Risk of Metastasis in Men with Grade Group 2 Prostate Cancer Managed with Active Surveillance at a Tertiary Cancer Center

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Purpose: We studied the risk of metastatic prostate cancer development in men with Grade Group 2 disease managed with active surveillance at Memorial Sloan Kettering Cancer Center.

Materials and Methods: A total of 219 men with Grade Group 2 prostate cancer had disease managed with active surveillance between 2000 and 2017. Biopsy was performed every 2 to 3 years, or upon changes in magnetic resonance imaging, prostate specific antigen level or digital rectal examination. The primary outcome was development of distant metastasis. The Kaplan-Meier method was used to estimate treatment-free survival.

Results: Median age at diagnosis was 67 years (IQR 61–72), median prostate specific antigen was 5 ng/ml (IQR 4–7) and most patients (69%) had nonpalpable disease. During followup 64 men received treatment, including radical prostatectomy in 36 (56%), radiotherapy in 20 (31%), hormone therapy in 3 (5%) and focal therapy in 5 (8%). Of the 36 patients who underwent radical prostatectomy 32 (89%) had Grade Group 2 disease on pathology and 4 (11%) had Grade Group 3 disease. Treatment-free survival was 61% (95% CI 52–70) at 5 years and 49% (95% CI 37–60) at 10 years. Three men experienced biochemical recurrence, no men had distant metastasis and no men died of prostate cancer during the followup. Median followup was 3.1 years (IQR 1.9–4.9).

Conclusions: Active surveillance appears to be a safe initial management strategy in the short term for carefully selected and closely monitored men with Grade Group 2 prostate cancer treated at a tertiary cancer center. Definitive conclusions await further followup.

Abbreviations and Acronyms

AS = active surveillance

mpMRI = multiparametric magnetic resonance imaging

MRI = magnetic resonance imaging

PSA = prostate specific antigen

Key Words: prostatic neoplasms, watchful waiting, neoplasm grading

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Most patients with favorable risk prostate cancer do not need immediate treatment and can instead have disease managed with active surveillance in an effort to avoid or delay the side effects of radical therapy.[1] In the context of AS, patients are regularly monitored for signs of disease progression, which then prompts curative intervention. Originally AS was used very restrictively around the world, for example, the group at Hopkins restricted their cohort to patients with low risk prostate cancer, predominately a subgroup with very low risk (defined as clinical stage T1c, PSA density less than 0.15 ng/ml, biopsy Gleason score 6 or less, 2 or fewer positive biopsy cores and a maximum of 50% involvement of any biopsy core with cancer).[2] The Toronto cohort also included some patients older than 70 years with Gleason score 3+4=7 (Grade Group 2) disease.[3] Over time AS inclusion criteria have been relaxed in cohorts to also include men with high volume Gleason score 6 (Grade Group 1) disease and PSA between 10 and 20 ng/ml as well as select men with intermediate risk disease with Gleason score 3+4=7 (Grade Group 2).[2–8]

The strongest predictor of oncologic outcome among men with prostate cancer is the histopathological grade group.[9] All published prospective AS cohorts that have reported long-term outcomes thus far have either reported only on Grade Group 1 or a mixture of low and intermediate risk disease (Grade Groups 1-3).[2–8]

The paucity of data on outcomes in men at the lower end of intermediate risk prostate cancer managed with AS contributes to uncertainty for physicians and patients engaging in shared decision making. We report our experience of 219 men with Grade Group 2 (Gleason score 3+4) prostate cancer managed with AS at Memorial Sloan Kettering Cancer Center.

PATIENTS AND METHODS

This study was approved by the institutional review board at Memorial Sloan Kettering Cancer Center. We queried our institutional database and identified 219 patients with Grade Group 2 prostate cancer managed with AS from 2000 to 2017. Patients were determined to be on AS if they were not treated within a year of diagnosis. Chart reviews were performed to assess if patients were followed on AS. Those who were followed on a watchful waiting basis (no biopsies, advanced age, hormonal treatment) were not included in the analysis. Management strategies evolved during this 17-year period and our contemporary management strategy is described here. Following diagnosis and confirmatory biopsy, patients underwent PSA testing and physical and digital rectal examinations every 6 months. In addition, patients underwent multiparametric (T2-weighted, diffusion weighted and/or dynamic contrast enhanced) magnetic resonance imaging performed every 18 months. Nontargeted systematic biopsy was performed every 2 to 3 years with MRI/ultrasound fusion biopsy of suspicious lesions identified on MRI. Historically, patients may have undergone with yearly biopsies. If there was a change in PSA or MRI a biopsy was performed before the 3-year period. Questionnaires were sent to patients to ascertain their treatment status. The majority of initial biopsies were performed at the institution. All but 15 biopsies (diagnostic and surveillance) were reviewed by subspecialty urological pathologists at the institution.

