SELECTION AND MANAGEMENT OF MEN FOR ACTIVE SURVEILLANCE IN LOW RISK PROSTATE CANCER

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Abstract

Aims:
To investigate:

1. Selection of men for active surveillance of prostate cancer
   a. Validation of risk calculators
   b. Suitability for inclusion of Gleason 3+4 disease.

2. Performance of prostate biopsy during AS
   a. Differences in quality of diagnostic biopsy between academic and referral centres.
   b. Optimization of biopsy templates
   c. Examination of prognostic indicators for disease progression

Methods:

Data were obtained from several difference sources:

- Men suitable for AS on prostate biopsy but undergoing upfront radical prostatectomy were pooled from 3 international academic institutions in Cambridge (UK), Toronto (Canada) and Melbourne (Australia).
- Prospectively maintained AS prostate cancer database at Princess Margaret Cancer Centre (PMCC) (1997-2012).

Analyses performed:

- Four risk calculators were assessed for their ability to predict different definitions of insignificant prostate cancer by area under the curve (AUC) of receiver operating characteristic curves and Brier scores for discrimination, calibration curves and decision curve analysis.
Men with biopsy Gleason 3+4 disease, suitable according to modified Royal Marsden, Sunnybrook Toronto and PRIAS selection criteria, were assessed for presence of adverse pathology at upfront radical prostatectomy.

Patients on AS at a tertiary referral centre (PMCC) were dichotomized depending on where their diagnostic biopsy was performed (interval versus external). Multivariate logistic regression was performed to examine for predictors of re-classification at the second, or confirmatory, biopsy.

Mapping of all patients with pathological progression at PMCC for location of disease progression enabled comparison of hypothetical biopsy templates (sextant and standard extended) to the institutional template used.

Men on AS at PMCC were evaluated for presence of disease progression at serial biopsy in the prostate transition zone (TZ). Multivariate Cox proportional hazards regression evaluated predictors of TZ progression.

At PMCC, men were dichotomized based on presence of cancer at their confirmatory biopsy. Pathological progression was investigated using a Cox proportional hazards regression model.

Results

All 4 models predicting presence of insignificant prostate cancer had weak discrimination at best (AUC 0.618-0.664).

Presence of Gleason 3+4 at biopsy, compared to 3+3 disease, increases risk of adverse pathology at radical prostatectomy if modified Sunnybrook Toronto criteria are used (19% versus 33%, p≤0.001). Using
a stricter protocol such as PRIAS, there was no statistical difference between the groups.

- External biopsy predicted both grade related re-classification (OR 4.14, C.I. 2.01-8.54, p<0.001) and volume related re-classification (OR 3.43, C.I. 1.87-6.25, p<0.001).
- Sextant and standard extended biopsy templates were inferior to the institutional biopsy template in detecting presence of cancer (84% and 99% versus 100%), and pathological progression (47.9% and 81.9% versus 100%).
- At each subsequent biopsy during AS, 2.7-6.7% of men had disease progression only in the TZ which would not have been detected if TZ biopsy was not performed. Predictors of TZ progression were maximum % single core (HR 1.99, C.I. 1.30-3.04, p=0.002), and MRI reporting cancer (HR 3.19, C.I. 1.23-8.27, p=0.02).
- Men with no cancer at confirmatory biopsy were less likely to have pathological progression (HR 0.47, CI 0.29-0.77, p=0.003). Sub-analysis showed this was predictive of volume-related progression (HR=0.36, CI 0.20-0.62, p=0.0006) and not grade-related progression.

Conclusions

- Utilization of models predicting suitability for AS should be used with caution as external validation in our cohort was weak.
- If considering biopsy Gleason 3+4 disease for AS, a stricter protocol such as PRIAS must be utilized.
• At PMCC, patients who had their initial diagnostic prostate biopsy for AS done externally, were more likely to have worse pathological features and re-classify on the second biopsy.

• For men on AS, sextant and standard extended biopsy are less likely to detect prostate cancer or disease progression than the template used at PMCC.

• TZ biopsy should be considered for all men having serial biopsy on AS, in particular those with high % core involvement or positive MRI findings.

• Absence of cancer on B2 is associated with a significantly decreased risk of volume-related but not grade-related progression.
Author’s Declaration

This is to certify that:

i) the thesis comprises only my original work towards the Doctor of Medical Science, except where indicated in the Preface

ii) due acknowledgement has been made in the text to all other material used

iii) the thesis is below the maximum word limit in length, exclusive of tables, figures, bibliographies and appendices.

Signature:

[Signature]

Lih-Ming Wong
**Preface and Acknowledgements**

Multi-author published work is included in this thesis for which I declare that I contributed >50% of the content of the work, and am the “primary author”. Writing of the initial draft, and subsequent editing in response to collaborators and editors, was performed by myself.

Publications already published are included as Portable Document Format (PDF) in the thesis. Chapter 5 is presented as a regular thesis chapter as it has been accepted for publication but is not available electronically yet. Work included in the Discussion contains content from an invited literature review on “Active Surveillance for prostate cancer and small renal masses: New evidences and criticisms” of the journal Anti-Cancer Agents in Medicinal Chemistry (ISSN: 1871-5206). This manuscript is still currently with the editor and awaiting peer review at time of printing of this thesis.

The co-authors for all publications are listed in each chapter. In particularly, I would like to acknowledge the contribution of others who actively collaborated in various work as below:

**Acquisition of data** – The robotic assisted radical prostatectomy database at Addenbrookes Hospital was commenced by Dr Naomi Sharma, updated by Dr Richard Johnston and myself in 2010-2011, with further update in 2013 by Dr Benjamin Thomas. Dr Niall Corcoran, my principle collaborator for work presented in chapter 4, had access to the prostatectomy databases from the
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**Analysis and Interpretation of data** – I am grateful for the assistance of Mr Narhari Timilshina, Dr Niall Corcoran and Dr Shabbir Alibhai who assisted me with statistical analysis and interpretation of the data in chapters 4-9.

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Austin Hospital, Melbourne.

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St. Vincent’s Hospital Melbourne.

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These studies were performed with institutional research and ethics review board approval.
Communications and Awards arising from this Thesis

Communications published during the research period of this thesis (included as chapters 4 to 9 in the thesis).

Evaluation of models predicting insignificant prostate cancer to select men for active surveillance of prostate cancer.
Prostate cancer and prostatic diseases. Epub 2015/2/10
doi:10.1038/pcan.2015.1

Wong L-M, Tang V, Peters J, Costello A, Corcoran NM
Feasibility for active surveillance in biopsy Gleason 3+4 prostate cancer: an Australian radical prostatectomy cohort

doi:10.1038/pcan.2014.48

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http://dx.doi.org/10.1016/j.eururo.2013.04.038
Chapters 4 and 5 are presented in raw Microsoft Word format as whilst accepted for publication, electronic versions are not yet available. Chapters 6 to 9 are presented in images of the publications.

**Other communications published during the research period of this thesis (related to this thesis, included in Appendix B).**

Eur Urol 2013 Aug;64(2):343
[http://dx.doi.org/10.1016/j.eururo.2013.04.018](http://dx.doi.org/10.1016/j.eururo.2013.04.018)

Toren P, Wong LM, Timilshina N, Alibhai SMH, Trachtenberg J, Fleschner NE, Finelli A. 
Active surveillance in patients with a PSA >10ng/ml. 
*Can Urol Assoc J*, 2014; 8(9-10). 
doi: 10.5489/cuaj.2121.

Chang MD, Davidson AJ, De Fontgalland D, Johnson D, Sutherland T, Wong LM 
An unusual general surgical presentation of advanced prostate cancer – a case for PSA testing in the unwell elderly man. 
ANZ Journal of Surgery. Article first published online: 12 NOV 2014 
Doi: 10.1111/ans.12917

An Increase in Gleason 6 Tumor Volume While on Active Surveillance Portends a Greater Risk of Grade Reclassification with Further Followup 
Journal of Urology. Article in Press (1/1/2016) 
[http://dx.doi.org/10.1016/j.juro.2015.09.081](http://dx.doi.org/10.1016/j.juro.2015.09.081)
Peer reviewed presentations and prizes arising from this thesis.

Prizes:
European Association of Urology Annual Congress, Milan. 2013
Best Poster, Poster Session 23

The significance of finding no prostate cancer on the active surveillance confirmatory biopsy: Implications for pathological re-classification.

Society of Urologic Oncology Annual Meeting, Bethesda.
3rd prize, Friday poster session

Active Surveillance: predictors of pathological re-classification on the second prostatic biopsy.

Presentations:

2015
• Prostate Cancer World Congress
• Societe International d’Urologie Annual Meeting

Wong L-M, Tang V, Peters J, Costello A, Corcoran NM
Feasibility for active surveillance in biopsy Gleason 3+4 prostate cancer: an Australian radical prostatectomy cohort

2014
• Asia Pacific Prostate Cancer Conference

Evaluation of models predicting insignificant prostate cancer to select men for active surveillance of prostate cancer.

2013
• European Association of Urology Annual Congress, Milan.
The significance of finding no prostate cancer on the active surveillance confirmatory biopsy: Implications for pathological re-classification.

• American Urologic Association Annual Meeting, San Diego.

External Diagnostic Prostate Biopsy In Active Surveillance: A Predictor Of Reclassification On Confirmatory Biopsy.


Active surveillance prostate re-biopsy schema: results of routine transition zone biopsies.


The significance of finding no prostate cancer on the Active Surveillance confirmatory biopsy: Implications for pathological re-classification.

Torrren P, Wong L, Timilshina N, Finelli A.

Outcomes Following Active Surveillance in Prostate Cancer Patients with a PSA >10.

- Canadian Urologic Association Annual Meeting, Niagara Falls.


The significance of finding no prostate cancer on the active surveillance confirmatory biopsy: Implications for pathological re-classification.


External Diagnostic Prostate Biopsy In Active Surveillance: A Predictor Of Reclassification On Confirmatory Biopsy.

2012

- American Urologic Association Annual Meeting, Atlanta.


Active Surveillance: predictors of pathological re-classification on the second prostatic biopsy.

- Society of Urologic Oncology Annual Meeting, Bethesda.


Active Surveillance: predictors of pathological re-classification on the second prostatic biopsy.
Canadian Urologic Association Annual Meeting, Banff.


Ultra-extended prostate biopsy improves detection of pathologic progression in patients on active surveillance for prostate cancer.
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CHAPTER 1: General Introduction And Background – Prostate Cancer

Prostate cancer epidemiology

In Australia, prostate cancer was the most common cancer diagnosed (excluding non-melanoma skin cancer) in 2011. It is projected, at 17,250 new cases, it will remain the most commonly diagnosed cancer in 2015. The risk of a male being diagnosed with prostate cancer by their 85th birthday is estimated to be 1 in 7 (Australian Institute of Health and Welfare Canberra, 2015b). In 2012, it was the 2nd most common cause of cancer deaths (Australian Institute of Health and Welfare Canberra, 2015a). In 2015, it is estimated the risk of a male dying from prostate cancer by their 85th birthday will be 1 in 28. The trend in incidence rates for prostate cancer has steadily increased between 1982-2011 (Australian Institute of Health and Welfare Canberra, 2015b). The number of deaths has increased from 963 (1968) to 3079 (2012). Over the same period, the age-standardised mortality rate decreased 36 deaths per 100,000 males to 28 deaths per 100,000 males (Fig 1-1). In 2013, prostate cancer was the 6th leading cause of male deaths (3,112), ranked similarly to breast cancer in women (2,862 female deaths). Whilst heart disease was the leading cause of death in Australia, overall, cancer deaths outnumbered circulatory disease for the first time in the 2013 report from the Australian Bureau of Statistics (Australian Bureau of Statistics, 2015).
The incidence of prostate cancer in Australia reflects utilization of prostate specific antigen (PSA) testing. Similar to other countries with higher uptake of PSA screening, such as Canada and United States of America (USA) (Baade, Youlden and Krnjacki, 2009), rates of prostate cancer detection in Australia increased dramatically in the 1990s followed by a decline due to fewer prevalent cases. In contrast, in countries with slower adoption of PSA screening, such as the United Kingdom and Denmark (Kvale et al., 2007), incidence shows a steady increase (Fig 1-2). The SEER (Surveillance, Epidemiology and End Results Program) database, shown as a comparison in Fig 1-2, is a population database from the United States (U.S.). Hence the shape of the incidence curve is similar to Australia’s (Fig 1-1) with spike in incidence in the 1990s.
Fig 1-2 Prostate Cancer incidence and mortality in 5 Nordic countries (1945-2005).

Source: Interpreting Trends in Prostate Cancer Incidence and Mortality in the Five Nordic Countries, Kvale et al.

Trends in death rates from prostate cancer, in recent years, have declined in developed countries (Fig 1-1, 1-2). Improvements in treatments with curative intent (Baade, Youlden and Krnjacki, 2009; Kvale et al., 2007) are accepted reasons for this. Screening for prostate cancer, using serum prostate specific antigen (PSA), is also likely to have a role in reduction of prostate cancer related mortality (Schröder et al., 2014) but this remains controversial.
Risk factors for prostate cancer

The pathogenesis of prostate cancer is complex and multi-factorial. There are few established risk factors and many postulated ones.

Age:
Increasing age is a well-accepted risk factor for prostate cancer. It is rare for men under the age of 40 to be diagnosed but the probability for a man to be diagnosed with prostate cancer by the age of 85 is 1 in 7 (14.3%) in Australia (Australian Institute of Health and Welfare Canberra, 2015b). The difference in estimates for diagnosis of prostate cancer (1 in 7) and risk of dying from prostate cancer (1 in 28) by the age of 85, demonstrates many men are living with their prostate cancer and dying of other causes. This difference in incidence and cancer-specific mortality is further highlighted by autopsy data. The probability of prostate cancer found at autopsy has revealed histological evidence of prostate cancer in up to 10% of men aged 20 (Sakr et al., 1993) and 80% in 71-79 year olds (Table 1-1)(Haas et al., 2008). This information illustrates how common prostate cancer is in the community but also emphasizes the indolent natural history of many with the disease.

Family history:
Men with a positive family history of first-degree relatives are at increased risk of developing prostate cancer. A genetic component is suggested by twin studies. Concordance for prostate cancer was substantially higher among monozygous twin pairs, 27.1%, than among dizygous twin pairs, 7.1% (Page et al., 1997). A large Swedish population database of 11.8 million people examined the risks of
incident of diagnosis and death from prostate cancer, defined by number of affected family members (Brandt et al., 2010). The study included 26,651 men with prostate cancer, of which 5623 were familial. Younger age of diagnosis, along with number of first-degree relatives, and brother over father were associated with increased risk of diagnosis (Table 1-2).

Table 1-1: Autopsy prevalence of prostate cancer in the world

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>US White (%)</th>
<th>US Black (%)</th>
<th>Japan (%)</th>
<th>Spain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21-30</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>31-40</td>
<td>31</td>
<td>31</td>
<td>20</td>
<td>9</td>
</tr>
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<td>41-50</td>
<td>37</td>
<td>43</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>51-60</td>
<td>44</td>
<td>46</td>
<td>22</td>
<td>24</td>
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<td>61-70</td>
<td>65</td>
<td>70</td>
<td>35</td>
<td>32</td>
</tr>
<tr>
<td>71-80</td>
<td>83</td>
<td>81</td>
<td>41</td>
<td>33</td>
</tr>
<tr>
<td>81-90</td>
<td></td>
<td></td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>

Table 1-2: Hazard ratios of diagnosis with prostate cancer according to number and type of affected first degree relatives.

