Comparison of Pathological and Oncologic Outcomes of Favorable Risk Gleason Score 3 + 4 and Low Risk Gleason Score 6 Prostate Cancer: Considerations for Active Surveillance

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Abbreviations and Acronyms

AS = active surveillance
BCR = biochemical recurrence-free
FIR = favorable intermediate risk
GG = Grade Group
GS = Gleason score
LNI = lymph node involvement
LR = low risk
NCCN® = National Comprehensive Cancer Network®
PSA = prostate specific antigen
RP = radical prostatectomy
SVI = seminal vesicle invasion

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Purpose: Recent NCCN® (National Comprehensive Cancer Network®) Guidelines® show that patients with biopsy Gleason score 3 + 4/Grade Group 2 but otherwise favorable features are active surveillance candidates. However, little is known about the long-term outcomes compared to that in men in the low risk Gleason score 6/Grade Group 1 group. We sought to clarify the risk of adverse features and oncologic outcomes in surgically treated, favorable Grade Group 2 vs 1 cases.

Materials and Methods: We queried our prospectively maintained radical prostatectomy database for all 8,095 patients with biopsy Grade Group 1 or 2 prostate cancer who otherwise fulfilled the NCCN low risk definition of prostate specific antigen less than 10 ng/ml and cT2a or less, and who underwent radical prostatectomy from 1987 to 2014. Multivariable logistic regression and Kaplan-Meier methods were used to compare pathological and oncologic outcomes.

Results: Organ confined disease was present in 93.9% and 82.6% of Grade Group 1 and favorable intermediate risk Grade Group 2 cases while seminal vesicle invasion was noted in 1.7% and 4.7%, and nodal disease was noted in 0.3% and 1.8%, respectively (all $p < 0.0001$). On multivariable logistic regression biopsy proven Grade Group 2 disease was associated with a threefold greater risk of nonorgan confined disease (OR 3.1, 95% CI 1.7–5.7, $p < 0.001$). The incidence of late treatment (more than 90 days from surgery) in Grade Group 1 vs 2 was 3.1% vs 8.5% for hormonal therapy and 6.0% vs 12.2% for radiation ($p < 0.001$). In the Grade Group 1 vs 2 cohorts the 10-year biochemical recurrence-free survival rate was 88.9% vs 81.2% and the 10-year systemic progression-free survival rate was 99% vs 96.5% (each $p < 0.001$).

Conclusions: Men at favorable risk with Grade Group 2 disease who are considering active surveillance should be informed of the risks of harboring adverse pathological features which impact secondary therapies and an increased risk of cancer progression.

Key Words: prostatic neoplasms, watchful waiting, neoplasm grading, prostatectomy, risk factors

Active surveillance protocols for low risk prostate cancer continue to be used with overall and cancer specific survival similar to that of active treatment strategies.[1–5] Inherent in AS cohorts are small numbers of men harboring GS 3 + 4 prostate cancer, now also referred to as GG2,[6] who are

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often treated with surveillance because of decreased life expectancy or multiple comorbidities and, therefore, are likely not active treatment candidates.[7] Recently NCCN Guidelines recommended AS as an option in men with FIR prostate cancer on biopsy (GG2, less than 50% positive biopsy cores and only 1 additional intermediate risk factor) who may otherwise be eligible for active treatment strategies due to younger age and life expectancy greater than 10 years.[8] Whether this group of men can be safely surveilled is unclear with mixed results reported in currently available information.[9,10] However, based on studies comparing active treatment vs observation, such as the PIVOT (Prostate Cancer Intervention versus Observation Trial)[11] and SPCG-4 (Scandinavian Prostate Cancer Group Study Number 4)[12] trials, an argument can be made for early definitive treatment of men at intermediate risk.

Several groups have used biopsy and surgical pathology specimens of men eligible for AS to evaluate surgical and pathological outcomes.[9,13–15] Yet patients in those studies had LR or very LR disease with no attention given to men at FIR. With the new NCCN Guidelines further investigation is warranted in this subset of men. Therefore, we used biopsy and surgical pathology information to compare a Gleason 6 (GS6 or GG1) low risk patient subset to patients with GS 3 + 4 (GG2) who otherwise met low risk criteria (PSA less than 10 ng/ml and cT2a or less) to evaluate the rates of adverse pathology findings and long-term cancer specific outcomes.

