alternatives for men diagnosed in 2005.

Conclusion
Costlier prostate cancer therapies were rapidly and widely adopted, resulting in additional national spending of more than $350 million among men diagnosed in 2005 and suggesting the need for comparative effectiveness research to weigh their costs against their benefits.

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INTRODUCTION

With approximately 180,000 new diagnoses per year,[1] prostate cancer has been cited as a litmus test for health care spending and reform due to its rising costs of care.[2] Over the past decade, newer and more expensive alternatives have been introduced for the treatment of prostate cancer. For men who choose surgery, minimally invasive radical prostatectomy (MIRP), which includes either laparoscopic or robotic-assisted surgery, is a costlier alternative to the traditional open RP due to the greater cost of disposables, equipment, and increased operating room time during a lengthy learning curve.[3] For men who choose radiation, intensity-modulated radiation therapy (IMRT) is a more expensive alternative to traditional three-dimensional conformal radiation therapy (3D-CRT) due to more intense physics planning and quality assurance time, as well as treatment delivery time and software and hardware costs.[4]

Despite interest from patients and providers in these newer technologies, and belief by advocates that they could improve outcomes, there was only limited comparative effectiveness data when they were introduced, and to date there have been no randomized trials testing their clinical efficacy compared to traditional, less expensive counterparts. The purpose of this study is to characterize the adoption of these more expensive therapies among Medicare beneficiaries and to estimate the excess health

Table 1. Baseline Patient Characteristics Stratified by Primary Curative Modality Chosen

Variable	Brachytherapy		External RT		Surgery		*P*
	No.	%	No.	%	No.	%	
Race							
White	13,247	80.44	13,326	77.14	9,498	79.86	< .001
Black	1,470	8.93	1,716	9.93	910	7.65	
Hispanic	842	5.11	1,058	6.12	904	7.60	
Asian	592	3.59	795	4.60	441	3.71	
Other/unknown	317	1.92	379	2.19	141	1.19	
Age at diagnosis, years							
65-69	5,591	33.95	3,969	22.98	7,435	62.51	< .0001
70-74	5,915	35.92	5,793	33.54	3,589	30.17	
75-79	4,962	30.13	7,512	43.49	870	7.31	
High school education in patient's census region, %							
< 75/unknown	3,453	20.97	3,906	22.61	2,377	19.98	< .0001
75-84	3,546	21.53	4,064	23.53	2,368	19.91	
85-89	3,118	18.93	3,255	18.84	2,213	18.61	
90+	6,351	38.57	6,049	35.02	4,936	41.50	
Median income, $							
< 35,000/unknown	5,244	31.85	6,686	38.70	3,590	30.18	< .0001
35,000-44,000	3,905	23.71	4,017	23.25	2,812	23.64	
45,000-59,000	3,921	23.81	3,634	21.04	2,736	23.00	
≥ 60,000	3,398	20.63	2,937	17.00	2,756	23.17	
Region*							
Northeast	4,936	29.97	4,362	25.25	1,414	11.89	< .0001
South	3,365	20.43	2,733	15.82	1,975	16.61	
Midwest	1,751	10.63	3,202	18.54	1,634	13.74	
West	6,416	38.96	6,977	40.39	6,871	57.77	
SEER registry							
San Francisco	605	3.67	592	3.43	488	4.10	< .0001
Michigan	1,137	6.90	2,029	11.75	916	7.70	
New Mexico/Georgia/Hawaii	1,526	9.27	1,145	6.63	770	6.47	
Iowa	614	3.73	1,173	6.79	718	6.04	
Seattle	1,092	6.63	745	4.31	909	7.64	
Utah	959	5.82	209	1.21	693	5.83	
Connecticut	978	5.94	1,552	8.98	448	3.77	
San Jose	433	2.63	375	2.17	246	2.07	
Los Angele	672	4.08	1,283	7.43	1,275	10.72	
Greater California	2,199	13.35	2,943	17.04	2,742	23.05	
Kentucky	1,178	7.15	1,261	7.30	684	5.75	
Louisiana	1,117	6.78	1,157	6.70	1,039	8.74	
New Jersey	3,958	24.03	2,810	16.27	966	8.12	
Population density							
Metropolitan	15,192	92.25	15,619	90.42	10,896	91.61	< .0001
Nonmetropolitan	1,276	7.75	1,655	9.58	998	8.39	
Marital status							
Not married	3,024	18.36	3,579	20.72	1,792	15.07	< .0001
Married	12,106	73.51	11,959	69.23	9,509	79.95	
Unknown	1,338	8.12	1,736	10.05	593	4.99	
Grade							
Well	224	1.36	224	1.30	158	1.33	< .001
Moderate	11,067	67.20	9,210	53.32	6,451	54.24	
Poorly/undifferentiated	4,849	29.44	7,530	43.59	5,211	43.81	
Unknown	328	1.99	310	1.79	74	0.62	
Clinical stage							
T1	7,880	47.85	7,246	41.95	5,149	43.29	< .001
T2	8,049	48.88	8,905	51.55	6,365	53.51	
T3	267	1.62	603	3.49	174	1.46	
T4	16	0.10	137	0.79	21	0.18	
Unknown	256	1.55	383	2.22	185	1.56	

(continued on following page)

Table 1. Baseline Patient Characteristics Stratified by Primary Curative Modality Chosen (continued)

Variable	Brachytherapy		External RT		Surgery		
	No.	%	No.	%	No.	%	*P*
Charlson score							
0	11,860	72.02	11,516	66.67	9,412	79.13	< .001
1	3,230	19.61	3,765	21.80	1,760	14.80	
2+	1,153	7.00	1,763	10.21	448	3.77	
Unknown	225	1.37	230	1.33	274	2.30	
Total	16,468	36	17,274	38	11,894	26	

NOTE. Education had 24 unknown, income had 26 unknown. For men diagnosed in 2002, well differentiated refers to a Gleason score of 2-4, moderately differentiated is Gleason 5-7, and poorly differentiated is Gleason 8-10, but for men diagnosed from January 1, 2003 onward, poorly differentiated was designated as Gleason 7. Region categorization: northeast: Connecticut and New Jersey; south, Atlanta, rural Georgia, Kentucky, and Louisiana; west: San Francisco, Hawaii, New Mexico, Seattle, Utah, San Jose, Los Angeles, and greater California; and midwest: Detroit and Iowa. Comorbidity is the Klabunde modification of the Charlson Index.[21]
Abbreviation: RT, radiation therapy.

care spending attributable to the increased utilization of these newer modalities.

METHODS

Data Source

Our study was approved by the Brigham and Women's institutional review board and a data-use agreement was in place with the Centers for Medicare and Medicaid Services; patient data were de-identified and the requirement for consent was waived. We used Surveillance, Epidemiology, and End Results (SEER) –Medicare data for analyses, composed of a linkage of population based cancer registry data from 16 SEER areas covering approximately 26% of the US population with Medicare administrative data. The Medicare program provides benefits to 97% of Americans age 65 years or older.[5]

Defining the Study Cohort and Exclusion Criteria

We identified 103,363 men age 65 years or older in the SEER registry with pathologically confirmed prostate cancer from 2002 to 2005, who had no history of other malignancies. We excluded men enrolled in a health maintenance organization or not enrolled in both Medicare Part A and Part B throughout the duration of the study because claims are not reliably submitted for such men. We also excluded men who were missing a date of diagnosis or had metastatic disease. This reduced the cohort to 71,674 men, of which 58,571 men underwent some form of treatment with follow-up through December 31, 2007. The focus of our study was men who underwent surgery or radiation, so we excluded 11,093 men who received primary androgen deprivation therapy and 1,205 who received cryotherapy. We also excluded 619 men who all received proton therapy at a single center because their trends results would not be generalizable. The final study cohort was 45,636 patients.

Determination of Surgery and Radiation Therapies

Treatment type was identified from Medicare inpatient, outpatient, and carrier component files (formerly physician/provider B files) based on the presence of Current Procedural Terminology, Fourth Edition (CPT-4) codes listed in Appendix Table A1 (online only). Brachytherapy and external RT were considered as part of a combination therapy if they were given within 6 months of each other.

Determination of Treatment Cost

To determine the cost of therapy, we summed the total amount paid by Medicare for inpatient, outpatient, and physician services within 12 months of prostate cancer diagnosis.[6] To ensure that we adequately captured the cost of treatment, we included in our cost analysis only men who began treatment within 6 months of the prostate cancer diagnosis. Using each subject as his own control, we subtracted health expenditures accrued in the 12 months before prostate cancer diagnosis, which we considered baseline annual health care costs, from 12-month expenditures after prostate cancer diagnosis.[7] This difference captures the cost of treatment and other services such as preoperative evaluation, imaging, laboratory tests, and treatment of complications within 1 year. The mean cost of each therapy was then tabulated and stratified by the year of diagnosis. All costs were adjusted to 2008 dollars using the 2007 Annual Report of the Boards of Trustees of the Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Fund Table 5.B.1 HI and SMI Average Per Beneficiary Costs (HI = Part A; SMI = Part B).

Determination of the Excess Direct Medical Spending on More Expensive Therapies at the National Level

To estimate the total amount spent nationwide on more expensive prostate cancer therapies for men of any age, we identified the total number of patients in the US diagnosed with nonmetastatic prostate cancer in 2005 from the SEER limited-use registry treated with surgery, external beam radiation, or brachytherapy plus external beam radiation.[8] We divided these figures by 0.26 to extrapolate national estimates of the number of people receiving each treatment since the SEER registry captures 26% of the US population. We multiplied the number in each treatment category (eg, surgery), by the proportion expected to receive the more expensive therapy to determine the expected number of people receiving the expensive therapy nationwide. The observed rates of utilization found in our cohort were adjusted for demographic differences between the cohort and the US population to develop expected utilization rates applicable to the US population. The number of people receiving each expensive therapy was then multiplied by the mean cost of each therapy to estimate national spending.[9]

Statistical Analyses

Temporal trends in use of the more expensive therapy were examined using the Mantel-Haenszel test for trend. The χ^2 test was used to determine the factors associated with the receipt of the more expensive therapy. A *P* value of lower than .05 was considered statistically significant. We developed directly standardized rates of utilization that would be expected in the general population by weighing each patient in our cohort by the ratio of patients in general population to SEER-Medicare for the strata of demographic characteristics to which each patient belongs.[10] All analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, NC).

