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Scientific Article

# Factors influencing prostate cancer patterns of care: An analysis of treatment variation using the SEER database

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**Abstract**

**Purpose:** The aim of this study is to describe the trends and factors that influence the initial treatment of men with localized prostate cancer (PC) in the United States between 2004 and 2014.

**Methods and materials:** The National Cancer Institute's Surveillance, Epidemiology and End Results database was used to identify patients with primary prostate adenocarcinoma between 2004 and 2014. Patients were staged in accordance with the American Joint Committee on Cancer 7th edition criteria and stratified according to the National Comprehensive Cancer Network guidelines risk group classification. Descriptive statistics describing treatment patterns by year of diagnosis, age, risk group, insurance status, and region were performed.

**Results:** A total of 460,311 male patients were identified with sufficient information to be categorized into National Comprehensive Cancer Network risk groups. Overall, 30.9% of patients had low-risk disease, 38.1% were intermediate risk, 20.2% were high risk, 4.4% were very high risk, 1.6% were node-positive, and 4.7% had metastatic disease. During the study period, there was a 60% decrease in brachytherapy monotherapy utilization for patients with PC, and no definitive treatment increased from 20.3% in 2004 to 26.3% in 2014. There were regional treatment variations and discrepancies in treatment by age. Radical prostatectomy was performed on a greater proportion of insured patients than patients with Medicaid or those who were uninsured, but radiation therapy and no definitive treatment was administered to a greater proportion of uninsured and Medicaid patients.

**Conclusions:** PC treatment shows declining trends in brachytherapy utilization, increases in conservative management, and stability of surgical procedures over time. There is wide variation by geographical region, age, and insurance status.



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## Introduction

The management of prostate cancer (PC) can vary from monitoring interventions such as active surveillance (AS) or expectant management to definitive treatment including radical prostatectomy (RP), external beam radiation therapy (EBRT), brachytherapy, androgen deprivation therapy (ADT), or any combination of these. Risk stratification on the basis of the local extent of disease and spread, Gleason score (GS), and pretreatment prostate-specific antigen (PSA) levels guides treatment recommendations and informs prognosis. Guidelines such as the National Comprehensive Cancer Network (NCCN) provide treatment recommendations on the basis of these risk strata.[1] However, there are multiple treatment options for any risk group and no consensus regarding the superiority of the various treatments within the risk groups.[2-4] Thus, treatments are ultimately based on factors that may include medical, demographic, psychologic, logistic, and other factors. Economic incentives may also drive treatment recommendations for certain providers.[5]

The aim of this study is to describe the initial treatment of localized PC in the United States between 2004 and 2014; assess how treatment was affected by NCCN risk group, age, geography, and insurance status; and evaluate treatment trends over time.

## Methods and materials

### Study population

Access to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database was granted to the authors after receipt of a signed data-use agreement. The University institutional review board determined that the data in this dataset do not rise to the level of human subjects research per the federal Common Rule, 45 CFR, Part 46 and university policies; therefore, formal institutional review board review was waived.

The statistical analysis software package SEER*Stat, Version 8.3.4 was used to identify patients who were diagnosed between 2004 and 2014 with any stage of prostate adenocarcinoma as their first malignancy. The patients were staged clinically in accordance with the American Joint Committee on Cancer (AJCC) 7$^{th}$ edition criteria. All subjects with a derived AJCC 6$^{th}$ or 7$^{th}$ edition T1a, T1b, or T1c stage were assumed to be clinically staged, and the original derived AJCC stage was used. For all other patients, the Collaborative Staging (CS) Extension, Clinical Extension Field was used to assign patients an AJCC T-stage. CS lymph node data were used to assess AJCC N-stage, and the "CS Mets at DX" data item was used to assess AJCC M-stage. All patients with unknown N-stage and M-stage were assumed to have N0 and M0 disease. CS site-specific factor 1 was used to provide the PSA laboratory value at diagnosis, and CS site-specific factors 7 and 8 were used to determine the GS.

### Staging and group classification

Patients were grouped in accordance with the NCCN Version 1.2015 guideline risk groups.[1] The low-risk (LR) group also included the NCCN very low-risk group due to insufficient data in the SEER database to distinguish very low-risk from LR patients. All patients with stage T1 not otherwise specified (NOS) were placed in the LR group if they had appropriate PSA levels and GS. All patients with lymph-node-positive disease were placed in a node-positive group, and patients with M1 disease were considered metastatic.

Patients who could not be categorized due to unknown AJCC T, N, or M stage; PSA levels; or GS were placed in the unknown category. Patients with T2-NOS or T3-NOS were also placed in the unknown category because they could not be stratified into LR versus intermediate-risk (IR) or high-risk (HR) versus very high-risk (VHR) groups. Patients were grouped by age at diagnosis into the following categories: $< 50$, 50-64, 65-74, or $\geq 75$ years old.

### Treatment

The SEER program surgery codes were used to classify patients into the following cohorts: no surgery, cryprostatectomy, hyperthermia, laser ablation, transurethral resection (TURP), TURP + other, local tumor destruction/excision NOS, simple prostatectomy, prostatectomy, surgery NOS, and unknown. For the purposes of this study, TURP + other included patients with any combination of TURP and cryosurgery, laser, or hyperthermia. Simple prostatectomy included those who underwent a segmental or simple prostatectomy, and prostatectomy included those who received an RP, prostatectomy with resection in continuity with other organs, or a prostatectomy NOS.

Radiation therapy (RT) was grouped into 5 categories: no RT, EBRT, brachytherapy, EBRT + brachytherapy, and unknown. Patients who received radioisotopes or radioactive implants were placed in the brachytherapy group. The unknown group consisted of patients who received RT NOS or those whose RT status was not known.

### Statistical analysis

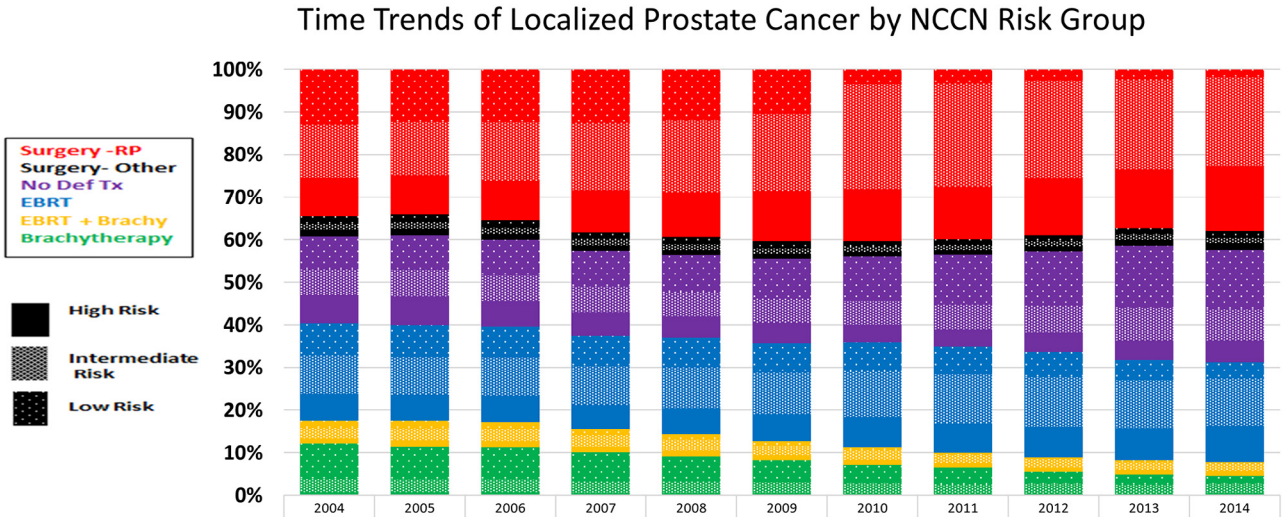
Descriptive statistics including the demographic characteristics of the study population and frequency distributions of the cohorts were performed with Microsoft Excel 2016 and MedCalc, Version 13.0.6.

