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Prostate Cancer

Multi-institutional Evaluation of Elective Nodal Irradiation and/or Androgen Deprivation Therapy with Postprostatectomy Salvage Radiotherapy for Prostate Cancer

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Abstract

Background: Outcomes with postprostatectomy salvage radiation therapy (SRT) are not ideal. Little evidence exists regarding potential benefits of adding whole pelvic radiation therapy (WPRT) alone or in combination with androgen deprivation therapy (ADT).
Objective: To explore whether WPRT and/or ADT added to prostate bed radiation therapy (PBRT) improves freedom from biochemical failure (FFBF) or distant metastases (DM).
Design, setting, and participants: A database was compiled from 10 academic institutions of patients with postprostatectomy prostate-specific antigen (PSA) >0.01 ng/ml; pT1-4, Nx/0, cM0; and Gleason score (GS) ≥7 treated between 1987 and 2013. Median follow-up was 51 mo.
Interventions: WPRT and/or ADT in addition to PBRT.
Outcome measurements and statistical analyses: FFBF and DM were calculated using cumulative incidence estimation. Multivariable analysis (MVA) utilized cumulative incidence regression.
Results and limitation: Median pre-SRT PSA was 0.5 ng/ml for 1861 patients. Median follow-up for patients not experiencing biochemical failure (BF) was 55 mo. MVA showed increased BF for PBRT versus WPRT (hazard ratio [HR] 1.82, $p < 0.001$) and no ADT versus ADT (HR 1.70, $p < 0.001$). WPRT was associated with a 5-yr FFBF of 62% versus 49% ($p < 0.001$) for PBRT. ADT use was associated with improved 5-yr FFBF (55% vs 50%, $p = 0.012$). No significant differences in DM cumulative incidence were found.
Conclusions: For patients with GS ≥7 receiving SRT, clinicians should weigh FFBF benefits of WPRT and ADT against toxicities. Future studies should explore the impact of WPRT on quality of life, clinical progression, and overall survival.
Patient summary: We evaluated patients with prostate cancer treated with radiation after surgery to remove the prostate. Both radiation to the pelvic lymph nodes and suppression of testosterone lowered the chance of increasing prostate-specific antigen (a marker for cancer returning).

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1. Introduction

Postprostatectomy radiation therapy (RT) improves outcomes for patients with positive surgical margins, pathologic T3 disease [1–3], and subsets with pelvic node involvement [4]. However, outcomes remain suboptimal, with 10-yr progression-free survival (PFS) rates between 56% and 61% [1,2]. Three randomized trials evaluating postprostatectomy RT in node-negative patients limited treatment to the prostate bed (PBRT) only, precluding evaluation of whether elective whole pelvic RT (WPRT) improves outcomes. RTOG 0534 investigated the role of androgen deprivation therapy (ADT) and WPRT with salvage RT (SRT); however, the results have not yet been reported. Despite no level 1 evidence, over 70% of radiation oncologists consider utilizing WPRT in the postprostatectomy setting [5]. Previous observational studies evaluating salvage WPRT were limited in size and drew different conclusions [6–9].

Questions also remain regarding the advantages of ADT given with SRT. RTOG 9601 demonstrated an 8.5% absolute reduction in the 12-yr incidence of distant metastases (DM) and a 5% improvement in 12-yr overall survival (OS) with long-term antiandrogen therapy [10]. The GETUG-AFU 16 trial showed short-term ADT given with SRT improved PFS, although no OS advantage has yet been shown [11]. However, WPRT was not utilized in the RTOG trial, and only 16% of patients in the GETUG-AFU trial received WPRT [10,11]. It remains uncertain whether WPRT is beneficial with or without ADT during SRT. Our analysis was performed to explore whether WPRT and ADT are associated with improved outcomes compared with salvage PBRT.

2. Patients and methods

Data collection for this database has been described previously [12]. Briefly, nine US academic centers signed an agreement with the Cleveland Clinic Foundation, the recipient data center that obligated all sites to comply with Health Insurance Portability and Accountability Act guidelines. A limited dataset of protected health information was assembled after Institutional Review Board approval. Inclusion criteria, data elements, and data collection and transference procedures were prespecified.

