Title:

Progression and treatment rates using an active surveillance protocol incorporating image guided baseline biopsies and multi-parametric MRI monitoring for men with favourable risk prostate cancer.

Running head:

Image-guided active surveillance in prostate cancer

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mpMRI

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ABSTRACT

Objective

To assess early outcomes since the introduction of an active surveillance (AS) protocol incorporating mpMRI guided baseline biopsies and image based surveillance.

Patients and Methods

A new AS protocol mandating image-guided baseline biopsies, annual mpMRI and 3 monthly PSA but which retained protocol re-biopsies was tested. Pathological progression, treatment conversion and triggers for non-protocol biopsy were recorded prospectively.

Results

Data from 157 men enrolled on this protocol (median: age 64years, PSA 6.8ng/ml, follow-up 39 months) was interrogated. 12 men (7.6%) left AS through patient choice. Of the 145 men who remained, 104 had re-biopsies either triggered by a PSA rise, MRI change or by protocol. Overall 23 men (15.8%) demonstrated disease progression; 20 from pathological changes and 3 from imaging changes. 17/23 of these switched to treatment giving a conversion rate of 11.7% (<4% per year). Of the 20 men with pathological progression 20% were detected from a PSA increase triggering a re-biopsy compared to 50% due to an mpMRI change. 30% however were detected solely from a protocol re-biopsy without prior PSA or MRI changes. Using PSA and MRI changes alone to detect progression demonstrated a sensitivity and specificity of 70.0% and 81.7% respectively.

Conclusion

An AS protocol with thorough baseline assessment and imaging based surveillance shows low rates of progression and treatment conversion. mpMRI changes were the principle trigger in detecting progression by imaging alone or pathologically. Protocol re-biopsy however still detected a significant number of pathological progressions without mpMRI or PSA changes.

Key Words

Active surveillance
Localised prostate cancer
Magnetic Resonance Imaging

Introduction

The incidence of low risk prostate cancer (LRPC) in the UK has grown rapidly in recent years with the increased uptake of PSA testing (1). Randomised trials have failed to show any disease-specific or overall survival benefit from treating men with LRPC by radical therapy in comparison to conservative management (2, 3). Therefore, the National Institute for Health and Care Excellence (NICE) and other guideline bodies have recommend active surveillance (AS) as a valid therapy option for men with LRPC (4). A number of studies have now reported excellent outcomes from AS, with systematic reviews concluding that AS is a safe and effective form of management (5, 6). Despite this, AS still has high early attrition rates and there is significant debate on the optimal follow up regime (7-9).

Multi-parametric MR imaging (mpMRI) is now an essential tool in initial staging as well as tumour identification (8). It is also now well recognised that many cancers are misclassified on first biopsy and repeat sampling can result in upgrading in up to 35% of cases amongst non-targeted cohorts (10, 11). mpMRI has therefore become an important tool in appropriate baseline selection for AS and in its follow-up (12-14). However, the optimal imaging schedule for mpMRI during surveillance is yet to be defined, with current UK 2014 guidelines only advising mpMRI at AS enrolment, without defining a protocol for subsequent scans (4).

Current unanswered questions in AS management are therefore whether (i) mpMRI-improved baseline risk stratification provides clinical benefit in reducing treatment conversion rates and (ii) how effective is mpMRI in detecting progressions and could this negate the need for routine protocol re-biopsies. To address these gaps in the knowledge we trialled a new AS protocol in our unit in 2011 which mandated early biopsy re-assessment and annual mpMRI. To comprehensively assess the pathological progression rates, we included image guided and systematic biopsies at the outset and in subsequent scheduled interval re-biopsies. Here we report on the early outcomes of this protocol.

Patients and Methods

Study cohort

Newly diagnosed patients selecting AS as preferred management were recruited from 2011 onwards into a prospective study in our institution (Cambridge University Hospital Trust, Cambridge, UK; Registration Number: 3592). Eligibility was restricted to men aged 50-80 years with histologically proven prostate adenocarcinoma, clinical stage T1-T2, PSA≤20ng/ml, histological grade group ≤2, <50% overall tumour core involvement and otherwise medically fit for radical treatment options (ECOG status 0 or 1). All men were treatment naïve with a first diagnosis of cancer. Our standard diagnostic pathway during the study period was 12-core sectoral trans-rectal prostate biopsy. A baseline mpMRI was performed at AS entry with the mpMRI used to guide a subsequent early transperineal re-biopsy performed using image-fusion software as previously reported (15). Where no lesion was identified standard sectoral biopsies were performed. The only exceptions were men who had already had previous negative biopsies and those first diagnosed using a transperineal image-fusion method (Table 1). Identification of higher risk tumours from an early re-biopsy mandated assignment to treatment unless the patient was very keen to remain on AS. For the purposes of this study, only men with a minimum of 12 months clinical follow-up were included.