## Results

A total of 536,639 male patients were diagnosed with primary PC between 2004 and 2014. Of these patients, 460,311 could be categorized into NCCN risk groups. Table 1 provides the demographics for patients stratified by NCCN risk group. A detailed distribution of all surgical and RT interventions within each risk group is available in eTable 1; available as supplementary material online only at www.practical.radonc.org).

The rates of treatment utilization from 2004 to 2014 among the patients with LR, IR HR, and VHR PC were calculated (Fig 1). Radical prostatectomy was the most commonly performed procedure (37% of patients), with utilization peaking in 2010. A progressive decline in brachytherapy utilization occurred between 2004 and 2014, with a 63% decrease noted for brachytherapy monotherapy (BM) and a 29% decrease for EBRT + brachytherapy. A concomitant increase in no definitive treatment (NDT) over this time period was also noted.

Rates of utilization of treatment modalities varied significantly across geographic areas (Fig 2.) The Los Angeles and Iowa registries showed the greatest utilization of RPs (approximately 40% of patients), whereas northern California and rural Georgia registries had the lowest RP rates (18%-27%). The lowest regional use of EBRT monotherapy was in Utah (7%), compared with the highest regional use in New Jersey (27%). BM was greatest in Utah (15%) and lowest in Los Angeles (2%).



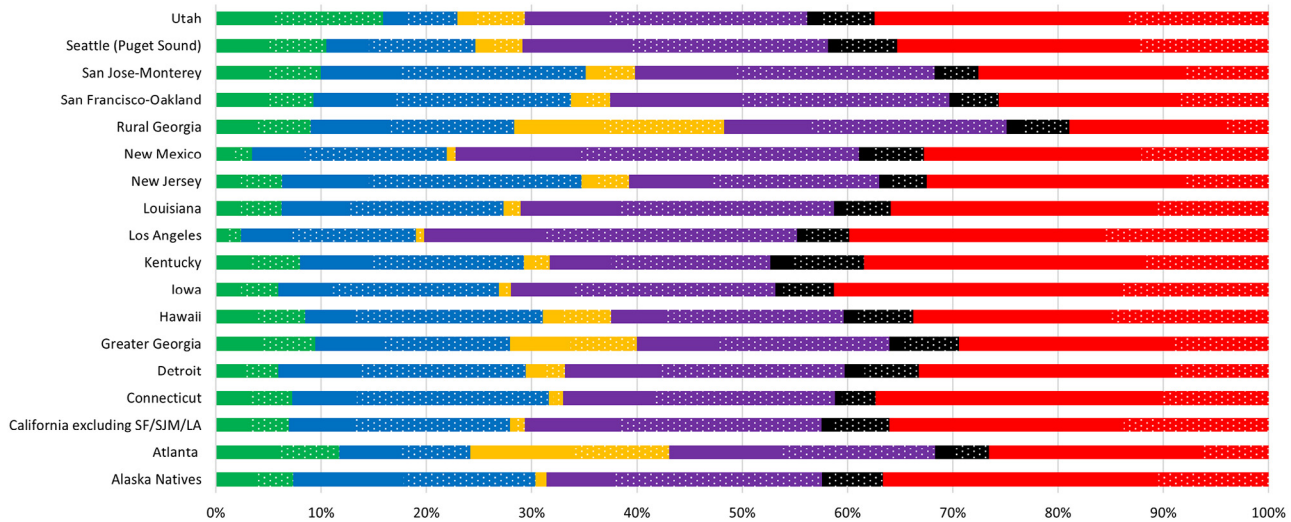

| | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| RP-low risk | 13.0% | 12.4% | 12.5% | 12.6% | 12.0% | 10.5% | 3.6% | 3.4% | 2.7% | 2.2% | 1.8% |
| RP-Intermediate | 12.4% | 12.4% | 13.8% | 15.8% | 16.8% | 18.1% | 24.6% | 24.2% | 22.9% | 21.2% | 20.8% |
| RP-High/VH | 9.1% | 9.2% | 9.3% | 9.9% | 10.5% | 11.8% | 12.2% | 12.3% | 13.3% | 13.8% | 15.2% |
| Other-low risk | 1.8% | 1.9% | 1.8% | 1.6% | 1.7% | 1.7% | 1.2% | 1.3% | 1.5% | 1.5% | 1.7% |
| Other-Intermediate | 1.3% | 1.5% | 1.3% | 1.5% | 1.3% | 1.2% | 1.2% | 1.2% | 1.2% | 1.3% | 1.2% |
| Other-High/VH | 1.7% | 1.6% | 1.5% | 1.3% | 1.2% | 1.3% | 1.2% | 1.2% | 1.2% | 1.4% | 1.5% |
| No Def Tx-low risk | 7.7% | 8.1% | 8.4% | 8.3% | 8.6% | 9.3% | 10.4% | 11.7% | 12.8% | 14.6% | 14.0% |
| No Def Tx-Intermediate | 6.1% | 6.2% | 5.9% | 6.0% | 5.8% | 5.7% | 5.5% | 5.8% | 6.3% | 7.6% | 7.3% |
| No Def Tx-High/VH | 6.6% | 6.7% | 5.9% | 5.7% | 5.0% | 4.8% | 4.1% | 4.0% | 4.6% | 4.6% | 5.1% |
| EBRT-low risk | 7.5% | 7.6% | 7.4% | 7.1% | 7.0% | 6.9% | 6.7% | 6.6% | 5.8% | 4.7% | 3.9% |
| EBRT-Intermediate | 9.1% | 8.8% | 8.9% | 9.0% | 9.5% | 9.7% | 10.8% | 11.6% | 11.6% | 11.2% | 11.1% |
| EBRT-High/VH | 6.3% | 6.1% | 6.2% | 5.7% | 6.1% | 6.3% | 7.0% | 6.8% | 7.2% | 7.6% | 8.4% |
| EBRT + Brachy-low risk | 1.7% | 1.7% | 1.7% | 1.4% | 1.3% | 1.0% | 0.8% | 0.6% | 0.5% | 0.5% | 0.3% |
| EBRT + Brachy-Intermediate | 2.4% | 2.8% | 2.8% | 2.7% | 2.6% | 2.2% | 2.2% | 1.9% | 1.9% | 1.9% | 1.9% |
| EBRT + Brachy-High/VH | 1.2% | 1.5% | 1.5% | 1.3% | 1.4% | 1.3% | 1.2% | 1.2% | 1.1% | 1.0% | 1.2% |
| Brachy-low risk | 8.3% | 7.8% | 7.6% | 6.9% | 5.8% | 5.1% | 4.3% | 3.8% | 2.8% | 2.3% | 1.9% |
| Brachy-Intermediate | 3.1% | 3.0% | 3.0% | 2.7% | 2.8% | 2.5% | 2.5% | 2.2% | 2.3% | 2.2% | 2.2% |
| Brachy-High/VH | 0.7% | 0.7% | 0.7% | 0.5% | 0.5% | 0.5% | 0.4% | 0.4% | 0.4% | 0.3% | 0.5% |