RESULTS

Utilization Trends

The characteristics of the study cohort are listed in Table 1, stratified by treatment modality. Of the cohort, 11,894 (26%) received surgery, 17,274 (38%) received external radiation, and 16,468 (36%) received brachytherapy with or without external radiation as their primary therapy (year-by-year analysis in Appendix Table A2, online only). Figures 1A-C demonstrate rapidly increased utilization of the

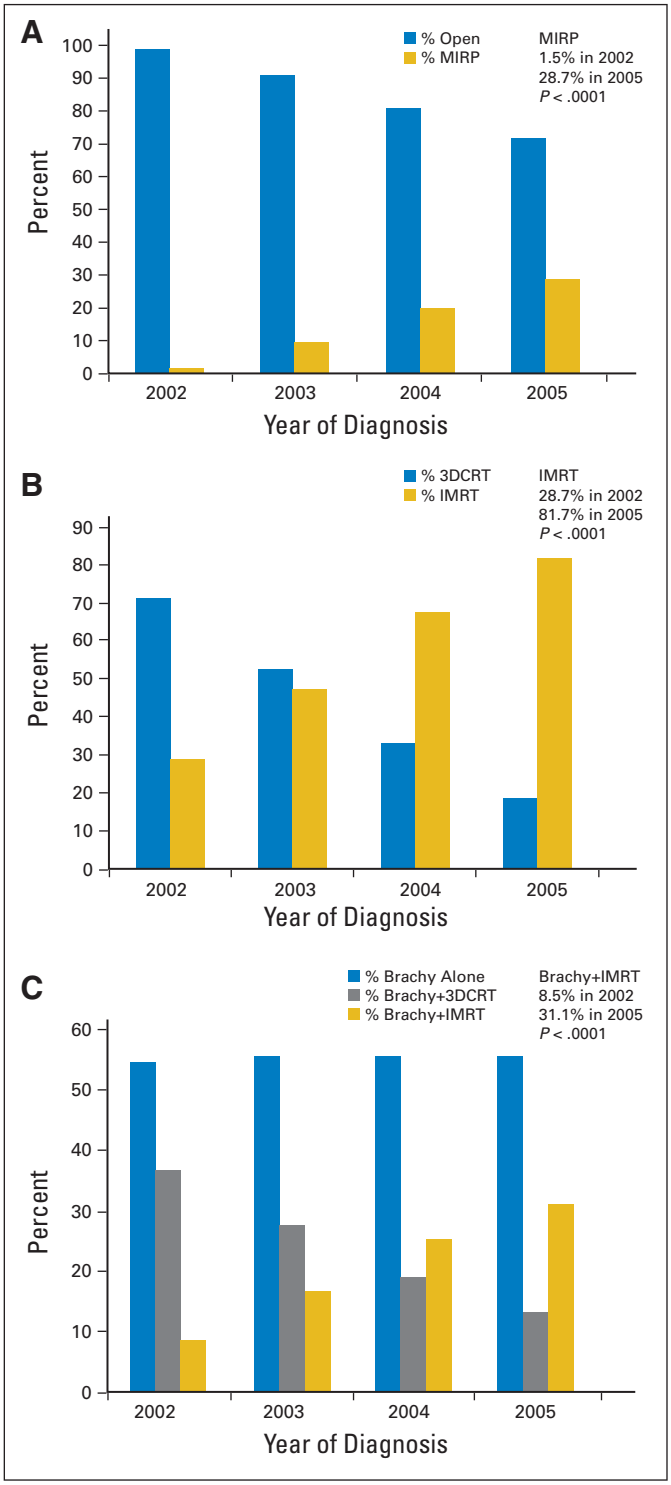

Fig 1. (A) Increasing use of minimally invasive radical prostatectomy (MIRP) among patients receiving surgery. (B) Increasing use of intensity-modulated radiation therapy (IMRT) among patients receiving external radiation. (C) Increasing use of supplemental IMRT among patients receiving brachytherapy (Brachy). 3D-CRT, three-dimensional conformal radiation therapy.

more expensive therapies over the study period. Among men undergoing surgery, MIRP was used by 1.5% of those diagnosed in 2002 versus 28.7% of those diagnosed in 2005 ($P < .001$), while IMRT was used by 28.7% in 2002 versus 81.7% in 2005 ($P < .001$) of those undergoing external radiation, and supplemental IMRT was used for 8.5% in 2002 versus 31.1% in 2005 ($P < .001$) among those receiving brachytherapy. Among just the subgroup of brachytherapy patients receiving supplemental external radiation, supplemental IMRT was used by 18.7% versus 70.2% ($P < .001$). Correspondingly, the use of each of the less expensive therapies (open RP, 3D conformal RT, and brachytherapy plus 3D conformal RT) decreased.

Predictors of Utilization

Table 2 presents a multivariable logistic regression of the factors associated with receiving more expensive therapy. Univariable analysis is listed in Appendix Table A3 (online only). The factors consistently associated with receiving the more expensive therapy regardless of whether they chose surgery or radiation were living in an area with median income $\geq$ $60,000, living in a metropolitan rather than rural area, having T1c disease, and being of Asian descent (all $P < .05$). The pattern of association with other demographic variables was less consistent. In our cohort of patients older than 65 years, the patients older than 75 years made up only 7% of those receiving MIRP, but were 33% of those receiving brachytherapy plus IMRT and 44% of those receiving IMRT. However, age was not a consistent significant predictor of utilization of more expensive therapies.

Cost of Therapy

Table 3 displays the mean cost of each primary therapy in 2008 dollars stratified by their year of diagnosis. Costs for each treatment declined significantly from 2002 to 2005 (all $P \leq .001$). For example, in constant 2008 dollars, IMRT costs fell by 15% from $37,125 to $31,574, brachytherapy plus IMRT costs fell by 16% from $43,723 to $36,795, and MIRP costs fell by 23% from $21,325 (in 2003 since the 2002 estimates are based on small numbers) to $16,469. Nevertheless, newer, more expensive treatments remained costlier than their less expensive alternatives over the study period. Specifically, among men diagnosed in 2005, the mean cost difference between IMRT and 3D-CRT was $10,986. Similarly, the cost difference between brachytherapy plus IMRT and brachytherapy plus 3D-CRT was $10,789, while the cost difference between MIRP and open RP was only $293. In Appendix Table A4 (online only), costs were alternatively estimated by matching controls from the Medicare 5% noncancer sample as outlined by Brown et al.[6]

Estimate of Excess Direct Medical Spending on Costlier Therapies at the National Level

Compared to the less costly alternative, the nationwide excess direct spending (Table 4) for the rapid adoption of more expensive therapies was $282 million for IMRT, $59 million for brachytherapy plus IMRT, and $4 million for MIRP for men diagnosed in 2005 (assuming that all treatments were reimbursed at Medicare rates).

DISCUSSION

Our study has several important findings. First, we found a rapid and substantial increase in the utilization of MIRP, IMRT, and brachytherapy plus IMRT, which are more expensive alternatives to traditional open RP, 3D-CRT, and brachytherapy plus 3D-CRT, respectively. Men who received the more expensive therapies tended to reside in wealthier areas, and in metropolitan as opposed to rural areas, possibly

Table 2. Multivariable Logistic Analysis of Factors Associated With More Expensive Therapy

Variable	MIRP *v* Open RP			IMRT *v* 3DCRT			Brachy/IMRT *v* Brachy/3DCRT		
	OR	95%CI	*P*	OR	95%CI	*P*	OR	95%CI	*P*
Outcome	MIRP			IMRT			Brachy/IMRT		
Age at diagnosis, years									
65-69	1.09	0.88 to 1.36	.4204	**1.18**	**1.09 to 1.28**	**< .001**	0.96	0.84 to 1.08	.4813
70-74	1.1	0.87 to 1.38	.4312	1.05	0.98 to 1.13	.1522	1.03	0.91 to 1.16	.6409
75+	1.00		ref	1.00		ref	1.00		ref
Comorbidity									
0	1.1	0.82 to 1.48	.5253	**1.14**	**1.03 to 1.26**	**.0135**	0.97	0.81 to 1.17	.7458
1	0.96	0.7 to 1.33	.8258	1.01	0.9 to 1.13	.876	0.99	0.81 to 1.21	.9107
2+	1.00		ref	1.00		ref	1.00		ref
Race									
White/Non-Hispanic	1.00		ref	1.00		ref	1.00		ref
Black/Non-Hispanic	0.91	0.71 to 1.15	.4284	**1.18**	**1.06 to 1.33**	**.0034**	1.17	0.99 to 1.38	.0608
Hispanic	**0.74**	**0.57 to 0.98**	**.0342**	**1.16**	**1 to 1.35**	**.0461**	**1.33**	**1.06 to 1.66**	**.0121**
Asian/Non-Hispanic	**1.51**	**1.18 to 1.93**	**.0011**	**1.49**	**1.27 to 1.76**	**< .001**	**1.43**	**1.11 to 1.86**	**.0062**
Other/unknown	1.03	0.65 to 1.66	.8868	1.21	0.97 to 1.51	.0894	1.27	0.84 to 1.93	.2561
High school education in patient's census region, %									
< 75	1.00		ref	1.00		ref	1.00		ref
75-84.99	0.99	0.8 to 1.22	.9448	**1.24**	**1.12 to 1.38**	**< .001**	1.06	0.9 to 1.25	.4966
85-89.99	**0.79**	**0.62 to 0.99**	**.0402**	**1.3**	**1.16 to 1.46**	**< .001**	**1.25**	**1.04 to 1.51**	**.0176**
90+	**0.74**	**0.58 to 0.93**	**.0111**	**1.52**	**1.35 to 1.73**	**< .001**	1.15	0.95 to 1.4	.1619
Median income, $									
< 35,000	1.00		ref	1.00		ref	1.00		ref
35,000-44,999	**1.49**	**1.24 to 1.79**	**< .001**	1.02	0.93 to 1.12	.6857	0.99	0.85 to 1.15	.8532
45,000-59,999	**1.91**	**1.57 to 2.33**	**< .001**	**1.13**	**1.02 to 1.26**	**.0228**	0.99	0.83 to 1.17	.8912
≥ 60,000	**3.1**	**2.49 to 3.85**	**< .001**	**1.47**	**1.29 to 1.67**	**< .001**	**1.31**	**1.07 to 1.59**	**.0075**
Region									
West	1.00		ref	1.00		ref	1.00		ref
Northeast	0.95	0.8 to 1.12	.5351	1.03	0.95 to 1.12	.4834	**2.17**	**1.91 to 2.47**	**< .001**
South	**0.73**	**0.61 to 0.88**	**.0009**	**0.74**	**0.67 to 0.82**	**< .001**	**1.65**	**1.43 to 1.91**	**< .001**
Midwest	**1.39**	**1.19 to 1.63**	**< .001**	**0.64**	**0.58 to 0.7**	**< .001**	**0.57**	**0.47 to 0.7**	**< .001**
Marital status									
Unmarried	1.00		ref	1.00		ref	1.00		ref
Married	0.99	0.84 to 1.16	.8818	1.04	0.96 to 1.12	.3355	1	0.88 to 1.13	.9599
Unknown	2.37	1.86 to 3.04	< .001	1.17	1.03 to 1.32	.0132	1.92	1.54 to 2.4	< .001
Population density									
Metropolitan	1.00		ref	1.00		ref	1.00		ref
Nonmetropolitan county	**0.75**	**0.58 to 0.97**	**.0307**	**0.76**	**0.67 to 0.85**	**< .001**	**0.52**	**0.41 to 0.66**	**< .001**
Grade/differentiation									
Well	1.00		ref	1.00		ref	1.00		ref
Moderately	1.09	0.62 to 1.93	.7538	1.13	0.86 to 1.49	.3752	0.86	0.5 to 1.46	.5726
Poorly	1.58	0.9 to 2.78	.1149	**1.73**	**1.32 to 2.28**	**< .001**	1.1	0.65 to 1.88	.7175
Unknown/missing	1.26	0.51 to 3.13	.6222	0.96	0.67 to 1.38	.8371	0.73	0.38 to 1.38	.3313
Clinical stage									
T1	1.00		ref	1.00		ref	1.00		ref
T2	**0.61**	**0.54 to 0.68**	**< .001**	**0.71**	**0.66 to 0.76**	**< .001**	**0.63**	**0.57 to 0.7**	**< .001**
T3	**0.53**	**0.33 to 0.86**	**.0104**	**0.67**	**0.57 to 0.8**	**< .001**	**0.71**	**0.53 to 0.94**	**.0169**
T4	0.36	0.08 to 1.62	.1853	**0.45**	**0.32 to 0.65**	**< .001**	0.71	0.23 to 2.23	.5637
Unknown/missing	0.29	0.15 to 0.56	.0002	0.72	0.58 to 0.9	.0038	0.8	0.51 to 1.25	.3183