Our primary end point was the incidence of distant metastasis in patients managed with AS using the Kaplan-Meier method. Patients were censored at the last date of contact with the clinic. Secondary end points included treatment-free survival, overall survival and radical prostatectomy outcomes. Grade progression was defined as an upgrade to Grade Group 3 (Gleason score 4+3) or higher. Volume progression was defined by MRI or number of cores. Univariate Cox regression was used to determine whether receiving treatment following active surveillance was associated with any diagnostic variable of interest including age at diagnosis, PSA at diagnosis, number of positive cores, percent cancer and total mm of cancer at diagnosis. Statistical analyses were performed using Stata® 15.0.

RESULTS

Patient characteristics are displayed in table 1. Among the 219 men with Grade Group 2 prostate cancer the majority enrolled in AS after 2010, including 113 (52%) between 2010 and 2014 and 68 (31%) between 2015 and 2017. Median age at diagnosis was 67 years (IQR 61–72), median PSA was 5 ng/ml (IQR 4–7) and the majority of patients (69%) had nonpalpable disease. Median number of positive cores was 2 (IQR 1–3) and median total length of cancer on diagnostic biopsy was 4 mm (IQR 2–6).

Table 1. *Patient characteristics*

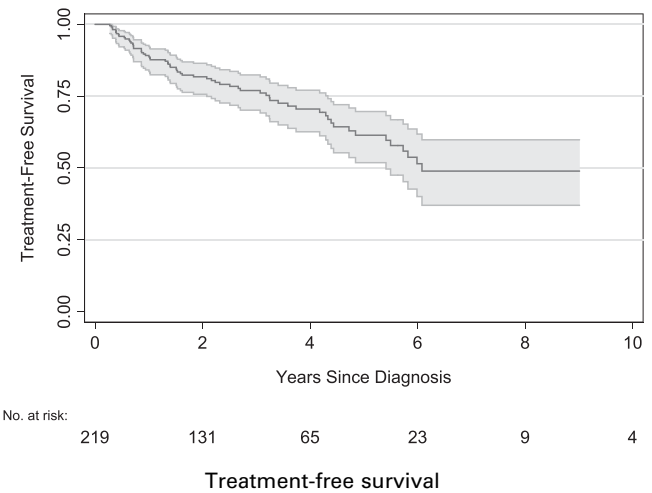
Median age at diagnosis (IQR)	67	(61, 72)
Median ng/ml diagnostic PSA (IQR)*	5	(4, 7)
Median pos cores at diagnosis (IQR)†	2	(1, 3)
Median total cores at diagnosis (IQR)†	12	(7, 14)
% Nomogram risk of locally advanced disease (IQR)*	50	(40, 60)
Median total Ca length (mm) at diagnosis (IQR)‡	4	(2, 6)
No. yr of diagnosis (%):		
2000–2004	7	(3.2)
2005–2009	31	(14)
2010–2014	113	(52)
2015–2017	68	(31)
No. clinical T stage (%):		
T1C or less	151	(69)
T2A	31	(14)
T2B	5	(2.3)
T2C	3	(1.4)
T3A	2	(0.9)
Unknown	27	(12)
No. Charlson comorbidity index (%):		
0	158	(72)
1	26	(12)
2	26	(12)
3 or Greater	9	(4.1)

* In 201 patients.
† In 213 patients.
‡ In 205 patients.

Median followup for those who did not die was 3.1 years (IQR 1.9–4.9). There were 55 men followed for at least 5 years and 5 men followed for 10 years. During followup 64 men received treatment, including radical prostatectomy in 36 (56%), radiotherapy in 20 (31%), hormone therapy in 3 (5%) and focal therapy in 5 (8%). Treatment-free survival was 61% (95% CI 52–70) at 5 years and 49% (95% CI 37–60) at 10 years (see figure). The triggers for treatment were mainly patient preference and/or disease progression by grade or volume upgrade (table 2). Of the 36 patients who underwent radical prostatectomy 32 (89%) had Grade Group 2 disease on pathology and 4 (11%) had Grade Group 3 disease. The majority of patients who underwent prostatectomy had organ confined disease, with 25 (69%) pT2 and 11 (31%) nonorgan confined disease (pT3). Three men experienced biochemical recurrence after radical prostatectomy.

