Comorbid Disease Burden is Independently Associated with Higher Risk Disease at Prostatectomy in Patients Eligible for Active Surveillance

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Purpose: Comorbid medical conditions are highly prevalent among patients with prostate cancer and may be associated with more aggressive disease. We investigated the association between comorbidity burden and higher risk disease among men eligible for active surveillance.

Materials and Methods: Using the National Cancer Data Base we identified 29,447 cases of low risk (Gleason score 6 or less, cT1/T2a, prostate specific antigen less than 10 ng/ml) prostate cancer managed with prostatectomy from 2010 to 2011. The primary outcome was pathological upgrading (Gleason score greater than 6) or up staging (T3-T4/N1). The association between Charlson score and upgrading/up staging was analyzed using multivariate logistic regression.

Results: The study sample comprised 29,447 men, of which 449 (1.5%) had Charlson scores greater than 1. At prostatectomy 44% of cases were upgraded/up staged. On multivariate analysis Charlson score greater than 1, age 70 years or greater, nonwhite race, higher prostate specific antigen and higher percentage of cores involved with disease were significantly associated with upgrading/up staging. After further adjusting for age, race, prostate specific antigen and core involvement, Charlson score remained a significant predictor of upgrading/up staging for younger white men. Specifically, white men less than 70 years old with Charlson comorbidity index greater than 1 had 1.3-fold higher odds of upgrading/up staging than men with Charlson comorbidity index 1 or less (OR 1.31, 95% CI 1.03–1.67, p=0.029).

Conclusions: Comorbidity burden is strongly and independently associated with pathological upgrading/up staging in men with clinically low risk prostate cancer. This finding may help improve disease risk assessment and clinical decision making in men with comorbidities considering active surveillance.

Key Words: prostatic neoplasms, comorbidity, neoplasm grading, neoplasm staging, watchful waiting

Abbreviations and Acronyms

CCI = Charlson comorbidity index

NCDB = National Cancer Data Base

PC = prostate cancer

PSA = prostate specific antigen

UGUS = upgrading and/or up staging

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Active surveillance is a management option for low risk prostate cancer intended to minimize overtreatment, especially in men with limited life expectancies or significant comorbidities. The major limitation of this approach is the misclassification of higher risk disease, which occurs in

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30% to 60% of patients on long-term active surveillance and carries a 10-year cancer specific mortality of 5% to 40% if untreated.[1–3] Retrospective data have demonstrated that aggressive treatment of intermediate and high risk disease offers a significant survival benefit regardless of comorbidity burden.[4,5] Clinical risk factors for misclassification and progression are currently poorly characterized.

Accumulating epidemiological data suggest that comorbid conditions, including obesity, metabolic syndrome, smoking and hypertension, may be associated with a higher risk of aggressive PC and recurrence after treatment.[6–13] It has recently been observed that obese patients, who frequently receive conservative treatment, are more likely to harbor occult, high risk disease, potentially leading to under treatment.[14–16] The impact of comorbidity burden on PC risk has not been established. Given the high prevalence of comorbidities among patients with prostate cancer, understanding the association between comorbidity and PC risk is important.[4,17] We investigated the impact of comorbidity on UGUS in a large cohort of American men with low risk prostate cancer who were candidates for active surveillance. We hypothesized that increased comorbidity burden may be associated with higher risk disease as seen in other hormone dependent cancers.[18]

MATERIALS AND METHODS

NCDB Participant User File

The NCDB, a joint project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons, is a comprehensive clinical oncology data set that captures 70% of all incident malignancies in the United States. After institutional review board approval we used the NCDB participant user file for PC diagnoses from 1998 to 2011.

Study Population

Using primary site coding from the International Classification of Diseases for Oncology, 3rd edition, we identified 106,173 patients with localized (cN0/cM0) PC diagnosed in 2010 to 2011 who underwent radical prostatectomy. We limited the study period to diagnosis years 2010 to 2011 to capture data on the number of positive and total biopsy cores, which were only available after 2009. We restricted the cohort to men with low risk PC based on D'Amico criteria (clinical stage T2a or lower, Gleason score 6 or less, PSA less than 10 ng/ml) (30,827). Cases with unknown pathological T stage or Gleason score were excluded from analysis (1,380).

Study Variables

Clinical variables included CCI, age and race. CCI was calculated based on ICD-9-CM secondary diagnosis codes and was categorized as 1 or less (1 or fewer comorbidities) or greater than 1 (2 or more comorbidities). Age was defined as less than 70, or 70 or greater. Race was categorized as white or nonwhite.

Demographic variables included income level and county of residence. Income level (defined by annual income quartiles) was categorized as low (less than $30,000), low middle ($30,000 to $34,999), middle ($35,000 to $45,999) and upper middle ($46,000 or greater). Income level was derived based on estimates from 2000 U.S. Census data. County was categorized as urban, metropolitan or rural based on data from the 2003 U.S. Department of Agriculture Research Service.

Pathological variables included clinical T stage (T1 or T2a), PSA (less than 4 or 4 to 10 ng/ml) and percentage of cores involved with disease at diagnosis. Percentage of positive cores was calculated by dividing the number of positive cores by the total number of cores biopsied and was categorized by tertile (less than 33%, 33% to 67%, greater than 67%).

Study Outcomes

The primary outcome was pathological UGUS in men with multiple comorbidities (CCI greater than 1) compared to relatively healthy men (CCI 1 or less). Upgrading was defined as an increase in Gleason score greater than 6 from initial biopsy to final pathological examination. Up staging was defined as the presence of pathological T3-4 or N1 disease.

Statistical Analyses

Baseline characteristics were compared between CCI groups (greater than 1 vs 1 or less) by logistic regression. The association between CCI score and UGUS was analyzed using multivariate logistic regression while adjusting for other covariates. Based on the fact that age, race and CCI were all associated with UGUS on preliminary analysis, 4 additional analyses were performed to assess the discrete effect of CCI on UGUS stratified by age and race in the 4 groups of age less than 70 years, white; age less than 70 years, nonwhite; age 70 years or greater, white; and age 70 years or greater, nonwhite. Goodness of fit of the multivariate models was assessed using the Hosmer-Lemeshow goodness of fit test. Statistical tests were performed using SAS® University Edition. For all tests 2-sided $p < 0.05$ was considered statistically significant.

RESULTS

The final sample consisted of 29,447 men (white 82.1%, middle to upper middle income 75.0%, metropolitan 82.1%) with low risk PC. Mean age of the cohort was 59.6 ± 6.9 years and most men were healthy. There were 449 men with 2 or more comorbidities (CCI greater than 1) who comprised 1.52% of the total cohort. More than 90% of the sample had clinical T1 disease with mean PSA 5.0 ± 1.9 ng/ml at diagnosis. The men with many comorbidities (CCI greater than 1) differed from the healthy men (CCI 1 or less) in terms of age, race and income level ($p < 0.001$). Men with comorbidities were more likely to be elderly, nonwhite and/or belong to a lower socioeconomic group (table 1).