

## Population-based Comparative Effectiveness of Salvage Radical Prostatectomy vs Cryotherapy

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<b>OBJECTIVE</b>	To characterize population-based practice patterns, disease-specific and overall mortality, and cost associated with salvage cryotherapy (SCT) vs salvage radical prostatectomy (SRP).
<b>METHODS</b>	We retrospectively identified 440 men who failed primary radiation therapy and subsequently underwent SCT (n = 341, 77.5%) or SRP (n = 99, 22.5%) between 1992 and 2009 from Surveillance, Epidemiology, and End Results–Medicare linked data. Propensity score analyses were used to compare overall and prostate cancer-specific mortality and associated Medicare expenditures for SRP vs SCT.
<b>RESULTS</b>	Men undergoing SCT were more likely to be white ( $P < .001$ ), less likely to be high school graduates ( $P = .008$ ), and experienced shorter median time from diagnosis to salvage therapy (44.1 vs 60.1, $P < .001$ ) and from primary radiotherapy to salvage therapy (38.7 vs 55.8 months, $P < .001$ ). In adjusted analyses, overall mortality was higher (21.6 vs 6.1 deaths/100 person years, $P < .001$ ) for SRP vs SCT. There was a trend for higher prostate cancer-specific death rates with SRP vs SCT (6.5 vs 1.4 deaths/100 person years, $P = .061$ ). Medicare expenditures for SRP vs SCT were more than 2-fold higher (\$19,543 vs \$8,088, $P < .001$ ).
<b>CONCLUSION</b>	SRP vs SCT is associated with higher overall mortality and greater health care expenditures. However, longer follow-up is needed to assess long-term functional outcomes and cancer control. UROLOGY 83: 653–657, 2014. © 2014 Elsevier Inc.

Prostate cancer is the most prevalent solid organ tumor among US men, with an estimated incidence of 241,740 cases and 28,170 prostate cancer-specific deaths in 2012.<sup>1</sup> Owing to stage migration observed over the past 3 decades, most incident prostate cancers present as localized disease.<sup>2</sup> Despite the popularity of traditional radiation therapies (external-beam and brachytherapy) as primary treatment options for localized disease,<sup>3</sup> 63% of men will experience biochemical recurrence within 10 years of radiotherapy,<sup>4</sup>

and it is estimated that 25%–32% will experience local failure.<sup>5</sup>

Salvage radical prostatectomy (SRP) and salvage cryotherapy (SCT) are performed with curative intent for clinically localized radiorecurrent prostate cancer, with 5-year progression-free survival approaching 60% for both.<sup>6,7</sup> Although SRP historically has a longer follow-up with acceptable oncologic outcomes, it is accompanied by significant morbidity owing to radiation-induced fibrosis and tissue-plane obliteration.<sup>8</sup> Conversely, SCT (particularly third-generation technology) has gained popularity, possibly because of improved technique and fewer complications.<sup>9</sup> Although several systematic reviews have assessed SRP and SCT morbidity and survival,<sup>6,10</sup> there is a dearth of directly comparative studies. Moreover, consensus regarding the optimal management of primary radiotherapy failures remains elusive.<sup>11</sup> Through our population-based approach that provides insight beyond referral centers in which salvage therapy outcomes largely originate, we sought to compare the use, patterns of care, outcomes, and costs of SRP vs SCT.

### MATERIALS AND METHODS

#### Data

Our study was approved by the University of California, Los Angeles Review Board; patient data were deidentified, and the

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Jim C. Hu 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.

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requirement for consent was waived. We used Surveillance, Epidemiology, and End Results (SEER)—Medicare data for analysis, which currently comprises a linkage of cancer registry data from 20 SEER regions with Medicare administrative data. The Medicare program provides benefits to 97% of Americans aged  $\geq 65$  years.<sup>12</sup>

We identified 345,803 men aged  $\geq 65$  years who were diagnosed with prostate cancer between 1992 and 2007, with Medicare follow-up through 2009. After excluding men not enrolled in both Medicare Part A and B or who were enrolled in a Medicare health maintenance organization because of unreliable claims submissions during the study period, 103,508 men treated with primary radiotherapy were subsequently identified. Of this group, 430 were found to have received SRP ( $n = 99$ ) or SCT ( $n = 341$ ). Patients were grouped into SRP or SCT cohorts based on *International Classification of Diseases, Ninth Revision* (ICD-9), *Physicians Current Procedural Terminology Coding System, 4th edition*, and *Healthcare Common Procedure Coding System* codes (60.62, C2618, 55840, 55842, 55845, and 55873), with SRP defined as surgery after 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 restricted our cohort to men with prostate cancer diagnosed as their only cancer.

