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Multiparametric Magnetic Resonance Imaging Is an Independent Predictor of Salvage Radiotherapy Outcomes After Radical Prostatectomy

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Abstract

Background: The Stephenson nomogram is widely used to estimate the success of salvage radiotherapy (sXRT) for prostate cancer (PCa) recurrence after radical prostatectomy (RP).
Objective: To determine whether multiparametric pelvic magnetic resonance imaging (mpMRI) performed for biochemical recurrence after RP improves prognostication of sXRT relative to the Stephenson nomogram.
Design, setting, and participants: Men undergoing RP at our institution from 2003 to 2012 who had biochemical recurrence evaluated by mpMRI within 12 mo of sXRT were retrospectively reviewed. Exclusion criteria included PCa treatment prior to RP, adjuvant XRT after RP, salvage cryotherapy before sXRT, and hormone refractory disease prior to sXRT.
Outcome measurements and statistical analysis: Multivariable Cox regression analyses (adjusting for Stephenson nomogram covariates) associated mpMRI findings with prostate-specific antigen (PSA) recurrence and metastasis after sXRT. The mpMR images were compared in a binary fashion: no lesion versus vesicourethral/seminal vesical bed/prostate fossa lesions.
Results and limitations: Among 473 sXRT patients, 57%(204) had lesions on mpMRI: 26% (124) vesicourethral, 28%(135) seminal vesical bed/prostatic fossa, 7%(34) nodal, and 1% (3) bone. Median PSA at mpMRI with lesions was 0.46 versus 0.40 ng/ml without lesions. After excluding nodal/bone lesions, 29% of men developed PSA recurrence and 14% metastasis (median follow-up 45 mo after sXRT). For patients with a pre-sXRT PSA of $\leq$0.5 ng/ml, negative mpMRI was associated with increased PSA recurrence (39% vs 12%, $p < 0.01$) and metastasis (16% vs 2%, $p < 0.01$) at 4 yr after sXRT. For patients with a PSA of $\leq$0.5 ng/ml, the addition of mpMRI to the propensity score (created using variables from the original Stephenson nomogram) improved the c-statistic from 0.71 to 0.77 for PSA recurrence (hazard ratio [HR] 3.60, $p < 0.01$) and from 0.66 to 0.77 for metastasis (HR 6.68, $p < 0.01$). Limitations include evolutions in MRI technique and lack of a cohort of men undergoing mpMRI electing against sXRT.
Conclusions: Pre-sXRT mpMRI improves clinicopathologic variables to estimate sXRT success, particularly in the early sXRT setting.
Patient summary: Men who have biochemically recurrent prostate cancer after radical prostatectomy often receive salvage radiotherapy. In our study, multiparametric pelvic magnetic resonance imaging prior to salvage radiotherapy was a significant predictor of prostate-specific antigen failure and metastasis after radiotherapy.

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1. Introduction

Approximately 70 000 radical prostatectomies (RPs) are performed for prostate cancer (PCa) annually in the USA [1,2], and ~30% of these men experience biochemical recurrence (BCR) [3]. At 10 yr, only 10% of men with BCR will die of PCa [4]. Salvage radiotherapy (sXRT) may achieve durable prostate-specific antigen (PSA) remissions, and Stephenson nomograms are widely used in this setting to estimate the success of sXRT [5,6]. On this basis, the "early" delivery of sXRT at PSA ≤0.5 ng/ml has been advocated due to improved PSA recurrence and metastasis rates [7].

However, some patients may not benefit from sXRT, particularly those who harbor distant disease at the time of sXRT. Indeed, 50% of men undergoing sXRT with a PSA between 0.2 and 0.5 ng/ml experience a PSA recurrence at 10 yr [6]. Accordingly, the updated Stephenson nomogram's concordance index for PSA recurrence is only 0.68 [6], supporting the need for further research to identify the optimal sXRT candidate. Moreover, minimizing overtreatment with sXRT may improve quality of life for patients, considering the toxicities [8,9] associated with sXRT.

Advanced PCa imaging may become sensitive enough to identify patients with distant metastases, and improve upon existing clinical and pathologic predictors of sXRT success. Nevertheless, a median PSA value of ~2 ng/ml per positive scan limits the utility of C11-choline [10] and prostate specific membrane antigen [11] positron emission tomography (PET) and computed tomography (CT) scans in the early sXRT setting. Instead, multiparametric pelvic magnetic resonance imaging (mpMRI) has sensitivity of >90% at PSA levels of ~1 ng/ml with an area under the curve of 0.93 [12] and 0.91 [13] for identifying local recurrences after BCR.