<table>
<thead>
<tr>
<th>Affected relatives</th>
<th>n</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>21028</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father only</td>
<td>3636</td>
<td>2.12</td>
<td>2.05-2.20</td>
</tr>
<tr>
<td>Brother only</td>
<td>1377</td>
<td>2.96</td>
<td>2.80-3.13</td>
</tr>
<tr>
<td>Father and one brother</td>
<td>402</td>
<td>5.51</td>
<td>5.00-6.09</td>
</tr>
<tr>
<td>Two brothers</td>
<td>144</td>
<td>7.71</td>
<td>6.54-9.08</td>
</tr>
<tr>
<td>Father and two brothers</td>
<td>36</td>
<td>8.51</td>
<td>6.13-11.80</td>
</tr>
<tr>
<td>Three brothers</td>
<td>28</td>
<td>17.74</td>
<td>12.26-25.67</td>
</tr>
</tbody>
</table>

Adapted from: Brandt et al, Age-Specific Risk of Incident Prostate Cancer and Risk of Death from Prostate Cancer Defined by the Number of Affected Family Members. (Brandt et al., 2010)

Although familial clustering of PCa is well established, no single high-risk susceptibility or “causal” gene has been found. Genome wide scans recently identified common variants associated with an increased risk; the genotype relative risks of these variants were typically small. Although these variants might explain a large proportion of the overall PCa susceptibility, they explain only a small proportion of the observed familial excess risks. Whilst this small proportion of men (5-10%) will have dominantly inherited susceptibility genes with high penetrance, they are estimated to contribute 30-40% of early onset
disease (Bratt, 2002). Hereditary prostate cancer is diagnosed on average 6-7 years earlier than sporadic disease but otherwise clinically behaves like the sporadic form.

Whilst no single gene has been demonstrated to definitively cause cancer, several genes (such as HPC-1, BRCA 1 and BRCA 2) have been shown to occur more frequently in men with prostate cancer. The BRCA2 gene has had some publicity with the first man to receive a prophylactic prostatectomy due to the perceived increased risk (Chustecka, 2013). It is a tumour suppressor gene, with autosomal dominant inheritance with incomplete penetrance. It is seen in men with family history’s of breast and ovarian cancer. It is estimated the BRCA2 gene only affects 1.2% of men with prostate cancer but germ line mutations are thought to confer a 8.6 fold increased risk of prostate cancer in men ≤ 65 years. This is greater than the BRCA1 gene (present in 0.44% of cases, increased risk 3.4-fold) (Breast Cancer Linkage Consortium, 1999). Studies do suggest however, that BRCA2 mutations confer a more aggressive prostate cancer phenotype with higher probability of nodal involvement and distant metastasis (Castro et al., 2013).

Ethnicity or race is an intricate blend of genetic and environmental factors. Men of African descent in the USA have a consistently higher incidence (Fig 1-3) and death rate (Fig 1-4) from prostate cancer than white males (Division of Cancer Prevention and Control Centers for Disease Control and Prevention, n.d.). This may reflect genetic susceptibility (Bock et al., 2009) though socio-economic factors such as access to healthcare have also been shown to be important.
(Major et al., 2012). Studies examining risk of poorer prognosis prostate cancer in black men in the United Kingdom (UK), Africa and Caribbean countries have confirmed a higher incidence of prostate cancer compared to white and South Asian men (Kheirandish and Chinegwundoh, 2011). In the UK, black men were also diagnosed up to 5 years earlier than white men and had higher age-adjusted PSA levels at diagnosis (Ben-Shlomo et al., 2008). However, both black and white men in the UK had very similar clinical stage and Gleason scores (similar to US SEER data, (Clegg et al., 2002)) with 75% of both groups diagnosed with localized disease and Gleason score ≤7 (Ben-Shlomo et al., 2008). Thus, it has been postulated that the higher mortality rates from prostate cancer in US may not be from more aggressive disease, but caused by less privileged socioeconomic status and poorer access to health services (Evans et al., 2008).

**Fig 1-3: Prostate Cancer Incidence Rates* by Race and Ethnicity, U.S., 1999-2012**

Incidence source: Combined data from the National Program of Cancer Registries as
submitted to CDC and from the Surveillance, Epidemiology and End Results program as submitted to the National Cancer Institute in November 2014. 

*Rates are per 100,000 and are age-adjusted to the 2000 U.S. standard population (19 age groups – Census P25-1130). Incidence rates are for state registries that meet USCS publication criteria for all years, 1999–2012. Incidence rates cover about 92% of the U.S. population.

†Hispanic origin is not mutually exclusive from race categories (white, black, Asian/Pacific Islander, American Indian/Alaska Native).

Fig 1-4: Prostate Cancer Death Rates (*) by Race and Ethnicity, U.S., 1999-2012

Mortality source: U.S. Mortality Files, National Center for Health Statistics, CDC.

*Rates are per 100,000 and are age-adjusted to the 2000 U.S. standard population (19 age groups – Census P25-1130). Death rates cover 100% of the U.S. population.

†Hispanic origin is not mutually exclusive from race categories (white, black, Asian/Pacific Islander, American Indian/Alaska Native).

South East Asian countries consistently show a lower incidence of clinically detected prostate cancer than western societies. Epidemiological migration studies however show that Japanese that move to Hawaii adopt an increased risk of prostate cancer approaching that of white American men (Breslow et al.,
Hence influence of environmental factors on “ethnicities” must be considered.

Many exogenous factors that might cause progression from latent to clinical prostate cancer have been studied. Dietary differences between various ethnicities have been extensively investigated but overall, findings are mostly observational, tenuous and inconsistent. Intake of dietary fat, particularly in the western world, has been blamed for increased incidence of many cancers, including prostate. The Health Professionals Follow-up Study, a prospective cohort study involving over 50,000 US men, demonstrated a trend in the association between higher total fat consumption and risk of advanced prostate cancer (RR=1.79, p=0.06) (Giovannucci et al., 1993). High alpha linolenic acid intake, found in both vegetable oils and meats, is thought to be related to increased risk (Giovannucci et al., 1993; Gann et al., 1994), however alpha linolenic acid contributes minimally to total fat intake (1%) (Marshall and Z. Chen, 1999). A negative or protective association was initially found between Lycopene, the main carotenoid in tomatoes, and prostate cancer (Giovannucci et al., 1995; Gann et al., 1999). However when studied in larger cohort studies (Schuurman et al., 2002), these findings were not reproduced. A similar discrepancy in findings exists with Vitamin E. The Alpha Tocopherol, Beta Carotene Trial suggested alpha tocopherol (Vitamin E) supplementation could decrease prostate cancer risk (Heinonen et al., 1998). Conversely the Selenium and Vitamin E Chemoprevention Trial (SELECT), a randomized trial involving 35,000 men found no evidence of protection (Lippman et al., 2009), and even a 17% increased risk for those who took Vitamin E alone with longer follow-
up (Klein et al., 2011). Obesity and prostate cancer studies show that overall, the association is weak, but observations suggest that obese men tend to be diagnosed with more advanced, higher grade disease (Freedland and Platz, 2007). Finally, when considering dietary and lifestyle issues, it should be remembered the biggest killer of men is cardiovascular disease. As many men with prostate cancer have indolent disease, cardiovascular disease represents a greater competing threat than their prostate cancer. Thus maintaining a “healthy heart” diet and exercise regime remains an important recommendation to maintain quality of life for all men (Moyad, 2011).

**Diagnosis of prostate cancer**

After consideration of many of the risk factors outlined above in the clinical history, traditionally prostate cancer is diagnosed using serum prostate specific antigen (PSA), digital rectal examination; followed by transrectal ultrasound guided prostate biopsy. More recent advances, such as imaging with multiparametric magnetic resonance imaging (mpMRI) and biomarkers, will be covered in the discussion section of this thesis.

PSA is a kallikrein related serine protease, detected in the blood, secreted by the prostatic epithelium that assists with liquefaction of semen. Whilst it is organ-specific, unfortunately it is not cancer specific. Thus non-cancerous conditions affecting the prostate such as benign prostatic hypertrophy (BPH), prostatitis and infection can cause an elevation in PSA. PSA is used as a continuous variable with higher values associated with increased sensitivity of diagnosing prostate
cancer. Low PSA levels do not preclude cancer being present (Thompson et al., 2004). Since PSA was first described in 1979 (Wang et al., 1979) and described as a serum marker for prostate cancer in 1987 (Stamey et al., 1987), the search for a better biomarker for prostate cancer has proved elusive. It is used for screening of prostate cancer, diagnosis, as well as in follow-up for evaluation of treatment given.

Digital rectal examination (DRE) is an integral part of the clinical assessment for suspected prostate cancer. In the ERSPC screening study, DRE was considered an ancillary test in many countries, only performed in the setting of an elevated PSA (>3.0ng/ml)(Schröder et al., 2009). Theoretically, as the majority of prostate cancers are anatomically located in the peripheral zone of the gland, they may be palpable on DRE when their volume is 0.2ml or larger. A suspicious DRE, independent of the PSA level, results in detection of prostate cancer in about 18% of patients. Limited reproducibility between examiners hampers utilization (Gosselaar, Kranse, et al., 2008). The positive predictive value of DRE increases with higher PSA (2-4ng/ml) to 30-48.6% (Carvalhal et al., 1999; Gosselaar, Roobol, et al., 2008), and an association between an abnormal DRE with more aggressive Gleason scores (>7) exists (Gosselaar, Roobol, et al., 2008).

Transrectal ultrasound (TRUS) has traditionally been the mainstay to visualize the prostate. However, it lacks definition and the ability to identify cancers within the gland reliably. The classical hypoechoic lesion in the peripheral zone describing cancer is estimated to only diagnose 60% of cancers as the lesions may also be isoechoic or hyperechoic. Furthermore, smaller lesions are likely to
be missed (Lee, Torp-Pedersen, Littrup, et al., 1989). Because of the poor positive predictive value of grayscale ultrasound, and the fact that >50% of prostate cancer is multifocal, systematic zonal biopsies, rather than ultrasound guided lesion biopsies of the prostate have been traditionally taken (Lee, Torp-Pedersen, Siders, et al., 1989). The standard “systematic” biopsy generally entails a total of 12 cores (Hodge et al., 1989). Two cores the ipsilateral apex, middle and base of the prostate, then repeated on the contralateral side. Any suspicious lesions on ultrasound may warrant additional cores. Studies demonstrated additional cores of the transition zone and seminal vesicles did not increase the yield of prostate cancer detected (Terris et al., 1997; Epstein et al., 1997). Complications from transrectal ultrasound guided prostate biopsy are well recognized and include bleeding, sepsis (Nam et al., 2010), exacerbation of lower urinary tract symptoms with possible urinary retention, and impotence (Fujita et al., 2009).

Prostate cancer found on core biopsy or operative specimens is graded on histological appearance. The Gleason score was originally described by Donald Gleason in 1966 (Gleason, 1966). Five classic different patterns of tumor growth (1-5) were initially described. These 5 patterns, designated as grades, describe progressive loss of normal prostate glandular architecture with pattern 5 being the worst grade. However, only Gleason grades 3-5 are now reported because of the advent of immunohistochemistry staining for basal cells. Most cases diagnosed with Gleason 1 or 2 in the original era are now referred to as adenosis (Epstein et al., 2005). The Gleason score is the sum of the two most common patterns and ranges from 6 to 10, with 10 being the most aggressive. For needle biopsies, the worst grade should always be incorporated into the Gleason score,
even if comprises <5% of the cancer. The Gleason score, in use now for over 40 years, is a powerful prognostic indicator for prostate cancer (Albertsen, P.C. et al., 1998; Pierorazio et al., 2013).

There have been multiple modifications to the scoring system with the most recent being in 2014 (Epstein et al., 2015). Here it was recommended that all cribriform glands be included in pattern 4, and to replace Gleason scores with 5 grades based on grouping of grading patterns. This new grading system ranges from 1 to 5, with grade 1 being 3+3=6 tumours; grade 2, 3+4=7; grade 3, 4+3=7; Grade 4, Gleason score 8; and grade 5, Gleason scores 9 and 10 tumours. Validation studies have been performing confirming the new ISUP grading system significantly predicts radical prostatectomy TNM pT and N stage, in addition to tumour volume and biochemical recurrence-free survival (Samaratunga et al., 2015). As all the publications in this thesis were analyzed and written using the previous Gleason scoring system, for sake of consistency only the Gleason scoring system will be used.

Traditionally, the Gleason score, together with PSA and DRE findings, have been used to categorize prostate cancer into 3 broad risk groups:

• low risk: Gleason score 6 and PSA <10ng/ml and cT1/cT2a
• intermediate risk: Gleason score 7 or PSA 10-20ng/ml or cT2b
• high risk: Gleason score ≥8 or PSA >20 or cT2c

These risk categories provide a simple means to estimate prognosis in prostate cancer (D"Amico et al., 1998) but will likely evolve given the newer ISUP grading system.
**Prostate cancer staging**

The 2009 TNM (tumour, node, metastasis) classification for prostate cancer is shown in Table 1-3 (Sobin, Gospodariwicz and Wittekind, 2009).

**Table 1-3: The 2009 TNM (tumour, node, metastasis) classification. (Sobin, Gospodariwicz and Wittekind, 2009)**

<table>
<thead>
<tr>
<th>T - Primary tumour</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Clinically inapparent tumour not palpable or visible by imaging</td>
</tr>
<tr>
<td>( T_{1a} )</td>
<td>Tumour incidental histological finding in 5% or less of tissue resected</td>
</tr>
<tr>
<td>( T_{1b} )</td>
<td>Tumour incidental histological finding in more than 5% of tissue resected</td>
</tr>
<tr>
<td>( T_{1c} )</td>
<td>Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA] level)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour confined within the prostate(^1)</td>
</tr>
<tr>
<td>( T_{2a} )</td>
<td>Tumour involves one half of one lobe or less</td>
</tr>
<tr>
<td>( T_{2b} )</td>
<td>Tumour involves more than half of one lobe, but not both lobes</td>
</tr>
<tr>
<td>( T_{2c} )</td>
<td>Tumour involves both lobes</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour extends through the prostatic capsule(^2)</td>
</tr>
<tr>
<td>( T_{3a} )</td>
<td>Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement</td>
</tr>
<tr>
<td>( T_{3b} )</td>
<td>Tumour invades seminal vesicle(s)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic walls</td>
</tr>
</tbody>
</table>

**N - Regional lymph nodes\(^3\)**

<table>
<thead>
<tr>
<th>N</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
</tbody>
</table>

**M - Distant metastasis\(^4\)**
<table>
<thead>
<tr>
<th>Mx</th>
<th>Distant metastasis cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td></td>
<td>M1a Non-regional lymph node(s)</td>
</tr>
<tr>
<td></td>
<td>M1b Bone(s)</td>
</tr>
<tr>
<td></td>
<td>M1c Other site(s)</td>
</tr>
</tbody>
</table>

1. **Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.**
2. **Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.**
3. **Metastasis no larger than 0.2 cm can be designated pN1 mi.**
4. **When more than one site of metastasis is present, the most advanced category should be used.**

**Prostate cancer screening**

The influence of the introduction of the PSA test, increasing prostate cancer diagnosis, was shown in Fig 1-1 and 1-2. Utilization of PSA to screen for prostate cancer with initially described in 1991 (Catalona et al., 1991). An effective public health screening program is dependent on test, disease and treatment characteristics. Ideally, the disease is prevalent with high associated morbidity or mortality. There should be effective treatment available and the test ought to be safe, inexpensive with high sensitivity and specificity. Prostate cancer is certainly a prevalent disease but the associated severity of morbidity/mortality, particularly considering the earlier stage shift caused by screening, is contentious. PSA testing is safe and inexpensive however it has difficulties in discriminating benign prostatic hypertrophy from prostate cancer.

Two large randomized control trials, based in Europe and the US, have investigated the association between prostate cancer screening and mortality. The Prostate Lung Colorectal and Ovarian Screening Trial (PLCO) contained
75,000 men and after 13 years of follow-up, found no mortality benefit for organized annual screening (Andriole et al., 2012). However, the study was deeply flawed as nearly half of the control arm underwent screening, so ultimately can only really be considered a trial of regular screening versus opportunistic screening. The European Randomized Study of Screening for Prostate Cancer (ERSPC) was conducted across 8 European countries and involved over 150,000 men. At last report, with 13 years follow-up, the rate ratio of prostate cancer mortality was 0.79 (0.69-0.91) favouring the screening arm (Schröder et al., 2014). The absolute risk reduction of death from prostate cancer at 13 years was 0.11 per 1000 person-years or 1.28 per 1000 men randomised. This translates into saying to prevent one death from prostate cancer at 13 years, 781 men would need to be screened and 27 cancers would need to be detected.

