



National Trends in the Recommendation of Radiotherapy After Prostatectomy for Prostate Cancer Before and After the Reporting of a Survival Benefit in March 2009

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Abstract

We used the Surveillance, Epidemiology, and End Results database to determine whether any changes in postprostatectomy radiotherapy (PPRT) recommendations occurred after the publication of the Southwestern Oncology Group 87-94 update in 2009 and what factors were associated with PPRT recommendations. To our knowledge, our study is the first to use a large national contemporary cohort to demonstrate an increase in PPRT uptake after the dissemination of survival benefit data. Still, absolute PPRT utilization rates remain low, suggesting that the oncologic community remains unconvinced that PPRT is needed for most patients with adverse features after prostatectomy.

Background: Three randomized trials demonstrated that postprostatectomy adjuvant radiotherapy improves biochemical disease-free survival for patients with adverse pathologic features, and 1 trial found adjuvant radiotherapy improves overall survival. We sought to determine whether postprostatectomy radiotherapy (PPRT) utilization changed after publication of the survival benefit in March 2009. **Patients and Methods:** The Surveillance, Epidemiology, and End Results database was used to identify men diagnosed with prostate cancer from 2004 to 2011 who met criteria for enrollment in the randomized trials (positive margins and/or pT3-4 disease at radical prostatectomy). Joinpoint regression identified inflection points in PPRT utilization. Logistic regression was used to evaluate factors associated with PPRT recommendation. **Results:** Of 35,361 men, 5104 (14.4%) received a recommendation for PPRT. In joinpoint regression, 2009 was the inflection point in PPRT utilization. In multivariable analysis, PPRT recommendations were more likely after March 2009 than before 15.8% vs. 13.5%, adjusted odds ratio (AOR; 1.09; 95% confidence interval [CI], 1.02-1.16; $P = .008$), in men with pT3 (vs. pT2, AOR, 2.81; 95% CI, 2.53-3.11; $P < .001$), pT4 (vs. pT2 AOR, 4.62; 95% CI, 3.85-5.54; $P < .001$), or margin positive (AOR, 1.46; 95% CI, 1.34-1.58; $P < .001$) disease and in men who were younger (per year decrease, AOR, 1.02; 95% CI, 1.02-1.03; $P < .001$), married (AOR, 1.10; 95% CI, 1.02-1.19; $P = .01$), or lived in metropolitan areas (AOR, 1.30; 95% CI, 1.16-1.47; $P < .001$). **Conclusion:** PPRT recommendations increased after the reporting of a survival benefit in March 2009, but absolute utilization rates remain low, suggesting that the oncologic community remains unconvinced that PPRT is needed for most patients with adverse features. Further work is needed to identify patients who might benefit most from PPRT.

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Introduction

In 2014, there will be an estimated 238,590 new cases of prostate cancer and 29,480 deaths due to prostate cancer in the United States alone.¹ Radical prostatectomy remains a standard and widely accepted treatment option for patients with localized NOM0 prostate cancer.^{2,3} Nevertheless, many patients who receive prostatectomy for localized prostate cancer might have adverse pathologic features at surgery such as extracapsular extension, seminal vesicle invasion, and/or involved surgical margins.⁴⁻⁶ Three randomized controlled trials (RCTs) have demonstrated that adjuvant

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radiotherapy (RT) for patients with adverse pathologic features after surgery for prostate cancer improves biochemical recurrence-free survival (bRFS) and 1 of those trials found an overall survival benefit.⁷⁻⁹ Furthermore, these trials found that nearly 2 thirds of patients with adverse pathological features at surgery will go on to develop biochemical recurrence if not treated with postoperative RT.

The European Organisation for Research and Treatment of Cancer (EORTC) 22911, Southwestern Oncology Group (SWOG) 87-94, and German ARO 96-02/AUO AP 09/95 trials were initially published in 2005,¹⁰ 2006,¹¹ and 2009,¹² respectively. Results from the initial publications demonstrated improved bRFS and an update to the SWOG trial in March 2009 published in the *Journal of Urology* demonstrated that adjuvant RT was associated with increased overall survival.⁷ Previous studies have attempted to characterize the trends in postprostatectomy RT (PPRT) use and recommendations after publication of the RCTs using the Surveillance, Epidemiology and End Results (SEER) and SEER-Medicare linked databases.^{13,14} These studies did not show an increase after the RCTs demonstrated improved bRFS; however, the study cohorts were not able to include data from patients who were diagnosed and received surgery after 2009 when the survival benefit was published because SEER did not yet release information beyond 2007 at the times of the studies. Recent updates to the SEER program include data up to 2011, allowing for more rigorous and accurate exploration of PPRT recommendation trends after the publication of the survival benefit in 2009.

