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Prostate Cancer

Utility of Risk Models in Decision Making After Radical Prostatectomy: Lessons from a Natural History Cohort of Intermediate- and High-Risk Men

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Abstract

Background: Current guidelines suggest adjuvant radiation therapy for men with adverse pathologic features (APFs) at radical prostatectomy (RP). We examine at-risk men treated only with RP until the time of metastasis.
Objective: To evaluate whether clinicopathologic risk models can help guide postoperative therapeutic decision making.
Design, setting, and participants: Men with National Comprehensive Cancer Network intermediate- or high-risk localized prostate cancer undergoing RP in the prostate-specific antigen (PSA) era were identified (n = 3089). Only men with initial undetectable PSA after surgery and who received no therapy prior to metastasis were included. APFs were defined as pT3 disease or positive surgical margins.
Outcome measurements and statistical analysis: Area under the receiver operating characteristic curve (AUC) for time to event data was used to measure the discrimination performance of the risk factors. Cumulative incidence curves were constructed using Fine and Gray competing risks analysis to estimate the risk of biochemical recurrence (BCR) or metastasis, taking censoring and death due to other causes into consideration.
Results and limitations: Overall, 43% of the cohort (n = 1327) had APFs at RP. Median follow-up for censored patients was 5 yr. Cumulative incidence of metastasis was 6% at 10 yr after RP for all patients. Cumulative incidence of metastasis among men with APFs was 7.5% at 10 yr after RP. Among men with BCR, the incidence of metastasis was 38% 5 yr after BCR. At 10 yr after RP, time-dependent AUC for predicting metastasis by Cancer of the Prostate Risk Assessment Postsurgical or Eggener risk models was 0.81 (95% confidence interval [CI], 0.72–0.97) and 0.78 (95% CI, 0.67–0.97) in the APF population, respectively. At 5 yr after BCR, these values were lower (0.58 [95% CI, 0.50–0.66] and 0.70 [95% CI, 0.63–0.76]) among those who developed BCR. Use of risk model cut points could substantially reduce overtreatment while minimally increasing undertreatment (ie, use of an Eggener cut point of 2.5% for treatment of men with APFs would spare 46% from treatment while only allowing for metastatic events in 1% at 10 yr after RP).
Conclusions: Use of risk models reduces overtreatment and should be a routine part of patient counseling when considering adjuvant therapy. Risk model performance is significantly reduced among men with BCR.
Patient summary: Use of current risk models can help guide decision making regarding therapy after surgery and reduce overtreatment.

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1. Introduction

The use of screening based on prostate-specific antigen (PSA) screening and the application of anatomic radical prostatectomy (RP) has greatly increased our understanding for the disease spectrum of localized prostate cancer (PCa) [1–4]. Large prospectively followed cohorts and randomized controlled trials have suggested that low-grade, low-stage PCa has limited metastatic potential and can be safely surveyed [5–8]. Currently, active surveillance for low-risk and very low-risk PCa has gained greater acceptance with treatment preferentially utilized in men having intermediate- and high-risk disease [9,10].

Men with intermediate- and high-risk PCa more commonly have disease of a higher pathologic stage that is more prone to disease progression [11]. These men may require additional therapy beyond surgical extirpation to prevent the development of clinical metastasis. Three randomized clinical trials have examined the use of secondary local therapy with irradiation of men with adverse pathologic features (ADFs) following RP (defined as positive surgical margins, extraprostatic extension, or seminal vesicle invasion) [12,13]. All three showed a reduction in biochemical recurrence (BCR) with the SWOG 8794 trial (but not European Organization Research and Treatment of Cancer [EORTC] 22911 or ARO 96-02) additionally demonstrating a benefit in overall survival and reduction of metastasis when adjuvant radiation therapy is administered [14–18]. Based on these data, the American Urological Association (AUA), American Society for Radiation Oncology (ASTRO), and American Society of Clinical Oncology (ASCO) guidelines suggest discussion of adjuvant radiotherapy for patients with APFs after surgery [12,13]. Although BCR rates for men with APFs at RC can be high (up to 60% at 10 yr following surgery), it is not clear that all men would benefit from additional local treatment immediately following surgery [19]. Thus to spare morbidity, many providers use salvage radiation therapy at the time of BCR, but this approach may compromise oncologic outcomes [20,21].

