Prostate Int 5 (2017) 139–142

Contents lists available at ScienceDirect

Prostate International

journal homepage: https://www.journals.elsevier.com/prostate-international

Original Article

# Management and outcomes of Gleason six prostate cancer detected on needle biopsy: A single-surgeon experience over 6 years

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ARTICLE INFO

*Article history:*
Received 16 February 2017
Received in revised form
25 March 2017
Accepted 30 March 2017
Available online 7 April 2017

*Keywords:*
Prostate cancer
Gleason 6
Active surveillance

ABSTRACT

**Objective:** To assess the management and oncological outcomes in men diagnosed with Gleason score (GS) 6 prostate cancer on needle biopsy in a regional centre, as compared with published international data.

**Materials and methods:** A retrospective analysis was conducted of patients who were diagnosed with GS 6 prostate cancer via transrectal ultrasound-guided or transperineal biopsy between June 2009 and September 2015 under the care of a single surgeon. Data were obtained from a prospectively collected database.

**Results:** A total of 166 patients were diagnosed with GS 6 prostate cancer. The mean age was 61 (range 46–79) years, with mean prostate-specific antigen of 6.7 (0.91–26.8) ng/mL at diagnosis. Of 166 patients, 117 (70.5%) patients were enrolled into the active surveillance program with 82 (70%) meeting Prostate Cancer Research International Active Surveillance (PRIAS) criteria, 44 patients underwent immediate definitive treatment (88.6% radical prostatectomy and 9.1% radiotherapy) and five watchful waiting. With a median follow-up of 1.8 years, 37 (31.6%) patients on AS had definitive treatment [30 cases (81%) were attributable to disease progression, 4 cases (10.8%) to an abnormal magnetic resonance imaging result and 3 cases (8.1%) for patient preference]. In the 35 patients who underwent radical prostatectomy immediately after diagnosis, the GS was ≥7 in 29 cases (82.9%), and the final pathology was pT3a in 16 (51.6%) and pT3b in one (2.9%). In patients who underwent radical prostatectomy after being on AS, the proportion of GS ≥7 prostate cancer was 29/32 (90.6%), with pT3a in six (18.8%) and pT3b in three (9.4%) cases. Overall, 23.5% of patients had a multiparametric magnetic resonance imaging scan.

**Conclusion:** This single-surgeon cohort of GS 6 prostate cancer patients demonstrates a high proportion of cases managed with active surveillance, with comparable rates to international literature. The majority of cases who underwent immediate definitive treatment had significant disease, indicating that patients are being appropriately selected for active surveillance.



## 1. Introduction

Gleason score (GS) 6 prostate cancer is generally considered low risk of morbidity and mortality; autopsy studies and cystoprostatectomy case series suggest that a significant proportion of males harbour G6PCa for years without symptoms.[1–3] The challenge of balancing the potential harms arising from over diagnosis of a largely benign disease, and the need to be vigilant for higher grades of prostate cancer has given rise to the era of active surveillance (AS).

There is increasing long-term evidence for AS for managing GS 6 prostate cancer with deferred curative treatment until there is disease progression. Seven major AS trials now demonstrate carefully selected low-risk prostate cancers can be successfully managed without curative intent, with 99.7% cancer-specific survival rates, from a combined cohort of more than 4,000 patients.[4–10] Furthermore, the recently published randomised ProtecT study showed that mortality from prostate cancer was low, irrespective of treatment modality or AS.[11] However, the efficacy of AS is limited by the accuracy of the investigations used in the selection protocols. With the advent of multiparametric magnetic

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http://dx.doi.org/10.1016/j.prnil.2017.03.007

resonance imaging (mpMRI) and fusion biopsies, the risk of inadequate sampling of prostate biopsies is likely to be significantly reduced,[12] and incorporation of these emerging diagnostic tools into selection criteria will improve the accuracy of patient selection into AS.

We report on our experience of patients who were diagnosed with GS 6 prostate cancer from prostate needle biopsy between June 2009 and September 2015, at the time when multiparametric prostate MRI was being introduced. All patients were under the care of a single surgeon in a nonmetropolitan centre, and we compare outcomes of management with data from national and literature.

