National Comprehensive Cancer Network® Favorable Intermediate Risk Prostate Cancer—Is Active Surveillance Appropriate?

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Abbreviations and Acronyms

AS = active surveillance
FIR = favorable IR
GG = Grade Group
IR = intermediate risk
LR = low risk
MRI = magnetic resonance imaging
NCCN® = National Comprehensive Cancer Network®
PSA = prostate specific antigen
RP = radical prostatectomy
TRUS = transrectal ultrasound
UIR = unfavorable IR

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Purpose: We compared pathological and biochemical outcomes after radical prostatectomy in patients at favorable intermediate risk who fulfilled current NCCN® (National Comprehensive Cancer Network®) Guidelines® for active surveillance criteria to outcomes in patients who met more traditional criteria for active surveillance.

Materials and Methods: We queried our institutional review board approved prostate cancer database for patients who met NCCN criteria for very low risk (T1c, Grade Group 1, 3 or fewer of 12 cores, 50% or less core volume and prostate specific antigen density less than 0.15 ng/ml), low risk (T1-T2a, Grade Group 1 and prostate specific antigen less than 10 ng/ml) or favorable intermediate risk (major pattern grade 3 and less than 50% positive biopsy cores) and who had 1 intermediate risk factor, including T2b/c, Grade Group 2 or prostate specific antigen 10 to 20 ng/ml. Men at intermediate risk who did not meet favorable criteria were labeled as being at unfavorable intermediate risk. Patients at favorable intermediate risk were compared to those at very low and low risk, and those at unfavorable intermediate risk to identify differences in rates of adverse pathological findings at radical prostatectomy, including Gleason score Grade Group 3-5, nonorgan confined disease or nodal involvement. Time to biochemical recurrence was compared among the groups using Cox regression.

Results: A total of 3,686 patients underwent radical prostatectomy between January 1, 2014 and December 31, 2015. Of these men 1,454, 250 and 1,362 fulfilled the criteria for low, favorable intermediate and unfavorable intermediate risk, respectively. The rate of adverse pathological findings in favorable intermediate risk cases was significantly higher than in low risk cases and significantly lower than in unfavorable intermediate risk cases (27.4% vs 14.8% and 48.5%, respectively, each $p < 0.001$). Time to biochemical recurrence differed significantly among the risk groups ($p < 0.001$).

Conclusions: Relative to men at low risk those at favorable intermediate risk represent a distinct group. Care should be taken when selecting these patients for active surveillance and monitoring them once they are in an active surveillance program.

Key Words: prostatic neoplasms; watchful waiting; prostatectomy; neoplasm recurrence, local; risk factors

PROSTATE specific antigen screening amid much recent debate has led to the detection and treatment of many clinically indolent prostate cancers.[1] Concerns regarding this overtreatment have led to the development

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and adoption of AS protocols with the goal of limiting treatment side effects without compromising cancer control. Despite initial reluctance and skepticism about such a strategy[2] appropriately selected AS cohorts have experienced low rates of cancer specific mortality and metastases at long-term followup.[3–5] As such AS has gradually become a well accepted management strategy for clinically localized, low risk prostate cancer.[6,7]

Despite generally widespread agreement on the role of AS in the management of clinically localized prostate cancer identifying appropriate candidates for AS has been a topic of some debate. Multiple, proposed, institution specific AS protocols and national guidelines are available, of which most include only patients at low risk.[4,8–12] Recently certain guidelines, including those of NCCN, have expanded to include select IR prostate cancer cases with more favorable clinical characteristics.[13–15] However, the data supporting the safety of AS in these patients at FIR are limited relative to the data supporting AS in patients at low risk. In fact, a recent expert consensus review identified the inclusion of IR group cases as an "unresolved issue in AS."[16]

Thus, we reviewed our prospectively collected prostatectomy database and assessed the pathological and biochemical outcomes in patients treated with RP who would have met AS inclusion criteria according to the updated NCCN Guidelines. In particular we focused on these outcomes in men at FIR and compared them to outcomes in those in the LR and UIR groups. Our goal was to help inform the appropriateness of AS in IR prostate cancer cases with favorable characteristics.

MATERIALS AND METHODS

After obtaining institutional review board approval we retrospectively reviewed our prospectively collected database of 3,669 patients who underwent RP from January 2004 through December 2015. The database was queried for men who would have been considered AS candidates based on current NCCN Guidelines.[14] We identified patients in our cohort as meeting certain risk criteria, including very low risk (T1c, GG 1, 3 or fewer/12 cores, 50% or less core volume and PSA density less than 0.15 ng/ml), low risk (T1-T2a, GG 1 and PSA less than 10 ng/ml) and favorable intermediate risk (major pattern grade 3, less than 50% positive biopsy cores and only 1 intermediate risk factor, that is T2b/c, GG 1 or PSA 10 to 20 ng/ml). For comparison purposes all other patients at intermediate risk (T2b/c, GG 2/3 and PSA 10 to 20 ng/ml) were also identified.

Three groups were the main focus of our study, including 1) the LR cohort composed of NCCN very low and low risk groups, in which AS has become well accepted, 2) the FIR group, which was recently included for AS in NCCN Guidelines, and 3) the UIR group, composed of all other patients at IR, who are typically advised against AS. A high/very high risk group was also identified for comparison purposes.

We compared demographic characteristics among the groups, including patient age, highest PSA before surgery, biopsy findings and clinical tumor stage using the chi-square test for categorical data and ANOVA or the Kruskal-Wallis test for continuous data. Pairwise comparisons were performed as indicated using the chi-square test or the Fisher exact test for categorical data when expected frequencies were low, and the t-test for independent groups or the Wilcoxon rank sum test for continuous data.

The study primary end point was the rate of adverse pathological outcomes at prostatectomy. An adverse outcome was defined as Gleason score primary pattern 4/5 (GG 3-4), nonorgan confined disease (pT3-pT4) or lymph node involvement. Rates of adverse findings were compared across groups using the chi-square test. Risk group categorization was assessed as an independent predictor of adverse findings using multivariate logistic regression and controlling for demographic variables.

The study secondary end point was recurrence-free survival. Recurrence was defined as any postoperative PSA greater than 0.2 ng/ml with secondary confirmation or as the need for postoperative radiation or systemic therapy such as androgen deprivation therapy in the adjuvant or the salvage setting. Kaplan-Meier curves were generated to assess time to recurrence with associated 2 and 5-year PSA recurrence-free survival in each defined risk group. Findings were compared across groups by the log rank test. Cox regression was applied to evaluate the value of risk group as an independent predictor of time to recurrence while controlling for year of surgery. For statistical analyses significance was considered at $p < 0.05$. All analyses were performed with SPSS®, version 21.

RESULTS

A total of 3,686 consecutive patients underwent RP between January 1, 2004 and December 31, 2015. We excluded 107 patients from analysis due to the lack of sufficient preoperative information to determine the risk group. Data on 3,579 patients were available for analysis. Of these men 1,704 (47.6%) would have fulfilled AS criteria (very low, low or favorable intermediate risk) based on current NCCN Guidelines. Stratification by NCCN risk group yielded 1,454, 250 and 1,362 patients in the LR, FIR and UIR groups, respectively, representing the main analytical data set of 3,066 patients. A total of 513 patients were in the high or the very high risk group.

The table lists cohort demographics and clinical characteristics. Mean patient age was 59.7 years. As a whole patients with intermediate risk disease tended to be older with higher preoperative PSA and more advanced clinical stage than men at LR. Overall followup in the cohort was 37 months and it differed among the groups, including 27 months in