AS follow up

Following baseline assessment as above, the protocol incorporated: 3-monthly PSA testing, annual repeat mpMRI and scheduled protocol interval re-biopsy at 12 months after completing baseline assessment and then at year 3. Outpatient review was performed annually (Figure 1). 3 consecutive PSA rises or a reported change in mpMRI (increase in number of lesions, lesion size, or stage progression) triggered an earlier targeted image–fusion re-biopsy. 2 cores were taken of target lesions in addition to 2 cores taken from each of 12 anatomical sectors(15). Progression on AS was defined as pathological progression on a re-biopsy or progression on MRI from T2 to T3. Pathological progression was defined as a Grade Group increase between diagnostic and repeat biopsy. In all cases of progression, on-going participation in AS or conversion to treatment was re-discussed.

Magnetic Resonance Imaging

All mpMRI were performed on a 3T Discovery MR750-HDx or 1.5T MR450 system (GE Healthcare, Waukesha, USA) with a surface phased-array coil, including standard anatomical and functional diffusion-weighted imaging using multiple b-values, as previously described (16). Images were reported by expert uro-radiologists and reviewed in a multi-disciplinary team (MDT) setting. A reported lesion (score of ≥3 on a Likert scale) of any size on baseline imaging was considered an MRI positive lesion for the purposes of subsequent analysis. This study predated the PRECISE grading criteria, however, for consistency a 5-point Likert scale was prospectively used throughout the study period, informed by PIRADS versions 1 and 2 following their publication with a score ≥3 considered suspicious (17, 18). For the purposes of robust assessment of this protocol re-biopsies were done by transperineal biopsies with image guided and systematic biopsies when suspicious lesions were present on MRI. Those with no mpMRI lesion had systematic biopsies only (transperineal or transrectal) . All mpMRI changes and re-biopsy results were reviewed and discussed in multi-disciplinary meetings before triggering a change in the AS pathway.

Statistical analysis

The measured outcomes were patient adherence to AS, pathological progression and rates of conversion to treatment. The ability of PSA and mpMRI changes to detect all progression events was compared to the outcome from protocol interval re-biopsies (considered the reference standard for this study). Data from men who were scheduled protocol re-biopsies but declined the procedure were kept in the analysis to allow overall assessment of progression. Kaplan Meier curves were used to describe treatment-free and progression-free survival outcomes. Time was measured from date of enrolment to AS, and censored at date of last follow-up. Cox regression analyses were performed to calculate hazard ratios with 95% confidence intervals (CI) to explore predictors of time to progression and conversion to treatment. All available clinical variables were included in a first pass analysis. P values <0.05 were considered significant. As no variables showed significant association this was not developed further. Statistical analysis was performed in Stata 14 (Texas, USA).

Results

Baseline cohort characteristics

157 men were managed using this protocol and met minimum follow up criteria (Figure 2). Of these men only 12 (7.6%) dropped out from AS through patient choice. The baseline cohort characteristics of the remaining 145 men are shown in Table 1. The median age, PSA and follow-up was 64 years, 6.8ng/ml and 39 months, respectively. 95/145 men (65.5%) had low-risk disease by the 2014 NICE risk criteria, 124 (85.5%) had Grade Group 1 (Gleason 6) disease and 135 (93.1%) had cT1 disease. Over half of the cohort (55.2%) was identified as having a lesion on baseline mpMRI. There were 2 deaths within the cohort, neither attributable to prostate cancer. 104/145 men had a repeat biopsy episode during surveillance, with 116 repeat biopsies performed in total. In 29/116 (25.0%) cases this was triggered by mpMRI or PSA changes with the remaining 87 performed as protocol re-biopsies (Table 2). 41 men declined any repeat further re-biopsies.

Pathological progression and conversion to treatment

Of the 145 men who stayed on AS, 23 men progressed over the median follow-up of 39 months equating to an overall progression rate of 15.9%. In 20 this was due to a pathological upgrade following either a protocol or triggered re-biopsy. Three additional patients with known Grade Group 2 disease had stage progression from T2 to T3 on mpMRI and converted to radiotherapy treatment without repeat biopsy or further evaluable histology. Details of these men are shown in Table 3. If we consider pathological progression only amongst those who underwent further re-biopsies within our study, the progression rate is 19.2%. 17/23 men with progression chose to convert to active treatment, and 6 others with only Grade Group changes elected to stay on AS. This resulted in an annual conversion rate of under 4% per year, Only 5 men converted to treatment within the first 24 months equating to an overall treatment-free survival of 96.6% at 2 years.