## 2. Patients and methods

A 6-year retrospective study from 1 June 2009 to 30 September 2015 was undertaken. It was approved by the Central Coast Human Research and Ethics Committee (Ref no: 0314-019C). Patients were selected from a prospectively maintained database of patients under the care of a single surgeon. All men diagnosed with G6PCa on transrectal ultrasound (TRUS) or transperineal biopsy were included. All biopsies performed were saturation protocol (16–30 cores depending on prostate volume). Data collected included demographics, diagnostic biopsy and prostate-specific antigen (PSA) results, subsequent biopsy results, MRI reports where available and the results of final pathology if progressing to definitive surgical therapy. Patients who were lost to follow-up or care transferred were excluded from subsequent analysis.

### 2.1. Definitions

Disease progression reclassification on repeat needle biopsy was defined as significant increasing volume of disease or upstaging of GS on serial prostate biopsy. Insignificant disease at prostatectomy was defined as stage T2 or less, GS 6 or less, and less than 0.5 mL of tumour volume.

### 2.2. Data analysis

Data were analysed using GraphPad Prism 6.0 (GraphPad Software Inc., La Jolla, CA, USA). Continuous variables were analysed using the Student unpaired *t* test and categorical variables with Fisher's exact test, with a significance level set at 5% for all calculations.

## 3. Results

### 3.1. Patient demographics

A total of 166 patients were diagnosed with GS 6 prostate cancer via needle biopsy during the study period. The mean age at diagnosis was 61.2 (range 46.2–78.7) years, with mean PSA 6.7 (range 0.91–26.8) ng/mL, PSA density 0.2 (range 0.02–0.7) and TRUS prostate volume 48.5 (range 15–125) mL at diagnosis. Baseline characteristics of the AS and immediate therapy cohort are outlined in Table 1.

Of this cohort of patients, 117 (70.5%) patients were enrolled into the AS program ($n = 82$, 70% meeting Prostate Cancer Research International Active Surveillance (PRIAS) criteria), and 44 (27%) underwent immediate definitive treatment ($n = 4$, 9.1% meeting PRIAS criteria); 35 patients underwent radical prostatectomy (RP), four patients received radiotherapy, one patient was commenced on androgen deprivation therapy and five cases were suitable for watchful waiting.

### 3.2. Active surveillance

After enrolment in AS, the mean time until the first repeat biopsy was 103 days (standard deviation 30.2 days), and time between subsequent biopsies was 1.43 years (standard deviation 0.52 years).

Excluding nine patients who were lost to follow-up or whose care was transferred, 66 (61%) patients remain on AS with a median follow-up of 1.9 years (maximum 5.59 years). Thirty-seven (31.6%) patients progressed to definitive treatment after a median of 1.07 years (range 0.34–3.53) on surveillance. Of these, 30 cases (81%) treatment was precipitated by disease reclassification at repeat biopsy, four cases (10.8%) were attributable to an abnormal MRI and three patients (8.1%) elected treatment owing to anxiety (see Table 2). Five cases have crossed to watchful waiting (4.27%).

Excluding the nine cases lost or transferred, 44 (40.7%) patients on AS had disease reclassification on a subsequent biopsy; nine (20.5%) were reclassified on the basis of GS being upgraded, 17 (38.6%)% on the basis of increasing number of biopsy cores or maximum core involvement with cancer, and 18 (40.9%) met both of these criteria. Of patients who received an immediate confirmatory repeat biopsy at approximately 3 months, 18 cases (27.7%) were reclassified. The median time from diagnosis to reclassification was 1.28 years. Patients enrolled in AS who fell outside the PRIAS criteria were more likely to be reclassified on the basis of biopsy (57.6% vs. 30.6%) and in less time (median 1.11 years vs. 1.53 years) than PRIAS patients. In these 44 patients, 30 (68.2%) have undergone definitive treatment, and 14 patients (31.1%) remain on AS and are being further investigated with mpMRI.

### 3.3. Outcomes of treatment with RP

There were 35 patients who underwent RP immediately after diagnosis. The final GS was $\geq 7$ in 29 cases (82.9%), and extracapsular disease was present in 16 (51.6%) cases as pT3a, and one case (2.9%) as pT3b; eight cases with extracapsular extension also had a positive surgical margin. Two patients had insignificant disease on final pathology; one of these patients met the PRIAS criteria for enrolment into AS, but elected to have a laparoscopic RP performed.

