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Impact of Postoperative Radiotherapy in Men with Persistently Elevated Prostate-specific Antigen After Radical Prostatectomy for Prostate Cancer: A Long-term Survival Analysis

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Abstract

Background: Prostate cancer (PCa) patients with prostate-specific antigen (PSA) persistence after radical prostatectomy (RP) are at increased risk of mortality, although the natural history of these men is heterogeneous and the optimal management has not been established.
Objective: To develop a model to predict cancer-specific mortality (CSM) and to test the impact of radiotherapy (RT) on survival in this setting.
Design, setting, and participants: We identified 496 patients treated with RP and lymph node dissection at two referral centers between 1994 and 2014 who had PSA persistence, defined as a PSA level between 0.1 and 2 ng/ml at 6–8 wk after RP.
Outcome measurements and statistical analyses: A multivariable model predicting CSM was developed. We assessed whether the impact of postoperative PSA levels on survival differed according to baseline CSM risk. The nonparametric curve fitting method was then used to explore the relationship between baseline CSM risk and 10-yr CSM rates according to postoperative RT.
Results and limitations: Median follow-up for survivors was 110 mo. Overall, 49 patients experienced CSM. The 10-yr CSM-free survival was 88%. Pathologic grade group and pathologic stage were independent predictors of CSM (all $p = 0.01$). The association between CSM-free survival and PSA at 6–8 wk differed by the baseline CSM risk, whereby the effect of increasing PSA was evident only in patients with a CSM risk of $\geq$10%. Postoperative RT was beneficial when the predicted risk of CSM was $\geq$30% ($p = 0.001$ by an interaction test). Our study is limited by its retrospective design.
Conclusions: Increasing PSA levels should be considered as predictors of mortality exclusively in men with worse pathologic characteristics. Postoperative RT in this setting was associated with a survival benefit in patients with a CSM risk of $\geq$30%. Conversely, individuals with a CSM risk of $<$30% should be initially managed expectantly.
Patient summary: Not all patients with prostate-specific antigen persistence have a poor prognosis. Pathologic characteristics should be used to estimate the risk of cancer-specific mortality in these individuals and to identify patients who could benefit from postoperative radiotherapy.

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1. Introduction

Radical prostatectomy (RP) is associated with excellent oncologic outcomes in patients with localized prostate cancer (PCa), with approximately 75% of such patients being free from recurrence at 10-yr follow-up [1–3]. Following surgery, prostate-specific antigen (PSA) is expected to become undetectable at approximately 6 wk postoperatively. However, up to 20% of patients with adverse pathologic characteristics fail to achieve an undetectable PSA after RP [4–8]. These individuals are at increased risks of recurrence and mortality compared with patients with initially undetectable postoperative PSA [4,7–10]. Considerable heterogeneity has been noted in the clinical outcomes of patients with PSA persistence after surgery [9,11]. A detectable PSA after RP has the potential to reflect persistent local or distant PCa cells not removed by surgery as well as benign prostatic tissue left behind during the procedure. While in the former case, timely administration of additional cancer therapies might improve oncologic outcomes [12,13], in the latter scenario, additional postoperative treatments may represent overtreatment and, thus, possibly expose these men to unnecessary side effects [14–16]. While subanalyses of prospective randomized trials have found a benefit to postoperative radiotherapy (RT) in men with PSA persistence [12,13], to date no study identified the optimal candidate for this approach in order to maximize oncologic benefit for those most likely to experience disease progression, while sparing the use of RT in those less likely to benefit from it.

We hypothesized that the impact of postoperative RT on disease progression and mortality varies according to an individual's risk of cancer-specific mortality (CSM). As such, we aimed at developing a novel predictive tool to identify patients with PSA persistence at a higher risk of CSM. We subsequently evaluated the impact of postoperative RT on CSM according to the risk of dying from PCa. We relied on a large contemporary cohort of patients with PSA persistence after RP treated at two high-volume tertiary referral centers.