NOTE. Boldface indicates statistical significance.
Abbreviations: MIRP, minimally invasive radical prostatectomy; Open RP, open radical prostatectomy; IMRT, intensity-modulated radiation therapy; 3DCRT, three-dimensional conformal radiation therapy; Brachy, brachytherapy; ref, referent.

due to the greater availability of newer technologies in these locations or greater marketing efforts directed toward their inhabitants. Of note, Asian race was consistently associated with 1.5-fold odds of receiving a more expensive therapy compared with white race, but the underlying reasons for this could not be determined from this study. Men undergoing the more expensive therapies also tended to have lower stage disease, which may reflect increased screening in more affluent populations, or perhaps a provider bias of offering these therapies to patients who will likely be cured of their prostate cancer and thereby have more time to benefit from any perceived reduction in long-term toxicity.

There are no randomized trials assessing whether newer treatments such as MIRP or IMRT have any clinical benefit over their less-expensive counterparts; the only available data currently come

Table 3. Mean Cost of Each Primary Therapy Among Medicare Enrollees, Stratified by Year of Diagnosis

	$						
Year	3DCRT	IMRT	Brachy	Brachy+ 3DCRT	Brachy+ IMRT	Open RP	MIRP
2002	22,384	37,125	21,117	28,770	43,723	18,070	29,988
2003	23,542	37,418	19,476	27,320	43,364	17,423	21,325
2004	22,023	33,237	18,308	26,756	39,453	16,930	17,645
2005	20,588	31,574	17,076	26,006	36,795	16,469	16,762
P trend	< .001	< .001	< .001	< .001	< .001	< .001	.001

Abbreviations: 3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; Brachy, brachytherapy; Open RP, open radical prostatectomy; MIRP, minimally invasive radical prostatectomy.

from retrospective studies. For instance, an observational, population-based study comparing outcomes after MIRP versus open RP found that MIRP appeared to be associated with a shorter length of stay (2 *v* 3 days), fewer transfusions (2.7% *v* 20.8%), fewer postoperative respiratory complications (4.3% *v* 6.6%), and fewer anastomotic strictures (5.8% *v* 14.0%). However, MIRP was also associated with an increased risk of genitourinary complications (4.7% *v* 2.1%) and diagnoses of incontinence (15.9 per *v* 12.2 per 100 person-years) and erectile dysfunction (26.8 *v* 19.2 per 100 person-years).[11] For external radiation, retrospective studies seem to consistently suggest that IMRT is associated with a significant reduction in long-term rectal bleeding compared to 3D-CRT. Zelefsky et al demonstrated that men treated to 81 Gy with IMRT versus conformal radiation experienced a significantly lower risk of ≥ grade 2 rectal bleeding, (2% *v* 14%, respectively), and other retrospective series have had similar findings.[12-14]

However, even if there is some underlying clinical benefit to these newer more expensive therapies, it is still important to ask whether the marginal benefit of these therapies is large enough to justify their higher cost.

We found that the rapid shift to more expensive therapies versus less costly counterparts resulted in a national cost burden of more than $350 million among patients diagnosed in 2005. Specifically, Medicare expenditures for IMRT were nearly $11,000 greater per case compared to 3D-CRT and were also nearly $11,000 greater per case for brachytherapy plus IMRT compared to brachytherapy plus 3D-CRT. While the Medicare expenditures for MIRP appeared to be only $236 more per case than for open radical prostatectomy, this surgical amount only approximates the difference in Medicare reimbursed surgeon fees between MIRP and open RP, and does not nearly reflect the full extent of the underlying cost difference between the surgical procedures. For instance, the most widespread form of MIRP presently is

Table 4. Estimates of Additional Direct Costs As a Result of Newer Technologies

	MIRP *v* Open RP						
Year	Utilization of MIRP From Our Cohort	Weighted Estimated Utilization of MIRP in US	Total No. in SEER Who Underwent Surgery	Estimated Total No. in the US Who Underwent Surgery	Estimated No. of MIRP in the US	Mean Cost Difference Between MIRP and Open RP ($)	Total Cost Savings If All MIRP in US Changed to Open RP ($)
2002	1.49	1.14	15,368	59,108	674	11,918	8,030,720
2003	9.48	7.78	14,760	56,769	4,417	3,902	17,233,683
2004	19.59	18.17	15,360	59,077	10,734	715	7,675,018
2005	28.66	25.17	13,866	53,331	13,423	293	**3,933,060**
	IMRT *v* 3D-CRT						
Year	Utilization of IMRT From Our Cohort	Weighted Estimated Utilization of IMRT in US	Total No. in SEER Who Underwent RT	Estimated Total No. in the US Who Underwent RT	Estimated No. of IMRT in the US	Mean Cost Difference Between IMRT and 3DCRT ($)	Total Saving Cost If All IMRT in US Changed to 3DCRT ($)
2002	28.65	23.35	10,656	40,985	9,570	14,741	141,071,333
2003	47.20	39.62	10,148	39,031	15,464	13,876	214,579,605
2004	67.31	58.80	10,006	38,485	22,629	11,214	253,763,625
2005	81.66	74.18	8990	34,577	25,649	10,986	**281,782,316**
	Brachy/IMRT *v* Brachy/3D-CRT						
Year	Utilization of Brachy/IMRT From Our Cohort	Weighted Estimated Utilization of Brachy/IMRT in US	Total No. in SEER Who Underwent Brachy + RT	Estimated Total No. in the US Who Underwent Brachy + RT	Estimated No. of Brachy/IMRT in the US	Mean Cost Difference Between Brachy/IMRT and Brachy/EBRT ($)	Total Cost Savings If All Brachy/IMRT in US Changed to Brachy/EBRT ($)
2002	18.66	15.51	2,914	11,208	1,738	14,953	25,993,709
2003	37.54	36.49	2,136	8,215	2,998	16,044	48,094,353
2004	57.26	53.72	1,931	7,427	3,990	12,697	50,658,293
2005	70.19	71.27	2,000	7,692	5,482	10,789	**59,146,252**

Abbreviations: MIRP, minimally invasive radical prostatectomy; Open RP, open radical prostatectomy; SEER, Surveillance, Epidemiology, and End Results database; IMRT, intensity-modulated radiation therapy; Brachy, brachytherapy; 3DCRT, three-dimensional conformal radiation therapy.

robotic-assisted prostatectomy, which requires at least a $1.4 million upfront investment to purchase the robot and then a $140,000 annual maintenance for the robot.[3] Importantly, while private health plans may reimburse a facility fee, Medicare does not reimburse for the use of the robot. Therefore, this fixed component of the costs cannot be accounted for by a Medicare claims–based analysis, which makes the cost difference between open RP and MIRP seem artificially small. Moreover, our Medicare-based cost estimates likely underestimate the true expense of the rapid shift to newer, more costly technologies, as Medicare typically reimburses a lower amount compared to private health plans.

Just as the newer technologies have been widely adopted without rigorous efficacy trials, they have also been adopted without robust cost-effectiveness analysis. To our knowledge, there are no data on the cost-effectiveness of MIRP. As for the cost-effectiveness of IMRT, a study by Konski et al suggested that based on its likely reduction in rectal toxicity, IMRTs incremental cost per quality-adjusted life year was $40,101, which meets the typical requirement that treatments have an incremental cost/quality-adjusted life year lower than $50,000 to be considered cost-effective.[15] However, that article was not published until 2006, and this study suggests that by then, 81% of external radiation patients were already receiving IMRT, making it likely that even if IMRT were found to not be cost effective, it would have been nearly impossible to reverse the nationwide trend in its use.

This research has implications for predicting the patterns of use of other newer and more expensive technologies in health care, as these trends are likely not unique to prostate cancer. It suggests that when a newer expensive technology becomes available and is reimbursed by health plans, it is likely to be rapidly adopted even before there is adequate data on its clinical benefits and cost effectiveness. This study may also inform the debate about the use of proton therapy for prostate cancer. Proton therapy carries a significantly higher price tag than IMRT, with some estimates showing it is about twice as expensive.[16] There are also significant marketing efforts promoting protons for prostate cancer and growing patient interest in receiving it. While protons are likely less toxic for certain pediatric and CNS tumors,[17,18] it remains unknown whether protons for prostate cancer are superior to IMRT in terms of cancer control or toxicity, and there is great uncertainty about whether proton therapy for prostate cancer could be cost-effective.[16,19] Nevertheless, if protons become more widely available, the trends seen in the rapid uptake of IMRT for prostate cancer may well be repeated with proton therapy.

Proponents of allowing the widespread adoption of higher-cost therapies before they are proven may point out that as a technology becomes more widely used, its costs will decrease over time. This is in fact reflected in Table 3, which shows the mean cost of IMRT falling by 20% from 2002 to 2005, and of MIRP falling by 12% over the same time period. These drops in the inflation-adjusted cost of each prostate cancer therapy are corroborated by other reports.[7] As the prices of these newer technologies falls, the likelihood that they will become cost effective can theoretically increase. However, it should be noted that the costs of the less-expensive therapies were also falling over that same time period. If the cost of the less expensive therapy is also falling, then the more expensive therapy may remain equally cost-ineffective despite its lower absolute price tag.

This study has certain limitations. First, we may have overestimated the excess costs of the new therapies because we could only look at direct Medicare costs, and could not factor in the potential indirect cost benefits, such as MIRP potentially leading to fewer missed working days for patients. In addition, our 12-month cost methodology cannot capture potential long-term savings from toxicity reduction, such as IMRT potentially reducing the need for late interventions for rectal bleeding. We also could not account for any potential long-term savings that could be due to higher cure rates and lower need for salvage therapies. Also, as more surgeons performing MIRP overcome their learning curves, the cost differentials between MIRP and open RP may fall. Conversely, we may have underestimated the excess costs because to be consistent with other cost studies we only accounted for direct Medicare payments and excluded payments made by beneficiaries and supplemental insurance. Accounting for these additional payments would have increased our estimated excess expenditures by approximately 30%. Finally, as mentioned above, the cost estimates were entirely based on patients enrolled in Medicare, and applying the mean Medicare costs to younger patients who may have private insurance that reimburses at higher rates likely leads to an underestimate of the true nationwide expenditures on the more expensive therapies.