There were 32 patients who underwent RP after being on AS, four patients met the PRIAS criteria for continued AS on repeat biopsy but instead progressed to RP; two of these elected definitive

**Table 1**
Patient characteristics at baseline (diagnosis)

| | Total ($n = 116$) | Active surveillance ($n = 117$) | Definitive therapy ($n = 49$) | *P* |
|---|---|---|---|---|
| | Mean ± SD | Mean ± SD | Mean ± SD | |
| Age (yr) | 61.2 ± 6.4 | 61.2 ± 6.4 | 61.8 ± 6.9 | 0.55 |
| PSA (ng/mL) | 6.8 ± 4.1 | 6.2 ± 3.0 | 8.1 ± 5.7 | <0.01 |
| Prostate volume (mL) | 48.4 ± 21.9 | 50.8 ± 23.1 | 43.1 ± 17.7 | 0.03 |
| PSA density (ng/mL/mL) | 0.16 ± 0.10 | 0.13 ± 0.06 | 0.21 ± 0.15 | <0.01 |

PSA, prostate-specific antigen; SD, standard deviation.

**Table 2**
Reasons for intervention on active surveillance

| Reason | *n* | % |
|---|---|---|
| Progression on biopsy | 30 | 77% |
| Abnormal mpMRI result (PIRADS ≥4) | 4 | 10% |
| Patient wish (without progression) | 5 | 13% |

mpMRI, multiparametric magnetic resonance imaging; PIRADS, Prostate Imaging Reporting and Data System.

treatment in the absence of disease progression, and two had PIRADS 5 disease with extracapsular extension on MRI. Median time to RP was 0.82 years (range 0.25–3.49). The proportion of GS ≥7 prostate cancer was higher in this cohort ($n = 29$, 90.9%) compared with upfront RP; however, a smaller percentage had extracapsular extension as six cases (18.8%) had pT3a pathology and three cases (9.4%) showed pT3b (total 10 cases, 30.3%); only four of these cases also had a positive surgical margin (refer to Table 3). Insignificant disease at final pathology was found in three patients in this group; one of these operations was performed at the patient's request, and two had their GS downgraded from their last biopsy. Patients who met the PRIAS criteria at enrolment were less likely to have positive surgical margins (7% vs. 22%) or extracapsular extension (21% vs. 33%).

### 3.4. Multiparametric MRI

mpMRI was used as a diagnostic aid in 39 of the G6PCa patients on AS. In 27 cases (69%) this investigation was unremarkable; however, in 11 cases (28.2%) an abnormal MRI result was noted (PIRADS ≥3). Extracapsular extension was reported in two (5.1%) cases. Seven patients who received an mpMRI have received definitive treatment (six RP, one radiotherapy), four of which were precipitated by an abnormal MRI. One patient showed disease progression on serial biopsy 12 months after a normal mpMRI, and subsequently underwent RP.

## 4. Discussion

AS is being used in a high proportion of our patients with GS 6 prostate cancer (70.5%). The majority of our patients on AS fulfilled the conservative PRIAS enrolment criteria (69.2%), with the remainder failing the volume criteria with more than two cores positive.

As the course of low-risk prostate cancer is protracted, and our cohort quite immature, the upstaging observed on repeat biopsies is likely attributable to misclassification of the initial biopsy, instead of true disease progression[13] in the time just prior to the introduction of mpMRI. Prior to the use of mpMRI, we performed a confirmatory biopsy at 3 months, to mitigate this risk of inadequate sampling inherent to systematic TRUS biopsies. Our median time to first biopsy was 103 days, compared with 1.1 years in the PRIAS trial.[13] We observed disease reclassification in 27.7% of men who had a confirmatory immediate repeat biopsy, which is a comparable figure to international literature.[14] Overall, disease reclassification was seen in 40.7% of the AS cohort, with a median time to reclassification of 1.28 years. Thus, early confirmatory biopsy detected disease misclassification in the majority of cases, and thus was able to trigger radical intervention in a more timely manner. With the use of mpMRI, immediate 3-month confirmatory biopsies are not performed, and then the next biopsy is a saturation at 12 months. In the PRIAS trial, 27% of the cohort experienced disease reclassification at repeat biopsy during follow-up, with a 1-year, 4-year, and 7-year repeat biopsy protocol.[13] As expected, patients who met the PRIAS criteria were less likely to have disease reclassification on serial biopsy and were more likely to persist on AS than patients who did not meet these criteria at enrolment.