Amongst the 20 men with pathological progression, 6 (30%) were detected by interval protocol re-biopsy with no prior increase in PSA or change in mpMRI characteristics. mpMRI changes, prompting a non-protocol biopsy, accounted for half of detected upgrading (n=10, 50%). Of note

however, in 10 further men, changes in mpMRI triggered a re-biopsy yet did not identify disease upgrading. Eight of these were found to have disease of the same grade on re-biopsy whereas the remaining 2 men had benign biopsies. In all these cases the PSA values were not significantly altered and would not in themselves have triggered a re-biopsy. Only 4 (20%) men were upgraded following changes in PSA alone triggering a re-biopsy. Of note, PSA changes did also trigger an additional 5 re-biopsies where no upgrade in tumour was detected. Of these, 1 biopsy remained Grade Group 1 and the rest were benign biopsies. Using mpMRI and PSA changes as the sole triggers for re-biopsy would therefore have detected 14/20 (70%) progressions, missed 6 (30%) and resulted in 15 additional biopsy procedures which failed to show pathological progression. Table 4 shows the sensitivity, specificity and predictive values of this approach, amongst only those men who underwent repeat biopsies (n=104). The sensitivity and specificity of using mpMRI and PSA was 70% and 81.7% respectively. Of the 17 men who converted to active treatment, 2 (8.7%) underwent robot-assisted laparoscopic prostatectomy. The remaining 15 men opted for radiotherapy and/or androgen deprivation therapy alone.

Subgroup analysis was performed on the 10 men diagnosed with pathological progression following MRI changes. In 5/10 cases upgrades were from MRI-defined targeted areas, in 2/10 cases although the targeted biopsy was unchanged/negative an upgrade was found in an adjacent sector. In the remaining 3 cases upgrades were in areas remote from the target.

The association between different variables and AS progression are shown in Supplementary Tables S1A and S1B. Prior negative biopsy before diagnosis demonstrated a non-significant trend to lower rates of AS progression in both univariate (HR 0.40; 95%CI 0.15-1.08 p=0.07) and multivariate analysis (HR 0.37; 0.13-1.07 p=0.06).

Discussion

We present here early outcomes from a prospectively applied structured AS regimen incorporating image-guided baseline risk assessment and mpMRI based follow-up. Conversion to treatment through patient choice in this study was 7.6% over a median 3.3 years of follow up. This compares very favourably to published drop-out rates of up to 36% over similar follow-up periods in other contemporary series (19). Only 11.7% of men in our series converted to treatment during AS. Over comparable follow-up periods, 33% converted to treatment in the Johns Hopkins Series (median follow-up 2.7 years) (20), 25% in the University of Miami series (2.9 years median follow-up)(21), 32% in the ERSPC series (3.9 years follow-up)(22), and in the largest published UK series 20% of men in the Royal Marsden series converted to treatment over just 1.8 years follow-up(23). Of note, these series did not include baseline MRI risk-stratification. These differences may be explained by stricter baseline assessment prior to inclusion in our series, with more conversions to treatment following early reclassification in older series. A number of publications have previously demonstrated that image-guided biopsies by any route are good at detecting disease, including in the context of selecting men for AS (24-26).

One of our key questions was how good mpMRI was in detecting pathological progression as a non-invasive monitoring tool. This was referenced against a comprehensive baseline biopsy assessment and using the same assessment in interval re-biopsies. In our cohort this was evaluable in the 104 men who did have a repeat biopsy either through the protocol or when triggered by a PSA rise or mpMRI change. This detected 20 pathological progressions. 50% of these were first detected by an MRI change and then confirmed on biopsies without a concomitant alteration in PSA levels. In this respect mpMRI proved very good at detecting changes translating into a disease upgrade. However a number of reported changes in mpMRI did not show pathological upgrading on re-biopsy and this affected the overall sensitivity and specificity of imaging as a stand alone AS tool (Table 3). This may of course be due to biopsy sampling errors and will likely improve with evolving MRI protocols and better hardware and software (15, 27). Our recent adoption (in 2016) of the standardised PRECISE reporting tool, for example, may also improve future consistency in reporting (17). For the present though our data supports the conclusions from a recent systematic review which suggests that mpMRI change should not itself drive a change to treatment but instead trigger re-biopsy because of the possibility that there is