Oncologic outcomes of men after RP have been thoroughly examined, and post-RP predictive tools such as the Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) and Eggener risk models have been developed [22,23]. These tools were primarily devised to determine a man's prognosis after initial treatment. Although it is possible that risk models might serve to stratify those men who would benefit most from adjuvant therapy, this has not been formally examined. In addition, because these risk models were developed utilizing surgical cohorts composed in large part of low-risk men with favorable outcomes, their applicability to contemporary surgical practice may be more limited [24]. We describe a natural history of a cohort of intermediate- and high-risk men treated by RP only until the time of metastasis. This cohort was chosen to reflect contemporary best practice patterns while not being confounded by the use of adjuvant or salvage therapy. We then evaluated commonly used prognostic variables and risk models for their ability to predict metastatic disease in these men and in the subsets of men for whom adjuvant and salvage radiation therapy might be considered.

2. Methods

2.1. Patient population

The cohort was selected from the men treated with RP at Johns Hopkins Medical Institutions between 1992 and 2009. Patients with National Comprehensive Cancer Network (NCCN) intermediate- or high-risk disease who did not receive neoadjuvant ($n = 77$), adjuvant ($n = 72$), or salvage ($n = 7$) treatment prior to detection of metastasis and had available clinical and pathologic information were included. NCCN guidelines were then used to categorize patients. The subset of 3089 patients who were NCCN intermediate or high risk formed our cohort.

After RP, PSA was measured every 3 mo for the first year, semiannually for the second year, and annually thereafter. BCR was defined by a postoperative PSA value $\geq$0.2 ng/ml with a confirmatory value. Metastasis was diagnosed by axial imaging or bone scan. The use of these data was approved by the Johns Hopkins institutional review board and followed the requirements for the Health Insurance Portability and Accountability Act.

2.2. Statistical analysis

Analyses were performed on two primary end points: BCR and metastasis. CAPRA-S scores were calculated using six clinicopathologic variables [22]; Eggener 15-yr PCa mortality rates were calculated as described previously [23]. Area under receiver operating characteristic curve (AUC) for time to event data was used to measure the discrimination performance of the risk factors [25]. Extension of the decision curve analysis (DCA) to survival data was used to evaluate the net benefit of risk models across clinically relevant threshold probabilities [26]. Both survival AUC and DCA were evaluated at 10 yr after RP and at 5 yr after BCR. Univariable and multivariable Cox proportional hazards regression was used to test the association of risk factors with outcome. Cumulative incidence curves were constructed using Fine and Gray competing risks analysis to estimate the risk of BCR or metastasis, taking censoring and death due to other causes into consideration [27]. The significance level was 0.05 for all statistical tests, and analyses were performed in R software v.3.1 (R Foundation, Vienna, Austria).

3. Results

A total of 3089 men with NCCN intermediate- or high-risk disease underwent RP in the PSA era and received no treatment prior to metastasis. Table 1 lists the preoperative and postoperative characteristics of these men. Most of the men in this cohort (91%) were intermediate risk. Gleason 7 PCa diagnosed at biopsy and pathologic Gleason 7 disease at RP was most prevalent. At 10 yr after RP, the cumulative incidence of BCR and metastasis was 13% and 6%, respectively. On multivariable analysis, Gleason score and pathologic stage were independent predictors of metastatic progression (Table 1).

Overall, 43% of the men had APFs at RP with most of the cohort classified as such due to the presence of pT3 disease (only 2% of the cohort had pT2 disease with positive margins). Cumulative incidence of metastasis among men

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