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Original article

Effects of perineural invasion on biochemical recurrence and prostate cancer-specific survival in patients treated with definitive external beam radiotherapy

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Abstract

Objectives: Perineural invasion (PNI) has not yet gained universal acceptance as an independent predictor of adverse outcomes for prostate cancer treated with external beam radiotherapy (EBRT). We analyzed the prognostic influence of PNI for a large institutional cohort of prostate cancer patients who underwent EBRT with and without androgen deprivation therapy (ADT).

Material and methods: We, retrospectively, reviewed prostate cancer patients treated with EBRT from 1993 to 2007 at our institution. The primary endpoint was biochemical failure-free survival (BFFS), with secondary endpoints of metastasis-free survival (MFS), prostate cancer-specific survival (PCSS), and overall survival (OS). Univariate and multivariable Cox proportional hazards models were constructed for all survival endpoints. Hazard ratios for PNI were analyzed for the entire cohort and for subsets defined by NCCN risk level. Additionally, Kaplan-Meier survival curves were generated for all survival endpoints after stratification by PNI status, with significant differences computed using the log-rank test.

Results: Of 888 men included for analysis, PNI was present on biopsy specimens in 187 (21.1%). PNI was associated with clinical stage, pretreatment PSA level, biopsy Gleason score, and use of ADT (all $P < 0.01$). Men with PNI experienced significantly inferior 10-year BFFS (40.0% vs. 57.8%, $P = 0.002$), 10-year MFS (79.7% vs. 89.0%, $P = 0.001$), and 10-year PCSS (90.9% vs. 95.9%, $P = 0.009$), but not 10-year OS (67.5% vs. 77.5%, $P = 0.07$). On multivariate analysis, PNI was independently associated with inferior BFFS ($P < 0.001$), but not MFS, PCSS, or OS. In subset analysis, PNI was associated with inferior BFFS ($P = 0.04$) for high-risk patients and with both inferior BFFS ($P = 0.01$) and PCSS ($P = 0.05$) for low-risk patients. Biochemical failure occurred in 33% of low-risk men with PNI who did not receive ADT compared to 8% for low-risk men with PNI treated with ADT ($P = 0.01$).

Conclusion: PNI was an independently significant predictor of adverse survival outcomes in this large institutional cohort, particularly for patients with NCCN low-risk disease. PNI should be carefully considered along with other standard prognostic factors when treating these patients with EBRT. Supplementing EBRT with ADT may be beneficial for select low-risk patients with PNI though independent validation with prospective studies is recommended. © 2018 Elsevier Inc. All rights reserved.

Keywords: Prostate cancer; Perineural invasion; PNI; External beam radiation therapy

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1. Introduction

Perineural invasion (PNI) on prostate cancer biopsy, defined by carcinoma disseminating along or around a nerve within the perineural space, has been found in 15% to 62% of prostate cancer specimens [1]. PNI has been frequently identified as an additional, independent risk factor along with Gleason score, clinical stage, and PSA in prostate cancer [2–17]. Some studies, however, have questioned the overall prognostic value of PNI [18–27]. Consequently, PNI has not yet gained universal acceptance as a standard factor to guide treatment decisions.

We previously reported our institutional outcomes for prostate cancer patients with or without PNI treated with external beam radiotherapy (EBRT) and showed that PNI predicted for worse biochemical recurrence risk after a median of 5-years follow up [10]. Here we present a long-term update of these results after a median follow-up time of 11 years.

2. Material and methods

2.1. Study design and participants

The study was approved by the institutional review board of the Johns Hopkins Medical Institutions (Baltimore, MD). The study cohort included all men with clinically localized prostate cancer who were consecutively treated with definitive radiation between January 1, 1993 and December 31, 2006. Clinical stage was determined by digital rectal exam and assigned according to the American Joint Commission on Cancer, seventh edition. Risk grouping was defined as per NCCN criteria. For biopsies performed at outside institutions, we required specimen review by genitourinary pathologists at our institution before treatment. Patients without complete clinical or pathologic information were excluded ($n = 22$), as were patients with less than 24 months of follow-up ($n = 36$).

2.2. Treatment

Patients were treated with definitive radiation using either 3-dimensional conformal radiation therapy (79%) or intensity-modulated radiation therapy (IMRT, 21%); IMRT was increasingly used toward the end of the study period. Treatment fields were determined by NCCN risk level. Low- and intermediate-risk patients were generally treated with an initial field that targeted the prostate and seminal vesicles, followed by a boost field to the prostate. For high-risk patients, treatment generally consisted of an initial whole pelvis field, which included the prostate, seminal vesicle, and pelvic lymph nodes, followed by a boost field to the prostate. For high-risk patients, seminal vesicles were also included in the boost field if there was high suspicion of involvement. The prescription dose for the initial field was 45 to 46 Gy, delivered in 1.8 to 2 Gy fractions. The prescription dose for the boost field varied over the study period, with higher doses administered in more recent years. Median total dose for the cohort was 70.2 Gy (range: 64.8–75.6 Gy).

The administration of ADT was determined by the treating provider and varied according to risk level. High-risk patients were treated with neoadjuvant-concurrent and long-term (2 years) adjuvant ADT, with ADT withheld or stopped early only in exceptional circumstances such as medical contraindications, treatment intolerability, or patient refusal. Low-risk patients were not treated with any ADT except in rare cases where patients had multiple minor risk factors and no medical contraindications. Important minor risk factors included >50% positive cores on biopsy, high percentage involvement of individual cores, African-American race, likelihood of poor compliance with treatment/follow-up, elevated PSA velocity, and PNI on biopsy. Intermediate-risk patients with just a single NCCN intermediate-risk factor were more likely to be treated with EBRT alone, while patients with Gleason 4 + 3 disease or multiple NCCN intermediate-risk factors or multiple minor risk factors were more likely to be treated with both EBRT and ADT. In cases of major medical comorbidities such as cardiovascular disease or diabetes, physicians were more likely to forgo ADT.

Among NCCN low-risk patients, 14% received neoadjuvant-concurrent ADT. Among NCCN intermediate-risk patients, 53% received neoadjuvant-concurrent ADT only, 11% received adjuvant ADT, and 36% received no ADT. Among NCCN high-risk patients, 20% received neoadjuvant-concurrent ADT only, 66% received both neoadjuvant-concurrent and adjuvant ADT, and 14% received no ADT. When administered, neoadjuvant ADT was initiated 2 months before the radiation start date and consisted of a luteinizing hormone-releasing hormone agonist and an oral anti-androgen. For NCCN high-risk men receiving adjuvant ADT, the luteinizing hormone-releasing hormone agonist was generally maintained for a goal of 2 years after completion of radiation, if tolerated without significant toxicities. Among NCCN high-risk men in our cohort, median duration of ADT was 28 months (range: 0–40 months).

Following treatment, patients underwent routine follow-up with serial PSA measurements and digital rectal examination, generally at 6-month intervals. The frequency of PSA measurements and digital rectal examinations was influenced by the PSA trend and clinical symptoms. Similarly, clinical imaging was obtained in the setting of concerning PSA trends or clinical symptoms. Salvage therapy was administered at the discretion of the treating provider, but major motivating factors generally included PSA doubling time, co-morbidity, and life expectancy.

2.3. Statistical analysis

The primary endpoint of our study was prostate cancer-specific survival (PCSS). Death due to prostate cancer was

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