no true pathological change (14). Whether rebiopsy in this context should be targeted alone, 'saturation target', or systematic
and targeted is another unanswered question in AS follow-up. Amongst our small subcohort of 10 men with pathological progression following mpMRI-changes, only 5 upgrades were detected on targeted cores, with upgrade detected in areas remote from the target in 3 cases. Further study is required in this area but these results may suggest a combination of systematic and targeted cores is necessary, as is generally accepted at primary biopsy(28).
Our data does raise the possibility that mpMRI based surveillance might result in more re-biopsies than a programme that relied only on PSA changes to trigger reinvestigation, particularly in centres where MRI reading and reporting is evolving. PSA changes alone found upgrading in 4 men in our cohort but also led to a similar number having biopsies with no change in pathology.

Nearly a third of pathological progressions were detected by scheduled protocol biopsies without evidence of an mpMRI or PSA change. This echoes the recent findings of Ma *et al* from Johns Hopkins who reviewed the results of 157 men who had template and systematic biopsies within an AS programme, and concluded that systematic re-biopsies were still needed in AS given the relatively low sensitivity of mpMRI in this context(29). Further work is needed in larger multi-centre trials to determine the true benefit and impact of mpMRI use in AS pathways before widespread adoption in national guidelines. For the present, our data suggest that PSA tests, mpMRI and protocol re-biopsy are all important contributing parts of an AS programme to detect early pathological progression. The importance of detecting early grade progression is of course debatable as is the significance of detecting increased core involvement or core positivity. There is no current national or international standard on this and grade progression remains a key marker of progression in AS(30).

One significant factor in our study is that a number of men declined invitation for scheduled interval re-biopsies during AS. In clinic consultations we found that many men take great reassurance from an unchanged annual mpMRI and stable PSA. This further reinforces the need for future research to embed standardised mpMRI reporting and assess how safe it is to omit protocol biopsies as routine practice.

As our cohort size was relatively small and with a short follow up, it is perhaps unsurprising that

we failed to find many predictors of progression or conversion to treatment. Neither a positive mpMRI lesion nor an initial Grade Group 2 diagnosis predicted progression or conversion to active treatment which is in contrast to other studies (31-33). We did observe that men with a prior negative biopsy appeared less likely to progress which supports the findings of a recent large Danish study that reported extremely low rates of prostate cancer mortality (0.7-3.6%) from a retrospective database review of men with first negative biopsies over a 20 year follow up period, underscoring the indolent nature of many of these tumours (34).

There are limitations to our study. Compliance to our re-biopsy protocol was incomplete, with a number of men not undergoing any additional biopsies within our follow-up period. Compliance with AS protocols however is known to be a universal problem in the published literature. In the PRIAS study for instance only 30% of men were still compliant to the protocol after 4 years of AS (35). This was attributed to compliance issues from both patients and clinicians (35). Our study also had relatively short follow up and we cannot say if our protocol will materially alter survival rates. Indeed this is an unknown factor in almost all contemporary AS protocols. As mentioned, our imaging reports did not include standardised reporting until 2016 and we are continuing to review if this will impact on triggers for re-biopsy. Re-biopsies did use an image guided fusion approach but there remains a possibility of sampling errors. Our protocol is also investigation heavy in that men had annual MRI and image-guided and systematic biopsies. Therefore we do not claim that this should be the adopted standard, instead we have used this protocol to test the value of MRI at baseline and in follow up to inform future safer and less intensive regimens. Future work to verify our findings, and to further refine the protocol (extending mpMRI and biopsy intervals) are currently underway. Finally, as this was not a clinical trial, we did not mandate central review or double reading of imaging or biopsies. All results were however discussed in team multi-disciplinary meetings thus reflecting real world practice.

Conclusions

In summary we report here the early outcomes of a structured AS protocol using mpMRI as a surveillance tool after thorough image-guided baseline assessment in men with favourable risk disease. Our data suggests low patient choice drop-out rates and treatment conversions in men optimally selected for AS. mpMRI is the primary trigger for detecting disease progression on re-biopsy but can miss some pathological progressions, suggesting that protocol re-biopsy should not

yet be abandoned. Our results justify the need for multi-centre trials to assess the true impact of an image based AS protocol with regards to clinical and patient benefit and with respect to health economic implications amongst men with favourable risk prostate cancer. This is particularly important as clinicians and patients are already increasingly using imaging as a primary surveillance tool.

