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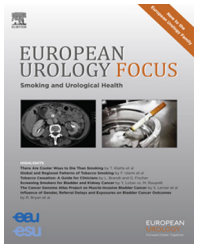


Prostate Cancer

# Adjuvant Radiotherapy in Prostate Cancer Patients Treated with Surgery: The Impact of Age and Tumor Characteristics

*Firas Abdollah* [a,†,*], *Pierre I. Karakiewicz* [b,†], *Giorgio Gandaglia* [c], *Deepansh Dalela* [a], *Dane E. Klett* [a], *Jonas Shiffmann* [b], *Francesco Montorsi* [c], *Alberto Briganti* [c], *Fred Saad* [b], *Markus Graefen* [d], *James O. Peabody* [a], *Mani Menon* [a], *Maxine Sun* [b]

[a] *Vattikuti Urology Institute and VUI Center for Outcomes Research Analytics and Evaluation, Henry Ford Hospital, Detroit, MI, USA;* [b] *Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Centre, Montreal, QC, Canada;* [c] *Department of Urology, Vita Salute San Raffaele University, Milan, Italy;* [d] *Martini Clinic, Prostate Cancer Center Hamburg-Eppendorf, Hamburg, Germany*

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## Abstract

*Background:* The overall mortality (OM) and cancer-specific mortality (CSM) benefits of adjuvant radiotherapy (aRT) in treating prostate cancer (PCa) patients with adverse pathologic characteristics at radical prostatectomy (RP) are unclear.
*Objective:* To test the impact of aRT on survival in PCa patients treated with RP according to adverse pathologic characteristics (Gleason score [GS] 8–10; pT3b/4, lymph node invasion [LNI]) and age categories (<70 vs ≥70 yr).
*Design, setting, and participants:* A total of 7616 patients with pT3/4 pN0/1 PCa treated with RP between 1995 and 2009 within the Surveillance Epidemiology and End Results–Medicare linked database were included.
*Outcome measurements and statistical analysis:* Cox regression analysis was used to test the relationship between aRT and CSM, as well as OM in the entire cohort. Stratification was performed according to tumor characteristics and age categories.
*Results and limitations:* In patients with fewer than two adverse pathologic characteristics, aRT did not improve CSM or OM. Conversely, in patients with two or more adverse pathologic characteristics, the 10-yr CSM-free rate was 92% in patients treated with aRT versus 82% in patients treated without aRT ($p < 0.001$). This survival improvement was confirmed in patients aged <70 yr ($p = 0.01$) but not in those ≥70 yr ($p = 0.1$). In multivariable analyses, aRT was an independent predictor of lower CSM risk (hazard ratio: 0.45; $p = 0.02$) only among patients aged <70 yr with two or more adverse pathologic characteristics. Similar trends were observed when OM was examined as an end point.
*Conclusions:* Age and tumor characteristics should be considered in the selection of optimal aRT candidates after surgery. Only patients aged <70 yr with two or more adverse pathologic characteristics (GS 8–10, pT3b/4, LNI) appear to benefit from aRT.
*Patient summary:* The usefulness of adjuvant radiotherapy after surgery for prostate cancer greatly depends on tumor characteristics and patient age. Only patients with advanced local tumor characteristics aged <70 yr seem to benefit from this treatment modality.


† Contributed equally.
* Corresponding author. Vattikuti Urology Institute and VUI Center for Outcomes Research Analytics and Evaluation, Henry Ford Health System, 2799 W. Grand Blvd, Detroit, MI, 48202–2689, USA. Tel. +1 313 916 9923.
E-mail addresses: firas.abdollah@gmail.com, fabdoll1@hfhs.org (F. Abdollah).

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## 1. Introduction

Prostate cancer (PCa) is the most common noncutaneous malignancy in men [1,2]. Most patients present with clinically localized tumors at diagnosis [3,4]. However, adverse pathologic features are still found in about a third of patients treated with radical prostatectomy (RP) [4–6]. These features consist of positive surgical margins (PSMs), extracapsular extension, seminal vesicle invasion, and/or lymph node invasion (LNI). Randomized clinical trials (RCTs) have shown that adjuvant radiotherapy (aRT) in node-negative PCa patients with adverse pathologic characteristics affords greater biochemical recurrence (BCR)–free survival; however, its role in long-term survival benefit is questionable [7–9]. Although the European Organization for Research and Treatment of Cancer (EORTC) 22911 trial [7] found no significant improvement in clinical progression and survival rates with the use of aRT, the SWOG S8794 study [8] demonstrated a 29% and 28% reduction in the risk of metastasis and overall mortality (OM), respectively. Differential tumor characteristics, intensity of salvage treatment, or insufficient power to detect survival end points could have contributed to the contradictory results, among other factors.