Despite limited comparative effectiveness research, newer and costlier prostate cancer therapies were rapidly and widely adopted, resulting in an excess national spending of more than $350 million among men diagnosed in 2005. This pattern of rapid adoption may provide some empirical evidence for why health care costs account for 17% of the US gross domestic product,[20] and suggests the need for increased comparative effectiveness research to accurately weigh costs and benefits.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Influence of Surgeon and Hospital Volume on Radical Prostatectomy Costs

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Abbreviations and Acronyms

RP = radical prostatectomy

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Study received institutional review board approval.

This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors.

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See Editorial on page 2037.

Purpose: While higher radical prostatectomy hospital and surgeon volume are associated with better outcomes, the effect of provider volume on health care costs remains unclear. We performed a population based study to characterize the effect of surgeon and hospital volume on radical prostatectomy costs.

Materials and Methods: We used SEER (Surveillance, Epidemiology and End Results)-Medicare linked data to identify 11,048 men who underwent radical prostatectomy from 2003 to 2009. We categorized hospital and surgeon radical prostatectomy volume into tertiles (low, intermediate, high) and assessed costs from radical prostatectomy until 90 days postoperatively using propensity adjusted analyses.

Results: Higher surgeon volume at intermediate volume hospitals (surgeon volume low $9,915; intermediate $10,068; high $9,451; p = 0.021) and high volume hospitals (surgeon volume low $11,271; intermediate $10,638; high $9,529; p = 0.002) was associated with lower radical prostatectomy costs. Extrapolating nationally, selective referral to high volume radical prostatectomy surgeons at high and intermediate volume hospitals netted more than $28.7 million in cost savings. Conversely, higher hospital volume was associated with greater radical prostatectomy costs for low volume surgeons (hospital volume low $9,685; intermediate $9,915; high $11,271; p = 0.010) and intermediate volume surgeons (hospital volume low $9,605; intermediate $10,068; high $10,638; p = 0.029). High volume radical prostatectomy surgeon costs were not affected by varying hospital volume, and among low volume hospitals radical prostatectomy costs did not differ by surgeon volume.

Conclusions: Selective referral to high volume radical prostatectomy surgeons operating at intermediate and high volume hospitals nets significant cost savings. However, higher radical prostatectomy hospital volume was associated with greater costs for low and intermediate volume radical prostatectomy surgeons.

Key Words: health expenditures, prostatectomy

Prostate cancer remains the most commonly diagnosed solid organ tumor of United States men with approximately 217,730 new cases in 2010.[1] Given the high incidence, prostate cancer contributes significantly to spiraling Unites States health care costs, tallying several billion dollars annually.[2] Moreover, prostate cancer has been singled out as a litmus test for health care reform. There is a lack of consensus regarding the best treatment, and treatments are increasingly costly with mediocre results.[3] Radical prostatectomy hospital and surgeon volumes are prostate cancer

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quality indicators, and regionalization of care may improve outcomes similar to other complex oncologic procedures.[4,5] Furthermore, higher RP surgeon and hospital volume are associated with better outcomes[6,7] and lower hospital charges.[8,9] However, little is known regarding the effect of provider volume on actual health care costs. Therefore, in this population based study we evaluated the effect of surgeon and hospital volume on RP costs.

MATERIALS AND METHODS

Data

Our study was approved by the Brigham and Women's institutional review board. Patient data were de-identified and the requirement for consent was waived. We used SEER-Medicare linked data for analyses, comprised of a linkage of population based cancer registry data from 16 SEER regions covering approximately 28% of the United States population with Medicare administrative data. The Medicare program provides benefits to 97% of Americans 65 years old or older.[10]

Study Cohort

We identified 15,347 men 65 years old or older diagnosed with prostate cancer from 2003 to 2007 who underwent RP during 2003 to 2009. We used the CPT Coding System, 4th edition to differentiate retropubic, perineal and minimally invasive RP, consistent with prior studies.[11] We excluded 2,616 men not enrolled in both Medicare Part A and Part B, or who were enrolled in a Medicare health maintenance organization (because their claims were not reliably submitted). A total of 1,683 men were excluded from study because of missing demographic or tumor characteristics, leaving a final cohort of 11,048 men.

Expenditures Related to Surgeon and Hospital Volume

To determine radical prostatectomy costs, we summed all Medicare health care expenditures from inpatient, outpatient and physician services within 3 months of radical prostatectomy. All costs were adjusted to 2010 dollars using the 2007 Annual Report of the Boards of Trustees of the Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Funds.[12]

Control Variables

Age was obtained from the Medicare file, and tumor characteristics, race, census tract measures of median household income and high school education, region, population density (urban vs rural) and marital status were obtained from SEER registry data. Comorbidity was assessed using the Klabunde modification of the Charlson index during the year before surgery. We determined RP surgeon and hospital volume by aggregating the number of procedures performed from 2003 to 2009. While we originally categorized provider volume into quartiles consistent with previous studies,[6] this process resulted in few very high volume surgeons operating at low volume hospitals and vice versa and, therefore, we categorized surgeon volume into tertiles. In terms of hospital volume thresholds, the low, intermediate and high volume hospitals performed 1 to 33, 34 to 99 and 100 to 738 RPs during the study period, respectively.

Statistical Analysis

Because men undergoing RP varied by surgeon volume in terms of demographic characteristics and geography, we used weighted propensity score methods to adjust for these differences. Propensity score methods permit control for observed confounding factors that might influence group assignment and outcome using a single composite measure, and attempt to balance patient characteristics among groups.[11]

To conduct the propensity score adjustment, we used a logistic regression model to calculate the propensity (probability) of undergoing RP by surgeon volume based on all covariates previously described, and then weighted each patient's data based on the inverse propensity of being in either of the treatment groups.[13] Covariate balance was checked after adjustment.

From a 3×3 table assessing the joint effect of hospital and surgeon volume on RP costs, skewness for the 9 hospital-surgeon volume combinations ranged from 2.3 to 15.1, indicating right skewed distributions, with most values concentrated below the mean and extreme values above the mean.[14] Because RP costs were not normally distributed and were heavily right skewed, propensity weighted median costs were compared by provider volume. However, we used mean costs in determining total cost savings, which is the product of RP mean costs and the number of RPs.

Potential Cost Savings from Selective Referral

We identified the total number of RPs performed in SEER registries in 2007.[15] Because SEER registries captured 28% of the United States population during the study period, we divided by 0.28 to estimate RPs performed nationally in 2007. To determine the total number of RPs performed nationally by low, intermediate and high volume surgeons, we multiplied total RPs by the respective proportions performed by the corresponding surgeon volume category from our SEER-Medicare cohort to estimate national cost savings of selective RP referrals as previously described.[16] All analyses were performed with SAS® version 9.2.

RESULTS

The demographics of our study population by surgeon volume are shown in table 1. Older, married and white men were more likely to undergo RP performed by high volume surgeons ($p < 0.005$). In addition, men residing in areas of greater income and education were more likely to undergo RP by high volume surgeons ($p < 0.001$). Moreover, there was significant geographic variation by RP surgeon volume ($p = 0.002$). However, men with clinically organ confined prostate cancer (clinical stage T2 or less) were more likely to undergo RP by high volume surgeons ($p = 0.014$). Men were also more likely to undergo minimally invasive RP by a high volume surgeon ($p < 0.001$). Propensity adjusted analyses are shown in table 1.

The adjusted median RP Medicare costs by surgeon and hospital volume are presented in table 2. RP costs decreased with higher surgeon volume at intermediate ($p = 0.021$) and high volume hospitals

Table 1. *Propensity model adjusted outcomes*

	Low Surgeon Vol	Intermediate Surgeon Vol	High Surgeon Vol	p Value
No. pts	3,524	3,637	3,887	
Surgical vol	1–16	17–38	39–320	
No. age at diagnosis (%):				
65–69	2,275 (63.4)	2,264 (63.4)	2,463 (63.4)	0.996
70–74	1,077 (30)	1,083 (30)	1,145 (30)	
75+	238 (6.6)	245 (6.6)	258 (6.6)	
No. Charlson score (%):				
0	2,903 (80.9)	2,886 (80.9)	3,094 (80.9)	0.974
1	543 (15.1)	559 (15.1)	612 (15.1)	
2+	144 (4)	148 (4)	161 (4)	
No. race (%):				
White	2,993 (83.4)	2,958 (83.4)	3,232 (83.4)	0.998
Black	237 (6.6)	249 (6.6)	253 (6.6)	
Hispanic	221 (6.1)	234 (6.1)	225 (6.1)	
Asian	139 (3.9)	152 (3.9)	156 (3.9)	
No. marital status (%):				
Not married	553 (15.4)	556 (15.4)	596 (15.4)	0.997
Married	3,037 (84.6)	3,036 (84.6)	3,270 (84.6)	
No. % with high school education (%):				
Less than 75	588 (16.4)	629 (16.4)	667 (16.4)	0.992
75–84.99	701 (19.5)	707 (19.5)	756 (19.5)	
85–89.99	641 (17.9)	671 (17.9)	707 (17.9)	
90+	1,660 (46.2)	1,586 (46.2)	1,735 (46.2)	
No. median income (%):				
Less than $35,000	975 (27.2)	1,007 (27.2)	1,104 (27.2)	0.997
$35,000–$44,999	806 (22.5)	833 (22.5)	869 (22.5)	
$45,000–$59,999	876 (24.4)	855 (24.4)	906 (24.4)	
$60,000 or Greater	933 (26)	898 (26)	987 (26)	
No. region (%):*				
Northeast	430 (12)	430 (12)	530 (12)	1.00
South	614 (17.1)	574 (17.1)	617 (17.1)	
Midwest	447 (12.5)	464 (12.5)	512 (12.5)	
West	2,098 (58.5)	2,125 (58.5)	2,206 (58.5)	
No. population density (%):				
Big metro	1,872 (52.2)	1,883 (52.2)	2,009 (52.2)	1.00
Metro	1,227 (34.2)	1,224 (34.2)	1,293 (34.2)	
Urban	183 (5.1)	185 (5.1)	209 (5.1)	
Less urban	248 (6.9)	241 (6.9)	285 (6.9)	
Rural	60 (1.7)	60 (1.7)	70 (1.7)	
No. grade (%):				
Well/moderately differentiated	2,119 (59)	2,119 (59)	2,271 (59)	0.986
Poorly/undifferentiated	1,470 (41)	1,473 (41)	1,595 (41)	
No. clinical stage (%):				
T3/T4	77 (2.1)	70 (2.1)	111 (2.1)	0.816
T2	1,689 (47.1)	1,715 (47.1)	1,822 (47.1)	
T1	1,823 (50.8)	1,808 (50.8)	1,932 (50.8)	
No. surgical approach (%):				
Minimally invasive RP	1,212 (33.8)	1,115 (33.8)	1,215 (33.8)	0.932
Perineal RP	130 (3.6)	137 (3.6)	104 (3.6)	
Retropubic RP	2,247 (62.6)	2,340 (62.6)	2,547 (62.6)	

* The weighted propensity score was adjusted for age, comorbidity, race/ethnicity, marital status, education, income, SEER region, population density, pathological grade, stage and hospital volume.

