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Treatment outcomes with permanent brachytherapy in high-risk prostate cancer patients stratified into prognostic categories

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ABSTRACT

PURPOSE: To determine whether a previously reported substratification system can be extrapolated to patients with high-risk prostate cancer treated with permanent interstitial brachytherapy.

METHODS AND MATERIALS: Four hundred six National Comprehensive Cancer Network patients with high-risk prostate cancer treated with permanent prostate brachytherapy with or without supplemental external beam radiotherapy were stratified into good (prostate-specific antigen >20 or Gleason score ≥8 or ≥T3), intermediate (prostate-specific antigen >20 and ≥T3), and poor (Gleason score ≥8 with ≥1 additional high-risk feature) prognostic cohorts. Because of only 1 patient with intermediate high-risk disease, the analysis was performed on patients in the good and poor cohorts. Biochemical failure (BF), prostate cancer–specific mortality (PCSM), distant metastasis, and overall mortality were assessed as function of prognostic group. Multiple parameters were evaluated for impact on outcome.

RESULTS: With a median followup time of 7.9 years, 10- and 14-year rates of BF and PCSM for the entire cohort were 7.8% and 3.7%, respectively. The BF rate was significantly greater in the poor prognostic category (16.8% vs. 7.8%, $p = 0.041$). The poor prognostic category was the strongest predictor of BF in univariate and multivariate analyses. No statistically significant differences in PCSM, distant metastasis, or overall mortality were identified between the good and poor prognostic categories.

CONCLUSIONS: Patients with high-risk prostate cancer treated with a brachytherapy approach have excellent long-term biochemical control and cancer-specific survival. The poor prognostic high-risk category had a higher rate of BF compared with the good prognostic category without a higher rate of PCSM or distant metastasis.

Keywords: Brachytherapy; High risk; Prognostic categories; Overall mortality

Introduction

The National Comprehensive Cancer Network (NCCN) defines high-risk prostate cancer according to the following criteria: clinical stage T3, Gleason score 8–10, and/or prostate-specific antigen (PSA) >20 ng/mL. The most recent update of the NCCN practice guidelines also designates a ''very high risk'' to those patients with stage T3b–T4, primary Gleason pattern 5, or greater than four biopsy cores with Gleason score 8–10 (1). This subdivision in the high-risk stratum reflects the inherent heterogeneity of the disease process and underscores the need to better characterize the prognostic factors in this complex group of patients.

Many investigators have appealed for a critical review of the current prostate cancer risk classification system with a focus on better identifying those disease features that place high-risk patients at greatest probability of cancer-related mortality (2, 3). Both PSA velocity and the percentage of positive biopsy cores have been proposed as potential

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surrogates for aggressive biology, although the utility of these metrics remains the subject of vigorous debate (4–7). Additionally, there have been attempts to stratify patients with high-risk prostate cancer based on the number of risk factors present (8, 9). Joniau *et al.* (2) recently substratified patients with high-risk prostate cancer into prognostic subgroups using different combinations of accepted risk factors. This substratification system was found to be predictive of the risk for prostate cancer–specific mortality (PCSM) in the population of high-risk patients who underwent radical prostatectomy as primary treatment.

Interstitial low-dose–rate (LDR) brachytherapy with supplemental external beam radiotherapy (EBRT) has been shown to be an effective local treatment for high-risk prostate cancer (10). Even in the most unfavorable subset of patients with high-risk prostate cancer, treatment outcomes have been remarkably good with this therapeutic regimen (11–13). In the following study, we apply the substratification criteria of Joniau *et al.* to 406 patients with high-risk prostate cancer who received brachytherapy with or without supplemental EBRT as definitive local treatment. The primary goal of the analysis is to determine whether this substratification system can be extrapolated to the brachytherapy population and more specifically whether it is predictive of PCSM in patients who receive brachytherapy as primary treatment.