Results from Sweden, a country involved in the ERSPC trial, are the most supportive of population prostate cancer screening. In their population of 20,000 men, with median follow-up of 14 years, screening was found to decrease the relative risk (RR) of dying from prostate cancer by nearly 50% (RR 0.56, 95% CI 0.39-0.82, p=0.002). In this cohort, to prevent one prostate cancer death, the number needed to be screened (NNS) was 293 and the number needed to be treated (NNT) was 12 (Hugosson et al., 2010). The differences in results between the Swedish sub-population and overall ERSPC trial may be affected by a younger age of commencement of screening (median age at baseline was 56 years versus 60.8 years), differences in randomization (done prior to informed consent and thus avoids pre-selection bias and possible contamination of control
arm), and a very low background rate of opportunistic PSA-screening at time of study.

With longer follow-up, the benefits of prostate cancer screening seen in the ERSPC trial have increased. With the natural history of the majority of prostate cancers being one of long lead-time and long natural course, any benefits of screening should become more evident with longer follow-up. From the initial ERSPC report published at 9 years follow-up (Schröder et al., 2009) to the latest update with 13 years follow-up, the number needed to screen and treat changed from 1410 and 48 to 781 and 27 respectively.

Guidelines on the public health impact of screening for prostate cancer are polarized and confusing for many. Both the United States Preventative Services Task Force (USPSTF) and Canadian Task Force on Preventive Health Care recommend against PSA-screening for prostate cancer (Moyer, 2012; Krahn, 2014). They conclude that “many men are harmed as a result of prostate cancer screening and few, if any, benefit”. Those in favour of PSA screening are concerned that if PSA screening decreases or stops, men will invariably present with more advanced and incurable disease. Since publication of the ERSPC trial results, and subsequent USPSTF recommendation, guidelines from urological entities have taken a more balanced approach. The American Urological Association’s guideline on prostate cancer screening released in 2013 differs considerably from the previous consensus statement issued in 2009. The new guideline only recommends PSA testing for men aged 55-69, with shared decision-making between doctor and patient to discuss the potential harms of
screening and treatment (RACS, 2013). For men in the age group 40-54 years, there has been a major shift away from screening. This is because the two large RCTS (ERSPC and PLCO) did not include men under the age of 55 years, and thus evidence for screening in this group is lacking. Previous recommendations in this area were guided by a large retrospective population study from Sweden by Lilja et al. In this study of 21,277 men a single PSA measurement in men between the age of 33 to 50 years was highly predictive of subsequent prostate cancer diagnosis and advanced stage at diagnosis (Lilja et al., 2012). However, it is not possible to know if this stratification result in subsequent decrease in morbidity or mortality from prostate cancer.

Results of prostate cancer screening studies are comparable to screening studies for other cancers with similar length of follow up. A Cochrane review examined the effect of breast cancer screening with mammography on mortality in 7 randomised control trials with 13 year follow-up. Overall, the risk reduction found was 0.81 (95% CI 0.74-0.87), similar to what is reported for prostate cancer. However, concerns regarding suboptimal randomization in several of the trials were noted, and differential misclassifications of cause of death resulted in biases in utilization of breast cancer mortality as an outcome (Gøtzsche and Jørgensen, 2013). Thus, if only including “adequately randomised trials”, the Cochrane review calculated 2000 women needed to be screened to prevent one breast cancer death. However, a UK Independent Breast Screening Review found the number needed to screen was only 235 (Independent UK Panel on Breast Cancer Screening, 2012). The disagreement in risk reductions seen from these meta-analyses stem from differences in selection criteria for inclusion, age at
which regular screening starts, the period over which it continues, and the
duration of follow-up after screening.

In Australia, screening for bowel cancer using the faecal occult blood test (FOBT)
is recommended from the age of 50 years. A Cochrane review showed FOBT,
compared to no screening had a relative risk of 0.86 (95% CI 0.80-0.92, high
quality evidence). In the same report, screening using flexible sigmoidoscopy
showed a relative risk of 0.72 (95% CI 0.65 to 0.79, high quality
evidence)(Holme et al., 2013). A large UK randomized trial of 170,432 patients
examined the effect of screening with a single flexible sigmoidoscopy between
the ages of 55-64. In the sigmoidoscopy arm, the incidence of colorectal cancer
was reduced by 23-33% (depending on either intention-to-treat or per-protocol
analyses). The NNS to prevent one colorectal cancer diagnosis or death were 191
and 489 respectively (Atkin et al., 2010).

Despite several large randomized control trials, the relationship between PSA
screening and prostate cancer mortality remains provocative. However, what the
trials have showed us that that over-diagnosis and over-treatment of prostate
cancer is real issue. PSA testing invariably leads to patient anxiety about
presence of prostate cancer and often then subsequent prostate biopsy. Biopsy
finding cancer has often previously invariably segued to treatment. The
morbidity associated with prostate biopsy and any of the treatment modalities
are increasingly being balanced against the numbers needed to screen and treat
to save one man from dying of prostate cancer. Several papers have documented
the natural history of prostate cancer, managed conservatively with a
combination of observation and palliative treatment, such as androgen deprivation therapy. A Swedish prospective population cohort of 223 men with localized prostate cancer at diagnosis was followed for 30 years (Popiolek et al., 2013). In total, 17% of men died of prostate cancer, with 18.4% progression to metastasis and 41.4% local progression events. Thus, a significant number of men, 64% never developed symptomatic progression and were never treated with hormonal therapy. In this cohort, overall progression and mortality remained stable during the first 15 years of follow-up with a rapid increase seen between 15-20 years, which then stabilized (Fig 1-5).

**Figure 1-5: Prostate cancer specific survival in Swedish population cohort with localized prostate cancer managed conservatively** (Popiolek et al., 2013)
The drop in prostate cancer specific survival reported by Popiolek et al may be artifact from small sample size. In a similar publication, Albertsen examined data from the Connecticut Tumour Registry with 767 men. They reported constant mortality rates from 15 to 20 years follow-up (Albertsen, P.C., Hanley and Fine, 2005). With increasing Gleason score, the proportion of men dying from prostate cancer, relative to non-prostate cancer mortality, grew (Fig 1-6).

Other studies, with shorter follow-up have confirmed low prostate cancer specific mortality in men similar Gleason scores. In a Swedish population registry combining low and intermediate risk prostate cancer (Gleason score ≤7, PSA ≤20 ng/ml) managed with surveillance and/or treatment with curative intent, the calculated cumulative 10 year prostate cancer-specific mortality in the surveillance arm was 3.6% (95% C.I. 2.7-4.8%). Furthermore, the 10 year risk of dying from competing causes was 19.2% (95% C.I. 17.2-21.3%) in the surveillance arm (Stattin et al., 2010). When examining an older population with median age of 78 years (Albertsen, P.C. et al., 2009), the 10 year prostate cancer-specific mortality was higher at 8.3%, but so was the corresponding 10 year risk of dying of competing causes 59.8%.
Figure 1-6: Survival and Cumulative Mortality From Prostate Cancer and Other Causes Up to 20 Years After Diagnosis, Stratified by Age at Diagnosis and Gleason Score (Albertsen, P.C., Hanley and Fine, 2005)
Models to predict prognosis of men diagnosed with prostate cancer.

There have been many predictive models created to assist clinicians with prognostication and management of patients worried about prostate cancer. The Partin tables (1) were one of the first to estimate pathological staging using PSA, DRE and Gleason score. The classifications suggested by D’Amico (low, intermediate and high) showed significant differences in freedom from disease at 10 years after radical treatment, are simple to remember, and still used today by many urologists(2). Various on-line prediction tools from different institutions around the world are available and easily accessible (3-7). They can help predict presence of cancer for men deciding whether to have a prostate biopsy(5, 7), and the risk of biochemical recurrence after different forms of treatment(3). The UCSF-CAPRA score can predict likelihood of metastasis, cancer-specific mortality and overall mortality(4). However, it is increasingly being realized that the performance of these predictive models deteriorates when applied to a different population from which they are derived from(8).

Management of low risk prostate cancer

In the past, all prostate cancer was treated in a “radical” manner with curative intent. The term radical refers to the approach of treating the whole gland, either by surgical removal (radical retropubic prostatectomy) or ablation by energy source, most commonly radiotherapy. Radical retropubic prostatectomy involves removal of the whole prostate gland between urethra and bladder, along with the seminal vesicles and adjacent soft tissues to ensure a negative surgical margin. Radiotherapy can be delivered using external beam or by brachytherapy
(implantation of radioactive seeds). Unfortunately, all treatments are potentially associated with side effects. After surgery, erectile dysfunction rates are reported to be between 29-100% though using improved nerve-sparing techniques (Walsh, P.C., Partin and Epstein, 1994), this number more recently has been reported to be between 31-86% (Dubbelman, Dohle and Schröder, 2006). Another chronic adverse effect seen with radical prostatectomy is stress urinary incontinence. This has been reported to be in the range of 14-31% (Penson et al., 2008) but lack of standardization in reporting makes comparisons difficult. A more digestible outcome is the rate of men undergoing surgical procedure post-prostatectomy for incontinence, which is reported to be 5-6% (Nam et al., 2012).

With external beam radiotherapy (EBRT), erectile dysfunction rates are similar to surgery with potential toxicity (≥grade 2) in the urinary tract (15.9%) and bowel (11%) (Ataman et al., 2004). Improved targeting techniques, such as intensity modulated radiation therapy (IMRT), may decrease toxicity in surrounding organs but this needs to be balanced against increased toxicity from dose escalation. In addition, increased risk of developing secondary malignancies in the bladder and rectum, has been seen following both external beam and brachytherapy radiotherapy (9, 10). Brachytherapy involves careful selection of patients, with consideration of prostate volume size and anatomical configuration of pubic arch, do to greater risk short-term urinary obstruction (1.5-22%) (Budäus et al., 2012). Long-term toxicity suggest possibility of lower erectile dysfunction rates (16%), with chronic urinary (33.8%) and bowel (21%) problems also existing (A. B. Chen et al., 2006).
With the uptake of PSA screening, it is estimated that 81% of men with prostate cancers now diagnosed have localized disease (Siegel, Naidshadham and Jemal, 2013). However, the evidence from the screening studies suggest that many men need to be diagnosed and treated to prevent one death from prostate cancer. Thus many men are being exposed to complications from biopsy (overdiagnosis) and treatment (overtreatment) with significant ramifications on their quality of life. To minimize the harms of overtreatment, the management of men with low-risk prostate cancer with active surveillance was proposed. This involves the monitoring of men diagnosed with low-risk prostate cancer with the intent to intervene radically if their disease is found to worsen.

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Kvale, R., Auvinen, A., Adami, H. O., Klint, A., Hernes, E., Møller, B., Pukkala, E.,


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CHAPTER 2: Active Surveillance For Prostate Cancer –

Literature Review

In this chapter, a literature review on active surveillance is performed, and the thesis research hypotheses and aims presented.

Definition

Active surveillance (AS) is a management strategy for men with low risk prostate cancer that involves regular monitoring and if their disease is found to worsen, treating with curative intent. Increasing acceptance of AS coincides with the evidence from screening studies (Schröder et al., 2014) and recommendations from government tasks forces (Lin et al., 2011; Bell et al., 2014) highlighting concerns with over-diagnosis and over-treatment. Urologists however take a more cautious view. Being clinicians at the coal face of the disease, we have genuine concerns that if we stop diagnosis by stopping screening, the numbers of men presenting with incurable locally advanced and/or metastatic disease will dramatically increase. Instead, for early grade cancer we should uncouple diagnosis from treatment. Active surveillance provides a means to do this.

Occasionally, there is still confusion in differentiating between AS and watchful waiting (WW). Both are expectant management strategies for prostate cancer that involve monitoring of PSA. However, their intent is vastly different. With AS, the disease is monitored to avoid or delay potential side effects of treatment. With any progression of disease, the intent is to intervene with radical treatment to cure the patient (e.g. radical prostatectomy and radiotherapy). Patients are
generally younger with less comorbidity. Watchful waiting is an older concept where the disease is monitored with the focus more on quality of life. After initial assessment of the patient’s age and comorbidities, a decision is made that the patient would not likely benefit from definitive treatment due to the prolonged natural history of most prostate cancer. In layman’s terms, the patient is “more likely to die with his prostate cancer than of it”. Disease progression may be monitored if purely biochemical or radiological without symptoms, or if symptomatic, non-curative treatment measures such as androgen deprivation and/or palliative radiotherapy commenced.

**Rationale**

In the previous chapter, the background behind the development of AS was presented. This can be summarized as:

- Prostate cancer is common but most is indolent and not clinically significant.
- Screening for prostate cancer is associated with a large amount of over-diagnosis and over-treatment to reduce one death from prostate cancer.
- All the radical treatments for prostate cancer can be associated with significant adverse effects on the patient’s quality of life.
- Active surveillance provides a method of de-coupling diagnosis from treatment.
Utilization

There has been a noticeable shift in practice patterns documented globally in the management of low risk prostate cancer towards AS. Until recent years, treatment would invariably follow diagnosis (Hoffman et al., 2014) as clinicians did not fully appreciate the indolent natural history of low grade prostate cancer. The Surveillance, Epidemiology and End Results Medicare data were analyzed for the period 2004-2007 (Filson et al., 2014). During this time, there were 7,347 men with localized prostate cancer treated expectantly of which the proportion receiving AS, as opposed to WW, rose from 9.7% to 15.3% during the study interval. A similar analysis of the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry was performed between 1990-2007 (Cooperberg, Broering and Carroll, 2010). Patients were stratified using the Cancer of the Prostate Risk Assessment (CAPRA) score. Unfortunately the registry was unable to differentiate between men on WW and AS. For low risk prostate cancer (CAPRA score 0-2), the proportion of patients receiving WW/AS each time period analyzed varied from 5.3-12.8% whereas >50% of these men with low risk disease were consistently receiving radical prostatectomy. The treatment delivered was shown to vary with age, comorbidity, and socioeconomic status, along with clinical site. Patients having radical prostatectomy tended to be younger, healthier, more like to have private insurance, and more likely to have higher socioeconomic status. A more contemporary analysis (2012-2013) from the Michigan Urological Surgery Improvement Collaborative (MUSIC) (Womble et al., 2015) suggests increased uptake of AS. In their cohort of D’Amico low risk patients, 49% were managed initially by AS. The Victorian Prostate Cancer Registry, Australia documented
that from 2008-2012, for 1816 men with National Comprehensive Cancer Network (NCCN) very low/low risk prostate cancer, 36% were managed by AS. This increase in utilization of AS for appropriate patients is likely to increase even further with time.

**How to perform Active Surveillance**

Active surveillance involves a process of selecting men, whom the clinician deems to have indolent, or non-aggressive, prostate cancer, and then actively monitoring them for presence of more aggressive disease, which would then trigger radical treatment.

Traditionally, the process of selection and monitoring has been based on the triad of PSA, digital rectal prostate examination and histopathology obtained from transrectal ultrasound guided prostate biopsy.

However, as will be demonstrated, there is global variation in the application of the subtleties of selection and monitoring of men for AS. Exploration of these nuances forms the basis of this thesis.

**Selection of patients for Active Surveillance**

Eligibility for AS is built on the foundation of work published by Stamey (Stamey et al., 1993), later refined by Epstein (Epstein et al., 1994). Stamey examined prostates in 139 consecutive cystoprostatectomies, identifying prostate cancer in 55 (40%). From radical prostatectomy series, a subset of patients was identified
with potentially biologically insignificant tumor. In Stamey’s series, 80% of patients had tumours <0.5ml, and were unlikely to reach clinically significant size. Epstein was then able to show serum PSA level, PSA density, and needle biopsy pathologic findings such as number of positive cores and percentage of core involved with cancer were accurate predictors of tumor extent (Epstein et al., 1994). Thus the eligibility criteria for AS, published by various international institutions, are summarized in Table 2-1.