($p = 0.002$). However, surgeon volume did not affect RP costs at low volume hospitals ($p = 0.917$). Conversely, RP costs increased with higher hospital volume for low ($p = 0.010$) and intermediate ($p = 0.029$) volume surgeons. However, RP costs did not vary by hospital volume for high volume surgeons ($p = 0.974$). Extrapolating nationally, selective referral from low and intermediate to high volume RP surgeons at intermediate and high volume hospitals netted more than $28.7 million in annual cost savings.

DISCUSSION

High risk surgical procedures such as pancreatectomy[4] and esophagectomy[5] have decreased morbidity and mortality when performed at high volume hospitals. Similarly, higher hospital volume is associated with decreased morbidity for colon[17] and breast[18] cancer surgeries. In addition, hospital volume is inversely related to in-hospital mortality and length of stay after RP.[8] However, surgeon rather than hospital volume has been shown to be the principal determinant of RP outcomes, as intensive care admissions and lengths of hospitalization have decreased in the last 20 years.[19,20] In addition, RP hospital and surgeon volumes have been analyzed to assess whether centralization may be beneficial to minimize morbidity, mortality and costs.[8,21,22] Given that the majority of radical prostatectomies are performed by surgeons performing fewer than 10 a year,[23] selective referral of radical prostatectomies to high volume surgeons may lead to significant cost savings, particularly with the reality of accountable care organizations looming on the horizon.

Our study has several important findings. Higher surgeon volume was associated with a reduction in RP costs at intermediate and high volume hospitals where most RPs are performed, and selective referral to high volume surgeons at intermediate and high volume hospitals nationally would reduce health care costs by more than $28.7 million. This amount exceeds the $19 million the National Cancer Institute allocated to funding surgery related research in 2010 for prostate cancer.[24] However, it is likely that our cost estimates underestimate the actual cost savings of selective referrals as Medicare reimburses a lower amount com-

Table 2. *Propensity score weighted median Medicare costs by surgeon and hospital volume**

	Median Medicare Costs			
	Low Surgeon Vol	Intermediate Surgeon Vol	High Surgeon Vol	p Value
Low hospital vol	$9,638	$9,529	$9,582	0.817
Intermediate hospital vol	$9,915	$10,011	$9,420	0.032
High hospital vol	$11,257	$10,638	$9,611	0.004
p Value	0.009	0.009	0.945	

* For differences in costs across combinations of surgeon volume and hospital volume $p = 0.001$, from a test statistic that is a function of the interaction terms between surgeon volume and hospital volume, as well as a function of the main effects of surgeon volume and hospital volume.

pared to private health plans. Moreover, we did not assess indirect RP costs, ie costs of treating post-prostatectomy incontinence and erectile dysfunction, which may be greater for less experienced, low volume surgeons. Others have shown that higher surgeon volume is associated with lower hospital charges,[9] suggesting that as RP surgeons gain experience, they become more efficient, and have better outcomes with lower costs.[6,21] Correspondingly, high RP volume surgeon costs were not affected by changes in hospital volume in our study.

We also found that higher RP hospital volume was associated with higher costs for low and intermediate volume surgeons, and this contrasts evidence demonstrating an inverse relationship between hospital volume and RP charges.[8] However, RP costs for high volume surgeons were unaffected by hospital volume. Increased RP surgeon volume portends improved perioperative outcomes,[21,22] which may be the more important determinant to offset costs vs other high risk procedures such as pancreatectomy[4] and esophagectomy.[5] These high risk procedures require dedicated anesthesia, perfusionists and intensive care nursing, suggesting hospital volume may be more important. Higher volume hospitals tend to be academic medical centers with the mission of furthering research, education and clinical care, accepting patients regardless of clinical presentation and financial risk.[25] Thus, higher volume hospitals may have better information technology, documentation and compliance with reimbursement guidelines to offset potential financial risks. Moreover, our finding that higher volume hospitals are associated with higher RP costs may reflect the greater availability of technology based services such as advanced imaging modalities at larger, high volume centers. Although our findings pertain to Medicare RP, there is wide variation in payments by private health plans to hospitals across and within local markets, suggesting that hospitals have significant market power to negotiate higher than competitive prices.[26] The Medicare Payment Advisory Commission found that hospitals with substantial negotiating leverage may allow unit costs to increase because they obtain higher private insurance rates to offset negative Medicare margins.[27] Efforts to slow spending growth and limit costs are under way with policies that encourage high growth (or high cost) hospitals to behave like low growth, low cost hospitals.[28] Moreover, this decreased hospital negotiating power may contribute to our observation that low volume hospital RP costs were unaffected by RP surgeon volume.

On univariable analysis there was significant geographic variation in RP costs, consistent with prior reports demonstrating regional differences in Medicare costs for patients with similar conditions and access to the same advanced technology.[28] These regional differences are not due to differences in the prices of medical services, levels of illness or the sociodemographic characteristics of a region, but rather are secondary to a greater quantity of medical services delivered in high cost areas.[28] Furthermore, decision making among physicians is highly correlated with regional differences in capital spending. For instance, high spending regions are more likely to use subspecialists and intensive care units, while they are less likely to discuss palliative care.[13] However, despite regional cost variation, quality of care may not necessarily be better in regions of greater use and may, in fact, be significantly worse than the quality of care in low expenditure areas.[29] The culture in medical communities is an important determinant of the quantity of medical care delivered and how much it costs,[29] and may be the rate limiting step when attempting to decrease costs and attenuate regional variation in health care spending.

Our findings must be interpreted in the context of the study design. SEER-Medicare is limited to men 65 years old or older and our results may not be generalizable to younger men undergoing RP. For instance, 32% of men undergoing RP are 65 years old or older and, therefore, 1 Medicare RP approximates 3 overall RPs[30] and our Medicare volume thresholds may not accurately portray overall provider volume. In addition, our findings of cost differences by provider volume are accentuated for private health plans, as their reimbursements for RP are more generous than Medicare, and high volume tertiary care vs low volume community hospitals negotiate richer contracts. To exclusively assess the independent effect of provider volume on RP costs, we used propensity scores requiring categorization of provider volume. However, we performed median regression (since RP costs were right skewed and log transformation did not normalize costs) with provider volume as a continuous variable and found similar results. Higher RP surgeon volume was associated with lower costs while higher RP hospital volume was associated with higher costs. Because we only accounted for direct Medicare payments and excluded payments made by beneficiaries, we underestimated RP costs and potential cost savings. Accounting for these additional payments may net additional cost savings resulting from selective referral.[16] While limited access, supply and geographic distances may preclude selective referral to high volume surgeons, there is tremendous heterogeneity in RP surgical technique and outcomes that contributes to the cost differences that we observed. Characterizing, disseminating and standardizing RP surgical technique and health care delivery by high volume surgeons may be a more feasible mechanism to attain RP cost savings. SEER-Medicare does not

characterize biochemical recurrence, which may contribute to greater indirect RP costs for treating recurrence beyond our 90-day post-RP study period. Finally, we did not distinguish RP performed with vs without robotic assistance. However, less than 40% of all RPs were performed with robotic assistance during the study period.[11] While private health plans may reimburse a facility fee, Medicare does not reimburse for the use of the robot, and this fixed component of the costs cannot be accounted for by a Medicare claims based analysis.

CONCLUSIONS

RP costs were lowest at low volume hospitals and were unaffected by surgeon volume. However, selective referral to high volume surgeons at intermediate and high volume hospitals was associated with lower RP costs. Although RP costs were lowest for high volume surgeons and did not vary by hospital volume, higher hospital volume was associated with higher RP costs for low and intermediate volume surgeons. These findings must be considered by health reform initiatives that seek to balance the seemingly countervailing goals of reducing health care costs while improving quality of care.

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EDITORIAL COMMENTS

Williams et al found that higher surgeon volumes were associated with lower costs for radical prostatectomy when operating at high or intermediate volume hospitals. Surgeries at higher volume hospitals did not reduce costs for low and intermediate volume surgeons. This suggests that the surgeon is the main determinant of cost and that even efficient hospitals cannot compensate for lower surgeon experience.

When extrapolated nationally the net savings are approximately $29 million. While the savings are not impressive compared with the multiple billion dollars of costs for prostate cancer care annually, there are many reasons for patients to search for surgeons with more experience. Several studies have demonstrated that rates of postoperative and late urinary complications are significantly reduced if the procedure is performed at a high volume hospital and by a surgeon who performs a high number of such procedures (reference 6 in article). Furthermore, higher volume surgeons have lower rates of positive surgical margins after radical prostatectomy.[1] Despite these advantages, instituting policies that encourage referral to high volume surgeons has many obstacles and currently are driven by patient demand.

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The impact of case volume on the outcomes of complicated surgical procedures has been well documented throughout the medical literature. Begg et al was one of the first groups to specifically link open radical prostatectomy surgeon and hospital volume with short-term and long-term morbidity (reference 6 in article). The higher volume urologists (and hospitals) tended to have fewer complications compared with their lower volume counterparts. We found a similar volume/outcome relationship when looking at minimally invasive RP. The higher volume surgeons tended to have fewer complications and their patients had shorter hospital stays than the lower volume surgeons.[1]

Williams et al explore the impact of volume on RP costs, and their findings are somewhat contrary to what I expected based on the previously described positive association of RP volume and perioperative outcomes. RP costs were found to be the lowest at low volume hospitals regardless of surgeon volume. Furthermore, for low and intermediate volume surgeons, higher hospital volume was associated with higher costs. These findings are thought provoking, and show that the impact of volume on cost is a complicated matter and deserves further study. Based on these results, I question whether regional referral to high volume centers/surgeons will actually result in significant cost savings in the surgical care of prostate cancer. But if high volume centers/surgeons provide superior outcomes, then a higher cost is justifiable.

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REPLY BY AUTHORS

While $29 million is a relatively small amount, our study of Medicare radical prostatectomies likely underestimates the potential cost savings pocketed from selective referral among privately insured men. Moreover, surgeon experience contributes to the preservation of functional outcomes[1] and recurrence-free survival,[2] and it was beyond the scope of our study to estimate the downstream cost savings of

avoiding diagnostic and therapeutic interventions such as potency/pelvic floor rehabilitation, imaging, and salvage radiation and/or androgen deprivation therapy.