MATERIALS AND METHODS

After obtaining approval from our institutional review board we queried our prospectively maintained, single institution prostatectomy registry from 1987 to 2014 to identify all patients with biopsy proven GS6 (GG1) or GS 3 + 4 (GG2) who underwent RP. These men otherwise fulfilled LR NCCN criteria, including clinical stage cT2a or lower and PSA less than 10 ng/ml. Patients with disease on prostate biopsy were included in analysis. Participation was based on biopsy pathology findings alone and cases were accordingly designated as LR GG1 or FIR GG2. The surgical approach and the need for pelvic lymph node dissection, including the template performed, were at surgeon discretion. All biopsy specimens were reviewed at our institution, and surgical pathology was processed and analyzed by a genitourinary pathologist as previously characterized.[16] As previously described,[15] all Gleason scores and grade groupings represent the results of our internal review.

The preoperative variables extracted included patient age at surgery, preoperative PSA, PSA doubling time, clinical T stage, and primary and secondary Gleason grades on biopsy. Prostatectomy pathological variables included primary and secondary GSs, pT and pN stages, and surgical margin status. Pathologically unfavorable disease was defined as advanced stage (SVI, invasion into adjacent organs or LNI) and/or pathological Gleason score 4 + 3 or greater (GG3 or greater).[9] TMN stage was determined according to the 2002 AJCC (American Joint Committee on Cancer), 6th edition.[17] GS was assigned according to the 2005 ISUP (International Society of Urological Pathology) Consensus Conference on Gleason Grading of Prostatic Carcinoma.[18] We also included the newer Grade Group designations[6] as this simplified system is now commonly applied in prostate cancer research studies.

In addition to descriptive statistics, we used the chi-square test to compare categorical variables and the Wilcoxon rank sum test to compare continuous variables. Patient age, year of surgery, PSA doubling time, percent of the surface with cancer, and clinical GS and GG were analyzed in multivariable prediction models using logistic regression to look for rates of GS or GG upgrading and/or downgrading, up staging and the development of unfavorable disease in each group. BCR survival, systemic progression-free survival, cancer specific survival and overall survival were compared between the LR GG1 and the FIR GG2 groups using Kaplan-Meier curves and the log rank test. All tests were 2-sided with $p = 0.05$ considered significant.

RESULTS

Of the 8,095 patients included in analysis 6,360 had LR GS6 or GG1 disease and 1,735 had FIR GS 3 + 4 or GG2 disease. Table 1 lists baseline clinical and demographic characteristics. Median age at surgery was 60 (IQR 55–65) vs 63 years (IQR 57–67) and preoperative PSA was 5.0 (IQR 3.8–6.5) vs 5.3 ng/ml (IQR 4.3–6.8) in the GG1 and GG2 cohorts, respectively. Clinical stage was T1 in 75.9% of the patients with GG1 and in 65.5% with GG2 vs stage T2a in 24.1% with GG1 and in 34.5% with GG2.

Table 1 also shows the pathological features of each cohort following prostatectomy. Of GG1 cases stage was pT2a-2b in 2,321 (36.6%), pT2c in 3,642 (57.5%), pT3a in 264 (4.2%) and pT3b in 106 (1.7%). Of GG2 cases stage was pT2a-2b in 440 (25.4%), pT2c in 1,008 (58.1%), pT3a in 202 (11.6%) and pT3b in 80 (4.6%). Pathological GS/GG was concordant in 4,716 GG1 cases (74.4%), downgraded in 162 (2.6%) and upgraded to GG2 or greater in 1,459 (23.0%). Among GG2 cases 1,102 (63.6%) showed concordant pathology at prostatectomy while 419 (24.1%) were downgraded and 213 (12.3%) were upgraded. Overall 12.3% of GG2 cases were upgraded to unfavorable risk disease compared to 3.2% of GG1 cases.

Patients with GG2 on final pathology were more likely to have nonorgan confined disease (17.4% vs 6.1%, $p \leq 0.0001$) and positive surgical margins (20.7% vs 15.3%, $p < 0.0001$) compared to patients with GG1 disease. Those with GG2 were more likely