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Conflict of Interests Statement

The authors all certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

Legends to figures

Figure 1:

The study active surveillance protocol, represented on a vertical timeline.

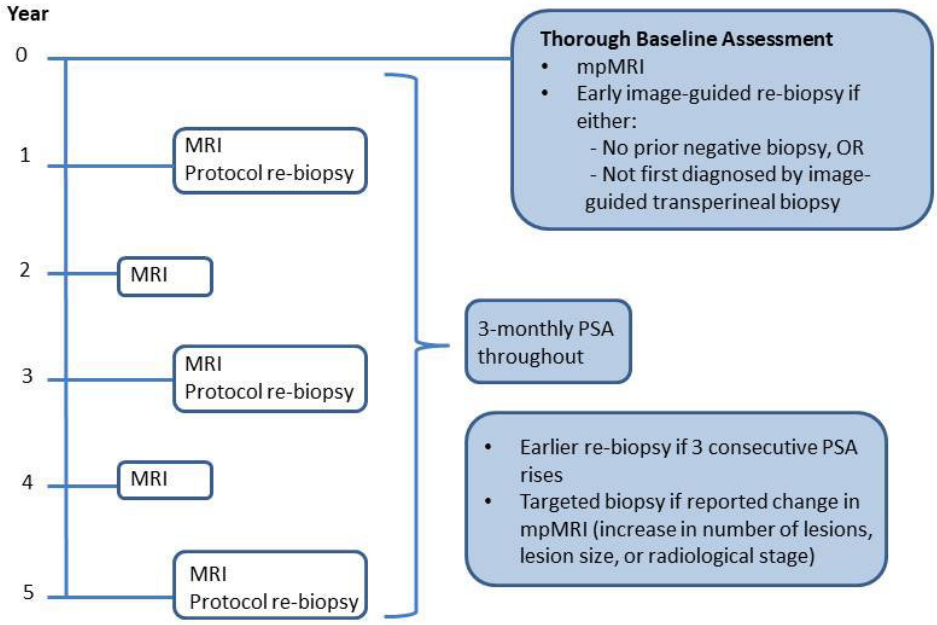

Figure 2: Flow chart of patients recruited to Active Surveillance at CUH between 2011 and 2015.

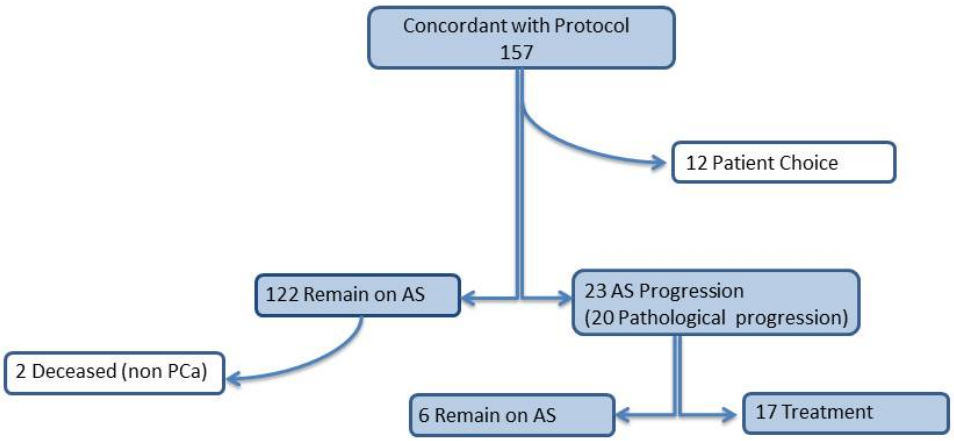

Table 1. Baseline Cohort Information for men within the AS study cohort from 2011 to 2015(n=145).

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	Median	**IQR**	**Range**	**Unit**
Age	64	59-68	44-79	Years
PSA	6.8	5.2-9.4	0.54-18.4	ng/ml
PSA Density	0.13	0.09-0.18	0.02-0.42	ng/ml/cc
Follow-up	39	27-51	15-63	Months
	N	**%**		
Grade Group 1	124	85.5		
Grade Group 2	21	14.5		
cT1	135	93.1		
cT2	6	4.1		
cT Unknown	4	2.8		
MRI Lesion (at baseline)	80	55.2		
No MRI Lesion	65	44.8		
NICE Low Risk Group	95	65.5		
NICE Intermediate Risk	50	34.4		