As for the counterintuitive finding that higher volume radical prostatectomy hospitals cost more rather than drive down costs with greater efficiency and less waste of costly resources, one may turn to Massachusetts, a vanguard for health care reform. Recently the Department of Justice investigated Partners HealthCare, a network led by Massachusetts General and Brigham and Women's Hospitals, for anticompetitive behavior following a report from the state attorney general attributing 75% of spending trends to price increases and 25% to increased use.[3] Shortly thereafter, Partners HealthCare volunteered $40 million to decrease premiums for small groups and individuals. Similarly, hospital mergers in Toledo, Ohio resulted in higher reimbursements passed onto consumers as higher premiums, co-pays and other costs, and consequently a Federal Trade Commission challenge followed.[4]

While there is complex interplay among radical prostatectomy hospital and surgeon volume, patient demand, outcomes and health care costs, a paradigm shift to a capitated accountable care organization model will place the onus on health care providers to rein in radical prostatectomy costs and improve outcomes.

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Original Article

Utilization and Expense of Adjuvant Cancer Therapies Following Radical Prostatectomy

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BACKGROUND: We sought to identify the costs of adjuvant therapies following radical prostatectomy (RP) and factors associated with their receipt. **METHODS:** We used SEER-Medicare data from 2004-2006 to identify 4247 men who underwent RP, of whom 600 subsequently received adjuvant therapies. We used Cox regression to identify factors associated with receipt of adjuvant therapies. Health care expenditures within 12 months of diagnosis were compared for RP alone versus RP with adjuvant therapies. **RESULTS:** Biopsy Gleason score, prostate-specific antigen, risk group, and SEER region were significantly associated with receipt of adjuvant treatments (all $P<.001$). Higher surgeon volume was associated with lower odds of receiving adjuvant therapies (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.46-0.78 [$P<.001$]). Factors associated with increased receipt of adjuvant therapies were positive surgical margins (HR, 3.02; 95% CI, 2.55-3.57 [$P<.001$]), high-risk group versus low-risk group (HR, 7.65; 95% CI, 5.64-10.37 [$P<.001$]), lymph node–positive disease (HR, 5.36; 95% CI, 3.71-7.75 [$P<.001$]), and treatment in Iowa (HR, 1.93; 95% CI, 1.12-3.32 [$P = .019$]) and New Mexico/Georgia/Hawaii (HR, 1.92; 95% CI, 1.09-3.39 [$P = .025$]) versus San Francisco SEER regions (baseline). Age, race, comorbidities, and surgical approach were not associated with use of adjuvant therapies. The median expenditures attributable to postprostatectomy hormonal therapy, radiation therapy, and radiation with hormonal therapy versus were $1361, $12,040, and $23,487. **CONCLUSIONS:** Men treated by high-volume surgeons were less likely to receive adjuvant therapies. Regional variation and high-risk disease characteristics were associated with increased receipt of adjuvant therapies, which increased health care expenditures by 2- to 3-fold when radiotherapy was administered. ***Cancer* 2011;117:4846–54.** © *2011 American Cancer Society.*

KEYWORDS: prostatectomy, adjuvant therapy, utilization, expenditures, outcomes.

Prostate cancer remains the most commonly diagnosed solid organ tumor among men in the United States, with approximately 192,000 incident cases in 2009.[1] The majority of these tumors are localized, and radical prostatectomy (RP) remains the most popular treatment option.[2] However, 21%-37% of men experience biochemical recurrence (BCR) after radical prostatectomy.[3] Recent studies have shown that postprostatectomy radiotherapy improves prostate cancer-specific survival[4] and significantly decreases overall mortality when used in the adjuvant[5] or salvage setting in selected men with high-risk disease.[6] Furthermore, the benefit of hormonal therapy needs to be carefully balanced against the significant inherent risks of cardiovascular and thromboembolic disease, along with the substantial health care costs of implementing this treatment.[7-9] Hormonal therapy as it pertains to the adjuvant setting, either alone or in combination with radiotherapy, has been less extensively evaluated, with no definitive guidelines on who should receive treatment or when to initiate it.[8,9]

Although there are few contemporary characterizations of secondary therapies,[6,10,11] a study of Medicare beneficiaries from the early 1990s demonstrated that 35% of men receive secondary therapies following RP.[12] However, this may not reflect contemporary practice patterns due to the downward stage migration that followed the advent of prostate-specific antigen (PSA) screening.[13] The purpose of our population-based study was to evaluate factors associated with the use of adjuvant cancer therapies following RP and estimate the associated health care expenditures of these treatments.

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MATERIALS AND METHODS

The study was approved by the Brigham and Women's Institutional Review Board. Patient data were de-identified and the requirement for consent was waived. We used Surveillance, Epidemiology, and End Results (SEER)-Medicare data for analysis, which comprise a linkage of population-based cancer registry data from 16 SEER areas with Medicare administrative data and cover approximately 26% of the United States population. The Medicare program provides benefits to 97% of Americans aged $\geq$65 years.[14]

Study Cohort

We identified 4247 men aged $\geq$65 years who were diagnosed with prostate cancer in 2004 and 2005 and underwent RP through 2006 based on the Physician's Current Procedural Terminology Coding System, 4th edition, (CPT-4): codes 55840, 55842, 55845 for open RP and code 55866 for minimally invasive RP. CPT-4 code 55899 (unspecified male genitourinary procedure) may sometimes be used with an open RP administrative code to specify minimally invasive RP with robotic assistance for private health plans,[15] but Medicare does not recognize this coding schema, and very few men had this combination of codes; therefore, this schema was not used to identify minimally invasive RP. We excluded men not enrolled in both Medicare Part A and B, or who were enrolled in a Medicare health maintenance organization (because their claims are not reliably submitted). Because SEER only captures positive margin characteristics for American Joint Commission on Cancer pathological T2 and T3a disease, we excluded 292 men with pathological stage T3b, 63 men with pathological stage T4, and 412 men with missing margin status from our cohort. Patients with lymph node–positive disease (n = 45) were included in the study. In addition, to increase the sensitivity for detecting additional postoperative radiation therapy, we restricted our cohort to patients with prostate cancer diagnosed as their only cancer. A total of 204 patients with other cancers, including nonmelanoma skin cancers, were excluded from the analysis.

Outcomes

We examined the utilization of adjuvant therapy (radiation and/or hormonal) after RP in patients with pathological T2 and T3a disease.[12,16] According to the American Urological Association 2007 guidelines, additional radiation and/or hormonal therapy should be administered to patients with adverse pathological features and/or positive surgical margins.[17]

Control Variables

Age was obtained from each patient's Medicare file; race, census tract measures of median household income and high school education, region, population density (urban vs rural), and marital status were obtained from SEER registry data. Comorbidity was assessed using the Klabunde modification of the Charlson index during the year before surgery.[18] The Klabunde modification uses comorbid conditions identified by the Charlson comorbidity index and incorporates the diagnostic and procedure data contained in Medicare physician (Part B) claims. Variables were categorized as in Table 1. Additionally, we used PSA, Gleason grade, and clinical stage to stratify men to low, intermediate, and high-risk disease.[19] However, tumor stage was missing/unknown for almost one-third of our patients, and we therefore used a modified risk stratification without clinical stage, resulting in a low-risk designation for 29% of our cohort. Therefore, we used a modified risk classification defined as follows: PSA $<$10 and biopsy Gleason score $<$7 = low; PSA 10-20 or Gleason score 7 = intermediate; PSA $>$20 or Gleason score $>$7 = high.

Because surgeon rather than hospital volume is the more significant determinant of outcomes following open RP,[20] we determined surgeon volume for each type of procedure by aggregating the number of procedures performed from 2004-2006. Surgeon volume was categorized into quartiles, consistent with a prior study.[21]

Expenditures Related to the Use of Adjuvant Cancer Therapies

We compared baseline health care expenditures in the 12 months prior to prostate cancer diagnosis for men who underwent RP alone versus those who underwent adjuvant treatment postprostatectomy. To determine the total expense of adjuvant treatment, we summed the total health care expenditures from the beneficiary, Medicare, and supplemental private insurance for inpatient, outpatient, and physician services within 12 months of prostate cancer diagnosis. Approximately 50% of men who received adjuvant therapies did so within 6 months, and we were able to capture costs for 275 of the 600 that received therapy. To ensure that we adequately captured the cost of treatment, we excluded men who underwent RP and adjuvant therapies beyond 6 months following prostate cancer