Herein, we used the SEER program to determine whether any changes in PPRT recommendations occurred after the publication of the SWOG 87-94 update in March 2009 and what factors (sociodemographic or cancer-specific) were associated with PPRT recommendations.

Patients and Methods

Study Design

Sponsored by the National Cancer Institute, the SEER program collects and publishes cancer incidence, survival, and treatment data from population-based cancer registries; the 17 tumor registries encompass nearly 28% of the US population and capture approximately 97% of incident cancers.^{15,16} The SEER program was used to identify 38,419 men with N0M0 prostate cancer who had positive margins and/or pT3-4 disease after radical prostatectomy from 2004 to 2011. The inclusion period was limited to 2004 to 2011, because 2004 represents the year that SEER initiated collection of prostate-specific antigen (PSA) data and 2011 represents the most recent year for which full information is available. Patients were not selected if they had a previous cancer diagnosis, brachytherapy as a treatment, or preoperative radiation. Patients were excluded if PSA information was missing (n = 3080) or if radiation recommendations were not documented (n = 175), leaving 35,361 patients for study analyses.

Men were classified as having PPRT recommended versus not having PPRT recommended, as previously described.¹³ Patients were defined as having received a PPRT recommendation if PPRT was received, recommended but unknown if administered, or refused (assuming that if PPRT was refused, then it also must have been recommended) as classified by the SEER program.^{13,16} SEER

aims to capture complete information on first course treatment, including PPRT. Tumors were classified according to SEER site-specific factor 3 (pathologic extension) for prostate, as pT2, pT3, or pT4 and margins were categorized as involved versus uninvolved.¹⁷ Of note, SEER does not capture margin status for pT3b tumors (seminal vesicle invasion), so these cases were conservatively classified as having uninvolved margins. Gleason score was categorized as Gleason 8 to 10 versus Gleason ≤ 7 . Income (computed as median household income) and educational status (computed as the percentage of residents ≥ 25 years of age with at least a high school education) were both determined at the county level by linking to the 2000 US Census.¹⁸ Residence type (metropolitan vs. nonmetropolitan) was also determined at the county level by linking to the 2013 US Department of Agriculture rural-urban continuum codes.¹⁹ SEER regions were classified as west, east, southwest, Alaska, and northern plains. The demographic characteristics of race and marital status were classified as white (non-Hispanic), black, non-black Hispanic, Asian or Pacific Islander, Native American, or other race and married versus unmarried, respectively.

Statistical Analysis

Univariable joinpoint regression analysis (Joinpoint Regression Program, Version 4.1.0)²⁰ was used to analyze trends in the percent of men who received PPRT recommendations. The Joinpoint Regression Program takes trend data and tests whether any statistically significant changes in trends occur using the Monte Carlo permutation method.²¹ Points at which statistically significant changes in trends occur are termed “joinpoints.”

Univariable and multivariable logistic regression analyses were used to determine whether any changes in PPRT recommendations occurred after March 2009 and what factors were associated with PPRT recommendations. Multivariable models were adjusted for year of diagnosis, race, age, residence, marital status, educational status, income, SEER region, PSA, Gleason score, pathologic T stage, and margin status. Logistic regression *P* values were 2-sided with the threshold of .05 used to determine statistical significance. Logistic regression analyses were completed using STATA 13.0 (StataCorp, College Station, TX). This study was approved by the institutional review board; a waiver for informed consent was obtained.

Results

Baseline Clinical and Demographic Characteristics

Table 1 displays baseline clinical and demographic characteristics. The median age of the study cohort (n = 35,361) was 62 (interquartile range [IQR], 57-67). Most men were white (72.7%), married (77.3%), and from metropolitan areas (90.1%). The median PSA was 6.4 ng/dL (IQR, 4.8-9.7 ng/dL), 21.5% of patients had Gleason 8 to 10 disease, 69.1% had pT3-4 disease, and 45.2% had involved margins after prostatectomy.

Recommendations for Adjuvant Radiation Therapy

Among 35,361 patients who had adverse pathologic features after prostatectomy for prostate cancer, 5104 (14.4%) patients were recommended PPRT from 2004 to 2011. Joinpoint regression model detected an apparent significant increase (by the Monte Carlo permutation method) in the rate of PPRT recommendations after 2009 (Figure 1).

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