**Figure 1** The distribution of surgical and radiation therapies among patients with National Comprehensive Cancer Network low-, intermediate-, or high-risk prostate cancer, stratified by year of treatment. The colors represent each treatment group: radical prostatectomy (red), other surgical therapy including cryotherapy, transurethral resection, laser ablation, and high-intensity focal ultrasound (black), no definitive therapy, which may include active surveillance, expectant management, or primary androgen deprivation therapy (purple), brachytherapy monotherapy (green), external beam radiation therapy (blue), and external beam radiation + brachytherapy (yellow). The patterns represent National Comprehensive Cancer Network risk groups: high risk (solid color), low risk (dark cross-hatch), and intermediate risk (light cross hatch). Androgen deprivation therapy status is unknown. The percentiles in the data table reflect the proportion of the identified therapy-risk group combination for each year. RP, radical prostatectomy.

**Table 1** Demographic characteristics of all risk-grouped patients with prostate cancer in the surveillance, epidemiology, and end results database from 2004 to 2014

| | Age cohort (y) | | | | | Race | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| NCCN risk group | <50 | 50-64 | 65-74 | >75 | Row total (%) | American Indian/ Alaska Native | Asian or Pacific Islander | Black | Unknown | White | Row total (%) |
| **High (n)** | 1880 | 32,285 | 34,889 | 23,975 | 93,029 (17.3%) | 391 | 5610 | 15,167 | 2183 | 69,678 | 93,029 (17.3%) |
| **Row percentile per risk group** | 2.00% | 34.70% | 37.50% | 25.80% | | 0.40% | 6.00% | 16.30% | 2.30% | 74.90% | |
| **Column percentile per risk group** | 11.20% | 14.70% | 17.60% | 23.70% | | 19.90% | 22.20% | 19.00% | 11.80% | 17.00% | |
| **Overall percentile** | 0.40% | 6.00% | 6.50% | 4.50% | | 0.07% | 1.00% | 2.80% | 0.40% | 13.00% | |
| **Intermediate (n)** | 5827 | 76,021 | 66,375 | 27,215 | 175,438 (32.7%) | 591 | 8191 | 27,815 | 3516 | 135,325 | 175,438 (32.7%) |
| **Row percentile per risk group** | 3.30% | 43.30% | 37.80% | 15.50% | | 0.30% | 4.70% | 15.90% | 2.00% | 77.10% | |
| **Column percentile per risk group** | 34.70% | 34.60% | 33.40% | 26.90% | | 30.00% | 32.30% | 34.80% | 19.00% | 32.90% | |
| **Overall percentile** | 1.10% | 14.20% | 12.40% | 5.10% | | 0.10% | 1.50% | 5.20% | 0.70% | 25.20% | |
| **Low risk (n)** | 5742 | 66,798 | 53,585 | 16,312 | 142,437 (26.5%) | 422 | 5834 | 19,287 | 3833 | 113,061 | 142,437 (26.5%) |
| **Row percentile per risk group** | 4.00% | 46.90% | 37.60% | 11.50% | | 0.30% | 4.10% | 13.50% | 2.70% | 79.40% | |
| **Column percentile per risk group** | 34.20% | 30.40% | 27.00% | 16.10% | | 21.40% | 23.00% | 24.10% | 20.70% | 27.50% | |
| **Overall percentile** | 1.10% | 12.40% | 10.00% | 3.00% | | 0.08% | 1.10% | 3.60% | 0.70% | 21.10% | |
| **Metastatic (n)** | 538 | 6476 | 6531 | 8130 | 21,675 (4.0%) | 147 | 1217 | 4137 | 182 | 15,992 | 21,675 (4.0%) |
| **Row percentile per risk group** | 2.50% | 29.90% | 30.10% | 37.50% | | 0.70% | 5.60% | 19.10% | 0.80% | 73.80% | |
| **Column percentile per risk group** | 3.20% | 2.90% | 3.30% | 8.00% | | 7.50% | 4.80% | 5.20% | 1.00% | 3.90% | |
| **Overall percentile** | 0.10% | 1.20% | 1.20% | 1.50% | | 0.03% | 0.20% | 0.80% | 0.03% | 3.00% | |
| **Node Positive (n)** | 282 | 3708 | 2660 | 765 | 7415 (1.4%) | 42 | 343 | 1059 | 57 | 5914 | 7415 (1.4%) |
| **Row percentile per risk group** | 3.80% | 50.00% | 35.90% | 10.30% | | 0.60% | 4.60% | 14.30% | 0.80% | 79.80% | |
| **Column percentile per risk group** | 1.70% | 1.70% | 1.30% | 0.80% | | 2.10% | 1.40% | 1.30% | 0.30% | 1.40% | |
| **Overall percentile** | 0.05% | 0.70% | 0.50% | 0.10% | | 0.01% | 0.06% | 0.20% | 0.01% | 1.10% | |
| **Unknown** | 1969 | 25,989 | 27,257 | 21,113 | 76,328 (14.2%) | 273 | 2985 | 9614 | 8503 | 54,953 | 76,328 (14.2%) |
| **Row percentile per risk group** | 2.60% | 34.00% | 35.70% | 27.70% | | 0.40% | 3.90% | 12.60% | 11.10% | 72.00% | |
| **Column percentile per risk group** | 11.70% | 11.80% | 13.70% | 20.80% | | 13.90% | 11.80% | 12.00% | 45.90% | 13.40% | |
| **Overall percentile** | 0.40% | 4.80% | 5.10% | 3.90% | | 0.05% | 0.60% | 1.80% | 1.60% | 10.20% | |
| **Very high (n)** | 559 | 8552 | 7416 | 3790 | 20,317 (3.8%) | 102 | 1143 | 2924 | 246 | 15,902 | 20,317 (3.8%) |
| **Row percentile per risk group** | 2.80% | 42.10% | 36.50% | 18.70% | | 0.50% | 5.60% | 14.40% | 1.20% | 78.30% | |
| **Column percentile per risk group** | 3.30% | 3.90% | 3.70% | 3.70% | | 5.20% | 4.50% | 3.70% | 1.30% | 3.90% | |
| **Overall percentile** | 0.10% | 1.60% | 1.40% | 0.70% | | 0.02% | 0.20% | 0.50% | 0.05% | 3.00% | |
| **Column Total** | 16,797 | 219,829 | 198,713 | 101,300 | 536,639 | 1968 | 25,323 | 80,003 | 18,520 | 410,825 | 536,639 |
| **Column percentile** | 3.1% | 41.0% | 37.0% | 18.9% | | 0.4% | 4.7% | 14.9% | 3.5% | 76.6% | |
| **$\chi^2$ *P*-value** | | | | | $P < .0001$ | | | | | | $P < .0001$ |

NCCN, National Comprehensive Cancer Network.