Table 1. Demographics of the Study Population

Characteristic	Categories	Total	No Adjuvant Therapy	Hormonal or Radiation	*P*	Hormonal Therapy	Radiation Therapy
Year of surgery	2004	1779	1503 (84.49)	275 (15.46)	.028	138 (7.76)	221 (12.42)
	2005	2058	1776 (86.30)	282 (13.70)		139 (6.75)	214 (10.40)
	2006	410	367 (89.51)	43 (10.49)		17 (4.15)	39 (9.51)
Age (years)	65-69	2620	2240 (85.50)	379 (14.47)	.624	177 (6.76)	310 (11.83)
	70-74	1332	1154 (86.64)	178 (13.36)		95 (7.13)	137 (10.29)
	≥75	295	252 (85.42)	43 (14.58)		22 (7.46)	27 (9.15)
Charlson comorbidity index	0	2956	2543 (86.03)	413 (13.97)	.501	194 (6.56)	343 (11.60)
	1	1018	865 (84.97)	153 (15.03)		85 (8.35)	106 (10.41)
	≥2	273	238 (87.18)	34 (12.45)		15 (5.49)	25 (9.16)
Race	White	3366	2893 (85.95)	473 (14.05)	.328	226 (6.71)	384 (11.41)
	Black	307	265 (86.32)	42 (13.68)		22 (7.17)	31 (10.10)
	Hispanic	356	310 (87.08)	45 (12.64)		25 (7.02)	30 (8.43)
	Asian	186	150 (80.65)	36 (19.35)		20 (10.75)	25 (13.44)
	Other	32	28 (87.50)	4 (12.50)		1 (3.13)	4 (12.50)
Marital status	Unmarried	605	523 (86.45)	82 (13.55)	.632	35 (5.79)	67 (11.07)
	Married	3469	2971 (85.64)	497 (14.33)		247 (7.12)	393 (11.33)
Education: % of census tract with at least a high school degree	<75	785	672 (85.61)	112 (14.27)	.074	57 (7.26)	83 (10.57)
	75-84.99	785	682 (86.88)	103 (13.12)		60 (7.64)	76 (9.68)
	85-89.99	791	656 (82.93)	135 (17.07)		63 (7.96)	113 (14.29)
	≥90	1885	1635 (86.74)	250 (13.26)		114 (6.05)	202 (10.72)
Median income in census tract of residence	<$35,000	1106	938 (84.81)	168 (15.19)	.367	88 (7.96)	124 (11.21)
	$35,000-44,000	975	842 (86.36)	132 (13.54)		64 (6.56)	102 (10.46)
	$45,000-59,000	1072	912 (85.07)	160 (14.93)		76 (7.09)	134 (12.50)
	≥$60,000	1093	953 (87.19)	140 (12.81)		66 (6.04)	114 (10.43)
SEER region	San Francisco	171	151 (88.30)	20 (11.70)	.029	10 (5.85)	17 (9.94)
	Detroit	303	273 (90.10)	30 (9.90)		16 (5.28)	20 (6.60)
	Iowa	195	156 (80.00)	39 (20.00)		20 (10.26)	30 (15.38)
	Seattle	352	312 (88.64)	40 (11.36)		19 (5.40)	33 (9.38)
	Utah	284	255 (89.79)	29 (10.21)		8 (2.82)	24 (8.45)
	Connecticut	127	108 (85.04)	19 (14.96)		10 (7.87)	18 (14.17)
	San Jose	103	82 (79.61)	21 (20.39)		8 (7.77)	18 (17.48)
	Los Angeles	569	496 (87.17)	73 (12.83)		38 (6.68)	51 (8.96)
	Greater California	1171	987 (84.29)	183 (15.63)		89 (7.60)	149 (12.72)
	Kentucky	215	181 (84.19)	34 (15.81)		18 (8.37)	28 (13.02)
	Louisiana	316	276 (87.34)	40 (12.66)		23 (7.28)	29 (9.18)
	New Jersey	265	226 (85.28)	39 (14.72)		20 (7.55)	32 (12.08)
	New Mexico/Georgia /Hawaii	176	143 (81.25)	33 (18.75)		15 (8.52)	25 (14.20)
Population density	Metropolitan	3989	3430 (85.99)	558 (13.99)	.292	271 (6.79)	443 (11.11)
	Rural	258	216 (83.72)	42 (16.28)		23 (8.91)	31 (12.02)
Clinical stage	T1c	2218	1938 (87.38)	279 (12.58)	<.001	133 (6.00)	224 (10.10)
	T2	737	619 (83.99)	118 (16.01)		60 (8.14)	94 (12.75)
	T3	39	22 (56.41)	17 (43.59)		13 (33.33)	10 (25.64)
Gleason grade	≤6	1687	1599 (94.78)	88 (5.22)	<.001	29 (1.72)	71 (4.21)
	7	2073	1752 (84.52)	320 (15.44)		143 (6.90)	259 (12.49)
	≥8	469	280 (59.70)	189 (40.30)		120 (25.59)	143 (30.49)
PSA	<10	3141	2764 (88.00)	377 (12.00)	<.001	173 (5.51)	303 (9.65)
	10-20	495	391 (78.99)	104 (21.01)		49 (9.90)	84 (16.97)
	>20	170	117 (68.82)	53 (31.18)		33 (19.41)	39 (22.94)
Risk stratification	Low	1242	1188 (95.65)	54 (4.35)	<.001	17 (1.37)	41 (3.30)
	Intermediate	2265	1950 (86.09)	314 (13.86)		130 (5.74)	260 (11.48)
	High	637	408 (64.05)	229 (35.95)		146 (22.92)	171 (26.84)

SEER indicates Surveillance, Epidemiology, and End Results; PSA, prostate-specific antigen.
Data are presented as No. (%).

Table 2. Adjuvant Therapy by Surgeon Volume, Surgical Approach, Pathological Stage, and Surgical Margin

Independent Variable	Category	n	Adjuvant Therapy	Hormonal or Radiation	*P*	Hormonal Therapy	Radiation Therapy
Pathological stage	T2	3547	3201 (90.25)	345 (9.73)	<.001	148 (4.17)	275 (7.75)
	T3a	700	445 (63.57)	255 (36.43)		146 (20.86)	199 (28.43)
Positive surgical margin	Yes	822	563 (68.49)	259 (31.51)	<.001	129 (15.69)	213 (25.91)
	No	3425	3083 (90.01)	341 (9.96)		165 (4.82)	261 (7.62)
Surgeon volume in quartiles (no. of surgeons by approach)	Low (MIRP, 85; RRP, 396)	1027	867 (84.42)	159 (15.48)	.001	63 (6.13)	134 (13.05)
	Intermediate (MIRP, 21; RRP, 169)	1130	944 (83.54)	186 (16.46)		94 (8.32)	149 (13.19)
	High (MIRP, 12; RRP, 91)	1159	998 (86.11)	161 (13.89)		90 (7.77)	120 (10.35)
	Very high (MIRP, <11[a]; RRP, 37)	931	837 (89.90)	94 (10.10)		47 (5.05)	71 (7.63)
Surgical approach	MIRP	1120	998 (89.11)	122 (10.89)	<.001	59 (5.27)	97 (8.66)
	RRP	3127	2648 (84.68)	478 (15.29)		235 (7.52)	377 (12.06)
Positive lymph nodes	Yes	45	11 (24.44)	34 (75.56)	<.001	31 (68.89)	11 (24.44)
	No	4201	3635 (86.53)	566 (13.47)		263 (6.26)	463 (11.02)

MIRP indicates minimally invasive radical prostatectomy; RRP, retropubic radical prostatectomy.
Data are presented as No. (%).
[a] The actual number of MIRP surgeons is not presented because the National Cancer Institute precludes the reporting of table cells of n<11.

diagnosis. We then subtracted baseline health care expenditures, allowing subjects to serve as their own controls. We considered the difference in health expenditures between men receiving adjuvant treatment versus RP alone to be the health care expenditures attributable to hormonal therapy, radiotherapy, and both treatments in combination. Moreover, the health care expenditures included therapies, consultations, imaging, laboratory tests, and treatment of complications. All costs were adjusted to 2008 dollars using the 2007 Annual Report of the Boards of Trustees of the Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Fund.[22]

Statistical Analysis

Unadjusted analysis using the Pearson chi-square statistic was performed to compare demographic and biopsy tumor characteristics for patients receiving RP and adjuvant treatment versus RP alone, adjusting for clustering by surgeon, surgical approach, surgeon volume, and clinical characteristics.[23] A 2-sided result of $P<.05$ was considered statistically significant. Adjusted analysis was performed with a Cox multivariable regression model to assess the association of the covariates on the use of adjuvant therapies.

All tests were considered statistically significant at $\alpha = 0.05$. All analyses were performed with SAS version 9.1.3 (SAS Institute, Cary, NC).

RESULTS

The demographics of our study population are summarized in Table 1. We observed a temporal trend in the administration of adjuvant therapy after RP; patients were more likely to receive adjuvant therapy after RP performed in 2004 versus 2005 or 2006 (15.5%, 13.7% and 10.5%, $P = .028$). Moreover, whereas age, comorbidities, income, and education were not associated with receipt of adjuvant therapies, there was significant geographic variation for utilization of adjuvant therapies, with the San Jose versus Detroit region having the highest versus lowest utilization rates (20.4% vs 9.9%, $P<.001$). Furthermore, more aggressive tumor characteristics (higher Gleason grade, preoperative PSA, clinical stage, and risk stratification) were associated with receipt of adjuvant cancer therapy (all $P<.001$).

In assessing the effect of surgical approach, surgeon volume, and pathological features on the use of adjuvant therapies (Table 2), patients undergoing minimally invasive RP versus retropubic RP were less likely to receive additional cancer therapy (10.9% vs 15.3%, $P<.001$), and higher surgeon volume was associated with lower utilization of adjuvant cancer therapy ($P = .001$). Moreover, patients with pathological stage T3a versus T2 disease were more likely to receive additional therapy (36.4% vs 9.7%, $P<.001$), and patients with positive versus negative surgical margins were more likely to receive adjuvant cancer therapy (31.5% vs 10.0%, $P<.001$). Finally, patients with positive lymph nodes were more likely to receive adjuvant therapy (75.6% vs 13.5%, $P<.001$).

Table 3. Unadjusted and Adjusted Model for Predictors of Adjuvant Cancer Treatment

Covariate (Referent)	Categories	Univariate HR (95% CI)	Multivariate HR (95% CI)	Multivariate *P*
Age (≥75 years)	65-69	0.98 (0.71-1.34)	1.12 (0.81-1.55)	.477
	70-74	0.9 (0.65-1.26)	0.96 (0.69-1.35)	.823
Race (white)	Black	1.01 (0.74-1.39)	1.11 (0.79-1.55)	.555
	Hispanic	0.91 (0.67-1.24)	0.85 (0.62-1.17)	.316
	Asian	1.47 (1.05-2.06)	1.26 (0.88-1.8)	.203
SEER region (San Francisco)	20 = Michigan	0.89 (0.5-1.56)	0.90 (0.51-1.6)	.723
	22 = Iowa	1.76 (1.01-3.06)	1.93 (1.12-3.32)	.019
	25 = Seattle	1.82 (1.06-3.11)	1.10 (0.64-1.89)	.738
	26 = Utah	1 (0.58-1.7)	1.16 (0.65-2.08)	.612
	2 = Connecticut	0.94 (0.53-1.65)	1.37 (0.73-2.58)	.323
	31 = San Jose	1.32 (0.71-2.48)	1.71 (0.92-3.17)	.089
	35 = Los Angeles	1.82 (0.98-3.35)	1.30 (0.79-2.14)	.307
	41 = Greater California	1.15 (0.7-1.89)	1.48 (0.93-2.36)	.098
	42 = Kentucky	1.39 (0.87-2.2)	1.40 (0.8-2.45)	.233
	43 = Louisiana	1.41 (0.81-2.44)	1.33 (0.77-2.3)	.301
	44 = New Jersey	1.14 (0.67-1.95)	1.51 (0.87-2.61)	.141
	New Mexico/Georgia/Hawaii	1.33 (0.77-2.28)	1.92 (1.09-3.39)	.025
Risk stratification (low)	Intermediate	3.34 (2.5-4.46)	2.86 (2.14-3.83)	.001
	High	10.28 (7.64-13.84)	7.65 (5.64-10.37)	<.001
Surgical margin (negative)	Positive	3.65 (3.1-4.29)	3.02 (2.55-3.57)	<.001
Lymph nodes (negative)	Positive	12.73 (8.99-18.02)	5.36 (3.71-7.75)	<.001
Surgical approach (RRP)	MIRP	0.72 (0.59-0.88)	0.89 (0.72-1.1)	.285
Surgeon volume (low)	Intermediate	1.06 (0.86-1.31)	1.02 (0.82-1.27)	.855
	High	0.89 (0.72-1.11)	0.86 (0.69-1.08)	.203
	Very high	0.64 (0.49-0.82)	0.60 (0.46-0.78)	<.001
Year (2004)	2005	1 (0.85-1.19)	0.99 (0.83-1.18)	.903
	2006	0.85 (0.61-1.18)	0.86 (0.62-1.19)	.356

HR indicates hazard ratio; CI, confidence interval; RRP, retropubic radical prostatectomy; MIRP, minimally invasive radical prostatectomy.