All patients were ≥18 yr old, treated at tertiary referral centers, received open or laparoscopic radical prostatectomy (RP), and underwent SRT for a detectable postoperative prostate-specific antigen (PSA) level of >0.01 ng/ml. This analysis was limited to patients with pathologic Gleason score (GS) ≥7 to examine a higher-risk subset shown to have increased rates of disease progression after SRT [12,13]. Exclusion criteria were as follows: (1) undetectable PSA at RT; (2) ADT initiated either before RP or more than 6 mo before SRT; (3) histologically positive lymph nodes; and (4) incomplete pathologic staging or follow-up details to assess biochemical failure (BF), DM, and vital status. Overall, 1861 patients treated with SRT between 1987 and 2013 were included.

Treatment was at practitioner discretion with patient informed consent. The use of WPRT and ADT (including type/duration) was not prespecified, randomly assigned, or mandated by uniform standards. The WPRT target volume for elective nodal RT was influenced by best practices and guidelines [14] that evolved during the study period. Details of field design, including the extent of nodal coverage, were not available; patients were coded as having received nodal RT or not. Details regarding specific ADT agents were not available; patients were coded as having received neoadjuvant/concurrent ADT or not. Neoadjuvant/concurrent ADT was defined as having started either during SRT or within 6 mo prior to SRT. There was no centralized pathology review, uniform staging, or standardized follow-up.

BF following SRT was defined as serum PSA >0.2 ng/ml with a confirmatory rising value or by initiation of salvage ADT after SRT [15]. Rates of freedom from BF (FFBF) and DM were estimated from the date of SRT completion to the date of last recorded follow-up using the cumulative incidence method with nonprostate cancer death as a competing risk [16]. FFBF and DM rates were initially calculated comparing WPRT versus PBRT alone and ADT versus no ADT. Cumulative incidence analyses were repeated to analyze the four possible combinations of treatments assessed in this study (PBRT/no ADT, WPRT/no ADT, PBRT/ADT, and WPRT/ADT) in an effort to assess the FFBF and DM rates with each possible treatment combination.

Multivariable analysis (MVA) was performed by competing risk regression to assess whether ADT and/or WPRT was associated with reductions in BF and/or DM [17]. Variables included in each MVA were selected based on their known prognostic significance from previous studies using this database [12] and included commonly recognized prognostic variables. Interaction tests were performed within the competing risk regression for biochemical recurrence and DM by adding ADT and RT coverage, ADT and GS, and GS and RT coverage, each as a variable in both models. This method tests each variable individually and specific variables as interaction terms within the model. ADT use was included as a binary variable rather than a time-dependent covariate since ADT duration use was not reported by all centers. PSA doubling time was not analyzed due to the inclusion of patients treated with early SRT at PSA levels <0.2 ng/ml in whom PSA doubling time could not be accurately estimated. A p value of <0.05 was statistically significant. Only total GS was available for all patients; therefore, GS 7 (grade group 2–3 as defined by the International Society of Urologic Pathology [18]) patients were not subdivided into primary pattern 3 (grade group 2) versus 4 (grade group 3). SRT dose was evaluated as a binary variable (<66 vs ≥66 Gy) rather than as a continuous variable due to a separate analysis from this dataset and supported by existing literature [19,20]. Given the limited size of the GS 8–10 (grade group 4–5) grouping, it was not further subdivided. All statistical analyses used R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

The median follow-up was 51 mo (interquartile range [IQR]: 24–90 mo) for all patients and 55 mo (IQR: 26–101 mo) for patients who did not experience BF. Median age at RP, median age at SRT, SRT dose, and pre-SRT PSA were 61 yr, 64 yr, 66 Gy, and 0.5 ng/ml, respectively. Intensity-modulated RT (IMRT), three-dimensional conformal RT (3D-CRT), and two-dimensional RT (2D-RT) were used in 40%, 30%, and 31% of patients, respectively. WPRT was administered in 13% of patients with GS 7 and 20% with GS 8–10. The use of WPRT increased in recent years from 8.7% between 1987 and 1994 to 11.9% between 2005 and 2013 ($p = 0.053$). ADT was given with SRT to 319 (17%) patients (13% GS 7, 30% GS 8–10). Duration of ADT was documented for 267 patients (median 6 mo, range 1–122 mo). ADT use increased over time from 1.7% between 1987 and 1994 to 18.8% between 2005 and 2013 ($p < 0.001$). Extraprostatic extension (EPE), seminal vesicle invasion (SVI), pre-SRT PSA,

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