| | Alaska Natives | Atlanta | California excluding SF/SJM/LA | Connecticut | Detroit | Greater Georgia | Hawaii | Iowa | Kentucky | Los Angeles | Louisiana | New Jersey | New Mexico | Rural Georgia | San Francisco-Oakland | San Jose-Monterey | Seattle (Puget Sound) | Utah |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Brachy - <65 | 4% | 6% | 3% | 3% | 3% | 4% | 4% | 2% | 3% | 1% | 2% | 2% | 2% | 4% | 5% | 5% | 5% | 6% |
| Brachy - 65+ | 4% | 6% | 4% | 4% | 3% | 5% | 4% | 4% | 5% | 1% | 4% | 4% | 2% | 5% | 4% | 5% | 5% | 10% |
| EBRT - <65 | 10% | 6% | 6% | 6% | 8% | 6% | 5% | 5% | 7% | 5% | 7% | 8% | 5% | 8% | 8% | 8% | 4% | 2% |
| EBRT - 65+ | 13% | 7% | 15% | 18% | 16% | 12% | 18% | 16% | 15% | 12% | 15% | 20% | 13% | 12% | 17% | 17% | 10% | 5% |
| EBRT + Brachy - <65 | 1% | 10% | 1% | 0% | 2% | 6% | 2% | 0% | 1% | 0% | 1% | 2% | 0% | 8% | 1% | 2% | 2% | 2% |
| EBRT + Brachy - 65+ | 0% | 9% | 1% | 1% | 2% | 6% | 4% | 1% | 2% | 1% | 1% | 3% | 1% | 11% | 2% | 3% | 3% | 5% |
| No Def Tx - <65 | 6% | 11% | 9% | 9% | 9% | 8% | 5% | 6% | 6% | 11% | 9% | 8% | 12% | 8% | 13% | 10% | 10% | 8% |
| No Def Tx - 65+ | 20% | 14% | 19% | 17% | 17% | 16% | 17% | 19% | 15% | 24% | 21% | 16% | 26% | 19% | 20% | 19% | 19% | 19% |
| Other - <65 | 1% | 2% | 1% | 1% | 2% | 1% | 1% | 1% | 2% | 1% | 1% | 1% | 1% | 2% | 1% | 1% | 1% | 1% |
| Other - 65+ | 5% | 3% | 5% | 3% | 5% | 5% | 5% | 5% | 7% | 4% | 4% | 4% | 5% | 4% | 4% | 3% | 5% | 5% |
| Prostatectomy - <65 | 26% | 20% | 22% | 27% | 24% | 20% | 18% | 27% | 27% | 24% | 25% | 25% | 21% | 15% | 17% | 19% | 23% | 24% |
| Prostatectomy - 65+ | 10% | 6% | 14% | 10% | 9% | 9% | 15% | 14% | 12% | 16% | 11% | 8% | 12% | 4% | 8% | 8% | 13% | 14% |

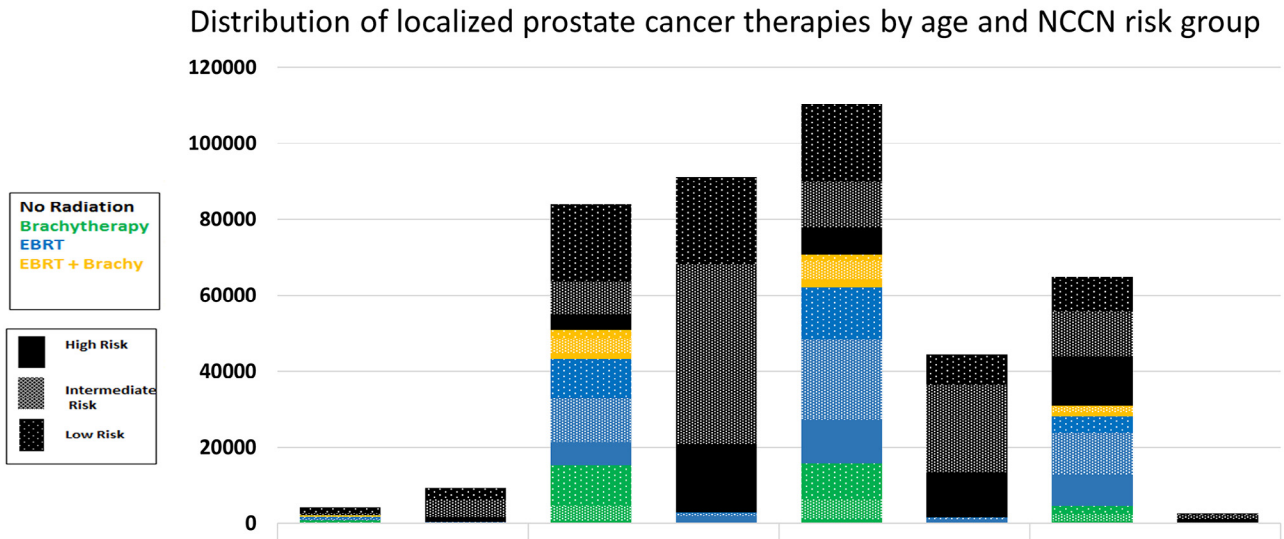
**Figure 2** The distribution of surgical and radiation therapies among all patients in the Surveillance, Epidemiology, and End Results database stratified by region and age <65 or 65 + years. The colors represent each treatment group: radical prostatectomy (red), other surgical therapy including cryotherapy, transurethral resection, laser ablation, and high-intensity focal ultrasound (black), no definitive therapy, which may include active surveillance, expectant management, or primary androgen deprivation therapy (purple), brachytherapy monotherapy (green), external beam radiation therapy (blue), and external beam radiation + brachytherapy (yellow). The solid colors represent patients aged <65 years, and the patterned color represents patients aged ≥65 years. Androgen deprivation therapy status is unknown. The percentiles in the data table reflect the proportion of the identified therapy-age group combination for each region. RP, radical prostatectomy; EBRT, external beam radiation therapy.

NDT ranged from a low of 19% (Kentucky) to a high of 37% (New Mexico).

Treatment utilization varied greatly by age and NCCN risk group in patients with nonmetastatic PC (Fig 3). In patients aged <65 years, RP was the most common treatment modality. However, in patients aged ≥65 years, RT was the most common treatment modality, followed by NDT and then RP. Utilization of RP decreased as the risk group increased, whereas the use of EBRT was lowest in the LR group and highest in the HR group. There was also some variability in treatment on the basis of marital status that was also age-dependent. The highest utilization of RP was found among men aged <65 years who were married (61%), whereas the utilization for men aged <65 years who were widowed, single, or divorced was equivalent to approximately 45% (eFig 1; available as supplementary material online only at www.practical.radonc.org).

For patients aged <65 years, 56.55% of insured patients received a RP but only 33.46% and 37.86% of Medicaid and uninsured patients, respectively, received an RP (Fig 4). Only 23.5% of insured patients aged < 65 years received a form of RT (brachytherapy, EBRT, or EBRT + brachytherapy), whereas 32.7% and 25.1% of Medicaid and uninsured patients aged <65 years, respectively, received a form of RT. In patients aged ≥65 years, a slightly greater proportion of insured patients received RP and RT compared with Medicaid and uninsured patients. However, a smaller proportion of insured patients received NDT compared with Medicaid or uninsured patients.

