Gleason Upgrading with Time in a Large Prostate Cancer Active Surveillance Cohort

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Purpose: We report the percentage of patients on active surveillance who had disease pathologically upgraded and factors that predict for upgrading on surveillance biopsies.

Materials and Methods: Patients in our active surveillance database with at least 1 repeat prostate biopsy were included. Histological upgrading was defined as any increase in primary or secondary Gleason grade on repeat biopsy. Multivariate analysis was used to determine baseline and dynamic factors associated with Gleason upgrading. This information was used to develop a nomogram to predict for upgrading or treatment in patients electing for active surveillance.

Results: Of 862 patients in our cohort 592 had 2 or more biopsies. Median followup was 6.4 years. Of the patients 20% were intermediate risk, 0.3% were high risk and all others were low risk. During active surveillance 31.3% of cases were upgraded. On multivariate analysis clinical stage T2, higher prostate specific antigen and higher percentage of cores involved with disease at the time of diagnosis predicted for upgrading. A total of 27 cases (15% of those upgraded) were Gleason 8 or higher at upgrading, and 62% of all 114 upgraded cases went on to have active treatment. The nomogram incorporated clinical stage, age, prostate specific antigen, core positivity and Gleason score. The concordance index was 0.61.

Conclusions: In this large re-biopsy cohort with medium-term followup, most cases have not been pathologically upgraded to date. A model predicting for upgrading or radical treatment was developed which could be useful in counseling patients considering active surveillance for prostate cancer.

Key Words: prostatic neoplasms, watchful waiting, neoplasm grading, nomograms

Abbreviations and Acronyms

AS = active surveillance

GS = Gleason score

PSA = prostate specific antigen

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Study received research ethics board approval.

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See Editorial on page 8.

ACTIVE surveillance is an established management strategy for localized prostate cancer.[1,2] In our series from Sunnybrook Health Sciences Centre 10-year prostate cancer specific survival rates were 97.2%.[3] The incidence of prostate cancer is expected to increase, due to an aging population, even in the absence of formal PSA screening programs.[4] A recent comprehensive review of prostate AS emphasized the need for confirmatory prostate biopsies to reduce the risk of tumor under sampling at the time of

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diagnostic biopsy.[5] Most AS programs advocate serial prostate biopsies, aimed at detecting under sampling or biological tumor progression with time which may lead to active treatment.[3,6–8]

Several AS series have recently reported rates of pathological upgrading with medium-term followup.[8,9] Porten et al examined 377 patients enrolled in an AS program with a median followup of 47 months.[8] The majority of patients were low risk at diagnosis (77%), with 20% being diagnosed with intermediate risk disease. In this cohort 34% of patients had upgrading of primary or secondary Gleason grades on subsequent biopsies. The Royal Marsden series considered adverse histology as upgrading to GS 4+3 or greater, or more than 50% core involvement.[9] With a median followup of 5.7 years, 54 of 412 patients (13.1%) had adverse histology on subsequent biopsies using these more stringent criteria.

In this study we determined the proportion of cases upgraded in a large prospectively collected AS cohort and determined the factors that predicted for upgrading. Furthermore, we generated a nomogram to help clinicians and patients predict the risk of upgrading or radical treatment 5 years from diagnosis.

PATIENTS AND METHODS

A prospective, single-arm, cohort study was initiated in November 1995 to test the feasibility of an AS strategy in low and favorable intermediate risk prostate cancer. A total of 251 patients were enrolled into the clinical trial which closed in 2002.[3] Thereafter, prospective recruitment of patients continued into our centralized database (www.asure.ca), with these patients also included in this analysis. Research Ethics Board approval was obtained from the Sunnybrook Health Sciences Centre.

Patients were eligible for AS if they had low risk localized prostate cancer with GS 6 or less and PSA 10 ng/ml or less.[3] Patients older than age 70 years with PSA up to 15 ng/ml or GS 3+4 or less were also considered for AS. A small proportion of patients who did not meet these eligibility criteria elected for AS.

Patients underwent PSA and digital rectal examination 3 monthly for 2 years and 6 monthly thereafter. A confirmation 8 to 14-core biopsy, based on the Vienna nomogram,[10] was performed 1 year after initial diagnostic biopsy to identify high grade cancer missed on the original biopsy. When possible, particular attention was paid to the site of the previous biopsy and to the anterolateral horn.[3] Subsequent biopsies were performed every 3 to 4 years (until aged 80). All prostate biopsies were centrally reviewed by a uropathologist.

Definitive therapy was discussed with patients with clinical progression, histological upgrading, or a PSA doubling time of less than 3 years. To ensure completeness of data collection the AS database was cross-referenced against the Sunnybrook prostate biopsy database, radical prostatectomy database and deaths database. For the purposes of this study, histological upgrading was defined as any increase in primary or secondary Gleason grade on repeat biopsy, compared to all previous prostate biopsies, as in previous reports from our institution (eg G3+3 to G3+4 or higher; G3+4 to G4+3 or higher etc).[11]

We used 2 sets of covariates to look for predictive factors of Gleason upgrading at any time. Baseline covariates included age (years), baseline PSA, T-stage (T1 or T2), GS (GS6 or less, or GS7), percentage cores involved on diagnostic biopsy, risk group (low vs intermediate/high) and number of cores taken at first biopsy. Clinic covariates included PSA velocity (continuous and dichotomous (greater than 2, or 2 ng/ml per year or less) calculated from time of diagnosis to time of upgrading, PSA doubling time, number of biopsies, total number of cores taken and time per biopsy (last biopsy date minus first biopsy date divided by number of biopsies). Age, baseline PSA, percentage and number of cores, number of biopsies and total cores were analyzed as continuous variables and natural log transformations were applied to provide more normal distributions. Univariate logistic regression analysis was used with $p < 0.05$ considered statistically significant. Backward stepwise selection procedures were used in the multivariate logistic regression analysis until only significant covariates ($p < 0.05$) were left in the model. R^2 (higher the value, better the model) and Hosmer-Lemeshow ($p < 0.05$ indicating lack of fit) were used to estimate model fitting.

To develop a nomogram to predict the likelihood of pathological upgrading or radical therapy we included commonly used clinical variables including clinical stage, age, PSA, core positivity and Gleason score. A model was constructed on the basis of the results of conditional cumulative incidence analysis and this model served as the starting point for the development of a computerized prediction tool. The discriminatory power of the model was quantified using the concordance index (CI). Calibration of the model was assessed using jackknife predictions of pathological upgrading or radical therapy as previously published.[11]

To assess Gleason upgrading over time, we used generalized estimating equations to adjust for correlated categorical data due to repeated measures (repeat biopsies) over time. Time from diagnosis (years) was considered as a continuous variable. Univariate and multivariate analyses were performed as previously described. Kaplan-Meier upgrade-free survival curves were generated for patients with a PSA velocity greater than 2, or 2 ng/ml per year or less, and treatment-free survival curves were generated for patients with upgraded or nonupgraded score. All analyses were performed using SAS® v9.3 for Windows® and Graphpad Prism® 5.0.

RESULTS

Of 862 patients enrolled into our AS database as of August 2012, 592 had at least 1 repeat prostate biopsy. Median followup was 6.5 years (IQR 4.1 to 8.7). Of the patients 20% have been followed for 10 years or more. Baseline characteristics are