**Table 2-1: Published eligibility criteria for active surveillance.**

<table>
<thead>
<tr>
<th>Institution</th>
<th>Clinical stage</th>
<th>PSA (ng/ml)</th>
<th>PSA density (ng/ml/ml)</th>
<th>Biopsy Gleason score</th>
<th>No. of positive cores</th>
<th>% of single core</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal Marsden (Har die et al., 2005)</td>
<td>≤T2a</td>
<td>≤15</td>
<td>-</td>
<td>≤3+4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sunnybrook Hospital (Klotz et al., 2015)</td>
<td>≤T2a</td>
<td>≤10</td>
<td>-</td>
<td>≤3+3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PRIAS (van den Bergh et al., 2007)</td>
<td>≤T2a</td>
<td>≤10</td>
<td>&lt;0.20</td>
<td>≤3+3</td>
<td>≤2</td>
<td>-</td>
</tr>
<tr>
<td>MSKCC and PMCC (Adamy et al., 2011; Wong)</td>
<td>≤T2a</td>
<td>≤10</td>
<td>-</td>
<td>≤3+3</td>
<td>≤3</td>
<td>≤ 50%</td>
</tr>
</tbody>
</table>
et al., 2013)

| University of Miami (Soloway et al., 2010) | ≤T2a | ≤10 | ≤3+3 | ≤2 | ≤20% |
| UCSF (Dall'Era et al., 2008) | ≤T2a | ≤10 | - | ≤3+3 | ≤1/3 of total | ≤50% |
| John Hopkins (Tosoian et al., 2011) | ≤T2a | - | ≤0.15 | ≤3+3 | ≤2 | ≤50% |

PRIAS: Prostate Cancer Research International: Active Surveillance originating from the European Randomized study of Screening Prostate Cancer.

MSKCC: Memorial Sloan Kettering Cancer Center, New York.
PMCC: Princess Margaret Cancer Center, Toronto.
UCSF: University of California San Francisco.

Comparison of cohort selection criteria has been performed in various manners. Initial investigations compared cohort selection criteria on groups of men who were suitable for AS but underwent upfront radical prostatectomy, examining the outcome of adverse pathology present at radical prostatectomy (Suardi et al., 2010; Wong et al., 2012). These studies consistently showed that utilization of the stricter criteria, such as the PRIAS and John Hopkins’ criteria, limited the amount of upgrading and upstaging at radical prostatectomy but concurrently reduced the numbers of men suitable for AS. However, adverse pathology was always a surrogate outcome as we waited for longer-term results of AS to emerge. We now have two single institution cohorts, from Sunnybrook Toronto (Klotz et al., 2015) and John Hopkins (Tosoian et al., 2015), with published results on overall survival, cancer-specific survival and metastatic-free survival.
As can be seen in Table 2-1, the John Hopkins criteria are markedly more onerous than those used by Sunnybrook Toronto. One study showed that in a cohort of men undergoing radical prostatectomy, the proportion of men eligible according to Sunnybrook Toronto criteria was 30%, compared to John Hopkins 4% (Conti et al., 2009). Furthermore, at John Hopkins, repeat biopsies were performed yearly whereas Sunnybrook Toronto conducted them every 2-3 years. Table 2-2 shows a comparison of long-term results between the two institutions, and despite their differences in how AS was conducted, the 10-year cancer specific survival rates are both very high. Thus, it would appear that the Sunnybrook lenient criteria, would permit more men to experience AS without necessarily having worse outcomes.

Table 2-2: Comparison of long-term outcomes for men on AS, conducted at Sunnybrook Toronto and John Hopkins.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Follow-up Median (range)</th>
<th>Overall survival (10yrs)</th>
<th>Cancer specific survival (10yrs)</th>
<th>Metastatic free survival (10yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunnybrook Toronto</td>
<td>819</td>
<td>6.4 (0.2-19.8)</td>
<td>80%</td>
<td>98%</td>
<td>97.2%</td>
</tr>
<tr>
<td>John Hopkins</td>
<td>1298</td>
<td>5.0 (0.01-18.0)</td>
<td>93%</td>
<td>99.9%</td>
<td>99.4%</td>
</tr>
</tbody>
</table>

A variation on the cohort selection criteria outlined above is a nomogram, or risk calculator. These aim to take an individual patient’s variables and calculate a more precise probability of presence of indolent cancer. There are several of these nomograms for AS easily accessible to both patients and clinicians on the internet(SWOP – The Prostate Cancer Research Foundation, Rotterdam, 2013;
Memorial Sloan-Kettering Cancer Center, 2013). However, there are well-recognized limitations to how these risk calculators are derived (Steyerberg et al., 2010) and external validation is helpful to determine if the calculators perform as well in populations outside those they were derived in. In Chapter 4 of this thesis, a radical prostatectomy cohort, where histopathology is available from both biopsy and prostatectomy, is used to assess the performance of the published nomograms designed to aid selection for men on AS (Wong et al., n.d.).

In the selection criteria listed in Table 2-1, “age” is not a variable formally considered. Most centres do not have a strict upper age threshold where AS is no longer offered. However, consideration of competing co-morbidities and life expectancy is essential when considering management of any man with prostate cancer. These considerations are perhaps best reflected in the Sunnybrook Hospital cohort, where there have been subtle changes in how men are selected. Initially (1995-1999), Dr Klotz and colleagues accepted older men >70 years with PSA up to 15ng/ml, and Gleason scores ≤3+4 (Klotz, 2005). However since the year 2000, for men with favourable intermediate-risk disease (PSA 10-20 and/or Gleason score ≤3+4), only those with significant comorbidities and a life expectancy of less than 10 years were accepted (Klotz et al., 2015). It could be argued that this approach could be described more as “watchful waiting”, as opposed to “active surveillance”, as the intent of monitoring might be to intervene in a non-curative manner given life expectancy of <10 years.

Investigation of whether AS is suitable for men with Gleason 3+4 disease at biopsy is presented in Chapter 5 of this thesis. As is human nature, there is a
desire by clinicians, driven also in part by patients, to push the boundaries of what is possible. Reporting of outcomes of AS for highly motivated men with low volume Gleason 3+4 initially appeared to be similar to standard criteria, but with short follow-up (median 4.3 years, range 1.2-11.7 years) (Cooperberg et al., 2011). A subsequent report with longer follow-up (median 6.4 years, range 0.2-19.8 years) suggests outcomes such as development of metastasis and cancer specific survival may be worse for men with Gleason 3+4 on AS (Klotz et al., 2015). Further discussion on this will be presented in Chapter 5.

The role of biopsy

Repeated ultrasound guided prostate biopsy forms the foundation for monitoring men on AS as Gleason grade remains a powerful predictor of prognosis for prostate cancer. Traditionally this has been via the transrectal route but increasingly in some areas of the world such as Australia, transperineal biopsies is increasingly being utilized (Grummet et al., 2014).

The first positive prostate biopsy is also called the baseline or diagnostic biopsy. The technique used is an established “standard extended template” of 10-12 cores with laterally peripheral zone directed biopsies (Presti et al., 2003). Prostate sampling using this template carries a recognized risk of clinical undergrading of 20-30% (Conti et al., 2009). This sampling error may result in men being enrolled into AS with presence of more aggressive disease than was found at biopsy. To overcome this problem, an immediate or early re-biopsy, often termed the “confirmatory biopsy”, has been advocated before allowing patients
to commence AS. Adamy and colleagues proposed the confirmatory biopsy because at their institution (Memorial Sloan Kettering Cancer Center, MSKCC), when performing this re-biopsy within 3 months of diagnosis, up to 35% of men were found to no longer be suitable candidates for AS (Adamy et al., 2011). This paper also implies a difference in quality of biopsy performed. As many of the patients were referred to MSKCC for management with AS, most of them had diagnostic prostate biopsy previous done in the community. In Chapter 6, we specifically investigated whether prostate biopsy done in an academic centre (Princess Margaret Hospital) had advantages to those done in a non-academic setting.

The standard extended template of 10-12 cores with laterally peripheral zone directed biopsies is based on a systematic review from 2006. Here, comparison between the “extended” 10-12 template, with more laterally directed cores, and the then existing “sextant” 6 core template found the extended 12-core template detected 31% more cancer than sextant with similar adverse event rates (Eichler et al., 2006). This review also suggested taking >12 cores added no significant benefit, and schemes taking >18 cores more likely to be associated with increased risk of adverse events. Other studies have suggested the number of cores taken should be increased in older men with larger glands (Eichler et al., 2006; Remzi et al., 2005) using the “Vienna nomogram”. By adjusting for larger glands, they showed higher prostate cancer detection rates (36.7%) when compared to octant control group undergoing first (22%) and then repeat (10%) biopsies. When performing repeat prostate biopsies for active surveillance, the literature on diagnostic prostate biopsy has been extrapolated and applied to AS.
However, goals for diagnostic and surveillance biopsies, whilst similar are not the same. The purpose of diagnostic biopsy is to find cancer whereas for surveillance, diagnosis of cancer is already known and the objective is to seek presence of cancer that would exclude the patient from AS. This difference forms the basis of hypotheses in Chapters 7 and 8. Chapter 7 explores different hypothetical biopsy templates for AS whereas Chapter 8 specifically examines biopsy of the prostate transition zone during AS.

The frequency of serial prostate biopsy varies between institutions. John Hopkins requires patients to have yearly biopsies (Tosoian et al., 2011) whereas most others have described repeating the biopsy at 2-3 year intervals (Klotz et al., 2015; Bangma et al., 2012). At each subsequent interval prostate biopsy during AS, a proportion of men will be found to have worsened high-grade disease. This proportion is estimated to be 22-30% (Porten et al., 2011) with the most common increased grade found Gleason 3+4 disease (Wong et al., 2013). Various terms have been used to describe the phenomenon of upgrading including “progression” and “re-classification”. This is because we cannot adequately explain the biological cause for upgrading. It may signify previous biopsy sampling error, progression of existing disease, or development of new disease (Epstein, Walsh, P.C. and Carter, 2001).

For some men on AS, at time of confirmatory biopsy, a proportion (21-52%) will be found to have no cancer present (Dall’Era et al., 2012). Intuitively, both clinicians and patients are reassured by this result, which is a form of “down-grading” of disease. Investigation of the prognostic significance of “no cancer” at
confirmatory biopsy formed the basis of the manuscript presented in Chapter 9 of the thesis.

**The role of prostate specific antigen**

Selection of men for AS was traditionally limited to those with PSA <10ng/ml. The Royal Marsden however has accepted with men for AS with PSA <15 ng/ml. Regular monitoring with prostate specific antigen (PSA), together with digital rectal examination (DRE) and serial prostate biopsy, is recommended. The intensity of DRE and PSA follow-up is recommended every 3 months in most published series, however with increasing experience there is a trend to relax this follow-up to 6 monthly.

Increases in PSA above 10ng/ml, a threshold for AS eligibility, do not necessarily directly trigger treatment, as the fickleness in fluctuation of PSA is well known (Toren et al., 2014). In a paper included as a co-author in the appendices of this thesis, (Toren et al., 2014) the significance of men on AS with PSA >10 ng/ml was investigated. Of 698 men who were otherwise suitable for AS, three groups were identified: baseline (at diagnosis) PSA >10ng/ml (n=82), PSA rise >10ng/ml during surveillance (n=157), and those with PSA <10ng/ml throughout AS (n=459). Those with baseline PSA >10ng/ml were older and had larger prostates. When analysis for predictors of adverse pathology (parameters exceeding entry criteria) at biopsy was performed, PSA >10ng/ml at either baseline or during AS follow-up, was not significant for finding adverse pathology at subsequent biopsy. The direction of odds ratio (OR) for baseline
PSA >10ng/ml on multivariable logistic regression was protective (OR 9.78, 0.41-15.0, p=0.46) but with wide confidence interval. Caution must still be applied, particularly in the PSA rise >10ng/ml group as we found of the 22 men who had radical prostatectomy in this group, 5 (22.7%) had Gleason ≥8 disease.

PSA kinetics, such as PSA doubling time or PSA velocity, describes changes in PSA with time. These have also been examined for association with biopsy disease progression. In an earlier publication from the Toronto Sunnybrook group, PSA doubling time (PSA DT) was suggested as a potential trigger to recommend treatment due to findings that it predicted increased risk of biochemical recurrence (BCR) after definitive treatment (Klotz et al., 2010). Subsequent analysis with longer follow-up showed a threshold of PSADT <3 years to be associated with BCR, but this was only significant on univariate analysis. Other institutions have not been able to demonstrate an association between PSA DT (Ross et al., 2010) or PSA velocity (Whitson et al., 2011), and adverse pathology at biopsy or radical prostatectomy.

In the modern era of AS, a PSA >10ng/ml at baseline or during surveillance, on its own is unlikely to preclude AS or directly trigger radical treatment. In my practice, it usually activates further investigation such as earlier biopsy or imaging with MRI (Adamy et al., 2011).


**Triggers for exiting Active Surveillance**

As indicated above, the criteria in decision making to cease AS and move to radical therapy are closely tied to the selection, or inclusion, criteria. If PSA is the weakest parameter, the hardest end point is finding an increase in Gleason grade, also referred to as grade-progression or grade-reclassification. For most men included with Gleason score 3+3 disease, this means any presence of Gleason grade 4 on re-biopsy. For the few men included with Gleason 3+4 disease, increase of volume Gleason grade 4 disease to a Gleason score of 4+3 disease is the trigger.

Increase of volume of Gleason 3+3 disease remains a more contentious trigger for ceasing AS. When AS first began, it would not be uncommon for men with increasing number of positive cores or percentage of cores involved of Gleason 3+3 disease, to be recommended active treatment. There is some evidence to suggest higher volume of 3+3 disease could be associated with presence of Gleason grade 4 (Komisarenko et al., 2015). However, it is thought by some that Gleason 3+3 disease has no metastatic potential and hence if all measures are taken to exclude presence of higher-grade disease, Gleason 3+3 disease can be surveyed, regardless of volume of disease present. The evidence to support this theory comes from Sunnybrook Toronto cohort where only 2 of 28 patients with metastasis were not upgraded to Gleason score ≥ 7 before developing metastatic disease (Klotz et al., 2015).
Research problem and hypotheses

The primary aim of this thesis was to examine selection criteria for active surveillance. In particular, whether various published risk calculators for AS do in fact aid selection and if Gleason 3+4 disease was suitable for AS.

The secondary aims were to research approaches to improve the efficacy of prostate biopsy by examining operator variability in performing biopsy, the effect of different biopsy templates on surveillance biopsy, and the significance of negative biopsy on disease prognosis.

Thus, the hypotheses of this thesis are formally presented as follows:

- Risk calculators published to aid selection of men for active surveillance will not be useful due to methodological flaws in derivation.
- Gleason 3+4 disease found at biopsy will not be suitable for active surveillance.
- Prostate biopsy performed in the community is not as rigorous as an academic centre in selecting men for active surveillance.
- Addition of biopsy cores from the transition zone of the prostate will aid in detection of more aggressive disease not suitable for active surveillance.
- A negative biopsy during active surveillance will be associated with less likelihood of disease progression.
Justification and clinical impact of the research

Increasing number of men are being offered AS in preference to radical therapy.

This thesis addresses the need for continual improvement in the manner of which men are selected and monitored for AS.

Chapter References:


Increase in Gleason 6 Tumor Volume While on Active Surveillance Portends a Greater Risk of Grade Reclassification with Further Followup', The Journal of Urology. doi: 10.1016/j.juro.2015.09.081.


CHAPTER 3: Patients And Methods

Thesis overview

In this chapter, a synopsis of the databases sourced, identification and selection of patients, and statistical methods employed, will be presented. The specific details of methods relating to each manuscript will be described in each of the 5 respective chapters.

