# Long-Term Outcomes of Active Surveillance for Prostate Cancer: The Memorial Sloan Kettering Cancer Center Experience

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**Abbreviations and Acronyms**

ADT = androgen deprivation therapy

AS = active surveillance

MRI = magnetic resonance imaging

PSA = prostate specific antigen

RP = radical prostatectomy

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**Purpose:** We report oncologic outcomes for men with Grade Group 1 prostate cancer managed with active surveillance at a tertiary cancer center.

**Materials and Methods:** A total of 2,907 patients were managed with active surveillance between 2000 and 2017, of whom 2,664 had Grade Group 1 disease. Patients were recommended confirmatory biopsy to verify eligibility and were followed semiannually with prostate specific antigen, digital rectal examination and review of symptoms. Magnetic resonance imaging was increasingly used in recent years. Biopsy was repeated every 2 to 3 years or after a sustained prostate specific antigen increase or changes in magnetic resonance imaging/digital rectal examination. The Kaplan-Meier method was used to estimate probabilities of treatment, progression and development of metastasis.

**Results:** Median patient age at diagnosis was 62 years. For men with Grade Group 1 prostate cancer the treatment-free probability at 5, 10 and 15 years was 76% (95% CI 74–78), 64% (95% CI 61–68) and 58% (95% CI 51–64), respectively. At 5, 10 and 15 years there were 1,146, 220 and 25 men at risk for metastasis, respectively. Median followup for those without metastasis was 4.3 years (95% CI 2.3–6.9). Distant metastasis developed in 5 men. Upon case note review only 2 of these men were deemed to have disease that could have been cured on immediate treatment. The risk of distant metastasis was 0.6% (95% CI 0.2–2.0) at 10 years.

**Conclusions:** Active surveillance is a safe strategy over longer followup for appropriately selected patients with Grade Group 1 disease following a well-defined monitoring plan.

**Key Words:** prostatic neoplasms, watchful waiting

RANDOMIZED trials comparing observation to radical treatment with surgery or radiation have failed to demonstrate a clear long-term benefit of immediate treatment of low risk prostate cancer, thus supporting the use of initial conservative management of these men to reduce the risks of overtreatment and side effects.[1–4] First described in 2002,[5] active surveillance is a conservative management strategy that involves careful monitoring of disease progression with PSA and regular biopsy, with the intent to give curative treatment in the event that progression is detected. AS has become increasingly accepted as a primary treatment option for patients with favorable risk prostate cancer and is now

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recommended by a growing body of clinical guidelines worldwide.[6] The 2017 AUA/ASTRO/SUO guideline recommends AS as the best available option for very low risk localized prostate cancer and the preferable care option for most patients with low risk localized prostate cancer.[7] Although the U.S. Cancer of the Prostate Strategic Urologic Research Endeavor registry has documented minimal use of AS from 1990 to 2009 (approximately 10%), there has been a sharp increase in the uptake of AS between 2010 and 2013 (40%, 95% CI 35–46).[8] Several other contemporary population based registries around the world now report a similar pattern.[9–14] Sweden reports the highest rates of AS, with very high uptake (74%) among men with low risk prostate cancer and almost complete uptake (91%) among men with very low risk prostate cancer.[12]

Approximately 10 groups worldwide have now reported outcomes of prospective AS cohorts.[15–17] However, most series are small (fewer than 500 patients) and currently have a short median followup of approximately 5 years. Only 3 series (Prostate Cancer Research International Active Surveillance, Johns Hopkins and Toronto) comprise more than 900 patients and have reported followup at 10 or 15 years.[15,17–20] Moreover, because these cohorts used different eligibility criteria and regimens for followup, the 15-year prostate cancer mortality risk varies between 0.1% (Hopkins, restrictive criteria)[20] and 5.7% (Toronto,[19] inclusive criteria).[15,18–21] In order to provide accurate counseling for men considering contemporary AS estimates of oncologic outcomes from large-scale, long-term, contemporary prospective cohorts are needed. We used the long-term experience at our institution to estimate the oncologic safety of AS for men with Grade Group 1 prostate cancer.

## MATERIALS AND METHODS

After institutional review board approval we retrospectively queried our prospectively maintained database of patients with prostate cancer at Memorial Sloan Kettering Cancer Center. Between 2000 and 2017 we identified 2,907 patients diagnosed with low or intermediate risk prostate cancer who were managed with active surveillance during 2000 to 2017, identified as either patients with low or intermediate risk prostate cancer who had a confirmatory biopsy within 6 months of diagnosis and did not receive treatment within a year, or a review of their medical charts outlining an expectant management strategy. We performed a chart review of all patients to assess the expectant management strategy used. As reported previously,[22,23] patients were recommended confirmatory biopsy to confirm eligibility, although this was not standard practice in the earliest years of AS. Our protocol was initially to include Gleason score 6, 3 or fewer cores, with confirmatory biopsy and yearly biopsy, which was changed over time with the inclusion of MRI and newer biopsy techniques as well as developing knowledge about AS, to Gleason score 6 (Grade Group 1), no core limitations, or Gleason score 3+4 (Grade Group 2), clinical stage T2B or less, confirmatory biopsy and biopsy every 2 to 3 years. We report the outcomes for 2,664 men with Grade Group 1 disease. There was no restriction on number of positive biopsy cores or PSA.

