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Intermediate Endpoints After Postprostatectomy Radiotherapy: 5-Year Distant Metastasis to Predict Overall Survival

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Abstract

Background: Intermediate clinical endpoints (ICEs) prognostic for overall survival (OS) are needed for men receiving postprostatectomy radiation therapy (PORT) to improve clinical trial design.
Objective: To identify a potential ICE for men receiving PORT.
Design, setting, and participants: We performed an institutional review board–approved multi-institutional retrospective study of 566 men consecutively treated with PORT at tertiary care centers from 1986 to 2013. The median follow-up was 8.2 yr.
Outcome measurements and statistical analysis: Biochemical failure (BF), distant metastases (DM), and castrate-resistant prostate cancer (CRPC) were evaluated for correlation with OS and assessed as time-dependent variables in a multivariable Cox proportional hazards model and in landmark analyses at 1, 3, 5, and 7 yr after PORT. Cross-validated concordance (*c*) indices were used to assess model discrimination.
Results and limitations: OS at 1, 3, 5, and 7 yr after PORT was 98%, 95%, 90%, and 82%, respectively. In a time-varying model controlling for clinical and pathologic variables, BF (hazard ratio [HR] 2.32, 95% confidence interval [CI] 1.45–3.71; $p < 0.001$), DM (HR 6.52, 95% CI 4.20–10.1; $p < 0.001$), and CRPC (HR 2.47, 95% CI 1.56–3.92; $p < 0.001$) were associated with OS. In landmark analyses, 5-yr DM had the highest *c* index when adjusting for baseline covariates (0.78), with 5-yr DM also providing the greatest increase in discriminatory power over a model only including baseline covariates. These findings require validation in prospective randomized data.
Conclusions: While limited by the retrospective nature of the data, 5-yr DM is associated with lower OS following PORT, outperforming the prognostic capability of BF and CRPC at 1, 3, 5, or 7 yr after treatment. Confirmation of this ICE as a surrogate for OS is needed from randomized trial data so that it can be incorporated into future clinical trial design.
Patient summary: We assessed potential intermediate clinical endpoints prognostic for overall survival in a cohort of men receiving radiotherapy after prostatectomy. We identified the development of metastatic disease within 5 yr after treatment as the strongest predictor of overall survival.

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1. Introduction

The seminal analysis by Pound et al [1] describing the natural history of prostate cancer following prostatectomy demonstrated that in the absence of additional treatment intervention, the median time from biochemical recurrence after prostatectomy to the development of metastatic disease is 8 yr. Similarly, for men receiving salvage radiation therapy (SRT) for biochemical recurrence after prostatectomy, the median time from a "second" biochemical recurrence following SRT to the development of metastatic disease is greater than 9 yr [2]. Modern clinical trials of treatment for men with newly diagnosed metastatic castration-sensitive prostate cancer suggest that the median overall survival (OS) is approximately 5 yr [3,4]. In summary, although survival is highly variable, median survival for men who fail postprostatectomy radiation therapy (PORT) can be approximated 14 yr from the time of their "second" biochemical recurrence [5], with modern nomograms available to assist in estimating a man's prostate cancer–specific survival at the time of postprostatectomy biochemical recurrence [6]. While OS is the gold-standard primary endpoint for oncologic clinical trials, the long natural history of prostate cancer following prostatectomy poses challenges for evaluating novel treatments, as follow-up in excess of a decade is often required to show an improvement in survival. Clinical practice can change dramatically over the course of a decade, often leaving findings from trials out of date or obsolete by the time they are reported.

Robust intermediate clinical endpoints that can be used as a surrogate endpoint for OS are needed to expedite the ability of clinical trials to identify new effective therapies for men receiving PORT, and thereby allow these treatments to be implemented in clinical practice while still clinically relevant. The Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) working group recently established metastasis-free survival as an acceptable surrogate for OS for men with localized prostate cancer [7,8]. However, only a minority of men included in this analysis (8%) were treated with prostatectomy, and metastasis-free survival was not validated in the subset of surgically treated patients. Thus, data are lacking regarding intermediate endpoints for men receiving PORT. We therefore sought to identify an intermediate endpoint associated with OS in a large multi-institutional cohort of men receiving PORT.

