Original Study

Greatest Percentage Involved Core Length and Risk of Clinically Significant Prostate-Specific Antigen Failure After Radical Prostatectomy

Matthew D. Cheney,[1] Danjie Zhang,[2] Ming-Hui Chen,[2] Marian J. Loffredo,[3] Jerome P. Richie,[4] Anthony V. D'Amico[3]

Abstract

Radical prostatectomy (RP) has been increasingly used for high-risk prostate cancer (PC). Of 402 men who had undergone RP, an increasing greatest percentage of involved biopsy core length was significantly associated with an increased risk of clinically significant prostate-specific antigen failure, particularly in men with unfavorable intermediate- or high-risk PC. Men planning to undergo RP should be considered for randomized neoadjuvant trials of metastatic treatments that prolong survival.

Background: Radical prostatectomy (RP) can cure men with unfavorable intermediate- or high-risk prostate cancer (PC). However, some will experience short prostate-specific antigen (PSA) doubling time (PSADT) failure that requires additional treatment with increased toxicity. The present study investigated whether the greatest percentage of involved biopsy core length (GPC) can preoperatively identify men at risk of short PSADT failure. **Patients and Methods:** A total of 503 men with biopsy-proven PC underwent RP at an academic institution from January 2005 to December 2008. Men with incomplete pathologic information, those who had received neoadjuvant or adjuvant hormonal therapy or chemotherapy, and those who had undergone adjuvant radiation therapy were excluded. The median follow-up period was 4.89 years (interquartile range, 1.97-5.68 years). A competing risk regression was used to assess whether an increasing GPC value was associated with an increased PSADT at $<$ 10-month failure risk, adjusting for age, percentage of positive biopsy results, and risk group. **Results:** Of the 402 men, 34 (8.46%) developed PSA failure, 17 (50.0%) of whom had a PSADT of $<$ 10 months. An increasing GPC value was significantly associated with an increased PSADT of $<$ 10-month failure risk (adjusted hazard ratio, 1.03; 95% confidence interval, 1.01-1.06; $P = .015$). Men with a GPC $>$ 30% (median) versus $\leq$ 30% and unfavorable intermediate- or high-risk PC ($P = .011$), but not low or favorable intermediate-risk PC ($P = .57$), had a significantly greater incidence of PSADT $<$ 10-month failure estimates (30% vs. 0% at 5 years). **Conclusion:** Men planning to undergo RP for unfavorable intermediate- or high-risk PC with a GPC of $>$ 30% should be considered for randomized trials evaluating the effect on survival of the neoadjuvant use of treatment that extends survival in those with castrate-resistant metastatic PC.

Clinical Genitourinary Cancer, Vol. 13, No. 4, 338-43
Keywords: Biopsy, Doubling time, Percent positive biopies, Prognosis, Prostate cancer

Introduction

Interest is increased among urologic oncologists in radical prostatectomy (RP) for the initial treatment of men with high-risk prostate cancer (PC).[1,2] This concept might be driven in part by the lower volume, but high-grade, disease at presentation and advances in surgical techniques.[3,4] It remains unknown how many of these men will require adjuvant or salvage radiation therapy (RT) and/or androgen deprivation therapy (ADT) and experience the

[1]Harvard Radiation Oncology Program, Department of Radiation Oncology, Brigham and Women's Hospital and Dana Farber Cancer Institute, Boston, MA
[2]Department of Statistics, University of Connecticut, Storrs, CT
[3]Department of Radiation Oncology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, MA
[4]Department of Urology, Brigham and Women's Hospital, Boston, MA

Submitted: Sep 7, 2014; Revised: Nov 13, 2014; Accepted: Feb 27, 2015; Epub: Mar 5, 2015

Address for correspondence: Matthew D. Cheney, MD, PhD, Harvard Radiation Oncology Program, Department of Radiation Oncology, Brigham and Women's Hospital and Dana Farber Cancer Institute, ASBI/LL2, 75 Francis Street, Boston, MA 02115
E-mail contact: mcheney@lroc.harvard.edu

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2015.02.012

toxicities associated with multimodality treatment.[5,6] To this end, investigators have identified preoperative prognostic factors that can be used in addition to the highest Gleason score (GS), clinical tumor category (T stage), and PSA level to more accurately counsel men regarding their risk of disease recurrence and need for postoperative therapy.[7-9]

With the exception of the percentage of positive biopsy cores (PPB), consensus is lacking among genitourinary oncologists regarding the clinical utility of biopsy measures of tumor volume. Few studies are available that allow a comparison of multiple measures.[10] The greatest percentage of cancer involvement in a single biopsy core (GPC) is an easily calculated and frequently reported tumor volume metric. Recent evidence has suggested that the GPC value could provide important information regarding the risk of nonorgan-confined disease at RP.[11,12] However, study has been limited on the value of the GPC in determining which men with unfavorable intermediate (UI) and high-risk disease are likely to experience a clinically significant PSA recurrence after RP that can lead to metastasis and death from PC if left untreated.[10]