Herein, we evaluate the utility of mpMRI to predict PSA recurrence and metastasis after sXRT, and improve upon the clinical and pathologic variables of the original [5] and updated [6] Stephenson nomograms. We hypothesize that patients with negative mpMRI may be more prone to sXRT failure due to an increased risk of distant disease.

2. Patients and methods

2.1. Patient population

In this Institutional Review Board–approved study, men undergoing RP from January 2003 to December 2012 who had BCR (defined as PSA ≥ 0.2 or rising PSA before 0.2) and received sXRT (N = 1111) were identified using a prospectively maintained institutional prostatectomy registry. A retrospective chart review identified patients who received mpMRI for BCR after RP. The mpMRI was performed within 12 mo prior to sXRT. Exclusion criteria were as follows: PCa treatment prior to RP (radiotherapy, cryotherapy, or hormone therapy); adjuvant XRT after RP; other salvage therapy after RP but before sXRT; proton beam therapy in place of high-energy photons for sXRT; and hormone refractory disease prior to sXRT. A total of 473 men were retained (consort diagram can be found in Supplementary Fig. 1).

2.2. MRI technique

Our institutional mpMRI technique after RP has been described in detail [13]. In brief, 1.5 and 3T MR scanners are employed with an endorectal coil for BCR. T1-weighted, T2-weighted, diffusion-weighted, and gadolinium-based dynamic contrast-enhanced (DCE) images are obtained. Six sequences are obtained, each with a different slice thickness, field of view, and repetition time. Radiologists with experience in genitourinary MRI interpreted the studies.

Radiology reports were classified based on the lesions identified. The lesions on mpMRI were grouped according to location: vesicourethral, seminal vesical bed/prostate fossa, pelvic nodes, and pelvic bones. All indeterminate and suspicious findings on the basis of enhancement, nodularity, diffusion restriction, or abnormal contour were categorized as abnormal lesions for the anatomic area of question. If no lesion was present in any anatomic area, the mpMRI was categorized as negative. Patients with nodal/bony lesions were categorized as such regardless of the presence of other lesions.

2.3. Post-RP and sXRT follow-up

Patients were followed after RP in a risk-adapted manner with serial PSAs every 3–6 mo for the first 2 yr, and followed annually thereafter. Patients with detectable PSA were referred for radiotherapy consultation; mpMRI was performed according to urologist and radiation oncologist's discretion. The use of adjuvant hormone therapy at the time of sXRT, fractionation of sXRT, dosage of sXRT, and inclusion of pelvic nodal fields was at the discretion of the radiation oncologists. Patients usually received follow-up PSA at 3 mo after completion of sXRT and every 3–6 mo for first 2 yr, and followed annually thereafter if PSAs remained negative.

2.4. Outcomes

PSA recurrence after sXRT was defined as a 0.2 ng/ml PSA rise above the nadir or the initiation of salvage androgen deprivation therapy [5,6]. Distant (metastatic) recurrences were identified using a combination of traditional (bone scan and CT scan) or other modalities (mpMRI, C11-choline PET scan, and image-guided biopsy results) based on the discretion of the treating physician. Mortality information was gathered based on a combination of the electronic medical record, primary care physician correspondence, and death certificates.

2.5. Statistical analyses

Standard descriptive statistics were used to compare patients with and without MRI lesions. Univariable logistic regressions were used to identify associations between lesion on MRI and each of the following independent variables: PSA prior to RP, age, pT stage at RP, pN stage at RP, pathologic Gleason score at RP, margin status at RP, persistent detectable PSA at RP, months from RP to BCR, months from RP to MRI, PSA at MRI, and PSA doubling time before sXRT. Then both forced entry and forward stepwise (p = 0.05 for inclusion and p = 0.10 for exclusion) multivariable logistic regression models were created where the above variables were used as covariates against MRI lesion status.

For survival analyses, patients with a nodal or bony lesion on MRI were excluded, as these patients represented a higher-risk cohort (analyses including these patients did not change analyses meaningfully: Supplementary tables and figures available upon request). The mpMRI was categorized as a binary variable: no lesion versus any vesicourethral/prostate fossa/seminal vesicle lesion. Kaplan–Meier analyses and multivariable Cox regression models were used to compare oncologic outcomes between MRI lesion categories. Follow-up was measured in months starting from the date of sXRT completion, which served as time zero. The outcomes of interest were PSA recurrence and metastasis, and are defined above. When calculating PSA recurrence–free survival, men were censored if they did not have a PSA recurrence at last follow-up or died without a PSA recurrence. Similarly, when calculating

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