Methods and materials

From April 1995 to February 2012, 406 patients with NCCN high-risk prostate cancer (clinical stage T3 or Gleason score 8–10 and/or PSA >20 ng/mL) underwent permanent prostate brachytherapy by a single brachytherapist (GSM). The high-risk patients were subsequently assigned to three prognostic categories: good prognosis (1 high-risk factor), intermediate prognosis (PSA > 20 ng/mL and clinical T3), and poor prognosis (Gleason score 8–10 in combination with at least one other high risk factor) (2). All patients underwent brachytherapy >3 years before analysis. Before formulation of a treatment plan, all biopsy slides were reviewed by a single pathologist (EA). Our preplanning technique, intraoperative approach, and dosimetric evaluation have been described previously (14, 15). Calculation algorithms and seed parameters using preplanning and postoperative dosimetry were those recommended by the American Association of Physicists in Medicine Task Group No. 43 (TG43) (16). Patients were clinically staged by medical history and physical examination including digital rectal examination, serial PSA determinations, bone scans, and computed tomography of the abdomen/pelvis. Table 1 summarizes the clinical, treatment, and dosimetric parameters of the study population; 392 of the 406 patients received supplemental EBRT. In general, 45 to 50.4 Gy was delivered in 1.8 Gy fractions using 15–18 MV photons delivered via multifield technique. The target volume consisted of the prostate gland, seminal vesicles, and pelvic lymph nodes. The pelvic lymph nodes were treated superiorly to the L5-S1 interspace. In all cases, supplemental EBRT was delivered before brachytherapy.

At our center, there is not an institutional policy for the duration of androgen deprivation therapy (ADT) use in the high-risk prostate cancer population treated with brachytherapy. Individual patients are discussed in a multidisciplinary setting with input from the radiation oncologist, medical oncologist, and urologist. In this study, 280 patients received ADT; 52 (12.8%) received short course (≤6 months ADT) and 238 (58.8%) received extended course (>6 months ADT). ADT was initiated 3 months before implantation and consisted of a leutinizing hormone–releasing hormone agonist or antagonist with or without and anti-androgen. The median ADT duration was 4 and 24 months in the short course and extended course groups, respectively (range 3–36 months).

The brachytherapy target volume consisted of the prostate gland with periprostatic treatment margins including the proximal 1.0 cm of the seminal vesicles (14, 15). The minimum peripheral dose was prescribed to the target volume with margin; 393 of the patients were implanted with ^{103}Pd and 13 with ^{125}I. At implantation, the prostate gland, periprostatic region, and base of the seminal vesicles were implanted (14, 15). ^{103}Pd and ^{125}I monotherapy and boost doses were 125 and 90–100 Gy and 145 and 110 Gy, respectively. Within 2 h of implantation, a thin-slice (3 mm) CT scan was obtained for evaluation of postimplant dosimetric coverage. Evaluated dosimetric parameters include the percentage of the target volume receiving 100%, 150%, and 200% of the prescribed dose ($V_{100/150/200}$) and the minimum percentage of the dose covering 90% of the target volume (D_{90}).

Patients were monitored by physical examination including digital rectal examination and PSA measurement at 30- to 6-month intervals. The primary end point of the analysis was biochemical failure (BF). BF was defined as a PSA >0.40 ng/mL after nadir which has been demonstrated to be a particularly sensitive definition by identifying patients for whom treatment has failed (17). Patients who failed to achieve a PSA nadir <0.40 ng/mL were categorized as a BF. In cases where the post-implant PSA rose to a level >0.40 ng/mL but subsequently fell to a level <0.40 ng/mL, patients were considered to have experienced a "PSA spike" and were classified as biochemically controlled. PCSM, distant metastasis, and overall mortality were also calculated. At the time of biochemical and/or symptomatic failure, site-directed imaging was performed to identify or exclude the presence of distant metastasis. The cause of death was determined for each deceased patient. Patients with metastatic prostate cancer and or nonmetastatic castrate-resistant disease who died of any cause were classified as having a prostate cancer–specific death. All other deaths were attributed to the immediate cause of death. Multiple clinical, treatment,