For this thesis, six published manuscripts are included (Appendix B):

<table>
<thead>
<tr>
<th>Chapter 4</th>
<th>Evaluation of models predicting insignificant prostate cancer to select men for active surveillance of prostate cancer. (Wong, Neal, et al., 2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter 5</td>
<td>Feasibility for active surveillance in biopsy Gleason 3+4 prostate cancer: an Australian radical prostatectomy cohort</td>
</tr>
<tr>
<td>Chapter 6</td>
<td>Diagnostic Prostate Biopsy performed in a Non-Academic Center Increases the Risk of Re-classification at Confirmatory Biopsy for Men Considering Active Surveillance for Prostate Cancer. (Wong, Ferrara, et al., 2015)</td>
</tr>
<tr>
<td>Chapter 7</td>
<td>Should follow-up biopsies for men on Active Surveillance for prostate cancer be restricted to limited templates? (Wong, Trottier, et al., 2013)</td>
</tr>
<tr>
<td>Chapter 8</td>
<td>Regular Transition Zone Biopsy during Active Surveillance</td>
</tr>
</tbody>
</table>
for Prostate Cancer may Improve Detecting Pathological Progression. (Wong et al., 2014)

Chapter 9

A Negative Confirmatory Biopsy Among Men on Active Surveillance for Prostate Cancer Does Not protect them from Histological Grade Progression. (Wong, Alibhai, et al., 2013)

Data sources and variables

The data sources utilized for this thesis are summarized in Table 3-1.

For Chapter 4, radical prostatectomy data were pooled from 3 international academic institutions. These were Addenbrookes Hospital, Cambridge, United Kingdom; Princess Margaret Hospital, University of Toronto, Canada; and The Australian Prostate Cancer Centre@Epworth and Department of Urology Royal Melbourne Hospital, Australia.

Data analysed in Chapters 5 to 8 was from an Active Surveillance database compiled at Princess Margaret Hospital, University of Toronto, Canada.

Table 3-1: Data sources used in the thesis

<table>
<thead>
<tr>
<th>Chapter 4</th>
<th>Data type:</th>
<th>Dates and Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radical prostatectomy database</td>
<td>Collaboration between: 1. Addenbrooke's Hospital, Cambridge UK (2005-2011);</td>
</tr>
</tbody>
</table>
Baseline variables are those present at time of diagnosis of prostate cancer. These include age, year of diagnosis, family history of prostate cancer, DRE findings (clinical stage), serum PSA, TRUS prostate findings (prostate volume, presence of hypoechoic lesions, total number of cores taken), pathology from needle prostate biopsy (number of positive cores involved, Gleason score, maximum percentage of a single core involved, and location within prostate of where positive core(s) were found).
Variables from radical prostatectomy collected included date of surgery, and features from histopathology such as positive margin status, Gleason score, pT-stage, volume of cancer and lymph node status. Biochemical recurrence was collected from The Australian Prostate Cancer Centre@Epworth and Department of Urology Royal Melbourne Hospital, Australia (2003-2012) database for analysis presented in Chapter 5.

For men on active surveillance, date of each subsequent prostate biopsy, preceding PSA, pathology features at biopsy as outlined above, usage of 5 alpha reductase inhibitors (5ARI) and magnetic resonance imaging (MRI) was documented.

A summary list of abbreviations used in the thesis is provided in Appendix A.

**Identification of study patients**

In chapter 4, men suitable for AS were identified from the pooled collaborative radical prostatectomy dataset. Suitability was based on pre-selection criteria utilized in research by Kattan et al (Kattan et al., 2003) in creating their risk calculator to select men for AS. The aim of this “pre-selection” was to exclude men with high risk prostate cancer that would never be clinically considered for AS. Thus, men with pretreatment PSA>20, primary or secondary Gleason grade 4 or 5 cancer in biopsy, positive cores greater than 50%, total cancer in biopsy cores > 20 mm or benign tissue in all cores less than 40 mm were excluded.
For Chapter 5, modification of existing AS criteria was performed to theoretically allow Gleason 3+4 disease. The three AS criteria that were chosen to analyze were Royal Marsden, Sunnybrook Toronto and PRIAS, as these do not require the percentage of core involved with cancer parameter (not collected in the The Australian Prostate Cancer Centre@Epworth and Department of Urology Royal Melbourne Hospital, Australia database). The only adjustment to these inclusion criteria for the manuscript was changing the allowable Gleason score from 3+3 to 3+4.

In chapters 6 to 9, men on AS were identified according to the criteria of PSA <10 ng/ml, Gleason score (GS) ≤6, clinical stage ≤T2, ≤3 positive cores (PCore) for cancer, <50% of single core involved, and age ≤75 years. To ensure they had been entered into a surveillance program, a second, or confirmatory, biopsy (B2) after the initial diagnostic biopsy (B1) was required. As our understanding of what constitutes AS matured, further requirements for cleaner data were established. This meant excluding men with <10 cores at diagnosis for inadequate sampling, and excluding those with delayed confirmatory biopsy greater than 24 months for poor compliance.

**Outcomes measured in the thesis**

In Chapter 4, the ability of identified risk calculators to accurately predict suitability for AS, defined as presence of insignificant cancer, was assessed by
comparing the predicted to actual rates of insignificant cancer at radical prostatectomy.

In Chapter 5, adverse pathology at radical prostatectomy, defined as Gleason score $\geq 4+3$ and/or pathological stage $pT\geq 3$ was the primary endpoint. The secondary endpoint was biochemical recurrence (BCR), defined as a PSA $\geq 0.2$ ng/ml.

For Chapters 6 to 9, disease progression, or re-classification, at prostate biopsy was the main outcome. This was defined as increase in grade (Gleason score $\geq 3+4$) and/or volume ($\geq 4$ positive cores, $>50\%$ of single core involved with cancer) of prostate cancer.

**Statistical methods used in the thesis**

For comparison between different groups, continuous variables were assessed using ANOVA or the Student's t-test (parametric data), Wilcoxon Mann-Whitney or Kruskal-Wallis tests (non-parametric data); and chi-squared or Fisher's exact tests used to determine differences between groups of categorical variables.

Univariate and multivariate analysis was performed using logistical regression or Cox Proportional hazards regression as appropriate. Multivariate models were built with important clinico-pathological variables and forward stepwise regression was used. Collinearity was assessed between similar variables (e.g. PSA, prostate volume and PSA density). The number of covariables for the
multivariable model was carefully selected to avoid over-fitting (Peduzzi et al., 1996). Statistical analyses were performed using SPSS version 18.0 (IBM Corporation, Armonk, NY, USA). All statistical tests were two sided with p<0.05 considered to be statistically significant.

In Chapter 4, evaluation of prediction models was performed using area under the curve (AUC) of receiver operating characteristic curves and Brier scores for discrimination, calibration curves and decision curve analysis.

**Ethics statement**

For this thesis data were collaborated between 3 institutions. Ethics approval in all three centres was obtained for data collection and covered retrospective analysis of collected clinical information. With data sharing, patients' personal health information was de-identified. Records were kept in secure, password encrypted electronic files.

**Chapter references:**


CHAPTER 4: Evaluation Of Models Predicting Insignificant Prostate Cancer To Select Men For Active Surveillance Of Prostate Cancer

Introduction and PDF

In this chapter, external validation of all published risk calculators intended to aid selection of men for active surveillance (AS) was performed. These personalized risk assessors are appealing as they can theoretically individualize a man's risk and are easily accessible on the Internet. However, few have been robustly validated externally. We hypothesize that these risk calculators do not perform at an adequate level of accuracy for everyday non-educated use.
ORIGINAL ARTICLE

Evaluation of models predicting insignificent prostate cancer to select men for active surveillance of prostate cancer

L-M Wong1,2, DE Neal3, A Finelli3, S Davis3, C Bonner3, J Kapoor3, J Trachtenberg4, B Thomas5, CM Hovev3, AJ Costello3 and NM Corcoran3

BACKGROUND: In an era of personalized medicine, individualized risk assessment using easily available tools on the internet and the literature are appealing. However, unformed use by clinicians and the public raises potential problems. Herein, we assess the performance of published models to predict insignificant prostate cancer (PCa), using a multinational low-risk population that may be considered for active surveillance (AS) based on contemporary practice.

METHODS: Data on men suitable for AS but undergoing upfront radical prostatectomy were pooled from three international academic institutions in Cambridge (UK), Toronto (Canada) and Melbourne (Australia). Four predictive models identified from literature review were assessed for their ability to predict the presence of four insignificent PCa. Evaluation was performed using area under the curve (AUC) of receiver operating characteristic curves and Brier scores for discrimination, calibration curves and decision curve analysis.

RESULTS: A cohort of 460 men meeting the inclusion criteria of all four nomograms was identified. The highest AUCs calculated for any of the four models ranged from 0.618 to 0.664, suggesting weak positive discrimination at best. Models had best discriminative ability for a definition of insignificant disease characterized by organ-confined Gleason score ≤ 6 with a total volume ≤ 0.5 ml or 1.3 ml. Calibration plots showed moderate range of predictive ability for the Kattan model though this model did not perform well at decision curve analysis.

CONCLUSIONS: External assessment of models predicting insignificant PCa showed moderate performance at best. Uninformed interpretation may cause undue anxiety or false reassurance and they should be used with caution.

Prostate Cancer and Prostatic Disease (2015) 18, 137-143; doi:10.1038/pcan.2015.1; published online 10 February 2015

INTRODUCTION

Treatment paradigms for biopsy-determined small-volume, low-grade prostate cancer (PCa) have moved increasingly away from radical treatment and towards active surveillance (AS). The impetus for this comes from randomized PSA-screening trials10 suggesting that PCa is both over-diagnosed and over-treated. AS, with the intention of monitoring men with likely indolent PCa and intervening if more aggressive disease is subsequently found, aims to reduce the morbidity associated with management of such PCa.

Selection of men for AS has been traditionally guided by clinicopathological features found to be predictive of indolent PCa,2 defined as an organ-confined, well differentiated tumor (Gleason score ≤ 6) with a total volume not exceeding 0.5 ml.4 There are several methods to select patients with likely insignificant tumors following transrectal biopsy. The most common are cohort-based selection rules, which attempt to minimize the number of potentially significant cases within a population.5-19 We have previously shown that there are a number of drawbacks with this approach.11-13 With increased stringency of rules, fewer men are likely to have undiagnosed aggressive disease, but at the cost of excluding large numbers of men with biologically insignificant disease who are then ‘over-treated’. An alternative to cohort-based selection rules are personalized risk assessors, popularized as easy to use nomograms or online risk calculators.15-19 These tools have the theoretical advantage of individualizing risk for each patient’s circumstances. Few of these predictive tools have been robustly validated for accuracy and performance outside their derived populations, so their benefit and generalizability remain to be determined. Internal validation techniques, even utilizing statistical methods, such as boot-strapping, tend to overestimate a model’s predictive ability. Furthermore, many of the prediction models include in their analysis men with features of higher risk PCa at biopsy who were always unlikely to have insignificant disease at radical prostatectomy. This biases the pre-test probability and also results in overestimation of their model’s predictive ability.

In addition, the boundaries of what is permissible for AS are being challenged. Increased volume of disease (1.3 versus 0.5 ml)18 and low-volume Gleason 3+4 disease19 have been postulated as acceptable limits for AS. Although the selected predictive models were originally designed to predict the strict Epstein definition of insignificant disease, they may have comparable ability in predicting minor variation of the definition of insignificant disease. Herein, we assess the utility of these predictive tools to predict insignificant disease in a low-risk population that may be considered for AS based on contemporary practice.

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E-mail: theringuang@gmail.com

Received 23 October 2014; revised 8 December 2014; accepted 10 December 2014; published online 10 February 2015
MATERIALS AND METHODS

Data on men suitable for AS, meeting the selection criteria of the nomograms under assessment, but undergoing up-front radical prostatectomy, were pooled from three large tertiary institutions and retrospectively analyzed. Centers participating included Addenbrookes Hospital, Cambridge, UK (2005–2011); The Australian Prostate Cancer Centre/Epsom and Department of Urology, Royal Melbourne Hospital, Australia (2003–2012); and Princess Margaret Hospital, University of Toronto, Canada (2000–2012). Pathology for radical prostatectomy specimens was reported by genitourinary pathologists in all centers, as were needle biopsy specimens in Cambridge and Toronto. Data collection and transfer were performed with cross-institutional ethics approval.

A literature search was performed to identify all published predictive models for insignificant PCA found at radical prostatectomy.16–17 (Table 1). Although numerous terms such as “incident,” “minimal,” and “low-grade low-volume” are used across the literature, invariably these terms are subsequently defined as Epstein had originally described for “insignificant” cancer (Epstein 1994 #39; total tumor volume < 0.5 mL, organ-confined disease and absence of Gleason pattern 4 or 5 cancer). An early model was constructed by Kattan et al.18 and is incorporated into an easily available online pretreatment PCA risk calculator.19 Steyerberg and colleagues, in another online calculator, updated the Kattan model, but recalibrated the risk estimates based on a screening population of patients (European Randomized Study of Screening for Prostate Cancer).1 In Chun et al.11 and O'Brien et al.13 models predicting insignificant disease at radical prostatectomy, the actual proportion of men in their cohorts with insignificant disease was low (Table 1; both ~4% compared with 19.5% [Kattan] and 49% [Steyerberg]). The nomogram published by Nakashima et al.14 was only suitable for use in patients with 1 biopsy core positive for cancer. This was felt to be overly restrictive, clinically impractical and subsequently excluded from assessment.

For models where the regression equation was not published, corresponding authors were contacted for assistance. Available online risk calculators were accessed. When the regression equation was unobtainable, the probabilities were calculated by hand from the published graphical nomogram by two independent assessors (SD, CE), and results were cross-checked for consistency.