Results from the univariable Cox regression analyses are displayed in table 3. Diagnostic PSA (HR 1.08, 95% CI 1.03–1.13, p=0.003) and total millimeters of cancer at diagnosis (HR 1.07, 95% CI 1.01–1.14, p=0.021) were significantly associated with receiving treatment for prostate cancer and discontinuing AS.

The overall survival for the entire cohort of 219 men was 97% (95% CI 93–99) at 5 years and 77% (95% CI 48–92) at 10 years after diagnosis. Distant metastases did not develop in any men and no men died of prostate cancer during the followup. Two men had lymph node metastasis during followup. The first patient had multiple comorbidities (chronic obstructive pulmonary disease, coronary artery disease, aortic aneurysm and gastric cancer). He was followed on AS and experienced lymph node metastasis but later died of cardiac disease. The second patient was on AS for 4 months before receiving focal therapy. He had 2 positive biopsies and positive lymph nodes at radical prostatectomy 1.5 years later.



Treatment-free survival

Table 2. *Triggers for treatment*

	No. (%)
Pt preference	19 (30)
Biopsy vol progression	15 (23)
Biopsy grade progression	14 (22)
MRI result	9 (14)
Change in PSA or digital rectal examination	4 (6)
Prolaris® result (tissue based biomarker)	3 (5)

He was further treated with hormonal therapy and is still alive today.

DISCUSSION

With the growing acceptance of AS, long-term studies are essential to reassure patients and physicians of the safety and efficacy of the program. Patient preferences for curative therapy vis-à-vis side effects from treatment must be considered when making individualized treatment decisions for the select group of men with low-intermediate risk prostate cancer.

We report one of the world's largest cohorts of patients monitored by AS, which includes 219 men with intermediate risk prostate cancer. Similar to prior reports,[8,10] and as hypothesized, we have demonstrated that carefully selected men with intermediate risk features had a higher likelihood of receiving treatment than published estimates from cohorts of only Grade Group 1 cases. However, the chance of cure was not compromised and only 2 men had lymph node metastasis during followup, confirming the short-term safety of AS in carefully selected and monitored patients.

Current data suggest that men with Grade Group 2 (Gleason score 3+4) prostate cancer may be candidates for initial management with AS if they have low volume disease (fewer than 3 positive cores, less than 5% Gleason pattern 4), low PSA density (PSA/volume), favorable histology (no cribriform pattern), favorable genomic testing and favorable mpMRI findings.[8,11–14] More research is needed to identify the optimal selection criteria, monitoring methods and triggers for intervention for men with intermediate risk prostate cancer on AS. Risk profiling may be improved by combining clinical risk assessment with novel biomarkers and advanced imaging technology.

Table 3. *Factors associated with receiving treatment*

	HR	95% CI	p Value
Age at diagnosis (per 1 yr increase)	0.97	0.94, 1.00	0.053
Yr of diagnosis (per 1 yr increase)	1.00	1.00, 1.00	0.003
Diagnostic PSA (per 1 ng/ml increase)	1.08	1.03, 1.13	0.003
No. pos cores at diagnosis (per mm increase)	1.03	0.93, 1.15	0.6
% Ca at diagnosis (per % increase)	1.01	1.00, 1.02	0.058
Total mm Ca at diagnosis (per mm increase)	1.07	1.01, 1.14	0.021

Univariable Cox proportional hazards regression was used to determine if factors are associated with receiving treatment for prostate cancer.

This includes mpMRI, an important component of an AS program that is used to confirm eligibility and during surveillance, and future work is necessary to determine the most efficient use.[15] We used changes in volume of Grade Group 2 cores, upgrade to Grade Group 3 or higher and/or changes in MRI such as extraprostatic extension to trigger treatment. It is clear that the lack of predefined criteria for intervention explains the high rate of AS discontinuation on the basis of anxiety (30%) in our cohort.

