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A New Risk Classification System for Therapeutic Decision Making with Intermediate-risk Prostate Cancer Patients Undergoing Dose-escalated External-beam Radiation Therapy

Zachary S. Zumsteg[a], *Daniel E. Spratt*[a], *Isaac Pei*[a], *Zhigang Zhang*[b], *Yoshiya Yamada*[a], *Marisa Kollmeier*[a], *Michael J. Zelefsky*[a,*]

[a] *Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA;* [b] *Department of Epidemiology-Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA*

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Abstract

Background: The management of intermediate-risk prostate cancer (PCa) is controversial, in part due to the heterogeneous nature of patients falling within this classification.
Objective: We propose a new risk stratification system for intermediate-risk PCa to aid in prognosis and therapeutic decision making.
Design, setting, and participants: Between 1992 and 2007, 1024 patients with National Comprehensive Cancer Network intermediate-risk PCa and complete biopsy information were treated with definitive external-beam radiation therapy (EBRT) utilizing doses ≥81 Gy. Unfavorable intermediate-risk (UIR) PCa was defined as any intermediate-risk patient with a primary Gleason pattern of 4, percentage of positive biopsy cores (PPBC) ≥50%, or multiple intermediate-risk factors (IRFs; cT2b–c, prostate-specific antigen [PSA] 10–20, or Gleason score 7).
Intervention: All patients received EBRT with ≥81 Gy with or without neoadjuvant and concurrent androgen-deprivation therapy (ADT).
Outcome measurements and statistical analysis: Univariate and multivariate analyses were performed using a Cox proportional hazards model for PSA recurrence-free survival (PSA-RFS) and distant metastasis (DM). PCa-specific mortality (PCSM) was analyzed using a competing-risk method.
Results and limitations: Median follow-up was 71 mo. Primary Gleason pattern 4 (hazard ratio [HR]: 3.26; $p < 0.0001$), PPBC ≥50% (HR: 2.72; $p = 0.0007$), and multiple IRFs (HR: 2.20; $p = 0.008$) all were significant predictors of increased DM in multivariate analyses. Primary Gleason pattern 4 (HR: 5.23; $p < 0.0001$) and PPBC ≥50% (HR: 4.08; $p = 0.002$) but not multiple IRFs (HR: 1.74; $p = 0.21$) independently predicted for increased PCSM. Patients with UIR disease had inferior PSA-RFS (HR: 2.37; $p < 0.0001$), DM (HR: 4.34; $p = 0.0003$), and PCSM (HR: 7.39; $p = 0.007$) compared with those with favorable intermediate-risk disease, despite being more likely to receive neoadjuvant ADT. Short follow-up and retrospective study design are the primary limitations.
Conclusions: Intermediate-risk PCa is a heterogeneous collection of diseases that can be separated into favorable and unfavorable subsets. These groups likely will benefit from divergent therapeutic paradigms.

* Corresponding author. Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 22, New York, NY 10065, USA. Tel. +1 212 639 6802; Fax: +1 212 639 8876.
E-mail address: zelefskm@mskcc.org (M.J. Zelefsky).

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1. Introduction

Defining the optimal treatment algorithm for localized prostate cancer (PCa) represents a unique challenge in oncology. The vast majority of men with this disease will die of causes unrelated to their malignancy [1–3]. However, given its high prevalence and heterogeneous clinical behavior, PCa remains the second leading oncologic cause of mortality in men in the United States [4]. Differentiating indolent tumors from those that behave aggressively remains challenging, leading to overtreatment of men with relatively indolent disease and undertreatment of those with aggressive tumors [5–7].

Risk classification subgroups, such as those defined by the National Comprehensive Cancer Network (NCCN), have been proposed to stratify men into low-, intermediate-, and high-risk groups [8]. However, even within a given risk group, significant clinical heterogeneity remains, particularly for those with intermediate-risk disease, and more precise stratification is desirable [9]. Primary Gleason pattern, percentage of positive biopsy cores (PPBCs), and number of intermediate-risk factors (IRFs) have been shown to be independent predictors of outcome for localized PCa but are not included in the current NCCN system [10–14]. We have previously suggested stratifying intermediate-risk PCa into favorable and unfavorable categories based on these criteria to aid radiation and medical oncologists in treatment recommendations [15].

