Population Based Study of Predictors of Adverse Pathology among Candidates for Active Surveillance with Gleason 6 Prostate Cancer

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Abbreviations and Acronyms

AS = active surveillance
GS = Gleason score
PCa = prostate cancer
PSA = prostate specific antigen
PSAD = PSA density
RP = radical prostatectomy

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Purpose: Approximately a third of prostate cancer cases with a Gleason score of 6 are upgraded at radical prostatectomy. We studied trends and predictors of upgrading and up staging among men with Gleason 6 prostate cancer who were potential candidates for active surveillance in a population based cohort.

Materials and Methods: From 2007 to 2011, 13,159 men were diagnosed with Gleason 6, clinical stage T1c/T2 prostate cancer in the NPCR (National Prostate Cancer Register of Sweden). Of these men 4,500 underwent radical prostatectomy, including 2,205 with data on the extent of prostate cancer in the biopsy cores. Logistic regression was used to examine variables associated with adverse pathology (defined as upgrading to Gleason 7 or greater, or up staging to pT3 or greater) in the full group and in potential candidates for active surveillance using 6 current published protocols.

Results: Among Swedish men with clinically localized Gleason 6 prostate cancer approximately 50% had adverse pathology at radical prostatectomy. Of the men who met the study inclusion criteria of 6 different active surveillance protocols, adverse pathology was present in 33% to 45%. Predictors of adverse pathology were older age, higher prostate specific antigen, prostate specific antigen density greater than 0.15 ng/ml/cm^3, palpable disease and extent of cancer greater than 4 mm on biopsy. Larger prostate volume had an inverse relationship with adverse pathology.

Conclusions: More than a third of men meeting the most stringent active surveillance criteria had adverse pathology at radical prostatectomy in this population based cohort. Active surveillance programs should consider prostate specific antigen density and extent of cancer on biopsy for patient selection.

Key Words: prostatic neoplasms, watchful waiting, pathology, prognosis, neoplasm grading

MANY studies have demonstrated the frequent disparity between Gleason scores reported on prostate biopsy and at radical prostatectomy. In a recent review Epstein et al reported that about a third of cases with a biopsy Gleason score of 5-6 were upgraded at RP.[1]

This issue is particularly germane to men with presumed low risk prostate cancer considering active surveillance, for whom accurate pretreatment

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risk stratification is paramount. As reviewed by Dall'Era et al, in most AS programs candidates are chosen based on GS, clinical stage and PSA based parameters.[2] Depending on the particular inclusion criteria 4% to 82% of men were eligible for AS, and conversion to active treatment was reported in 11% to 33% of men on AS, with changes in tumor histology as the most common reason for discontinuing AS.[2]

A recent consensus conference concluded that AS is underused.[3] However, the limitations of current clinical staging and disparities in selection criteria among current protocols are important in evaluating obstacles for expanding the use of AS.

In this study we examined trends and predictors of upgrading/up staging in men with low risk prostate cancer who are potential candidates for AS from a large population based Swedish cohort. We hypothesized that upgrading and up staging remain common, but that additional predictors beyond PSA, clinical stage and GS could improve risk classification. These results are clinically important to lend insight into which factors are most essential to consider in the selection of men for AS and subsequent monitoring which is currently not standardized across institutions.

MATERIALS AND METHODS

The NPCR of Sweden contains information on tumor features and primary treatment for more than 97% of men diagnosed with PCa in Sweden since 1998.[4] It has been linked to several other population based health care registers to create a database with extensive longitudinal data called Prostate Cancer data Base Sweden (PCBaSe) 2.0, which includes information on socioeconomic factors, drug use, comorbidity and outcomes.

From 2007 to 2011, 45,532 men were registered with PCa in the NPCR. Because our goal was to examine contemporary low risk PCa, we limited our study to 17,437 men with Gleason 6 PCa. We excluded N1 or M1 disease, clinical stage T1a and T1b, and men who used 5α-reductase inhibitors. Among the 13,159 remaining men with clinical stage T1c-T2 Gleason 6 PCa, 4,630 underwent RP. Of these men 4,500 had complete pathology data and formed the final study population.