In adjusted analysis (Table 3), age, race, marital status, and surgical approach (minimally invasive RP vs retropubic RP) were not significantly associated with receipt of adjuvant therapies. However, risk stratification was significantly associated with use of adjuvant therapies as patients with intermediate (hazard ratio [HR], 2.86; 95% confidence interval [CI], 2.14-3.83 [$P<.001$]) and high-risk (HR, 8.3; 6.13-11.22 [$P<.001$]) versus low-risk disease were more than 2 and 8 times more likely to undergo adjuvant therapies. Survival estimates are shown in Figure 1 for the various risk groups. Men undergoing RP by very high-volume surgeons were less likely to receive adjuvant therapies (HR, 0.64; 95% CI, 0.49-0.84 [$P = .001$]). Moreover, patients with positive versus negative surgical margins were 3 times more likely to undergo adjuvant therapies (HR, 3.2; 95% CI, 2.71-3.78 [$P<.001$]). Men with positive versus negative lymph nodes were 5 times more likely to receive adjuvant therapies (HR, 5.36; 95% CI, 3.71-7.75 [$P<.001$]). In addition, there was greater use of adjuvant therapies in Iowa (HR, 1.93; 95% CI, 1.12-3.32 [$P = .019$]) and New Mexico/Georgia/Hawaii (HR, 1.92; 95% CI, 1.09-3.39 [$P = .025$]) versus San Francisco SEER regions.

Baseline health care expenditures in the 12 months prior to prostate cancer diagnosis did not differ for patients who underwent RP alone versus adjuvant therapies of hormonal therapy, radiation therapy, and hormone and radiation therapy. However, the 12-month post–prostate cancer diagnosis health care expenditures (Table 4) of patients who underwent RP alone versus adjuvant therapies of hormonal therapy, radiation therapy, and combination hormonal and radiation therapy were significantly greater for adjuvant therapies ($P<.001$).

DISCUSSION

Approximately 13%-34% of men who undergo prostatectomy will have adverse pathological features such as positive surgical margins or extracapsular extension/pT3a disease.[24,25] There is a lack of consensus regarding when to initiate treatment in such patients; however, 22%-34% of these patients will receive salvage secondary treatments within 3 years of BCR.[26,27] Whereas a recent population-based study demonstrated significantly greater use of additional cancer treatments (eg, radiation and/or hormonal therapy), within 6 months of minimally invasive

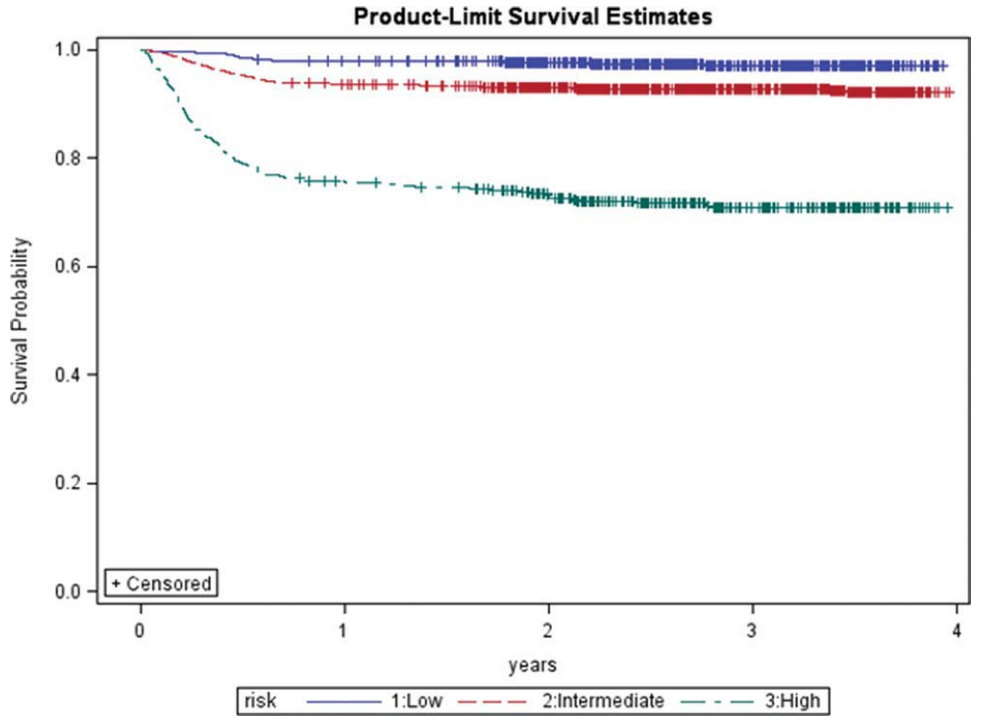

Figure 1. Estimated time to adjuvant therapy for the 3 risk groups with the number of subjects at risk at 1, 2, 3, and 4 years.

versus open RP, potential confounders such as surgical margin status and pathological stage and grade were unavailable in this analysis of Medicare beneficiaries.[16] In addition, there is an absence of population-based studies that assess use of adjuvant treatments after adjusting for surgical approach and surgeon volume. Aside from the lack of definitive guidelines on when to initiate adjuvant treatments after BCR and the appropriateness thereof, there is also concern of the added health care costs when adjuvant therapies are initiated.

Our paper has several important findings. First, higher surgeon volume was associated with decreased utilization of adjuvant cancer therapy independent of tumor characteristics. These findings would suggest that heterogeneity in practice patterns exist and that there is not uniform standardization of care. More experienced surgeons may prefer to manage positive surgical margins and extracapsular extension conservatively with surveillance versus adjuvant therapy. Similarly, Bianco et al.[28] found significant heterogeneity among BCR rates after adjusting for tumor characteristics and surgeon experience, and oncological outcomes vary due to measured and unmeasured characteristics of the treating surgeon. Thus, as Bianco et al. alluded to, there must be unmeasured characteristics of high-volume surgeons that result in decreased use of adjuvant therapies.

Second, we found that risk stratification was a significant predictor of adjuvant therapy use. Intermediate to high risk patients were approximately 3 to 8 times more likely to receive adjuvant therapy. Tumor biology as measured by pathological stage and grade have been previously shown to be powerful predictors for additional cancer therapy, whereas other patient variables including age and comorbidity have not.[12] Moreover, rapid PSA doubling time has also been shown to be significant predictors for secondary therapies.[29] Unfortunately, these endpoints are not captured in SEER-Medicare.

Third, positive surgical margin status was associated with increased utilization of adjuvant therapies, despite mixed evidence available during our study period regarding the impact of positive surgical margins on cancer recurrence and survival.[30] However, recently published randomized control trials demonstrate survival benefit from early adjuvant radiotherapy for positive surgical margins and high-risk features.[5,31] The interpretation of these trials is not without ongoing controversy, and further studies are warranted to clarify which patients would benefit most from adjuvant treatment.[32] Furthermore,

Table 4. Cost Analysis of Adjuvant Cancer Treatments

	Radical Prostatectomy	Radical Prostatectomy and Hormonal Therapy	Radical Prostatectomy and Radiation	Radical Prostatectomy and Radiation with Hormonal Therapy	*P*
Baseline health care expenditures in the year prior to prostate cancer diagnosis, median	$1861	$1272	$1380	$1333	.011
1-year postprostatectomy health care expenditures,[a] median	$15,022	$17,661			
	$28,442	$39,842	<.001		
Health care expenditures attributed to adjuvant therapies[b]	—	$1367	$12,040	$23,487	<.001

[a] We excluded patients who underwent radical prostatectomy and adjuvant therapies >6 months after initial treatment (radical prostatectomy) to ensure that we fully captured the expense associated with primary and adjuvant therapy.
[b] 1-year pre–prostate cancer diagnosis expenditures and expenditures of radical prostatectomy alone, respectively subtracted from 12-month postprostatectomy health care expenditures of various adjuvant therapies.

patients with lymph node–positive disease were more likely to receive adjuvant therapy, an increase that may be explained by prior studies demonstrating improved cancer-specific survival in such patients managed with adjuvant therapy.[33,34] With greater dissemination of evidence in favor of early adjuvant radiotherapy for adverse pathological features, more widespread adjuvant therapy use is expected and our results may underestimate current and future utilization of adjuvant therapies as practice patterns evolve.

Fourth, patient age, comorbidity status, and race were not significant predictors of adjuvant cancer therapy, consistent with previous studies.[11,12,29] One would expect that patient factors such as older age and more comorbidities would decrease the likelihood of receiving adjuvant therapies if treatment decisions were individualized. Moreover, these findings may highlight the need for guidelines based on life expectancy and postprostatectomy nomograms to better stratify which patients benefit most from adjuvant therapy. In addition, surgical approach was not a significant predictor for adjuvant therapy on multivariate analysis. Our findings contradict other studies that demonstrated greater use of secondary therapies following minimally invasive versus open RP, whereas other studies found no difference.[16,35] This difference may result from differences between the study populations: namely, a 5% random sample of Medicare beneficiaries[16] versus 100% of the Medicare beneficiaries in SEER tumor registry regions. Our study captures the entire surgeon Medicare experience in SEER regions versus a national 5% sampling of surgeon Medicare experience.

Finally, health care expenditures were $23,487 higher for combination radiation and hormonal therapy versus no treatment following prostatectomy. The additional expenditures for adjuvant hormonal therapy and radiotherapy were $1367 and $12,040, respectively versus RP alone. In particular, positive surgical margins, a surgeon-dependent variable, may increase the cost of cancer therapy significantly, particularly after level 1 evidence of improved survival from secondary radiation therapy.[4–6]

Our findings must be interpreted within the context of the study design. First, Medicare is limited to patients ≥65 years of age, and nerve-sparing may be performed more frequently in younger, potent men.[36] This factor, combined with the absence of margin status for pathological stage T3b and T4 disease, may lead to underestimation of the overall prevalence of adjuvant cancer treatments in patients undergoing RP.[24] Second, the SEER tumor registry does not contain detailed clinical information on PSA or biochemical recurrence, tumor volume, perineural invasion, and tertiary high Gleason grade, factors that increase the likelihood of adjuvant therapy use.[37–39] Third, we were unable to determine whether adjuvant radiotherapy was administered in an adjuvant versus salvage fashion, because postprostatectomy PSA data were unavailable. This observation is noteworthy, because initiation of adjuvant therapies is influenced by variation in provider practice patterns, whereas initiation of salvage therapy may be influenced by variations in PSA biochemical recurrence thresholds. Finally, our estimates of adjuvant therapy expenditures are lower than expenditures by private health plans versus Medicare.

Conclusions

Higher surgeon volume and geographic variation was independently associated with decreased use of additional therapy, demonstrating physician and regional practice pattern heterogeneity. Patients undergoing RP were

significantly more likely to undergo adjuvant treatments in the presence of higher risk stratification and positive surgical margins. Finally, adjuvant therapies significantly increased cancer-specific health care expenditures by 2- to 3-fold when radiotherapy was administered postoperatively.

Supplementary material for this article can be obtained at http://physiciandirectory.brighamandwomens.org/directory/profile.asp?dbasemain&setsize30&last_namehu&pict_id0009649.

CONFLICT OF INTEREST DISCLOSURES

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