2. Patients and methods

2.1. Population source

After Institutional Review Board approval, 982 patients treated with RP between 1994 and 2014 at two tertiary referral institutions (IRCCS Ospedale San Raffaele, Milan, Italy, and Mayo Clinic, Rochester, NY, USA) with available data on the first PSA value after surgery were identified. All patients had PSA persistence, defined as a PSA level of $\geq$0.1 ng/ml after RP. Among those, we selected patients who underwent a first PSA assessment between 6 and 8 wk after surgery (n = 612). Due to their increased risk of harboring distant metastases [17], patients with PSA levels >2 ng/ml at 6–8 wk after surgery (n = 100) were excluded from our analyses. Moreover, patients with incomplete pathologic data and pNx status were excluded from our study (n = 16). This resulted in a final cohort of 496 patients.

2.2. Covariates

All patients had complete data, including age at surgery, year of surgery, preoperative PSA, pathologic stage, pathologic grade group, surgical margin status, and lymph node invasion. Prostatectomy specimens were evaluated by high-volume, dedicated uropathologists. Postoperative RT was delivered to the prostate and seminal vesicle bed using previously described techniques [18–20]. Whole pelvis RT was administered to 7% and 80% of patients with pN0 and pN1 disease included in the postoperative RT group, respectively. Immediate androgen deprivation therapy (ADT) was defined as ADT administered within 90 d from surgery. The decision to administer postoperative RT $\pm$ ADT was based on the clinical judgment of each treating physician according to individual patient and cancer characteristics.

2.3. End points

The primary outcome of the study was CSM, which was defined as death from PCa. Other-cause mortality (OCM) was defined as death due to other causes. Follow-up time was defined as the time elapsed between surgery and CSM or last follow-up.

2.4. Statistical analyses

Our statistical analyses consisted of multiple steps. First, multivariable Cox regression analyses assessed predictors of CSM. Covariates consisted of pathologic stage, pathologic grade group, pN1 status, positive surgical margin status, and immediate ADT. The regression coefficients were then used to generate a model predicting 10-yr CSM. A leave-one-out cross validation was used to construct the Harrell c-index to assess discrimination of our novel model. The relationship between the predicted probability and the observed fraction of patients experiencing CSM at 10 yr was depicted using the calibration plot method.

Second, we assessed whether the impact of PSA level at 6–8 wk after surgery on CSM-free survival differed according to the risk of CSM. Locally weighted 10-yr Kaplan–Meier estimates by values of a continuous covariate (locally weighted scatterplot smoothing) method was used to graphically depict the relationship between PSA at 6–8 wk and 10-yr CSM-free survival in the overall population and after stratifying patients according to the median 10-yr CSM risk (<10 vs $\geq$10%) [21].

Third, we sought to assess whether the impact of postoperative RT was different by CSM risk. A multivariable Cox regression model predicting CSM was developed for patients who did not receive postoperative RT. The same covariates adopted in the nomogram developed for the overall population were used. The 10-yr CSM risk was calculated for each patient using the multivariate coefficients. We then tested an interaction with groups (postoperative RT vs no RT) and the probability of dying from PCa according to the newly developed model. The nonparametric curve fitting method was used to graphically explore the relationship between the risk of CSM and actual 10-yr CSM rates according to the administration of postoperative RT.

All statistical tests were performed using the R statistical package v.3.0.2 (R Project for Statistical Computing, www.r-project.org). All tests were two sided, with a significance level set at <0.05.

3. Results

3.1. Baseline characteristics

Table 1 depicts clinical and pathologic characteristics of patients included in our cohort. Median age at surgery was 64 yr. When patients were stratified according to receipt of postoperative RT, significant differences were observed with regard to the year of surgery, preoperative PSA and risk group, pathologic grade group, pathologic stage, nodal status, positive surgical margin status, and PSA level at

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