Patients were followed semiannually with digital rectal examination, total PSA measurement and a review of general health and symptoms. In more recent years MRI became increasingly used as an adjunctive tool to confirm eligibility and as part of monitoring every 18 months. Nontargeted systematic biopsy was generally repeated every 2 to 3 years. More recently, MRI/ultrasound fusion targeted biopsy of suspicious lesions on multiparametric (T2-weighted, diffusion weighted and/or dynamic contrast enhanced) MRI was more frequently used. Historically, biopsies may have been performed yearly. All cases (diagnostic and surveillance biopsies) were reviewed by subspecialty urological pathologists at the institution. If there was a change in PSA or MRI, biopsy was performed before the 3-year followup. Triggers for intervention included patient preference or progression to higher grade (defined as presence of any Gleason grade 4 on biopsy, ie Grade Group 2 or greater) or higher stage (T2c or T3) on digital rectal examination or imaging.

Time to progression, treatment, distant metastasis and death were estimated using the Kaplan-Meier method. Because of a small number of deaths from other causes, competing risks analysis was not performed. Patients without metastasis were censored at the last date of contact with the clinic. Because inclusion criteria for AS have changed over time, we hypothesized that the average age at diagnosis would be lower in more recent study years. To illustrate this we used locally weighted polynomial regression to plot the relationship between age at diagnosis and calendar year. Similarly, because inclusion criteria for AS were not restricted to very low risk disease (eg included high volume Grade Group 1) we hypothesized that the oncologic risk would increase over time. We calculated baseline (preoperative) risk of non-organ confined disease for all patients using the Memorial Sloan Kettering Cancer Center pre-RP nomogram,[24] a predictive model based on PSA, clinical T stage, Gleason grade, and number of positive and negative cores, and plotted the relationship between risk and calendar year using locally weighted polynomial regression. All statistical analyses were performed using Stata® 15.0.

## RESULTS

Between 2000 and 2017 a total of 2,907 patients were monitored by AS at our institution. We report the outcomes of men with Grade Group 1 prostate cancer (2,664; 92% of our AS population). The number of men in the AS cohort at our center increased sharply over time (supplementary figure, https://www.jurology.com).

Patient and tumor characteristics are described in table 1. Median age at diagnosis was 62 years (IQR 57–68). Consistent with the prevalence of PSA screening and early detection during this period

89% of men had nonpalpable tumors. The majority of patients presented with very low risk disease.

The risk of progression from Grade Group 1 to Grade Group 2 or 3 at 5, 10 and 15 years was 24% (95% CI 22–26), 36% (95% CI 33–39) and 41% (95% CI 35–46), respectively. While reasons for triggers for intervention were not routinely captured in the research database, it can be inferred that the main reason for intervention was grade progression, as it was highly correlated with treatment (fig. 1). Over time, 552 men received treatment. The treatment-free probability at 5, 10 and 15 years after the start of AS was 76% (95% CI 74–78), 64% (95% CI 61–68) and 58% (95% CI 51–64), respectively. Of the 552 men who proceeded to treatment, the majority underwent radical prostatectomy (66%), and the remainder received brachytherapy (6%), external beam radiation with or without hormonal therapy (21%), hormonal therapy (2.2%) or focal therapy (4.5%). Of the 363 men who underwent radical prostatectomy 23% had Grade Group 1 disease in the specimen, 62% displayed Grade Group 2, 10% showed Grade Group 3 and 5% showed Grade Group 4 or 5. At RP 69% of patients had organ confined disease, whereas 31% had pT3 or greater disease.

At 5, 10 and 15 years, respectively, there were 1,146, 220 and 25 men at risk (ie event-free and followed) for metastasis; 885, 145 and 20 men at risk for treatment; and 1,147, 222 and 26 men at risk for death. Median followup for those without metastasis was 4.3 years (95% CI 2.3–6.9). The probability of metastasis in this group was 0.1% (95% CI 0.03–0.4) at 5 years, 0.6% (95% CI 0.2–2.0) at 10 years and 1.5% (95% CI 0.4–5.2) at 15 years. Distant metastasis developed in 5 patients in this cohort and of these patients 3 (0.1%) had distant metastasis while on AS. Clinical information for these 5 patients is shown in table 2.