Comorbidities were classified using the Charlson comorbidity index as previously described.[5] A distinction was made between treatment at university and nonuniversity hospitals. Prostate volume was determined by transrectal ultrasound. PSAD was determined by dividing PSA by prostate volume. The number of biopsy cores was categorized as 6 or less, 7 to 9 or 10 or more. To quantify the extent of PCa on biopsy, the percentage of cores positive was classified like the UCSF (University of California San Francisco)-CAPRA (Cancer of the Prostate Risk Assessment) score as less than 34% vs 34% or greater.[6] Biopsy specimens were reviewed locally and central review was not performed.

Since 2007 the NPCR has collected detailed data on the extent of cancer within each biopsy core, which was available for 2,205 men. In these men we examined total biopsy length (less than 100, 100 to 150, greater than 150 to 200 and greater than 200 mm), extent of cancer (less than 4, 4 to 10, greater than 10 to 20 and greater than 20 mm) and ratio of cancer extent (less than 15% or 15% or greater). We then estimated the percentage of core involvement as average cancer extent in all positive cores divided by the average biopsy length per core. Average cancer in positive cores was defined as the extent of cancer in mm divided by the number of positive cores, and average biopsy length per core was defined as total biopsy length in mm divided by the number of biopsies.

We examined the frequency of adverse pathology (stage T3 or greater, or Gleason 7 or greater) and used logistic regression to examine predictors. Similar analyses were performed in the subset of men with 10 or more core biopsies. In addition, we substratified the study population using 6 published AS protocols,[2] namely 1) JH (Johns Hopkins)—clinical stage T2a or less, Gleason 3 + 3 or less, 2 or fewer positive cores, 50% or less core involvement with tumor, PSAD 0.15 ng/ml/cm^3 or less (393 cases, 131 events);[7] 2) UoT (University of Toronto)—PSA 10 ng/ml or less, Gleason 3 + 3 or less (1,821 cases, 828 events);[8] 3) USCF—clinical stage T2a or less, PSA 10 ng/ml or less, Gleason 3 + 3 or less, 33% or less positive cores, 50% or less core involvement (986 cases, 412 events);[9] 4) PRIAS (Prostate Cancer Research International: Active Surveillance)—clinical stage T2a or less, PSA 10 ng/ml or less, Gleason 3 + 3 or less, 2 or fewer total positive cores, PSAD 0.2 ng/ml/cm^3 or less (599 cases, 227 events);[10] 5) MSKCC (Memorial Sloan-Kettering Cancer Center)—clinical stage T2a or less, PSA 10 ng/ml or less, Gleason 3 + 3 or less, 3 or fewer positive cores, 50% or less core involvement (1,077 cases, 443 events);[11] and 6) UoM (University of Miami)—clinical stage T2a or less, PSA 10 ng/ml or less, Gleason 3 + 3 or less, 2 or fewer positive cores, 20% or less core involvement (511 cases).[12]

Among the men who met the criteria for each protocol we examined the frequency of upgrading/up staging and used similar logistic regression models to identify predictors of adverse pathology. Statistical analysis was performed using R version 2.15.2.

RESULTS

Table 1 shows the clinical features of 13,159 men in the NPCR with low risk PCa and the study population of 4,500 men who underwent RP. Men treated with RP were significantly younger, and had smaller prostates, lower PSA, fewer comorbidities, more biopsy cores sampled and more positive cores. In the final study population of men who underwent RP the median age was 62 years, median prostate volume was 35 ml and median PSA was 6.1 ng/ml. Most men had clinical stage T1c disease (74%), a comorbidity score of 0 (84%) and were treated at a nonuniversity hospital (82%). The median number