While most carefully selected men with Grade Group 2 prostate cancer do well on AS, men with intermediate risk features considering AS as a primary option should be informed of the increased oncologic risk over time. In the Toronto cohort men with intermediate risk prostate cancer had a 2.7-fold higher risk of metastasis than men with low risk disease, despite selective delayed intervention. Given the increased risk, careful patient selection and careful surveillance for early signs of disease progression are necessary.[16,17] Gleason score 7, PSA doubling time 3 years or less and 3 or more positive biopsy cores were associated with development of metastases in the Toronto cohort. Among the Toronto patients with Gleason score 3+4 disease in whom metastasis developed all had 5% or greater Gleason pattern 4 disease (in whom this information was available). In contrast, having a PSA greater than 10 ng/ml and Gleason score 6 in the Toronto cohort was not associated with an increased risk of metastatic disease.[16]

A recent 2017 review identified 5 published AS series that reported outcomes for men with intermediate risk features (with varying definitions), including Toronto (209 men), University of California San Francisco (90 men), Prostate Cancer Active Surveillance Study (115 men), European Randomized Study of Screening for Prostate Cancer (50 men), and Royal Marsden Hospital in Denmark (128 men).[10] Despite using varying definitions of intermediate risk disease, all studies found that men with Grade Group 2 prostate cancer had higher rates of clinical progression and were more likely to undergo treatment over time than men at lower risk. In contrast, a recent report on the AS experience at the Cleveland Clinic found that the 10-year metastasis-free survival was 97.4% for 514 men with very low/low risk prostate cancer and 99.0% for 117 men with intermediate/high risk with Grade Group 2 disease.[18] There were no deaths from prostate cancer during followup.

A limitation of the present study is that we could not calculate the total millimeters or percent of Gleason pattern 3 or 4 disease on diagnostic biopsy. We started reporting these calculations on all Grade Group 2 biopsies reviewed by our pathology department in 2015 so these data were only available for a small percentage of our cohort. As our cohort matures and we continue to monitor more patients with intermediate risk prostate cancer, we will record these parameters and report on their significance. We have recently shown that quantitation of Gleason pattern 4 conveys a net benefit to clinical decision making beyond standard clinicopathological variables in a cohort of patients with Grade Group 2 disease treated with radical prostatectomy.[19] Additional limitations include the retrospective study design with evolution in the AS protocol over time, short median followup for the end points of metastasis and death from prostate cancer and lack of recording of reasons for patient preference to undergo treatment. Definitive conclusions will need to await further followup.

CONCLUSIONS

Active surveillance appears to be a safe initial management strategy at a tertiary cancer center for carefully selected men with Grade Group 2 prostate cancer who are monitored closely according to a well-defined AS program. Men with Grade Group 2 disease considering AS should be informed about the relative lack of evidence on long-term oncologic outcomes with this approach. Future studies that elucidate which patients with intermediate risk prostate cancer have better long-term outcomes on AS are needed.

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EDITORIAL COMMENT

Whereas active surveillance is a preferred treatment option for many men with Grade Group 1 (Gleason score 3/3) prostate cancer, many believe that those with Grade Group 2 (Gleason score 3/4) disease should receive immediate treatment. The authors suggest that this may not be so given that in their cohort although the risk of treatment was higher than would be expected for men with Grade Group 1 disease, the risk of metastasis or death due to disease was extremely low. It should be recognized that the cancers in this analysis had many generally favorable features given what appears to be relatively low volume disease as assessed by PSA, T stage and tumor volume. Also, as stated by the authors, indications for intervention are not well-defined and only a minority experienced clear grade progression, a well recognized indication for treatment.

It is increasingly clear when making treatment decisions for those with Grade Group 2 prostate cancers, such cancers should be assessed in the context of other features which add substantial, incremental value to refined risk assessment. Grade Group 2 cancers that are associated with high PSA density (greater than 0.15 ng/ml), adverse genomic profiling, mpMRI PI-RADS (Prostate Imaging Reporting and Data System) scores of 4 and 5, have cribriform histology and are of higher volume should be considered for more immediate treatment or early confirmatory biopsy in healthy patients.[1-3] Those that are of low volume and do not share these characteristics seem to be suitable candidates for AS.

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REPLY BY AUTHORS

We thank Drs. Carroll and Chu for their positive comment on our experience with active surveillance for men with Grade Group 2 prostate cancer (Gleason 3+4=7) at Memorial Sloan Kettering Cancer Center. We agree entirely that treatment decision making for this subpopulation should involve a thorough risk stratification to assess eligibility for active surveillance, which may include PSA density, mpMRI, consideration of molecular markers and assessment of detailed histopathological biopsy features. At our center pathologists now routinely report Gleason pattern 4 quantification in biopsy cores in men with Grade Group 2 prostate cancer, which we have found added predictive value for adverse pathology on prostatectomy above standard clinicopathological parameters (reference 19 in article).