Additional variability was observed when considering race and insurance status (eFig 2; available as supplementary material online only at www.practical.radonc.org). Black race was associated with the lowest utilization of RP in all insurance cohorts (uninsured, Medicaid, or insured)




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| No RT - low risk | 35.72% | 32.75% | 24.34% | 25.29% | 18.48% | 18.04% | 14.08% | 11.17% |
| No RT - Intermediate | 9.53% | 50.47% | 10.11% | 51.92% | 10.98% | 51.59% | 18.06% | 47.52% |
| No RT - High | 4.38% | 13.66% | 4.95% | 19.65% | 6.51% | 27.13% | 20.10% | 37.92% |
| EBRT + Brachy - low risk | 4.50% | 0.03% | 2.68% | 0.00% | 1.64% | 0.00% | 0.59% | 0.00% |
| EBRT + Brachy - Intermediate | 4.55% | 0.00% | 4.54% | 0.01% | 4.14% | 0.01% | 2.13% | 0.04% |
| EBRT + Brachy - High | 1.70% | 0.00% | 1.98% | 0.01% | 2.07% | 0.02% | 1.52% | 0.04% |
| EBRT - low risk | 10.17% | 0.40% | 12.18% | 0.20% | 12.47% | 0.12% | 6.89% | 0.15% |
| EBRT - Intermediate | 7.57% | 1.12% | 13.84% | 0.91% | 19.17% | 0.76% | 16.81% | 0.61% |
| EBRT - High | 4.52% | 1.54% | 7.26% | 1.99% | 10.29% | 2.28% | 12.85% | 2.44% |
| Brachy - low risk | 13.38% | 0.01% | 12.70% | 0.01% | 8.63% | 0.01% | 3.12% | 0.08% |
| Brachy - Intermediate | 3.33% | 0.00% | 4.67% | 0.01% | 4.75% | 0.01% | 3.00% | 0.00% |
| Brachy - High | 0.65% | 0.00% | 0.75% | 0.01% | 0.87% | 0.01% | 0.85% | 0.04% |

**Figure 3** The distribution of surgical and radiation therapies among patients with National Comprehensive Cancer Network low-, intermediate-, or high-risk prostate cancer stratified by age for men treated between 2004 and 2014. The colors represent the treatment group: no radiation (black), brachytherapy monotherapy (green), external beam radiation therapy (blue), and external beam radiation + brachytherapy (yellow). The patterns represent the National Comprehensive Cancer Network risk groups: high (solid color), low (dark cross-hatch), and intermediate (light cross hatch) risk. Androgen deprivation therapy status is unknown. The percentiles in the data table reflect the proportion of the identified therapy risk-group combination for each column. The heights of all columns combined equal 100% (ie, entire cohort of National Comprehensive Cancer Network low-, intermediate-, and high-risk patients, n = 410,904). Men with very high risk National Comprehensive Cancer Network status (20,317 patients) are excluded for clarity. RP, radical prostatectomy.

compared with white, Asian, and Native American patients. The lowest utilization of RP was found in black patients with Medicaid insurance (27.7%), whereas the second highest RP utilization was in white patients with insurance (44.9%). The highest utilization of RP was in uninsured Asian patients (45.5%). In all insurance cohorts, black patients had the lowest use of prostatectomy but had a higher utilization of radiation therapies compared with white patients.

No clear trends were discerned when analyzing the distribution of therapies by median income or educational level (eFigs 3 and 4; available as supplementary material online only at www.practical.radonc.org). However, the utilization of brachytherapy was highest, and surgery lowest, in patients from geographic locations where the median household income was less than $25,000 per year in 2008.

## Discussion

The management of localized PC in the United States is undergoing increased scrutiny by patients, providers, and payers. With mature randomized trials calling into question the merits of both screening[6,7] and treatment[8,9] on cause-specific and overall survival (OS), one would anticipate shifts in care patterns across the United States. Nevertheless, trial data supporting oncologic outcomes do not necessarily shift practice patterns. Numerous other factors, such as regional access to treatment centers, consultation with a multidisciplinary team, insurance coverage, bias of providers, and economic incentives, may also affect treatment.

In the SEER database, treatment options differed by year, region of the country, age, and insurance status. Approxi-

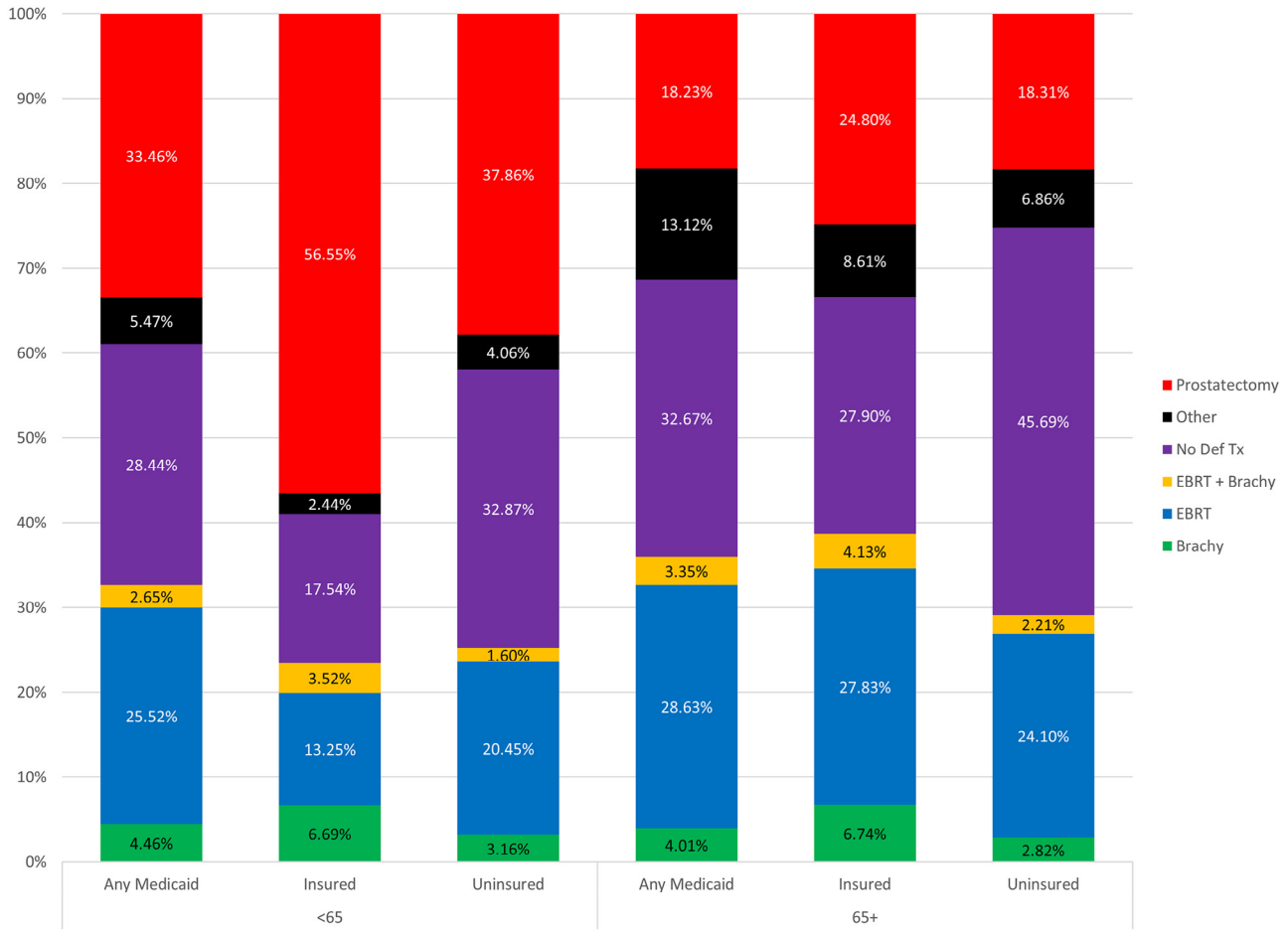



**Figure 4** The distribution of surgical and radiation therapies among patients stratified by insurance coverage for men treated between 2004 and 2014. The colors represent the treatment groups: radical prostatectomy (red), other surgical therapy including cryotherapy, transurethral resection, laser ablation, high-intensity focal ultrasound (black), no definitive therapy, which may include active surveillance, expectant management, or primary androgen deprivation therapy (purple), brachytherapy monotherapy (green), external beam radiation therapy (blue), and external beam radiation + brachytherapy (yellow). The percentiles in the data table reflect the proportion of the identified therapy risk group combination for each column. The heights of all columns combined equals 100%.

