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Trend of Adverse Stage Migration in Patients Treated with Radical Prostatectomy for Localized Prostate Cancer

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Abstract

Background: Two recent European studies showed an increasing proportion of non–organ-confined (NOC; pathologic stages T3–4) prostate cancer (PCa) in radical prostatectomy (RP) specimens.

Objective: To determine if the trend for NOC and pT3–4 PCa is also evident among contemporary North American patients.

Design, setting, and participants: Within the Surveillance, Epidemiology, and End Results database (2010–2014), we identified 58 558 patients with clinically localized PCa treated with RP. Only patients with clinical stage T1–2 and biopsy Gleason grade group (GGG) 1–3 PCa were included.

Outcome measurements and statistical analysis: Annual trend analyses and multivariable logistic regression models focused on the rate of NOC PCa, the rate of primary pathologic Gleason ≥4 PCa, and the rate of either NOC PCa and/or primary pathologic Gleason ≥4 PCa. Adjustment was made for clinical tumor characteristics (prostatic specific antigen [PSA], clinical stage, and biopsy GGG).

Results and limitations: The rate of NOC PCa increased during the study period (18.7% vs 24.2%; $p = 0.002$) and remained significant after adjustment (16.9% vs 22.3%; $p = 0.001$) Similarly, the rate of pathologic primary Gleason ≥4 PCa increased during the study period (16.8% vs 23.0%, $p = 0.001$) and remained significant after multivariable adjustment (10.8% vs 14.2%; $p = 0.002$). Moreover, virtually the same findings were recorded when both endpoints were combined. Our results were confirmed in multivariable logistic regression analyses in which year of diagnosis was modeled as a continuous variable or a categorical variable or when a cubic spline approach was used.

Conclusions: Rates of NOC PCa and primary Gleason ≥4 PCa increased over time among contemporary North American patients treated with RP. This finding may be related to better acceptance of active surveillance and watchful waiting by North American patients.

Patient summary: In this report, we looked at pathologic outcomes for contemporary North American patients treated with radical prostatectomy. We found an increase in non–organ-confined and more aggressive prostate cancer.

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1. Introduction

Non–organ-confined (NOC; pathologic stages T3–4) prostate cancer (PCa) and primary pathologic Gleason ≥4 PCa represent adverse pathologic characteristics at radical prostatectomy (RP) and both are associated with worse oncologic outcomes in patients with clinically localized PCa [1–4]. Gallina et al reported a decrease in NOC PCa in institutional databases for historical North American RP patients between 1988 and 2005. However, van den Bergh et al. [5] recently reported increasing rates of NOC PCa and unfavorable Gleason score (≥7) in RP patients in a multicenter analysis from four large European tertiary care centers [5]. Others also reported adverse stage migration in European RP patients, as evidenced by higher rates of NOC PCa [6]. Moreover, Dalela et al. [7] recently reported a significant increase in the incidence of metastatic PCa in North American patients aged 45–74 yr between 2009 and 2013 [7].

However, no contemporary large-scale North American analysis of population data has addressed the rate of adverse pathologic characteristics in patients with clinically localized PCa treated with RP. To address this gap, we examined rates of pathologic characteristics in a large contemporary cohort of patients treated with RP for clinically localized PCa. Specifically, we hypothesized that the proportions of NOC PCa and of primary pathologic Gleason ≥4 PCa are on the rise.

2. Patients and methods

2.1. Study population

Within the Surveillance, Epidemiology, and End Results (SEER) database (2010–2014), we identified 237 832 patients (Fig. 1) with histologically confirmed adenocarcinoma of the prostate (International Classification of Disease for Oncology code 61.9) aged 30–80 yr [8]. Exclusion criteria consisted of prostate-specific antigen (PSA) >50 ng/ml (ie, suspected metastatic disease) [9] or confirmed metastatic disease at diagnosis. Only patients who underwent RP with or without radiotherapy and who had clinical tumor stage T1–2, biopsy Gleason grade group (GGG) 1–3, and complete information on pathologic tumor characteristics were included. Patients treated with radiotherapy alone were excluded from the analyses. These selection criteria yielded 58 558 patients and represented the focus of the current analyses.