To identify men in our radical prostatectomy database, who were suitable for AS based on contemporary preoperative parameters, we first applied the Kattan “pre-selection” criteria.1 Thus, men with pretreatment PSA > 20, primary or secondary Gleason grade 4 or 5 cancer in biopsy, positive cores > 50%, total cancer in biopsy cores > 20% or benign tissue in all cores < 40 mm were excluded. For centers that reported cancer involvement of cores as a percentage rather than millimeters length, percentages were converted to millimeters by obtaining the average total core length of >200 random cores from each center. Insignificant disease at radical prostatectomy was defined by the classical Epstein criteria20 and three other, progressively less stringent potential definitions (Table 2). Our second definition allowed tumors of volume >1.3 mL,20 the third definition had no tumor volume restriction and the fourth allowed Gleason score 3+4 disease.21

Using the potential AS cohort as defined above, the performance of various prediction models was tested, assessing for both discrimination and calibration.22 Discrimination describes the model's ability to differentiate between those with versus those without the outcome of interest. In this case the presence of insignificant PCAs. The discriminatory ability of a predictive model is proportional to the area under the receiver operator

<table>
<thead>
<tr>
<th>Year and primary author</th>
<th>Population model derived from</th>
<th>Nomogram parameters</th>
<th>Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003 Kattan 1986–2000</td>
<td>&gt;6 cores at biopsy</td>
<td>Excluded: pretreatment PSA &gt;20, primary or secondary Gleason grade 4 or 5 cancer in biopsy, positive cores &gt;50, total cancer in biopsy cores &gt;20 mm or benign tissue in all cores &lt;40 mm. N=400 (after exclusion) 80/409 (19.5%) had insignificant cancer.</td>
<td>Three models: 1. Base: PSA, cT1, GS grade 2. Medium: add % cores positive and ultrasound volume 3. Full: replace % core involved with % of cancer/noncancer</td>
</tr>
<tr>
<td>2007 Steyerberg 1994–2004</td>
<td>Rotterdam section of the ERSPC</td>
<td>Lateralized sextant biopsies</td>
<td>Same exclusion criteria as Kattan. N=247. 121/247 (49%) had insignificant cancer.</td>
</tr>
<tr>
<td>2007 Nakashima 1997–2003</td>
<td>10–15 cores at biopsy</td>
<td>Only one positive core permitted. N=265 had radical prostatectomy. 134/265 (51.6%) had insignificant cancer.</td>
<td>Age PSA density Tumor length (mm) Gleason score not included in nomogram</td>
</tr>
<tr>
<td>2008 Chun 1992–2003</td>
<td>6–10 cores at biopsy</td>
<td>N=1132 67/1132 (3.3%) had insignificant cancer.</td>
<td>PSA</td>
</tr>
<tr>
<td>2011 O'Brien 1998–2009</td>
<td>Biopsy: 3–39 cores, median 12. N=2325 underwent RP 152/2525 (6%) had minimal cancer (&lt; 0.3 ml at RS GS)</td>
<td>Age Prostate volume PSA density % Positive biopsy cores Longest cancer length (mm)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under curve; ERSPC, European Randomized Study of Screening for Prostate Cancer; GS, Gleason sum; PRA1, Prostate Cancer Research International Active Surveillance; RS, radical prostatectomy. All defined insignificant cancer as: Insignificant cancer was defined as the total tumor volume < 0.5 ml using computer-assisted volumetric analysis of all separate tumor foci, confined to the prostate with no focal or established extracapsular extension and with no Gleason grade 4 or 5.
Table 2. Definitions of 'insignificant disease' prostate cancer used

<table>
<thead>
<tr>
<th>Definitions of insignificant disease</th>
<th>Frequency in our validation cohort (total n = 400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of cancer ≤ 0.5 ml and no GS 6.6; no Gleason pattern 4 or 5, and pT2 (Epstein)</td>
<td>23 (5.8%)</td>
</tr>
<tr>
<td>Volume of cancer ≤ 1.3 ml GS 6 pT2</td>
<td>67 (18.9%)</td>
</tr>
<tr>
<td>GS ≤ 6 pT2</td>
<td>203 (44.1%)</td>
</tr>
<tr>
<td>GS ≤ 3 + 4 pT2</td>
<td>350 (79%)</td>
</tr>
<tr>
<td>GS ≤ 3 + 4 pT2</td>
<td>350 (79%)</td>
</tr>
</tbody>
</table>

Abbreviations: GS, Gleason sum; pT2, organ-confined disease (cT2a TNM staging). *Pathology at radical prostatectomy.

Table 3. Briere scores of predictive models

<table>
<thead>
<tr>
<th>Model</th>
<th>Definition of insignificant disease</th>
<th>Briere score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kattan</td>
<td>EPSTEIN</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>pT2 GS ≤ 6, volume ≤ 1.3</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>pT2 GS = 6</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>pT2 GS ≥ 3 + 4</td>
<td>0.40</td>
</tr>
<tr>
<td>O'Brien</td>
<td>EPSTEIN</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>pT2 GS ≤ 6, volume ≤ 1.3</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>pT2 GS = 6</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>pT2 GS ≥ 3 + 4</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td>Chun</td>
<td>EPSTEIN</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>pT2 GS ≤ 6, volume ≤ 1.3</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>pT2 GS = 6</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>pT2 GS ≥ 3 + 4</td>
<td>0.67</td>
</tr>
<tr>
<td>Swerberg</td>
<td>EPSTEIN</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>pT2 GS ≤ 6, volume ≤ 1.3</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>pT2 GS = 6</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>pT2 GS ≥ 3 + 4</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.60</td>
</tr>
</tbody>
</table>

Abbreviations: GS, Gleason sum; pT2, organ-confined disease (cT2a TNM staging).

Table 4. Clinical pathological features, pre-radical prostatectomy, of men potentially suitable for AS by the Kattan exclusion rule

<table>
<thead>
<tr>
<th>n</th>
<th>400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center</td>
<td></td>
</tr>
<tr>
<td>Toronto</td>
<td>207 (49%)</td>
</tr>
<tr>
<td>Cambridge</td>
<td>132 (33.2%)</td>
</tr>
<tr>
<td>Melbourne</td>
<td>60 (17.8%)</td>
</tr>
<tr>
<td>Age (years) Mean</td>
<td>56.5</td>
</tr>
<tr>
<td>s.d.</td>
<td>5.9</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>6.6</td>
</tr>
<tr>
<td>s.d.</td>
<td>3.5</td>
</tr>
<tr>
<td>Prostate volume</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>52.9</td>
</tr>
<tr>
<td>s.d.</td>
<td>22</td>
</tr>
</tbody>
</table>

Stage

| CT1c | 404 (97.3%) |
| CT2a | 56 (22.9%)  |

Number of cores

| Median | 12 |
| IQR    | 10–13 |

Number of positive cores

| Median | 3 |
| IQR    | 2–4 |

Percent positive cores (p)

| Mean   | 25.3 |
| s.d.   | 11.8 |

Total cancer length (mm)

| Mean   | 5.9 |
| s.d.   | 4.2 |

Total noncancer length (mm)

| Mean   | 144.9 |
| s.d.   | 32.9 |

Length of cancer length (mm)

| Mean   | 3.6 |
| s.d.   | 2.5 |

Abbreviations: AS, active surveillance; IQR, interquartile range. *Pre-treatment PSA ≥ 20; primary serum Gleason grade 4 or 5 cancer in biopsy positive cores >50%, total cancer in biopsy cores >20 mm or benign tissue in all cores <40 mm were disqualified.

Results

A total of 3281 men were in the collaborative radical prostatectomy database. Of these, 460 (14%) men were considered potentially suitable for AS by the Kattan exclusion rule, and likely to have insignificant disease. A summary of their pertinent pre-operative clinical and pathological features is shown in Table 4.

Statistical analysis was performed using SPSS Version 18.0 (IBM, Armonk, NY, USA) or GraphPad Prism V5 (GraphPad Software, San Diego, CA, USA).

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Figure 1. Receiver operating curves—performance of the four nomograms to predict different definitions of insignificant disease: AUC, area under curve; GS, Gleason sum; pT2, organ-confined disease.

Figure 2. Calibration curves for the four nomograms. GS, Gleason Sum; pT2, organ-confined disease.

The frequency of insignificant cancer found at radical prostatectomy, for each definition used, is reported in Table 2. Receiver operator characteristics to assess the performance of the four published models to predict the Epstein definition of insignificant disease are shown in Figure 1. The AUC found for each model ranged from 0.563 (Chun), 0.612 (Kattan), 0.594 (O’Brien), and 0.601 (Steyerberg), suggesting weak positive discrimination at best. Ability to predict insignificant disease defined by a volume of 1.3 ml showed a similar range of AUC (0.577–0.664). When Gleason 3+4 disease was permitted, the AUC range was lower (range 0.527–0.607).

Calibration of each nomogram is seen in Figure 2. Here, the most striking observation is that only the Kattan nomogram (Figure 2a) has a good range of predicted probabilities of
patients on the internet. However, despite evidence in the literature suggesting caution with application of predictive models outside their derived populations, many clinicians and patients may be utilizing these tools inappropriately.

In our analysis, from a collaborative database of men who underwent upfront radical prostatectomy, we analyzed four models purposed to predict men with insignificant PCa, a surrogate for suitability for AS. Unlike several of the original model analyses, we adopted the approach by Kattan et al. and restricted inclusion to men who truly might be considered for AS. Thus men who had high-risk PCa at biopsy (for example, Gleason 8 disease), who would never be clinically considered for AS, were not analyzed, as previous work has indicated the low probability of low-risk disease in this scenario. In addition, as the boundaries defining ’insignificant cancer’ and suitability for AS are being challenged, we tested the performance of these predictive models using four progressively lenient definitions of insignificant cancer (Table 2).

Our receiver operator characteristic curves with calculated AUC (Figure 1) showed at best, modest performance of the different models (maximal AUC of 0.664). Not surprisingly, the models performed better in predicting the more stringent definitions of insignificant cancer (Epstein, and cancer volume ≤ 1.3 ml), as this is what they were originally designed for. The P-values for nearly all models, across the four definitions, were significant or approached significance. Thus the AUCs found, although moderate, are likely to statistically be better than tossing a coin (AUC = 0.5).

These results highlight the need for careful validation of predictive models. Internal validation, using the data set the model was originally derived from, statistically tends to overestimate both discriminative and calibration ability. In our external validation of both Chun and O’Brien nomograms, the AUCs calculated (0.563 and 0.533, respectively) were markedly lower than original reports (0.904 and 0.933, respectively). Their performance was even poorer than that demonstrated on similar analysis by Iyengar et al. (AUC 0.729 and 0.739, respectively). Furthermore, the calibration curves for all models (Figure 2), with the exception of Kattan, had restricted range of predicted probabilities to <0.4. This indicates that their originally reported high AUC was driven by the pre-test probability of insignificant disease in the derived population, rather than any discriminatory power. In both Chun and O’Brien models, only ~5% of their cohorts had defined ’insignificant disease’. Conversely, in an example of a model that was statistically sound but of limited clinical value, a different nomogram restricted its analysis to men with only one positive core at biopsy. To our knowledge, there is no published AS cohort that restricts eligibility to a single biopsy core. At last, the decision analysis curve for the best performing model (Kattan predicting Epstein insignificant disease) was no better than assuming all men had indolent disease. To put it simply, these models lack the ability to identify men with a high probability of insignificant disease.

Another possible reason for disparities between internal and external validation are true differences between the cohorts. The Kattan model was published in 2003, but derived from a population of men who had radical prostatectomy between 1986 and 2000. Changes in biopsy technique (ректant to extended") and Gleason grade reporting have occurred, and hence the patient seated in front of clinicians today differs to those this model was derived from. Geographical differences may also exist. The Steyerberg model updates the Kattan, but is derived from men with screen detected cancer. Hence, it may not be appropriate for populations such as the United Kingdom (a component of our validation cohort) with low prevalence of PSA and, furthermore, attempted validation was performed for definitions of insignificant disease with minor variations to what the nomograms were originally designed for. However, interestingly the

---

**Table 5. Multivariable logistic regression predicting insignificant prostate cancer (Epstein definition) at radical prostatectomy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>0.83</td>
<td>0.41-1.57</td>
<td>0.518</td>
</tr>
<tr>
<td>PSA (ng ml⁻¹)</td>
<td>0.89</td>
<td>0.83-0.95</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.96</td>
<td>0.92-0.98</td>
<td>0.003</td>
</tr>
<tr>
<td>Positive cores (per unit)</td>
<td>1.12</td>
<td>0.70-1.84</td>
<td>0.549</td>
</tr>
<tr>
<td>Percent positive cores</td>
<td>0.96</td>
<td>0.93-1.03</td>
<td>0.466</td>
</tr>
<tr>
<td>Prostate volume (ml)</td>
<td>1.02</td>
<td>1.01-1.03</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cancer length (mm)</td>
<td>1.04</td>
<td>0.95-1.13</td>
<td>0.370</td>
</tr>
<tr>
<td>Total non cancer length (mm)</td>
<td>1.02</td>
<td>0.99-1.01</td>
<td>0.777</td>
</tr>
<tr>
<td>Longest cancer length (mm)</td>
<td>0.93</td>
<td>0.81-1.05</td>
<td>0.209</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, Odds ratio.

---

**DISCUSSION**

As patients and physicians enthusiastically pursue AS as a strategy to minimize morbidity associated with overtreatment of PCa, the ability to accurately select men suitable for this approach is paramount. Predictive models to help select men for AS have been published with several easily accessible to clinicians and

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models showed similar performance in predicting Epstein and Wolters' definitions of Insignificant disease. Similarly, work to investigate whether these models could be used to predict pathological progression for men on AS was limited. At last, models can only be as good as the data available to create or validate them. It is increasingly apparent that transrectal ultrasound-guided prostate biopsy is an imperfect test with significant sampling error. The discrepancy in both grade and volume between biopsy and radical prostatectomy is difficult to model statistically.

Incorporation of advances in imaging, biomarkers and genetic tests may be able enhance these models. Developments in multiparametric magnetic resonance imaging, with standardized scoring and proposed ability to differentiate more aggressive tumors, offer the greatest potential for incorporation into individualized predictive models. Magnetic resonance imaging-guided biopsy, being cognitive, ultrasound-guided or in-bore, in addition presents a potential solution to overcoming the sampling error associated with standard transrectal prostate biopsy.

Furthermore, magnetic resonance imaging may be able to preoperatively directly assess tumor volume as a predictive variable. Transperineal template biopsies sample more of the gland but are still a binned form of biopsy. The emergence of biomarkers that can improve the predictive ability of established clinical pathological variables, and possibly predict more aggressive disease, are likely to be incorporated into models in the future.

Our study sample size (26-460) limits the statistical power of our analysis. However, it does represent multi-institutional data and is one of the largest cohorts of men with low-risk disease (using Kattan pre-selection criteria) that has undergone upfront radical prostatectomy published in the literature. The Kattan nomogram was itself derived from a similar cohort of 409 men. As fewer and fewer men undergo radical prostatectomy for low-risk disease, this data is of value. The cohorts were collected over 6-12 years, and thus more recently AS has become acceptable and increasingly adopted. Thus it must be remembered that although the patients analyzed had low-risk disease, they represent a surgical cohort, with all its unforeseen biases compared with a strict AS cohort. These may include age, family history, comorbidities, patient anxiety, imaging findings and institutional preferences for treatment. Being retrospective, differences in data collection between individual centers could not be controlled. Percentage of care involved by cancer, reported by Cambridge and Toronto, required conversion to millenniums of cancer using a median total core length and thus could have affected calculations. Furthermore, adverse pathology at radical prostatectomy may not correlate with longer-term outcomes such as biochemical recurrence and cancer-specific mortality, more clinically relevant outcomes.

For this investigation, we set out to ascertain the most effective published predictive model to guide clinicians in identifying men with insignificant PCA. Our results showed that the four models found all performed moderately at best, and only the Kattan model had any useful predictive range at calibration for our cohort. We would counsel to use these easily accessible models with care, as there is a danger that uneducated use, without understanding of how they are derived or their limitations, could result in false reassurance or anxiety.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ACKNOWLEDGEMENTS
Princess Margaret Hospital Prostate Precise database was conceived and maintained by the very generous financial and support of the Wambambo Family Foundation with administrative support by the Princess Margaret Cancer Centre Foundation. We acknowledge the support of The University of Cambridge Cancer Research UK and Hutchison Whampoa Limited. We acknowledge the support of the National Institute for Health Research, which funds the Cambridge Biomedical Research Centre, Cambridge, UK. We also acknowledge the support of the National Cancer Research Prostate Cancer Mechanisms of Progression and Treatment (PRoMPT) collaboration (grant code:090008/6175446), which has funded tissue and urine collections in Cambridge. We also acknowledge the support of the Cambridge Cancer Research Foundation. The Human Research Tissue Bank is supported by the NHS Cambridge Biomedical Research Centre.

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CHAPTER 5: Feasibility For Active Surveillance In Biopsy Gleason 3+4 Prostate Cancer: An Australian Radical Prostatectomy Cohort

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Key words: Prostate cancer, Gleason score, Active Surveillance, Outcomes, Radical Prostatectomy

Word Count:

- abstract: 255
- manuscript: 1826
Abstract:

Objective:
To examine the feasibility of active surveillance for low volume Gleason score (GS) 3+4 disease compared to GS 3+3 disease.

Patients and Methods:
Retrospective review of 929 patients, with biopsy proven GS 3+3 and 3+4 PCa, undergoing upfront radical prostatectomy (RP) was performed. Suitability for AS was adapted from protocols by Royal Marsden Hospital, University of Toronto, and PRIAS by allowing Gleason 3+4 disease.

The outcomes assessed were adverse pathology at RP (upgrading ≥ GS 4+3 and/or upstaging ≥pT3) and biochemical recurrence (BCR) after RP.

Results:
Adverse pathology at RP was compared between GS 3+3 versus 3+4 groups. When selecting patients using Royal Marsden (n=714) or University of Toronto (n=699) protocols, there was statistically significantly more adverse pathology at RP in GS 3+4 group (21% versus 31%, p=0.0028 and 19% versus 33%, p=<0.001 respectively). Using the more stringent PRIAS protocol (n=198), there was no statistical significant difference in groups.