### Outcomes

We examined overall and prostate cancer-specific mortality after SRP vs SCT. In addition, we characterized Medicare expenditures associated with each treatment.

### 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 modification of the Charlson index during the year before surgery.<sup>13</sup> ICD-9 codes were used to identify disease categories, whereas *Physicians Current Procedural Terminology Coding System, 4th edition* 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. Adjuvant androgen deprivation therapy (ADT) was defined as ADT use anytime between 6 months before and after primary therapy. "Additional ADT" was defined as ADT use at  $\geq 2$  years after SCT and use anytime after SRP.

### Expenditures

To best attribute the costs associated with each surgical setting, we assessed Medicare payments within 3 months of salvage therapy, which represents the traditional global payment period.<sup>14</sup>

### Statistical Analysis

Unadjusted analysis using the Pearson chi-square statistic was performed to compare demographic and tumor characteristics for SRP vs SCT.<sup>15</sup> Adjusted analyses were performed with weighted propensity scoring.<sup>16</sup> Propensity score methods control for all observed confounding factors that might 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 SRP vs SCT on the basis of described covariates and then weighting the data on the basis of the inverse propensity of being in either of the treatment groups.<sup>17</sup> After adjustment, covariate balance was assessed.

All tests were considered statistically significant at  $\alpha = 0.05$ . All analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC). Because of confidentiality, values  $< 11$  may not be reported directly or in a derivable way. Therefore, for outcomes with  $< 11$  patients, we present odds ratios.

## RESULTS

Among men experiencing radiotherapy failure, 341 (77.5%) underwent SCT and 99 (22.5%) SRP. Median follow-up for SRP vs SCT was 30 (interquartile range 18-44.4) vs 15 (interquartile range 4.8-33.6) months after salvage therapy. Although men undergoing SRP vs SCT experienced longer median time from primary to salvage therapy (55.8 vs 38.7 months,  $P < .001$ ) and from diagnosis to salvage therapy (60.1 vs 44.1 months,  $P < .001$ ), they experienced similar median time from prostate cancer diagnosis to primary therapy (3.0 months for both,  $P = .132$ ).

Men receiving SCT vs SRP (Table 1) were more likely to be white ( $P < .001$ ) and to live in areas with  $< 85\%$  high school graduation rates ( $P = .008$ ). In addition, men undergoing SCT vs SRP were more likely to have received previous ADT (50.4% vs 45.5%,  $P = .001$ ) and primary brachytherapy (43.7% vs 24.2%,  $P = .001$ ).

Propensity adjusted analyses is presented in Table 2. Overall survival was reduced (21.57 vs 6.14 deaths/100 person years,  $P < .001$ ) for SRP vs SCT. Similarly, there was a trend for higher disease-specific mortality for SRP vs SCT (6.54 vs 1.37 deaths/100 person years,  $P = .061$ ).

Health care expenditures in the 3 months before salvage therapy were higher for SRP vs SCT (median \$8,416 vs \$2,363,  $P < .001$ ). Similarly, SRP costs were 2-fold higher than SCT (median \$19,543 vs \$8,088,  $P < .001$ ). SRP vs SCT patients were more likely to require inpatient care in the 6 months surrounding surgery (58.6% vs 32.0%), at a median cost of \$23,321 vs \$10,497 ( $P < .001$ ).

## COMMENT

The optimal management of radiorecurrent prostate cancer remains controversial, particularly for younger men or those with life expectancy  $> 10$  years.<sup>11</sup> Current salvage treatment options include ADT, brachytherapy, cryoablative therapy, high-intensity focused ultrasound, and radical prostatectomy. Although SRP has the longest documented follow-up with acceptable oncologic outcomes, its use has been limited by greater perioperative morbidity, including rectal injury, urethrocutaneous fistula, lymphedema, urinary incontinence, and anastomotic stricture.<sup>18,19</sup> The use of SCT has increased in recent years owing to comparable oncologic outcomes and superior complication rates.<sup>5</sup> However, in the

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