To provide clinical evidence for this approach, we assembled a large cohort of men with intermediate-risk PCa undergoing definitive dose-escalated external-beam radiation therapy (EBRT). We compared prostate-specific antigen recurrence-free survival (PSA-RFS), incidence of distant metastasis (DM), and PCa-specific mortality (PCSM) in patients classified as favorable intermediate risk (FIR) or unfavorable intermediate risk (UIR). Given that androgen-deprivation therapy (ADT) has been shown to improve survival in high- but not low-risk PCa, we also investigated the effect of ADT on outcome for FIR and UIR groups.

2. Materials and methods

2.1. Patient selection and pretreatment evaluation

Between 1992 and 2007, 1208 patients with intermediate-risk PCa were treated with dose-escalated EBRT, defined as $\geq$81 Gy, at Memorial Sloan-Kettering Cancer Center and its affiliated satellite sites. Intermediate risk was defined according to NCCN criteria as patients with clinical stage T2b or T2c, Gleason score of 7, or prostate-specific antigen (PSA) of 10–20 ng/ml but without high-risk features (clinical stage T3a or higher, Gleason score 8–10, or PSA >20 ng/ml) [8]. A total of 184 patients had incomplete biopsy core information and were excluded because it was not possible to determine the PPBC, leaving 1024 patients to form our study cohort. Additionally, 511 and 582 patients with NCCN low-risk and high-risk PCa, respectively, representing all patients treated with EBRT to a total dose of at least 81 Gy from 1992 to 2007, were compared with subgroups of intermediate-risk patients. Institutional review board approval was granted prior to data collection.

2.2. Treatment

Detailed description of the radiation techniques used was provided previously [16]. Briefly, patients were simulated in the supine position with planning based on computed tomography. Patients received EBRT with 81 or 86.4 Gy in 1.8-Gy daily fractions, prescribed to the isodose line encompassing the planning target volume, with 15-MV photons. Radiation was not administered to the pelvic lymph nodes. The decision to use ADT was based on the clinical discretion of the treating radiation oncologist. ADT generally consisted of neoadjuvant and concurrent administration, and it was discontinued at the end of radiation therapy. The median duration of ADT was 6 mo for both FIR and UIR patients.

2.3. End points

PSA recurrence was defined according to the Phoenix definition as a serum PSA at least 2 ng/ml greater than the posttreatment nadir PSA. Local failure (LF) was defined as a positive postradiotherapy biopsy, clinical examination revealing a new or growing tumor, and/or magnetic resonance imaging showing a tumor in the prostate or seminal vesicles described as "suspicious" or "consistent" with locally recurrent disease. Distant metastatic disease was defined as PCa occurring in any anatomic location other than the prostate, seminal vesicles, or pelvic lymph nodes. All DMs were confirmed by either biopsy of at least one site, response to ADT initiation, or progression in combination with rising PSA in the setting of castration-resistant disease. PCSM was defined as death directly attributable to PCa or death in the setting of castration-resistant metastatic disease from unknown causes. Time to all events was calculated from the end of radiation therapy.

2.4. Definition of favorable versus unfavorable intermediate-risk prostate cancer

We defined FIR PCa as a patient with NCCN intermediate-risk disease and all of the following: a single NCCN IRF, Gleason $\leq$3 + 4 = 7, and <50% of biopsy cores containing cancer. All others were classified as UIR [15].

2.5. Statistical methods

Baseline clinical characteristics were compared using chi-square tests for categorical variables and an analysis of variance test for continuous variables. The Kaplan-Meier method was used to generate survival curves and to estimate actuarial event-time probabilities for PSA-RFS and DM. A Cox proportional hazards model was used to general hazard ratios and 95% confidence intervals for both univariate analysis (UVA) and multivariate analysis (MVA) for PSA-RFS and DM. The cumulative incidence method was used to estimate PCSM at a given time point, with death from causes other than PCa defined as a competing risk. Comparisons of PCSM for different subgroups were performed using a κ sample test. Multivariate competing-risk analysis for PCSM was performed using the Fine and Gray method [17]. All statistical analysis was performed using R v.2.14.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Table 1 shows the baseline clinical characteristics for our cohort. The median follow-up was 71 mo.

To investigate their utility as risk-stratification factors for intermediate-risk PCa, primary Gleason pattern, PPBC, and number of IRFs were included in a Cox proportional hazards analysis. As shown in Table 2, both primary Gleason pattern of 4 and PPBC $\geq$50% were highly significant predictors of PSA-RFS, DM, and PCSM in UVA and MVA. Multiple IRFs