**Table 1.** *Patient and tumor characteristics*

| | | |
|---|---|---|
| Median age at diagnosis (IQR) | 62 | (57, 68) |
| Median ng/ml diagnostic PSA (in 2,400) (IQR) | 5 | (4, 6) |
| Median pos cores at diagnosis (in 2,547) (IQR) | 1 | (1, 2) |
| Median total cores at diagnosis (in 2,483) (IQR) | 12 | (6, 13) |
| Median percent Ca at diagnosis (in 2,259) (IQR)* | 8 | (5, 20) |
| Median mm total Ca length at diagnosis (in 1,998) (IQR) | 1 | (1, 3) |
| Median nomogram risk of locally advanced disease (in 2,090) (IQR) | 35 | (31, 42) |
| No. yr of diagnosis (%): | | |
| 2000–2004 | 221 | (8.3) |
| 2005–2009 | 656 | (25) |
| 2010–2014 | 1,293 | (49) |
| 2015–2017 | 494 | (19) |
| No. clinical stage at diagnosis (%): | | |
| T1C or less | 2,359 | (89) |
| T2A | 248 | (9.3) |
| T2B | 34 | (1.3) |
| T2C | 23 | (0.9) |

Biopsy data are based on diagnostic biopsy.
* Highest reported percentage of cancer in any biopsy core.

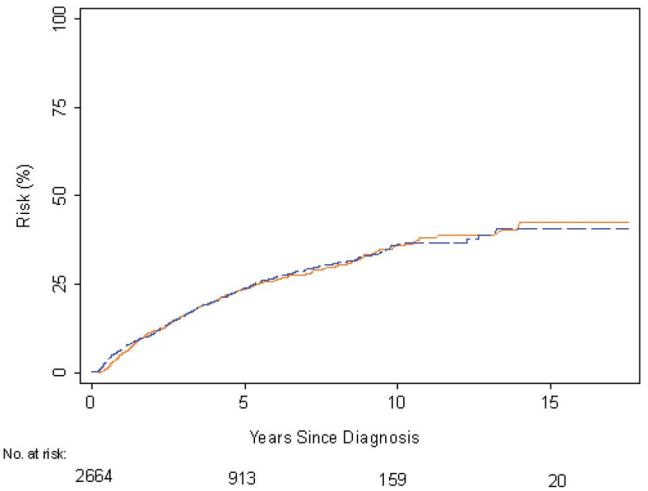


**Figure 1.** Risk of treatment and grade progression among patients with Grade Group 1 disease. Dashed blue line represents risk of grade progression and solid orange line represents risk of treatment.

The overall 10-year survival of men with Grade Group 1 prostate cancer was 94% (95% CI 92–95). Of the 2,664 patients in the cohort only 1 died of prostate cancer. The 10-year prostate cancer specific survival was 100% (95% CI 99–100). The patient had an unusual course of disease following diagnosis with Grade Group 1 prostate cancer (2 of 12 positive cores) at age 63. During a 3-year period the patient had 3 negative biopsies and 2 negative MRIs. The third MRI showed lesions suspicious of osseous metastasis, and symptomatic bone metastases developed consistent with prostatic origin 3 years after diagnosis. The patient received ADT and radiation therapy and ultimately died of disease 7 years after his initial diagnosis. Over time there was little to no change in the age at diagnosis or baseline risk of locally advanced disease (fig. 2).

## DISCUSSION

We have demonstrated that AS is a safe management strategy at a tertiary cancer center when patients are appropriately selected and a well-defined monitoring plan is followed, in particular for men with very low risk prostate cancer. The long-term risk of metastasis is very low. The current study confirms prior reports demonstrating a low incidence of oncologic events in men with low risk prostate cancer on AS.[15,18–20]

To date 10 groups worldwide have reported the results of prospective AS cohorts. Most cohorts, like

**Table 2.** *Clinical characteristics of patients with metastasis following active surveillance*

| | Pt 1 | Pt 2 | Pt 3 | Pt 4 | Pt 5 |
|---|---|---|---|---|---|
| Age at diagnosis | 76 | 45 | 58 | 63 | 60 |
| Yrs to metastasis from diagnosis | 8.8 | 7.6 | 11.8 | 3.5 | 1.8 |
| Yrs to metastasis from treatment | Pretreatment metastasis | 0.6 | 8.7 | Pretreatment metastasis | Pretreatment metastasis |
| First treatment | ADT | RP | RP | Radiotherapy + ADT | ADT |
| Grade Group at RP | - | 5 | 1 | - | - |
| Current status | Alive with disease | Alive with disease | Alive with disease | Died of disease | Alive with disease |
| Comments | Pt decision to remain on AS after upgrade to Grade Group 3; treated with ADT after metastatic diagnosis | Treated with prostatectomy after local progression; nodal + osseous metastasis after prostatectomy | Neuroendocrine differentiation on lumbar spine biopsy | Three neg biopsies + 2 neg MRIs; back pain + osseous metastasis on third MRI | Back pain + widespread osseous metastasis on MRI |