2. Patients and methods

2.1. Patients

Data for 566 men undergoing PORT at one of two university-based radiation oncology departments were retrospectively reviewed. This analysis was approved by each local institutional review board. Men with positive lymph nodes at the time of prostatectomy were excluded from the analysis.

2.2. Treatment and follow-up

PORT was defined as SRT to the prostate bed with or without SRT to pelvic lymph nodes. SRT was defined as radiation delivered for persistently elevated prostate-specific antigen (PSA) after prostatectomy or biochemical recurrence following prostatectomy (PSA $\geq$0.2 ng/ml followed by a sequential equal or higher PSA at least 1 mo later). RT was delivered using daily fractions of 1.8–2.0 Gy with three-dimensional conformal RT or intensity-modulated RT. Treatment doses ranged from 64.8 to 70.2 Gy. Patients were followed clinically according to national guidelines, with follow-up PSA values obtained 3 mo after treatment and then every 6–12 mo for 5 yr, and annually thereafter [9]. Post-treatment imaging was triggered by PSA recurrence or patient symptoms.

2.3. Endpoints

The primary endpoint of the analysis was OS, defined as the time from SRT to death from any cause, with censoring of patients lost to follow-up. We also repeated all the analyses for the endpoint of prostate cancer–specific mortality (PCSM), defined as the time from SRT to death secondary to prostate cancer, including any death in a man with metastatic or hormone-refractory disease. Intermediate endpoints assessed included biochemical failure (BF), distant metastasis (DM), and the development of castrate-resistant prostate cancer (CRPC). BF was defined as a rise above the post-PORT PSA nadir $\geq$0.2 ng/ml followed by a second PSA of equal or higher value [10]. DM was defined as any clinical or radiologic evidence of metastatic disease. Patients were considered to have CRPC on development of a rising PSA or radiographic evidence of progressive disease while receiving androgen deprivation therapy (ADT) with castrate testosterone levels.

2.4. Statistical analysis

The Kaplan-Meier product-limit method was used to estimate the OS distribution. To evaluate the effect of intermediate endpoints on OS, we first examined them as time-dependent covariates in a multivariate Cox proportional hazards model, adjusting for the following baseline covariates: Gleason score, T stage, log-transformed pre-PORT PSA, use of concurrent ADT, patient age, and year of SRT.

Landmark analysis using univariate and multivariate Cox proportional hazards models, adjusting for the same baseline covariates mentioned previously, was then used to assess the prognostic impact of the intermediate endpoints on subsequent survival at 1, 3, 5, and 7 yr after PORT. Only patients alive and not censored at the landmark time were included in each landmark analysis, and their intermediate endpoint status was assessed up to the landmark time. These models were applied to patients for whom BF, DM, and CRPC information was available to make the models comparable across all the intermediate endpoints. The time points were defined a priori on the basis of clinical follow-up. The hazard ratio (HR), 95% confidence interval (CI), and p value are reported, with significance evaluated at the 5% level.

Model discrimination was evaluated using the concordance index (c index) in landmark analyses to compare the predictive ability of the different intermediary events at the landmark times of interest. To assess the use of the intermediate events over the 7-yr time period we presented the global concordance measure–integrated area under the curve (AUC). Statistical analyses were performed using R version 3.3.3 (*survival*, *dynpred*, and *survAUC* packages).

3. Results

3.1. Patient characteristics

Analysis was based on data for 566 men receiving SRT from 1986 to 2013 for whom time to death or last follow-up was available. The median age was 63.1 yr (interquartile range [IQR] 57.8–68.6). Median pre-SRT PSA was 0.4 ng/ml (IQR

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