Therefore, in the present study, we investigated the ability of the GPC value to identify men at high risk of needing post-RP treatment of a clinically significant PSA recurrence. We selected the primary endpoint of a PSA doubling time (PSADT) failure of < 10 months, because it has been shown to correlate with a high risk of distant metastatic disease and PC-specific mortality (PCSM) in men who were observed after PSA failure without additional treatment until symptomatic or radiographic progression.[13,14]

Patients and Methods

Patient Characteristics and Treatment

The initial study cohort consisted of 503 consecutive men who had undergone RP from January 2005 to December 2008 at a single academic institution for biopsy-proven PC. Of the 503 men, 101 men were excluded from the analysis, leaving 402, who formed the final study cohort. Exclusions occurred because of inability to assign a GPC, PPB, or risk group value ($n = 88$) or receipt of neoadjuvant or adjuvant ADT and/or chemotherapy ($n = 13$) because such therapies can confound the primary study endpoint owing to their effect on micrometastatic disease. All patients who received adjuvant RT ($n = 5$) were excluded because of the receipt of adjuvant ADT.

The diagnosis was made using a transrectal ultrasound-guided prostate biopsy with a median of 12 cores (interquartile range [IQR], 10-12 cores). An academic pathologist performed the pathology review, and the GS, number of total cores, number of involved cores, and percentage of cancer involvement in each core were assessed and recorded. In the event of multiple, discontinuous tumor foci within a single core, the summed foci lengths, excluding intervening benign prostatic tissue, were used to define the percentage of cancer involvement.[15] The biopsy cores were generally 1 cm long, such that the lengths of core involvement in millimeters and the percentage of involvement were comparable. The GPC was defined as the greatest percentage of cancer involvement in a single core, irrespective of the core GS. The GPC was determined from the biopsy core with the greatest observed GS in 373 of 402 men (92.8%).

The T stage was assigned in accordance with the 2010 American Joint Committee on Cancer (AJCC) PC staging guidelines.[16] The risk groups were assigned according to the 2014 National Comprehensive Cancer Network (NCCN) guidelines, and the favorable intermediate (FI) and UI risk classifications were determined according to Zumsteg et al,[17] such that the UI risk group included men with intermediate-risk PC with GS 4+3, a PPB $\geq 50\%$, or multiple NCCN intermediate-risk factors.[18] The institutional review board approved the present study.

Follow-up and Determination of PSA Failure

The patients were generally seen postoperatively at 1 month, every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. A serum PSA level was obtained at each follow-up visit. PSA failure was defined as a PSA level ≥ 0.1 ng/mL on 2 consecutive occasions, with the assigned date corresponding to that of the first PSA level ≥ 0.1 ng/mL.[18] In the event of a persistently positive post-RP PSA level, the PSA failure date was defined as the date of the first follow-up PSA (generally at 1 month postoperatively). The data set was last updated on December 9, 2013.

Statistical Analysis

Distribution of Clinical Characteristics at Baseline Stratified by the Median GPC Value and Risk Group. The men were stratified according to risk group (low or FI risk vs. UI or high risk) and then substratified by the median GPC value of the cohort (30%). The distributions of both continuous and categorical clinical factors were enumerated and compared within the risk group substrata between men with a GPC value of $\leq 30\%$ versus $> 30\%$. A Fisher's exact test was used to compare the distributions of categorical factors, including the highest biopsy GS and 2010 AJCC clinical T stage.[16,19] A nonparametric Wilcoxon test was used to compare the distributions of continuous factors, including age, PSA, and PPB.[20]

Competing Risk Regression. The primary study endpoint was the interval to a PSADT < 10-month failure. The PSADT calculations were performed assuming first order kinetics and a minimum of 3 PSA values from 1 month after surgery to the initiation of salvage therapy or the last follow-up examination. A PSADT < 10-month failure was assigned to men with a persistently positive PSA level at ≥ 1 month after RP without evidence of residual prostatic tissue in the surgical bed on magnetic resonance imaging (MRI), because this has been associated with a high risk of distant metastatic disease.[21]

Given that a PSADT of ≥ 10-month failure is also possible, we modeled the interval to PSADT < 10-month failure using a competing risks method. Specifically, univariable and multivariable Fine and Gray's competing risk regression analysis was used to assess whether an increasing GPC was associated with an increased risk of PSADT < 10-month failure, adjusting for age, PPB, and risk group.[22] A PSADT of ≥ 10-month failure constituted the competing risk. The intervals to all other non-PSA failures or the end of the study were treated as censored. The GPC input was determined without regard to the highest core GS. Time 0 was defined as the date of surgery. Within the model, age, GPC, and PPB were considered continuous covariates. The risk group was considered a categorical covariate, with combined FI and low-risk men as the baseline group. Unadjusted hazard ratios (HRs) and