mately one-third of the patients had LR, one-third had IR, one-fifth had HR disease, and only a small proportion had VHR or metastatic disease, which is consistent with other population studies.[10,11] In general, RP accounted for the greatest proportion of localized PC treatment, with 43.4% of subjects receiving an RP; this is slightly lower than the CaPSURE and National Cancer Data Base (NCDB) data that showed that nearly half of all patients with PC received an RP.[10,11]

Trends in treatment for PC between 2004 and 2014 included a decline in brachytherapy use, both as BM and in combination with EBRT, an increase in NDT, and no substantial change in RP or EBRT use. The greatest change was the decrease in BM use by approximately 50% in all NCCN risk and age groups. Prior studies evaluating the use of BM over time showed increased utilization from 1994 to 2004.[12,13] Since then, several other studies have shown a decrease in brachytherapy use.[11,12,14] In the NCDB, the use of brachytherapy for nonmetastatic PC peaked at 16.7% in 2003 and steadily declined to 8.2% in 2010.[11] The CaPSURE database showed a linear decline in BM use between 1999 and 2011.[12] The SEER database also showed a decline in BM between 2004 and 2009.[14] A drop in BM in the HR group could be explained by studies showing inferior results with BM for HR patients,[2,15,16] and BM is not recommended by 2 national guidelines.[17,18] In the IR group, there is no consensus on BM. Studies have shown mixed results with the use of BM,[2,15,16,19,20] and the current national guidelines recommend BM for select groups of IR patients.[17,20]

Despite the lack of consensus on the role of brachytherapy, a recently published randomized trial, Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT), demonstrated superior biochemical failure-free survival for patients with unfavorable IR and HR PC who received brachytherapy

in addition to EBRT and ADT.[21-23] In the current study, the outcomes data are through 2014, but the official publication of the ASCENDE-RT trial was in January of 2017. Therefore, it remains to be seen whether this important randomized trial will change management.

Additionally, biochemical failure as an endpoint is undergoing increased scrutiny; as yet, there is no significant difference in metastasis-free survival, cause-specific survival, or OS in the ASCENDE-RT trial, although future results should be forthcoming. The Radiation Therapy Oncology Group 0232 trial is evaluating whether BM alone is equivalent to EBRT + brachytherapy for select IR patients, but the results have not yet been reported.

In LR patients, BM is an effective[2,15] and cost-efficient form of treatment.[24,25] The decline in the use of BM may be related to numerous factors.[26] First, the acceptance of AS as an appropriate treatment option[7,9] for eligible LR[1] patients during this time period would remove a proportion of patients who otherwise could have received BM. Second, the negative publicity highlighting poor patient outcomes from improperly placed prostate seed implants could be driving both patients and providers away from brachytherapy.[27] Third, insufficient training in brachytherapy procedures during residency contributes further to the decline[11,28] due to a lack of trained specialists. Lastly, the development and increased utilization of more highly reimbursed treatment methods, such as minimally invasive radical prostatectomy (MIRP), intensity modulated radiation therapy (IMRT), and proton therapy (PT),[29-35] may be incentivizing physicians to not utilize brachytherapy. The decline in BM has been found to correlate with a transition of 3-dimensional conformal radiation therapy (CRT) to IMRT, open RP to MIRP, and a surge of PT to treat PC.[31,32,35-37] Cost analysis studies have shown BM to be among the least expensive, and therefore less lucrative, initial treatments for PC.[24,25]

Although we did not find a significant increase or decrease in RP utilization, others have shown a significant increase in the use of RP.[11,38] Data from the NCDB showed a marked increase in the overall use of RP, from 46.1% in 1998 to 59.1% in 2010.[11] Regardless of overall trends, 3-dimensional CRT and open RP largely have been replaced by newer technologies, including MIRP, IMRT, and PT.[29,32,35,36] Both IMRT and MIRP are costlier than the alternatives, with a mean incremental increase in cost of $10,986 for IMRT versus 3-dimensional CRT and $293 for MIRP versus open RP.[29,30] PT also comes with a higher cost, with Medicare reimbursing approximately $13,000 more for PT compared to other standard PC treatments.[35,39]

The cohort of patients with NDT included AS, expectant management, and primary ADT because SEER did not discriminate between these forms of therapy. As a group, NDT increased between 2004 and 2014. LR and IR patients had the greatest increase in NDT, which is consistent with other reports from Medicare datasets that found that no active therapy increased from 16% to 23% between 1999 and 2007[36] and the SEER-Medicare database that showed an increase from 9.7% in 2004 to 15.3% in 2007 in patients undergoing AS.[40]

In the Scandinavian trial of RP versus AS, patients receiving an RP had improved OS, but this was only significant in men aged <65 years.[9] The Prostate Cancer Intervention versus Observation Trial found that RP did not significantly reduce OS or PC mortality compared with AS, although a reduced OS in subjects with IR and HR tumors was noted in subset analyses.[8]

Most recently, the landmark PROTECT trial has been reported and demonstrated no difference in OS or PC-specific mortality for patients undergoing EBRT + ADT versus radical prostatectomy versus AS[41] in a largely LR and favorable IR group of patients. Nevertheless, the PROTECT trial did show a difference in metastasis-free survival that was greater in the AS cohort, which has introduced a debate on whether AS is indeed inferior to definitive therapy. Currently, this increased risk of metastasis has not resulted in observable differences in OS or PC-specific mortality, but the conclusions of the study could change with additional follow-up. As a whole, the results in LR patients undergoing AS are consistent with those from randomized trials showing no OS benefit to RP[8,9]; EBRT +ADT[41] has been included in national guidelines,[19] which may explain the increased utilization of NDT seen in our study.

Nationally, we observed significant regional heterogeneity in treatment practice patterns for patients with PC. Iowa treated more than twice the number of patients with PC with RP compared with rural Georgia. Utah had the lowest proportion of patients with PC receiving EBRT but was the leader in BM treatment. New Jersey had the greatest fraction of patients with PC receiving EBRT; however, it was one of the regions least likely to recommend NDT.