In our cohort, radical therapy was triggered by disease reclassification on repeat biopsy or an abnormal MRI result in 87% of cases. Although some AS series strongly advocate using a PSA doubling time of less than 3 years as a marker for aggressive disease and thus a trigger for intervention,[5] it was not used in our cohort given the inaccuracies of PSA testing.[15]

It is agreed throughout the AS literature that favourable outcomes of surgery after progression are measured by high rates of organ-confined disease, low rates of extracapsular extension and positive surgical margins. In our study, patients receiving prostatectomy after initial management with AS showed more than 70% organ-confined disease at surgery. Compared to those treated with immediate prostatectomy, men undergoing delayed surgery were more likely to have positive GS 7 disease or higher, but were less likely to have extracapsular extension (49% vs. 19%, $P = 0.01$) and no more likely to have positive surgical margins (34% vs. 16%, $P = 0.09$) (Table 3), with similar findings reported in international literature.[16] This infers we are correctly selecting patients for immediate radical therapy. Compared with the PRIAS trial data, our rates of extracapsular extension in our delayed surgery cohort are inferior by approximately 10%; however, this is counterbalanced by our smaller rate of GS 6 disease on final pathology (47.3% vs. 9%), indicating that we are selecting more patients with significant disease for radical therapy.[15] Although low rates of positive surgical margins and extracapsular extension were seen in our cohort where strict enrolment criteria were met, recent evidence suggests that stricter AS criteria do not result in significantly better post-operative findings, with similar rates of biochemical recurrence seen after treatment.[17] Thus, our AS protocols are ensuring timely intervention in patients with significant disease, with the majority of patients treated with delayed surgery having organ-confined disease, and noninferior rates of extracapsular extension and positive surgical margins compared with immediate surgery.

Of our 117-patient AS cohort, four patients opted for radical therapy owing to anxiety. With this low rate of patients opting for radical therapies despite the absence of disease reclassification or progression, our data confirm published literature showing that with adequate counselling patients with low risk prostate cancer can live with low levels of anxiety.[18,19]

mpMRI was introduced as a diagnostic adjunct in our region in January 2013. Four patients have undergone radical therapy as the direct result of an abnormal mpMRI. We are increasingly using this investigation in our cohort after serial negative biopsies (21 patients, 55%) or as a second-line diagnostic investigation prior to repeat biopsy (17 patients, 45%). In addition, mpMRI is being utilised in our cohort in patients recently enrolled on AS that have

**Table 3**
Pathological findings in patients treated with radical prostatectomy (Gleason score 7a = 3 + 4, 7b = 4 + 3)

| | Total ($n = 67$) | Deferred (AS) ($n = 32$) | Immediate ($n = 35$) |
|---|---|---|---|
| T Stage | | | |
| T2 | 41 | 23 | 18 |
| T3a | 22 | 6 | 16 |
| ≥T3b | 4 | 3 | 1 |
| Gleason score | | | |
| ≤ 6 | 9 | 3 | 6 |
| 7a | 43 | 19 | 24 |
| ≥7b | 15 | 10 | 5 |
| Progression from last biopsy | | | |
| Downgrade | 2 | 2 | 0 |
| Same stage | 27 | 16 | 11 |
| Upgrade | 37 | 13 | 24 |

AS, active surveillance.

shown volume progression in the absence of GS upgrading. As mpMRI is further incorporated into our AS protocols and used with increasing frequency, we expect our rates of disease reclassification to fall significantly. Furthermore, in another analysis we have already demonstrated the increased accuracy of MRI fusion guided prostate needle biopsy as compared with standard prostate biopsy,[20] which concurs with international published literature,[12] and again expect this technique to improve our selection of patients into AS, and it has now become our preferred method of primary biopsy.

AS is being used in a high proportion of our patients diagnosed with GS 6 prostate cancer. Our rates of disease reclassification are comparable to international data. The majority of patients who underwent radical surgery after AS had significant disease that was organ confined, indicating that treatment is being triggered by our surveillance protocols in a timely manner. Disease misclassification in the pre-mpMRI era is likely to account for the higher proportion of patients progressing to definitive treatment from AS, seen early in our series, as compared with larger AS studies. Our future outcomes and data set maturation will be enhanced by refined selection criteria, increasing use of mpMRI fusion guided biopsy techniques, and this will likely improve the selection of appropriate patients for AS.

## Conflict of interest statement

The authors declared no conflict of interest.

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