ours, have a median followup of approximately 5 years and only 2 have reported outcomes at 10 to 15 years. Even in large cohorts (Johns Hopkins and Toronto) the number of men followed for more than 10 years is low.[17] Moreover, because these cohorts used different eligibility criteria and followup regimens, like the present study, the published risks of metastasis and prostate cancer mortality vary. The majority of the men in the Hopkins cohort met the more restrictive very low risk inclusion criteria (defined by the Epstein criteria 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) and nearly all have low volume disease.[25] As a result, the Hopkins cohort reported a 0.4% risk of metastasis and a 0.1% risk of prostate cancer mortality at 15 years.[20] The Toronto cohort is more heterogeneous and used more inclusive criteria (patients with low and intermediate risk prostate cancer, Gleason score 3+4=7 or less and PSA 20 ng/ml or less) and reported a 2.8% risk of metastasis and 5.7% 15-year risk of prostate cancer mortality.[19] In a separate report the Toronto group analyzed outcomes by grade among men with PSA less than 20 ng/ml, showing a 15-year metastasis-free survival of 94% for men with Grade Group 1 (Gleason 6); 84% for men with Grade Group 2 (Gleason 3+4), and 63% for men with Grade Group 3 disease (Gleason 4+3).[26] In comparison, we report a 0.6% risk of metastasis (95% CI 0.2–2.0) at 10 years and a 1.5% risk (95% CI 0.4–5.2) at 15 years, a fourfold lower rate of distant metastasis for Grade Group 1 at 15 years compared to the Toronto cohort.

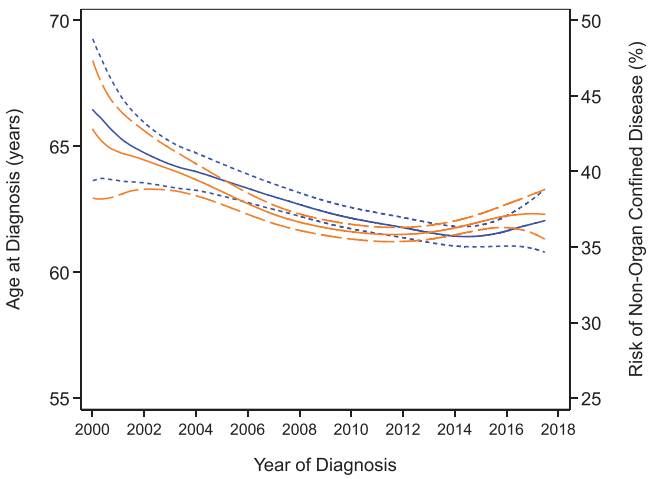


**Figure 2.** Age and risk of nonorgan confined disease at diagnosis over time for men with Grade Group 1 disease. Blue line with short dash confidence interval represents change in age at diagnosis over time. Orange line with long dash confidence interval represents change in risk of nonorgan confined disease at diagnosis over time.

While these rates align with those of other AS cohorts and support the oncologic safety of AS over longer term followup, we do note that the upper bound of the confidence interval at 15 years is clinically relevant (5.2% risk of metastasis). However, of the 5 patients with distant metastases only 2 might have been cured by early treatment. One man, who later died of the disease, had an unusual disease course and it is possible that his disease was likely metastatic already at diagnosis. One man was noncompliant with a treatment recommendation, and 1 had metastases after radical prostatectomy for Grade Group 1 disease and it is possible that he would have had a similar outcome if treated immediately.

This study is not without limitations. Because most patients were recruited to our AS program in recent years, the followup for metastasis and prostate cancer death is still of intermediate length. As such, we will continue to report longer followup as the cohort matures. Furthermore, we acknowledge that this is not a prospective protocol based AS cohort, but AS criteria were institution specific. Because expectant management in the early years of our study could entail either AS or watchful waiting, some men with monitoring more resembling watchful waiting have been included. This would have the effect of underestimating the safety of contemporary AS by including these men in our study. Furthermore, our AS program has been adapting to a number of changes over time. Very conservative initial eligibility criteria have expanded to include higher volume disease, integration of MRI and subsequent biopsy guidance. As such, there are fewer evaluable patients at 15 years and fewer patients with long established MRI followup. We did not see evidence of change in median age at diagnosis or baseline risk of locally advanced disease, despite broadening of AS criteria over time.

## CONCLUSIONS

Our experience confirms, on a large scale, prior reports that active surveillance is an oncologically safe strategy for men diagnosed with low risk prostate cancer. Active surveillance should be strongly recommended for such patients as it avoids treatment related morbidity without compromising cancer control.

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