Socioeconomic factors may explain some of the regional variability. Several studies have reported lower rates of RP in the African-American population, and a prior SEER study found that a majority of African-American men with PC were located in the Atlanta and San Francisco/Oakland region.[42-46] We also observed a lower rate of RP use in African-American men, which was sensitive to the insurance status of the patient. Curiously, the lowest utilization of RP in our study was in African Americans who were covered by Medicaid, which was far lower than the utilization in the uninsured population. Other studies have correlated income, education, and marital status to treatment decisions.[45,47]

Additionally, regional variations in PC treatment may be related to patient access to treatment centers. For example, New Jersey had the highest rate of EBRT use, which may be related to the fact that the state has one of the highest number of urology-owned RT centers in the United States. Urology-owned RT centers have substantially increased their use of IMRT compared with urologists who do not own linear accelerators.[5,48,49] However, multidisciplinary care

strongly influences the treatment patients ultimately receive. A SEER-Medicare study found that patients who only met with a urologist were most likely to receive an RP over RT. Yet, if the patient was referred to a radiation oncologist and a urologist, the patient was more likely to receive RT.[50] In our income analysis, RP use declined and BT use increased in households from areas with the lowest median income. When household incomes exceeded $50,000, no meaningful changes in practice patterns could be discerned, with the exception of very low utilization of EBRT + brachytherapy in the wealthiest ZIP codes.

Age played a large role in the treatments that patients received. In patients aged <65 years, RP was more commonly used than RT, even though RP and dose-escalated RT have been found to result in equivalent outcomes in young patients.[51-55] Prior to the dose-escalated RT era, biochemical disease-free survival in younger men was suboptimal,[56] and this earlier experience may be contributing to the longstanding trend of treating younger patients with RP.[42,57]

Furthermore, a training bias may exist among urologists purporting that incidence of late toxicity from radiation accelerates over time. Despite this bias, long-term comparative effectiveness data comparing EBRT, RT, and RP do not show increased toxicity for the radiation modalities.[37,58] In patients aged ≥65 years, RT was the most common treatment, followed by no treatment and RP. One factor that may increase EBRT use over RP in this population is the increased morbidity associated with RP in older men.[59] The majority of LR PC in patients aged <65 years was treated with RP, and the majority of patients aged ≥65 years were treated with a form of RT. AS, which is included in NDT, appears to be underutilized in both patients aged <65 and ≥65 years.

Patients aged <65 years with insurance received a greater proportion of RP compared with patients without insurance. CaPSURE data has also showed that patients who received RP were more likely to have private insurance compared with Medicare with or without supplementation, Veteran Affairs funding, or unknown coverage.[60] In patients of all ages, RT and NDT were administered to a greater proportion of uninsured and Medicaid patients than patients with insurance. This is an interesting finding, and although one might be able to explain a greater proportion of uninsured men receiving NDT because of financial pressures, this does not explain the increase in RT use.

The limitations of the SEER database can confound aspects of the analysis. These limitations include no information on medical comorbidities or patient performance status, which could influence treatment recommendations, no data on ADT or chemotherapy use, no records of EBRT dose and fields, and no classification of brachytherapy administration (high vs low dose rate). In addition, one-fourth of the patients were missing information on PSA level, GS, or clinical extent of the disease and thus could not be categorized into a risk group. Despite these shortcomings, the SEER database still provides a large population of patients with PC from multiple cancer registries across the United States and allows for a reflection of practice patterns throughout the nation.

## Conclusions

Practice patterns for localized PC were not found to be strictly influenced by outcomes data and varied significantly by patient age, insurance status, financial models, regional biases, and socioeconomic factors. This study may serve as a comparator for researchers evaluating trends in practice patterns in the future and against other datasets. As the national discussion shifts to value in medical care, these trends, along with outcomes data, could be useful to legislators and payers in crafting policies going forward.

## Supplementary data

Supplementary material for this article (https://doi.org/10.1016/j.adro.2017.12.008) can be found at www.practicalradonc.org.

## References

1. National Comprehensive Cancer Network. Prostate cancer version 1; 2015. http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed February 1, 2015.
2. Grimm P, Billiet I, Bostwick D, et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. *BJU Int*. 2012;109(suppl 1):22-29.
3. Thompson I, Thrasher JB, Aus G, et al. Guideline for the management of clinically localized prostate cancer: 2007 update. *J Urol*. 2007;177:2106-2131.
4. Wilt TJ, MacDonald R, Rutks I, Shamliyan TA, Taylor BC, Kane RL. Systematic review: Comparative effectiveness and harms of treatments for clinically localized prostate cancer. *Ann Int Med*. 2008;148:435-448.
5. Mitchell JM. Urologists' use of intensity-modulated radiation therapy for prostate cancer. *N Engl J Med*. 2013;369:1629-1637.
6. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: Results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet*. 2014;384:2027-2035.
7. Andriole GL, Crawford ED, Grubb RL 3rd, et al. Prostate cancer screening in the randomized prostate, lung, colorectal, and ovarian cancer screening trial: Mortality results after 13 years of follow-up. *J Natl Cancer Inst*. 2012;104:125-132.
8. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. *N Engl J Med*. 2012;367:203-213.
9. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med*. 2011;364:1708-1717.
10. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J Clin Oncol*. 2010;28:1117-1123.