Importantly, most patients included in the trials just cited had a pathologic T2–T3a and pN0 disease (with or without PSMs) [7–9]. In a 2013 report [10], we observed that such patients are unlikely to benefit from aRT. Only patients with at least two of these three characteristics—Gleason score (GS) 8–10, pathologic T3b/T4 disease, and LNI—had a survival improvement when treated with aRT [10]. Theoretically, even in these individuals, advanced age may undermine the beneficial impact of aRT on overall survival, as also noted in the EORTC trial [7]. Due to the limited sample size, however, we were unable to test this theory in our previous report [10]. To address this important issue, we decided to revisit the impact of aRT on cancer-specific mortality (CSM) and OM in a large contemporary population-based North American cohort, after stratifying patients according to adverse pathologic characteristics and age.

## 2. Materials and methods

### 2.1. Population source

Our study relied on the Surveillance Epidemiology and End Results (SEER)–Medicare linked database, which is 98% complete for case ascertainment. The SEER registries covered approximately 28% of the US population with Medicare administrative data. Medicare insurance includes approximately 97% of Americans aged ≥65 yr. Linkage to the SEER database is complete for approximately 93% of cases [11].

### 2.2. Study population

We identified a total of 44 536 patients diagnosed with nonmetastatic PCa (International Classification of Disease for Oncology site code 61.9; histologic code 8140) as the primary malignancy between 1995 and 2009 and treated with RP within 6 mo of diagnosis. Patient follow-up was available until December 31, 2011. Patients were not included if their original or current reason for Medicare entitlement was listed as a disability or a Medicare status code including disability. We also excluded men who were enrolled in a health maintenance organization, those who were not enrolled in both Medicare Part A and Part B for a minimum of 6 mo after diagnosis, or men whose claims data were missing from the time of RP through an event or end of follow-up in claims (2011), permitting complete capture of health services claims throughout the duration of the study.

Patients were excluded if aged ≥75 yr ($n = 4008$) and had an unknown clinical stage ($n = 689$), GS ($n = 1289$), pathologic stage ($n = 3958$), nodal stage ($n = 125$), and demographic data ($n = 390$). This yielded 34 077 assessable patients. For the purpose of this study, we excluded patients with pT2 disease ($n = 26\,158$) and those with a follow-up <6 mo ($n = 303$). The final population consisted of 7616 patients.

RP was defined using SEER surgery site codes 50 or 70. Given possible discrepancies between SEER and Medicare data on treatment assignment [12], we also identified patients from Medicare inpatient, outpatient, and carrier component files based on the presence of Current Procedural Terminology, Fourth Edition (CPT-4) billing codes (55810, 55812, 55815, 55840, 55842, 55845, and 55866) and International Classification of Diseases, Ninth Revision (ICD-9) codes (60.5x, 60.3x, 60.4x, and 60.62) [13]. We identified aRT and adjuvant hormonal therapy (aHT) as the administration of radiotherapy and hormonal treatment, respectively, within 6 mo from surgery [14]. Use of RT and HT was ascertained from Medicare claims using the CPT and ICD-9 codes as described previously by Goldin et al [13].

### 2.3. Covariates

The following information was extracted for all patients: age at diagnosis (dichotomized as <70 vs ≥70 yr according to the median), year of surgery, race, marital status, pathologic GS, clinical stage, and pathologic stage. The Charlson Comorbidity Index was derived from the Medicare claims 1 yr prior to PCa diagnosis using a commonly used and validated algorithm [15]. GSs were extracted from collaborative staging (CS) and grade categories for men diagnosed between 2004 and 2009 and 1995 and 2003, respectively [16]. While SEER provides detailed post-RP/autopsy GSs beginning in 2004 (CS site-specific factors 9 and 10), the variable grade categorizes GS score as 2–4, 5–7, and 8–10 for men diagnosed with PCa from 1995 through 2003.

For this analysis, tumor grade was categorized into two groups based on the SEER grading system: well/moderately differentiated (GS ≤7) and poorly differentiated (GS 8–10). Finally, the number of adverse pathologic characteristics (namely pathologic GS 8–10, pathologic stage T3b–T4, and LNI) was identified in each patient. As noted in a previously described methodology [10], the total number of these characteristics was used to calculate a risk score to stratify patients into two risk groups: <2 versus ≥2 risk score.

### 2.4. Outcomes

The cause of death was defined using the SEER cause of death code. Patients who died from PCa (ICD-9 185.9 or ICD-10 C619) were classified as CSM. Patients who died from any cause (including CSM) were classified as OM.

### 2.5. Statistical analyses

Descriptive statistics of categorical variables focused on frequencies and proportions. Means, medians, and interquartile ranges (IQRs) were reported for continuously coded variables. Chi-square and Mann-Whitney tests were used to compare the statistical significance of differences in proportions and medians, respectively.

Kaplan-Meier curves were used to estimate CSM-free and OM-free rates in the entire cohort, after stratifying patients according to aRT