2.2. Statistical analyses

Descriptive statistics included the frequency and proportion for categorical variables and the median and interquartile range for continuous variables. A χ^2 test was applied to determine the statistical significance of differences in proportions and a Mann-Whitney *U* test for differences in medians.

Adjusted and unadjusted annual trends for (1) NOC PCa, (2) primary pathologic Gleason ≥4 PCa, and (3) the combination of either NOC and/or primary pathologic Gleason ≥4 PCa were plotted. Three sets of univariable and multivariable logistic regression models were fitted to test the relationship between year of diagnosis (YOD) and these three endpoints. Specifically, the first set of logistic regression models focused on the rate of NOC PCa, the second set of separate models on the rate of primary Gleason ≥4 PCa, and the third set of separate models on the combination of NOC and/or primary Gleason ≥4 PCa. All multivariable models were adjusted for clinical tumor stage, biopsy GGG, and PSA.

In all three sets of models, YOD was coded in three different ways: (1) a continuous variable; (2) a categorical variable; and (3) a cubic spline [10]. The R software environment for statistical computing and graphics (version 3.4.0) was used for all statistical analyses. All tests were two-sided with the level of significance set at $p < 0.05$.

3. Results

3.1. Study population

Of 58 558 patients treated with RP, 20.6% had NOC PCa and 19.5% had pathologic primary Gleason ≥4 PCa (Table 1). Analyses stratified according to the presence (n = 12 086) or absence (n = 46 472) of NOC PCa revealed that patients with NOC PCa were significantly older (63 vs 61 yr; $p < 0.01$), had significantly higher median PSA (6.8 vs 5.4 ng/ml; $p < 0.01$), and more frequently harbored clinical stage T2 (33.6% vs 27.9%; $p < 0.01$) and biopsy GGG 3 (28.8% vs 12.0%; $p < 0.01$). Analyses stratified according to pathologic primary Gleason ≥4 PCa (n = 11 403) versus Gleason <4 (n = 47 155) demonstrated similar results. Patients with pathologic primary Gleason ≥4 PCa were also significantly older (63 vs 61 yr; $p < 0.01$), had significantly higher median PSA (6.7 vs 5.4 ng/ml; $p < 0.01$), and more frequently harbored clinical stage T2 (34.6% vs 27.7%, $p < 0.01$) but less frequently had biopsy GGG 1 (17.1% vs 53.2%; $p < 0.01$).

3.2. Annual rates of NOC PCa, primary Gleason ≥4 PCa, and both pathologic characteristics

The rate of NOC PCa increased during the study period (18.7% in 2010 vs 24.2% in 2014; p = 0.002). The estimated annual percentage change (EAPC) was 7.1% (Fig. 2A). After adjustment for clinical tumor characteristics (tumor stage, biopsy GGG, and PSA), the increase remained significant (16.9% in 2010 vs 22.3% in 2014, EAPC 2.6%; p = 0.001; Fig. 2B). Moreover, the rate of pathologic primary Gleason ≥4 PCa also increased during the study period (16.8% in 2010 vs 23.0% in 2014, EAPC 8.5%; p = 0.001; Fig. 3A) and remained significant after multivariable adjustment (10.8% in 2010 vs 14.2% in 2014, EAPC 2.6%; p = 0.002; Fig. 3B). Finally, the rate of combined NOC PCa and/or primary Gleason ≥4 PCa increased during the study period (28.3% in 2010 vs 36.8% in 2014, EAPC 7.1%; $p < 0.001$; Fig. 4A). After adjustment, the increase remained significant (25.0% in 2010 vs 33.8% in 2014, EAPC 3.0%; $p < 0.001$; Fig. 4B).

3.3. Multivariable logistic regression models predicting NOC PCa, primary Gleason ≥4, and both pathologic characteristics

Three sets of logistic regression models were fitted to test the relationship between YOD and the three different endpoints (NOC, primary pathologic Gleason ≥4 PCa, and the combination of NOC and/or Gleason ≥4 PCa). Adjustment was made for clinical tumor characteristics (clinical tumor stage, biopsy GGG, and serum PSA). Within each set of multivariable models, YOD was coded in three different