11. Martin JM, Handorf EA, Kutikov A, et al. The rise and fall of prostate brachytherapy: Use of brachytherapy for the treatment of localized prostate cancer in the National Cancer Data Base. *Cancer*. 2014;120:2114-2121.
12. Tseng YD, Paciorek AT, Martin NE, D'Amico AV, Cooperberg MR, Nguyen PL. Impact of national guidelines on brachytherapy monotherapy practice patterns for prostate cancer. *Cancer*. 2014;120:824-832.
13. Jani AB, Johnstone PA, Liauw SL, Master VA, Rossi PJ. Prostate cancer modality time trend analyses from 1973 to 2004: A surveillance, epidemiology, and end results registry analysis. *Am J Clin Oncol*. 2010;33:168-172.
14. Mahmood U, Pugh T, Frank S, et al. Declining use of brachytherapy for the treatment of prostate cancer. *Brachytherapy*. 2014;13:157-162.
15. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998;280:969-974.
16. Kibel AS, Ciezki JP, Klein EA, et al. Survival among men with clinically localized prostate cancer treated with radical prostatectomy or radiation therapy in the prostate specific antigen era. *J Urol*. 2012;187:1259-1265.
17. National Comprehensive Cancer Network. Prostate cancer: NCCN guidelines for prostate cancer updated. *Nat Rev Urol*. 2015;12:63.
18. Nag S, Beyer D, Friedland J, Grimm P, Nath R. American Brachytherapy Society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. *Int J Radiat Oncol Biol Phys*. 1999;44:789-799.
19. Goldner G, Potter R, Battermann JJ, et al. Comparison between external beam radiotherapy (70 Gy/74 Gy) and permanent interstitial brachytherapy in 890 intermediate risk prostate cancer patients. *Radiother Oncol*. 2012;103:223-227.
20. Davis BJ, Horwitz EM, Lee WR, et al. American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. *Brachytherapy*. 2012;11:6-19.
21. Rodda S, Morris WJ, Hamm J, Duncan G. ASCENDE-RT: An analysis of health-related quality of life for a randomized trial comparing low-dose-rate brachytherapy boost with dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2017;98:581-589.
22. Rodda S, Tyldesley S, Morris WJ, et al. ASCENDE-RT: An analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2017;98:286-295.
23. Morris WJ, Tyldesley S, Rodda S, et al. Androgen suppression combined with elective nodal and dose escalated radiation therapy (the ASCENDE-RT Trial): An analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2017;98:275-285.
24. Shah C, Lanni TB Jr, Ghilezan MI, et al. Brachytherapy provides comparable outcomes and improved cost-effectiveness in the treatment of low/intermediate prostate cancer. *Brachytherapy*. 2012;11:441-445.
25. Hayes JH, Ollendorf DA, Pearson SD, et al. Observation versus initial treatment for men with localized, low-risk prostate cancer: A cost-effectiveness analysis. *Ann Int Med*. 2013;158:853-860.
26. Petereit DG, Frank SJ, Viswanathan AN, et al. Brachytherapy: Where has it gone? *J Clin Oncol*. 2015;33:980-982.
27. Bogdanich W. Failed prostate procedures at the Philadelphia VA. New York Times. 2009:A1.
28. Compton JJ, Gaspar LE, Shrieve DC, et al. Resident-reported brachytherapy experience in ACGME-accredited radiation oncology training programs. *Brachytherapy*. 2013;12:622-627.
29. Nguyen PL, Gu X, Lipsitz SR, et al. Cost implications of the rapid adoption of newer technologies for treating prostate cancer. *J Clin Oncol*. 2011;29:1517-1524.
30. Bolenz C, Gupta A, Hotze T, et al. Cost comparison of robotic, laparoscopic, and open radical prostatectomy for prostate cancer. *Eur Urol*. 2010;57:453-458.
31. Sheets NC, Goldin GH, Meyer AM, et al. Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer. *JAMA*. 2012;307:1611-1620.
32. Hu JC, Gu X, Lipsitz SR, et al. Comparative effectiveness of minimally invasive vs open radical prostatectomy. *JAMA*. 2009;302:1557-1564.
33. Konski A, Speier W, Hanlon A, Beck JR, Pollack A. Is proton beam therapy cost effective in the treatment of adenocarcinoma of the prostate? *J Clin Oncol*. 2007;25:3603-3608.
34. The Lancet Oncology. Proton therapy for prostate cancer: Time for evidence. *Lancet Oncol*. 2014;15:775.
35. Zietman A. Proton beam and prostate cancer: An evolving debate. *Rep Pract Oncol Radiother*. 2013;18:338-342.
36. Dinan MA, Robinson TJ, Zagar TM, et al. Changes in initial treatment for prostate cancer among Medicare beneficiaries, 1999-2007. *Int J Radiat Oncol Biol Phys*. 2012;82:e781-e786.
37. Jarosek S, Elliott S, Virnig BA. Proton beam radiotherapy in the U.S. Medicare population: Growth in use between 2006 and 2009. Proton Beam Radiotherapy. Data Points # 10. In: Data Points Publication Series. Rockville, MD: Agency for Healthcare Research and Quality; 2011.
38. Stitzenberg KB, Wong YN, Nielsen ME, Egleston BL, Uzzo RG. Trends in radical prostatectomy: Centralization, robotics, and access to urologic cancer care. *Cancer*. 2012;118:54-62.
39. Winslow R, Martin TW. Prostate-cancer therapy comes under attack. Available at: https://www.wsj.com/articles/prostatecancer-therapy-comes-under-attack-1377734990. Accessed February 12, 2018.
40. Filson CP, Schroeck FR, Ye Z, Wei JT, Hollenbeck BK, Miller DC. Variation in use of active surveillance among men undergoing expectant treatment for early stage prostate cancer. *J Urol*. 2014;192:75-80.
41. Hamdy FC, Donovan JL, Lane JA, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375:1415-1424.
42. Harlan L, Brawley O, Pommerenke F, Wali P, Kramer B. Geographic, age, and racial variation in the treatment of local/regional carcinoma of the prostate. *J Clin Oncol*. 1995;13:93-100.
43. Klabunde CN, Potosky AL, Harlan LC, Kramer BS. Trends and black/white differences in treatment for nonmetastatic prostate cancer. *Med Care*. 1998;36:1337-1348.
44. Tewari AK, Gold HT, Demers RY, et al. Effect of socioeconomic factors on long-term mortality in men with clinically localized prostate cancer. *Urology*. 2009;73:624-630.
45. Mahmood U, Levy LB, Nguyen PL, Lee AK, Kuban DA, Hoffman KE. Current clinical presentation and treatment of localized prostate cancer in the United States. *J Urol*. 2014;192:1650-1656.
46. Mettlin CJ, Murphy GP, Cunningham MP, Menck HR. The National Cancer Data Base report on race, age, and region variations in prostate cancer treatment. *Cancer*. 1997;80:1261-1266.
47. Krupski TL, Kwan L, Afifi AA, Litwin MS. Geographic and socioeconomic variation in the treatment of prostate cancer. *J Clin Oncol*. 2005;23:7881-7888.
48. Bekelman JE, Suneja G, Guzzo T, Pollack CE, Armstrong K, Epstein AJ. Effect of practice integration between urologists and radiation oncologists on prostate cancer treatment patterns. *J Urol*. 2013;190:97-101.
49. Carreyrou J, Tamman M. Secrets of the system; A device to kill cancer, lift revenue. Available at: https://www.wsj.com/articles/SB10001424052748703904804575631222900534954. Accessed February 12, 2018.

50. Jang TL, Bekelman JE, Liu Y, et al. Physician visits prior to treatment for clinically localized prostate cancer. *Arch Int Med*. 2010;170:440-450.
51. Zelefsky MJ, Marion C, Fuks Z, Leibel SA. Improved biochemical disease-free survival of men younger than 60 years with prostate cancer treated with high dose conformal external beam radiotherapy. *J Urol*. 2003;170:1828-1832.
52. Kupelian PA, Elshaikh M, Reddy CA, Zippe C, Klein EA. Comparison of the efficacy of local therapies for localized prostate cancer in the prostate-specific antigen era: A large single-institution experience with radical prostatectomy and external-beam radiotherapy. *J Clin Oncol*. 2002;20:3376-3385.
53. Konski A, Eisenberg D, Horwitz E, Hanlon A, Pollack A, Hanks G. Does age matter in the selection of treatment for men with early-stage prostate cancer? *Cancer*. 2006;106:2598-2602.
54. Freedman GM, Hanlon AL, Lee WR, Hanks GE. Young patients with prostate cancer have an outcome justifying their treatment with external beam radiation. *Int J Radiat Oncol Biol Phys*. 1996;35:243-250.
55. Tward JD, Lee CM, Pappas LM, Szabo A, Gaffney DK, Shrieve DC. Survival of men with clinically localized prostate cancer treated with prostatectomy, brachytherapy, or no definitive treatment: Impact of age at diagnosis. *Cancer*. 2006;107:2392-2400.
56. Rosser CJ, Chichakli R, Levy LB, Kuban DA, Smith LG, Pisters LL. Biochemical disease-free survival in men younger than 60 years with prostate cancer treated with external beam radiation. *J Urol*. 2002;168:536-541.
57. Lai S, Lai H, Lamm S, Obek C, Krongrad A, Roos B. Radiation therapy in non-surgically-treated nonmetastatic prostate cancer: geographic and demographic variation. *Urology*. 2001;57:510-517.
58. Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. *N Engl J Med*. 2013;368:436-445.
59. Alibhai SM, Leach M, Tomlinson G, et al. 30-day mortality and major complications after radical prostatectomy: influence of age and comorbidity. *J Natl Cancer Inst*. 2005;97:1525-1532.
60. Sadetsky N, Lubeck DP, Pasta DJ, Latini DM, DuChane J, Carroll PR. Insurance and quality of life in men with prostate cancer: Data from the cancer of the prostate strategic urological research endeavor. *BJU Intl*. 2008;101:691-697.