There was no difference in BCR survival between biopsy GS 3+3 and 3+4 groups, regardless of which AS protocol assessed. Pre-operative PSA and clinical staging were the predictors for BCR.
Conclusion:

Presence of Gleason 3+4 at biopsy, when compared to 3+3, increases the risk of adverse pathology being present at radical prostatectomy for less stringent selection criteria. When considering AS, a stricter protocol such as PRIAS, limiting PSA density and number of positive cores to ≤2, appears to decrease the risk of adverse pathology. No differences in BCR were seen between biopsy 3+3 and 3+4 disease, regardless of AS selection criteria.
**Introduction**

Active surveillance (AS) is a recognized management for low risk prostate cancer, with the benefit of avoiding side effects of active treatments in men who are thought unlikely to die from prostate cancer. With longer follow-up of this group of men, the frequency of development of metastases (2.8%) and prostate cancer mortality (1.5%) has been shown to be low (88).

To date, mainstream AS practice has only included men with Gleason 3+3 disease. However, for Gleason 3+4 disease, there are preliminary reports of AS being used in highly motivated men (104), or those with significant comorbidity (88). Data from the Victorian Prostate Cancer Registry showed that 25.6% of men on AS had National Comprehensive Cancer Network (NCCN) intermediate risk (n=251/980) (141). Of these, 53.8% had Gleason 3+4 at biopsy. Additionally, of all men with NCCN intermediate risk category in the database, 8.9% were managed with AS. However, the long-term feasibility and safety of AS in this group of men remains to be elucidated.

For men suitable for AS but undergoing upfront radical prostatectomy, the literature reports the frequency of adverse pathology ranging from 7.1-50.6% (upgrading) and 2.4%-17% (upstaging), depending on the selection criteria used and population studied (96,142). Herein we examine the feasibility for AS for men with biopsy proven Gleason 3+4, in our Australian radical prostatectomy cohort.
Methods

Respective chart review of the Epworth Prostate Cancer Center database (2005-2013) was performed. Inclusion criteria were men with biopsy Gleason 3+3 and 3+4 disease, with total prostate biopsy cores taken ≥ 10, and undergoing upfront radical prostatectomy (RP). Men were selected as suitable for AS according to recognized protocols utilized by Royal Marsden Hospital (87), University of Toronto (88), and Prostate Cancer Research International Active Surveillance (PRIAS)(143). For the purposes of this study, these protocols were modified to allow biopsy Gleason 3+4, keeping other selection criteria the same (Table 5-1). RP pathology was obtained, with favorable pathology defined as GS ≤ 6 and ≤pT2c, and adverse pathology defined as GS ≥4+3 and/or ≥pT3.

Table 5-1: AS inclusion criteria used for this study

<table>
<thead>
<tr>
<th>Institution</th>
<th>Clinical Stage</th>
<th>PSA (ng/ml)</th>
<th>Biopsy GS</th>
<th>PSAD (ng/ml/ml)</th>
<th>No of +ve cores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal Marsden</td>
<td>T1-T2</td>
<td>≤ 15</td>
<td>≤ 3+4</td>
<td>-</td>
<td>≤ 50% total cores</td>
</tr>
<tr>
<td>University of Toronto</td>
<td>T1c/ T2a</td>
<td>≤ 10</td>
<td>≤ 6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PRIAS</td>
<td>T1c/ T2</td>
<td>≤ 10</td>
<td>≤ 6</td>
<td>&lt; 0.20</td>
<td>≤ 2</td>
</tr>
</tbody>
</table>

Patients were grouped according to biopsy Gleason score (Gleason 3+3 or Gleason 3+4), and differences between groups determined by Mann-Whitney U or Chi square test as appropriate. The primary endpoint was presence of adverse pathology at RP, defined as Gleason score ≥4+3 and/or pathological stage pT≥3. The secondary endpoint was biochemical recurrence (BCR), defined as a PSA ≥ 0.2 ng/ml. Patients who did not experience a recurrence were censored at the date of their last PSA reading. To assess differences in biochemical recurrence,
Kaplan-Meier curves were generated and compared using the log rank test. To
determine what variables predicted tumour upgrading/upstaging or biochemical
recurrence, binary logistic and Cox proportional hazards regression models were
fitted respectively, and odds/hazards ratios (OR/HR) calculated as appropriate.
All tests were 2-sided with significance assumed at <0.05. Analyses were
performed using SPSS (v18.0, IBM Corporation, Armonk, NY, USA).

Results
In total, 929 patients were identified with biopsy proven Gleason 3+3 and 3+4
prostate cancer that subsequently underwent upfront RP. Overall, the median
age of our cohort was 61.9yrs (IQR 57-66). Comparison of these two groups,
demonstrating baseline features at prostate biopsy as well as characteristics at
radical prostatectomy, are summarized in Table 5-2. At prostate biopsy, the
Gleason 3+4 group had more positive cores (4 vs 2, p<0.001) and higher
proportion of positive cores (33.3% vs 22.2%, p<0.001). Overall, at radical
prostatectomy, more patients with Gleason 3+4 at biopsy were upgraded to
≥4+3 (20.2% versus 11.9%, p<0.001), and upstaged to ≥pT3 disease (25.4%
versus 16.3%, p=0.001).
Table 5-2: Comparison of baseline characteristics between biopsy Gleason 3+3 and 3+4 groups.

<table>
<thead>
<tr>
<th></th>
<th>Gleason 3+3</th>
<th>Gleason 3+4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>399</td>
<td>530</td>
</tr>
<tr>
<td>Age (Years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>61 (57-66)</td>
<td>62 (58-66)</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>6.1 (4.8-8.5)</td>
<td>5.9 (4.6-7.9)</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cT1</td>
<td>323 (80.9%)</td>
<td>373 (70.4%)</td>
</tr>
<tr>
<td>cT2a</td>
<td>31 (7.8%)</td>
<td>68 (12.8%)</td>
</tr>
<tr>
<td>cT2b</td>
<td>38 (9.5%)</td>
<td>65 (12.3%)</td>
</tr>
<tr>
<td>≥ cT2c</td>
<td>6 (1.5%)</td>
<td>21 (4.0%)</td>
</tr>
<tr>
<td>% Positive cores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>22.2% (12.5-37.5)</td>
<td>33.3% (18.3-50.0)</td>
</tr>
<tr>
<td>Pathological Gleason Score - RRP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>138 (34.6%)</td>
<td>28 (5.3%)</td>
</tr>
<tr>
<td>3+4</td>
<td>214 (53.6%)</td>
<td>395 (74.5%)</td>
</tr>
<tr>
<td>4+3</td>
<td>41 (10.3%)</td>
<td>90 (17.0%)</td>
</tr>
<tr>
<td>8</td>
<td>5 (1.3%)</td>
<td>9 (1.7%)</td>
</tr>
<tr>
<td>9</td>
<td>1 (0.3%)</td>
<td>8 (1.5%)</td>
</tr>
<tr>
<td>pT stage - RRP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT2</td>
<td>334 (83.7%)</td>
<td>395 (74.5%)</td>
</tr>
<tr>
<td>pT3a</td>
<td>59 (14.8%)</td>
<td>120 (22.6%)</td>
</tr>
<tr>
<td>pT3b</td>
<td>6 (1.5%)</td>
<td>15 (2.8%)</td>
</tr>
<tr>
<td>Adverse Pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>94 (23.6%)</td>
<td>192 (36.2%)</td>
</tr>
<tr>
<td>no</td>
<td>305 (76.4%)</td>
<td>192 (63.8%)</td>
</tr>
<tr>
<td>Tumour volume (ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.5 (0.6-3.3)</td>
<td>1.9 (1.0-3.5)</td>
</tr>
<tr>
<td>Prostate volume (ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>49 (38.3-63.8)</td>
<td>46 (38.0-58.0)</td>
</tr>
</tbody>
</table>

The 929 patients were then categorized into suitability for AS, based on their prostate biopsy, according to the modified Royal Marsden (n=714), University of
Toronto (n=699) and PRIAS (n=198) protocols. Comparison of subsequent adverse pathology at RP, with AS criteria restrictions, was performed (Table 5-3).

**Table 5-3: Effect of selection criteria applied to biopsy groups on adverse pathology found at radical prostatectomy.**

<table>
<thead>
<tr>
<th>Biopsy GS</th>
<th>3+3</th>
<th>3+4</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Royal Marsden Hospital</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>328</td>
<td>386</td>
<td></td>
</tr>
<tr>
<td>Prostatectomy GS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6</td>
<td>123 (37%)</td>
<td>23 (6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3+4</td>
<td>167 (51%)</td>
<td>294 (76%)</td>
<td></td>
</tr>
<tr>
<td>≥ 4+3</td>
<td>38 (12%)</td>
<td>69 (18%)</td>
<td></td>
</tr>
<tr>
<td>pT Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>284 (86%)</td>
<td>304 (79%)</td>
<td>0.006</td>
</tr>
<tr>
<td>≥ 3</td>
<td>44 (14%)</td>
<td>82 (21%)</td>
<td></td>
</tr>
<tr>
<td>Favourable pathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse pathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Toronto</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>308</td>
<td>391</td>
<td></td>
</tr>
<tr>
<td>Prostatectomy GS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>118 (38%)</td>
<td>21 (5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3+4</td>
<td>161 (52%)</td>
<td>301 (77%)</td>
<td></td>
</tr>
<tr>
<td>≥4+3</td>
<td>28 (10%)</td>
<td>69 (18%)</td>
<td></td>
</tr>
<tr>
<td>pT Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>272 (88%)</td>
<td>306 (78%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 3</td>
<td>36 (12%)</td>
<td>85 (22%)</td>
<td></td>
</tr>
<tr>
<td>Favourable pathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse pathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PRIAS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>110</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Prostatectomy GS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 6</td>
<td>57 (51.8%)</td>
<td>9 (10%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3+4</td>
<td>45 (40.9%)</td>
<td>69 (79%)</td>
<td></td>
</tr>
<tr>
<td>≥ 4+3</td>
<td>8 (7.3%)</td>
<td>10 (11%)</td>
<td></td>
</tr>
<tr>
<td>pT Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>102 (92.7%)</td>
<td>78 (87%)</td>
<td>0.32</td>
</tr>
<tr>
<td>≥ 3</td>
<td>8 (7.3%)</td>
<td>10 (13%)</td>
<td></td>
</tr>
<tr>
<td>Favourable pathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse pathology</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
For both Royal Marsden and Toronto AS criteria, there were statistically significant differences in upgrading and upstaging comparing the biopsy 3+4 and 3+3 groups. Both selection criteria had similar proportion of men with consequent adverse pathology at radical prostatectomy (Royal Marsden 31%, Toronto 33%). The PRIAS criteria, being more stringent, had fewer suitable men in both Gleason 3+3 and 3+4 biopsy groups. However, the difference in adverse pathology at radical prostatectomy was less and not statistically significant (13% versus 19%, \( p=0.25 \)). Sensitivity analyses examining different combinations of PRIAS inclusion criteria found removing PSA density did not significantly affect adverse pathology (15% versus 23.3%, \( p=0.81 \)); and similarly allowing 3 positive cores rather than two had minimal effect (15.3% versus 21.1%, \( p=0.2 \)) (data not shown).

To examine biochemical recurrence (BCR) after radical prostatectomy, postoperative PSA data were available in 683 of 714 (95.7%) patients in the Royal Marsden Hospital protocol group, 670 of 699 (95.9%) patients in the Toronto protocol group, and 202 of 211 (95.7%) patients in the PRIAS protocol group. Median follow-up for men without BCR was 26mo (IQR 12-48.5). Kaplan-Meier analysis to compare BCR-free survival after radical prostatectomy is shown in Figure 5-1. For all three AS protocols, there were no statistical significant differences between biopsy Gleason 3+3 and Gleason 3+4 disease groups for BCR-free survival (log rank test, \( p=0.12 \), \( p=0.32 \) and \( p=0.72 \) respectively).
To examine for predictors of adverse pathology, logistic regression analysis was performed on all patients with biopsy proven Gleason 3+3 and 3+4 disease. Age (OR 1.07, 1.04-1.10, p<0.001), number of positive cores (OR 1.11, 1.05-1.17, p<0.001), pre-operative PSA (OR 1.09, 1.05-1.12, p<0.001), clinical stage (OR 1.48, 1.07-2.05, p=0.013) and Gleason score (3+3 versus 3+4, OR 1.58, 1.15-2.18, p=0.005) were all significant factors on multivariate analysis. However, when a sensitivity analysis was performed, limiting the same logistic regression analysis to men with ≤2 positive cores at biopsy, only age, number of positive cores and PSA remained significant variables. Significant predictors for BCR on cox regression were pre-operative PSA (HR 1.1, 1.06-1.13, p<0.001) and clinical stage (HR 1.91, 1.33-2.73, p<0.001).
Discussion

In our cohort of men with biopsy proven Gleason 3+3 and 3+4 disease who underwent upfront radical prostatectomy, there were significant differences in adverse pathology found at radical prostatectomy (23.6 vs 36.2%, p<0.001). Modified AS protocols were then used to allow presence of Gleason 3+4 disease at biopsy when selecting patients as suitable for AS. When comparing the biopsy 3+3 and 3+4 groups within the frameworks of these protocols, only the stricter PRIAS criteria was able to reduce the frequency of adverse pathology found at radical prostatectomy (13% versus 19%, p=0.25). Finally, when examining the long-term outcome of biochemical free recurrence, there was no statistical difference between biopsy 3+3 and 3+4 disease, regardless of which modified AS protocol was used.

Across the literature, there have been men with Gleason 3+4 disease, often highly motivated(104) or with some comorbidity(88), managed with AS. Our data suggests, for these men with Gleason 3+4 to be considered for AS, utilization of more stringent criteria such as PRIAS is advisable. PRIAS selection criteria are stricter in that only 2 positive cores at biopsy are allowed, and PSA density must be <0.20ng/ml/cc. Sensitivity analyses of the PRIAS selection criteria suggested dropping PSA density, or allowing 3 positive cores with a PSA density ≤0.20, did not significantly alter the amount of adverse pathology at radical prostatectomy. The allowable number positive cores we found differ to previous findings. Ploussard et al (144) found presence of more than 2 positive cores was significantly associated with higher frequency of Gleason ≥4+3 (27.1% vs 20.9%, p=0.002) and pT3-4 disease (41.1% vs 26.9%, p<0.001). Schiavina et al (145)
suggest even stricter interpretation, limiting PRIAS AS criteria to 1 positive core of GS 3+4 disease. They found this selection filter had similar outcomes for adverse pathology and biochemical recurrence when compared to GS 3+3 disease. A percentage amount of Gleason 4 disease ≤5%, relative to the total amount of cancer found at biopsy, has also been proposed as a method for selection with findings that this group of men had similar pathologic stages, total tumor volume, and insignificant tumor rate in RP(146).

Prospective data on AS for men with GS 3+4 disease has been gathered in the University of Toronto, Sunnybrook Hospital single-arm cohort study. Men with Gleason with 3+4 disease were accepted with conditions. Initially (1995-1999), all patients older than 70 years were allowed with PSA ≤15 or Gleason ≤3+4. Subsequently (>Jan 2000), the study was restricted to exclude men with PSA 10-20 and/or Gleason ≤3+4 with significant comorbidities and a life expectancy <10 years (88). In total, 25% of their cohort of 993 patients fulfilled D’Amico criteria for intermediate risk. Overall, only 1.5% of patients died of prostate cancer, and the 10 and 15-year actuarial cancer specific survival (CSS) rates were 98%, and 94% respectively. With so few men dying of prostate cancer, in the context of 25% of the cohort having “intermediate risk”, the authors argue that in a screened population, selected men older than age 70 years with intermediate-risk prostate cancer are candidates for surveillance. However, it should be noted that of the 28 men who developed metastases in this cohort, 12 (44%) had Gleason 3+4 at diagnosis.
In a different institution, it was demonstrated that men with intermediate risk (Gleason 3+4 and/or CAPRA 3-5) at baseline were older, had higher PSA values and greater tumour involvement (percentage of core involved) than low-risk men (147). Though follow-up was relatively short, comparison of their intermediate to low-risk group showed similar proportions of progression free survival (61% versus 54%) and progression to active treatment (35% versus 30%)(147). A composite definition of progression was used, including increase in Gleason grade, PSA doubling time ≤2 or 3 years, and progression to treatment. For men enrolled with 3+4 disease, biopsy Gleason 4+3 disease was considered grade progression. It remains to be demonstrated whether an increase in volume of 3+4 disease at biopsy should be used to trigger treatment.

Advances in imaging and biomarkers may be able to assist with selection of men with 3+4 disease, and deciding if treatment needs to be triggered. The Prostate Health Index (PHI) has been used to successfully predict pathological progression but based on standard Gleason 3+3 criteria(148,149). The Oncotype DX Genomic Prostate Score (GPS) test (Genomic Health, Redwood City, California, USA) is a 17-gene panel that was validated on a cohort of men having National Comprehensive Cancer Network (NCCN) very-low, low and intermediate risk prostate cancer undergoing radical prostatectomy within 6 months(150). The GPS demonstrated ability to predict adverse pathology at radical prostatectomy. Adverse pathology was defined as primary Gleason pattern 4 or any pattern 5 and/or pT3 disease. Cost of the GPS remains a significant barrier for wider uptake. Finally, the ability of multiparametric MRI to grade disease radiologically(151), predict re-classification(152), and guide placement of biopsy
needle either in-bore (153) or using ultrasound fusion (154), could assist selecting men with Gleason 3+4 disease for AS.

Patients on AS, whilst avoiding the consequences of radical treatment, are living with untreated cancer. Thus, they may suffer negative psychological effects and anxiety from fear of progression. As men with intermediate risk disease have higher risk of progression, it is possible that they could have more severe psychological effects. Alternatively, as many of these men are often highly motivated, they may be self-selected for calmer personality types. A systematic review suggested that patients undergoing AS reported good quality of life and did not appear to suffer negative psychological impacts (155). In particular, there has been documented low levels of anxiety for men on AS (156,157).

As our data were examined retrospectively, we were limited to the data fields previously collected. Percentage of core involvement with cancer was not collected, hence AS protocols requiring <50% of single core involved could not be tested. Without this variable, analysis to identify a threshold for percentage of core involvement, which might predict lesser risk of progression, could not be performed. In particular, we were unable to test the hypothesis of Huang et al. (146) examining a biopsy threshold of <5% containing Gleason 4 having equivalent outcomes at radical prostatectomy to men with only Gleason 3+3 disease. Also, a surgical cohort rather than an active surveillance one will contain unaccounted inherent biases such as age, comorbidities, patient anxiety and institutional factors. We were able to report biochemical recurrence post radical
prostatectomy but this is still only a surrogate for longer-term outcomes such as metastasis and cancer specific survival.

In conclusion, appropriately selected biopsy Gleason 3+4 disease may be considered for highly motivated patients. A stricter protocol such as PRIAS should be used with restriction of number of positive cores to ≤2, and consideration of PSA density ≤0.20, as this appears to minimize presence of potential adverse pathology. Adverse pathology in biopsy Gleason 3+4 disease did not translate into higher biochemical recurrence rates but it remains to be seen if this translates into harder endpoints such as metastasis free and cancer free survival.
CHAPTER 6: Diagnostic Prostate Biopsy performed in a Non-Academic Center Increases the Risk of Re-classification at Confirmatory Biopsy for Men Considering Active Surveillance for Prostate Cancer.

Introduction and PDF

This chapter of the thesis examines the issue of quality of prostate biopsy when selecting men for AS. Princess Margaret Cancer Centre (PMCC) in Toronto, is an academic, or tertiary referral centre. Hence, a proportion of patients are diagnosed with prostate cancer in the community and referred to PMCC, in this case to discuss AS.

It was anecdotally observed that men referred from external institutions who then had their confirmatory biopsy at PMCC were more likely to have worse disease found at the confirmatory biopsy. This manuscript presents the investigation into this hypothesis.
ORIGINAL ARTICLE

Diagnostic prostate biopsy performed in a non-academic center increases the risk of re-classification at confirmatory biopsy for men considering active surveillance for prostate cancer

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BACKGROUND: To examine whether diagnostic biopsy (B1), for patients on active surveillance (AS) for prostate cancer, performed at an outside referral center (external) compared with our in-house tertiary center (internal), increased the risk of re-classification on the confirmatory (confirmatory biopsy (B2).)

METHODS: Patients on AS were identified from our tertiary center database (1997–2012) with PSA < 10. Gleason sum (GS) ≤ 6, clinical stage ≤ T2a, ≤ 3 positive cores, < 50% of single core involved, age ≤ 75 years and having a B2. Patients who had < 10 cores at B1 and delay in B2 > 24 mo were excluded. Depending on center where B1 was performed, men were dichotomized to internal or external groups. All B2 were performed Internally. Multivariate logistic regression examined if external B1 was a predictor of re-classification at B2.

RESULTS: A total of 375 patients were divided into external (n = 71, 18.9%) and internal groups (n = 304, 81.1%). At B2, more men in the external group re-classified (26.8%) compared with the internal group (13.8%) (P = 0.008). On multivariate analysis, external B1 predicted grade-related re-classification (odds ratio (OR) 4.14, confidence interval (CI) 2.01–8.54, P < 0.001) and volume-related re-classification (OR 3.43, CI 1.87–6.25, P < 0.001). Other significant predictors for grade-related re-classification were age (OR 2.15 per decade, CI 1.32–3.57, P < 0.001), PSA density (OR 2.26 per unit, CI 1.44–4.73, P < 0.001), maximum % core involvement (OR 1.04 per percentage point, CI 1.01–1.09, P = 0.002) and time between B1 and B2 (OR 1.43 per 6 months, CI 1.21–1.71, P < 0.001).

CONCLUSION: At our Institution, patients on AS who had their initial B1 performed externally were more likely to have adverse pathological features and re-classify on internal B2.

Prostate Cancer and Prostatic Disease (2013) 18, 69–74; doi:10.1038/pcan.2014.48; published online 9 December 2014

INTRODUCTION

Patient selection for active surveillance (AS) currently remains heavily dependent on the volume and grade of disease found at prostate biopsy. Despite recent investigation into image-guided biopsy with multiparametric magnetic resonance imaging, template mapping saturation biopsy and biomarkers, the foundation for AS in most centers continues to be repeated transrectal ultrasound-guided prostate biopsy (TRUSPB). To minimize under-diagnosis of significant prostate cancer with standard TRUSPB, a second, otherwise known as the confirmatory, biopsy (B2) is recommended.1

Most published series on AS have arisen from larger academic centers.2 3 4 One would expect such institutions to frequently receive referrals for AS with initial diagnostic biopsy (B1) already performed. Berglund et al.6 examined a cohort of men where initial biopsy was performed at a referring institution and found 28% of men were upgraded and/or upstaged on repeat biopsy or at radical prostatectomy. Close examination of the published AS series reveals very few centers differentiate whether the B1 was from their center or performed elsewhere.7

Herein, we examine the effect of having had a B1 performed before the referral and the subsequent risk of re-classification. This information could assist with prioritization of which patients should undergo B2 or ancillary testing to ascertain their true disease state.

MATERIALS AND METHODS

We identified patients on AS from our prospectively maintained academic institutional database (1997–2012) with PSA < 10 ng mL−1. Gleason sum (GS) ≤ 6, clinical stage ≤ T2a, ≤ 3 positive cores for cancer, < 50% of single core involved, age ≤ 75 years and had at least a B2 after the initial B1 (n = 552). As our understanding of what constitutes AS has developed, from this data set, men with < 10 cores at diagnosis

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(n = 125) and those with delayed confirmatory biopsy (time > 24 months, n = 52) were excluded.

Patients were dichotomized depending on whether their diagnostic biopsy was performed in-house at the Princess Margaret Cancer Center (PMCC; Internal) or from an outside referral center (External). For all patients, B2 was performed at PMCC. A single operator (AF) performed the majority of biopsies at PMCC (75%) using an end-fire probe (C.6.5, ICT, Phillips, Bothell, WA, USA) under local anesthetic infiltration. At PMCC, B1 was performed using a standard extended 10–12 core template and all B2 were performed using a Bavarian template (13–17 cores) with cores of the transition zone taken. All B2 biopsies were read by one of four genitourinary pathologists.

The terms pathological 're-classification' and 'progression' have been used somewhat interchangeably in the literature to describe increases in Gleason grade and/or volume at repeat biopsy. For describing changes at B2, we prefer the term re-classification, as this is more likely a reflection of under-sampling at B1 than true disease transformation. The term 'progression' is best applied for biopsies performed later on as it becomes more difficult to distinguish between true disease transformation, development of new disease or repeated sampling error. Re-classification was subdivided into both grade (GSI ≥ 7) and volume (≥ 4 core positive cores, ≥ 50% single core involved). Grade-related re-classification was defined as men with grade-only and combined grade-and-volume re-classification. Volume-related re-classification describes men with volume-only and grade-and-volume re-classification.

Comparison between the internal and external biopsy groups, examining both the B1 and B2, were made using analysis of variance (continuous variables) and chi-squared test (nominal variables). Univariate and multivariate logistic regression were performed to assess if external B1 was a predictor for re-classification at B2. The model was built with important clinicopathological variables and forward stepwise regressions was used. A co-linearity check was performed for PSA, prostate volume and PSA density, with PSA density carried forward into the multivariate model. The number of covariates for the multivariable model was carefully selected to avoid over fitting. Model discrimination and calibration were assessed with c-statistics and the Hosmer-Lemeshow test. Analysis was done using SAS statistical software version 9.1 (Cary, NC, 125). All statistical tests were two sided with P < 0.05 considered to be statistically significant.

RESULTS
A total of 375 patients were included, divided into external (n = 71, 18.9%) and internal B1 groups (n = 304, 81.1%). Characteristics at the baseline biopsy are shown in Table 1. Baseline age, PSA and prostate volume were similar between the groups. Patients with external B1, compared with internal B1, were statistically more likely to have high-grade prostatic intraepithelial neoplasia reported (P = 0.01) and less likely to have a TRUS nodule identified (P = 0.003).

The second biopsy (B2), all performed at PMCC, was then examined comparing the external and Internal B1 groups. These results are shown in Table 2. At B2, a total of 61 patients (61/375 = 16.3%) re-classified. More men in the external group re-classified (26.6%) compared with the internal group (13.8% P = 0.008). At B2, patients with external B1 were more likely to have a statistically significant increase in all three pathological re-classification criteria: GS ≥ 7 (19.7% versus 7.5%, P = 0.03), positive core ≥ 3 (19.7% versus 8.2%, P = 0.004) and highest % core involved ≥ 50% (20.3% versus 8.5%, P = 0.005).

Table 3 summarizes the multivariate logistic regression analysis for re-classification at B2 (3b), with sub-analyses for grade-related (3b) and volume-related progression (3c) also performed. External biopsy was a predictor of overall re-classification (odds ratio (OR) 3.05, 1.48–6.19, P = 0.002), grade-related (OR 3.08, 1.23–7.66, P = 0.009) and volume-related re-classification (OR 3.14, 1.44–6.63, P = 0.003). Other predictors of re-classification at B2 were PSA density (OR 2.14 per unit, 1.53–3.91, P = 0.006) and increasing time between B1 and B2 (OR 1.46 per 6 months, 1.09–1.97, P = 0.01). To account for the possibility that more cores were taken at B1 internally compared with externally, and hence more cancer was

<p>| Table 1. Comparison of baseline biopsy characteristics between external and internal groups |
|---|---|---|</p>
<table>
<thead>
<tr>
<th>N</th>
<th>External diagnostic biopsy</th>
<th>Internal diagnostic biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>External</td>
<td>62.2 (6.4)</td>
<td>62.8 (6.7)</td>
</tr>
<tr>
<td>Internal</td>
<td>62.2 (6.4)</td>
<td>63.2 (6.9)</td>
</tr>
<tr>
<td>P</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Family history (n, %)</td>
<td>Yes</td>
<td>22 (30.9)</td>
</tr>
<tr>
<td>No</td>
<td>17 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (16.9)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>PSA (n, %)</td>
<td>Median (IQR)</td>
<td>5.1 (3.0–6.9)</td>
</tr>
<tr>
<td>P</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Total number of cores taken (n, %)</td>
<td>&gt; 10</td>
<td>71 (100.0)</td>
</tr>
<tr>
<td>≥ 10</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Picc (n, %)</td>
<td>1</td>
<td>53 (27.4)</td>
</tr>
<tr>
<td>2</td>
<td>14 (19.3)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>4 (5.6)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>Maximum percentage core involved</td>
<td>Median (IQR)</td>
<td>5 (5–10)</td>
</tr>
<tr>
<td>P</td>
<td>≤ 0.01</td>
<td></td>
</tr>
<tr>
<td>Prostate volume (n, %)</td>
<td>&lt; 50 ml</td>
<td>34 (37.9)</td>
</tr>
<tr>
<td>≥ 50 ml</td>
<td>22 (25.0)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>15 (17.1)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.95</td>
<td></td>
</tr>
<tr>
<td>SARI use at baseline (n, %)</td>
<td>Yes</td>
<td>7 (9.9)</td>
</tr>
<tr>
<td>No</td>
<td>64 (90.1)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>Presence of HGPIN (n, %)</td>
<td>Yes</td>
<td>14 (19.7)</td>
</tr>
<tr>
<td>No</td>
<td>57 (80.3)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Presence of ASAP (n, %)</td>
<td>Yes</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>No</td>
<td>68 (95.8)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Inflammation (n, %)</td>
<td>Yes</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>No</td>
<td>67 (94.4)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Previous negative bx before AS (n, %)</td>
<td>Yes</td>
<td>12 (16.9)</td>
</tr>
<tr>
<td>No</td>
<td>59 (83.1)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>TRUS nodule present (n, %)</td>
<td>Yes</td>
<td>13 (18.3)</td>
</tr>
<tr>
<td>No</td>
<td>89 (92.7)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (9.9)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>1.03</td>
<td></td>
</tr>
<tr>
<td>Year biopsy performed</td>
<td>&lt; 2005</td>
<td>62 (97.3)</td>
</tr>
<tr>
<td>≥ 2005</td>
<td>2 (3.1)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>MRI during AS (n, %)</td>
<td>Yes</td>
<td>20 (28.2)</td>
</tr>
<tr>
<td>No</td>
<td>51 (71.8)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.58</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AS, active surveillance; ASAR, atypical small acinar proliferation; HGPIN, high-grade prostatic intraepithelial neoplasia; IQR, interquartile range; MRI, magnetic resonance imaging; NA, not applicable; PIcore, number of positive cores; TRUS, transrectal ultrasound; SARI, 5 alpha reductase inhibitor.
Table 2. Characteristics of second prostate biopsy (B2), all performed internally

<table>
<thead>
<tr>
<th>Re-classification criteria (n, %)</th>
<th>External diagnostic biopsy (n = 71)</th>
<th>Internal diagnostic biopsy (n = 204)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cancer</td>
<td>29 (40.5)</td>
<td>134 (44.1)</td>
<td>0.03</td>
</tr>
<tr>
<td>≥3</td>
<td>28 (39.6)</td>
<td>147 (48.4)</td>
<td></td>
</tr>
<tr>
<td>≥4</td>
<td>11 (15.5)</td>
<td>19 (6.3)</td>
<td></td>
</tr>
<tr>
<td>≥4+</td>
<td>2 (2.8)</td>
<td>3 (0.9)</td>
<td></td>
</tr>
<tr>
<td>≥4+4</td>
<td>1 (1.4)</td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Positive cores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3</td>
<td>57 (80.3)</td>
<td>279 (91.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>&gt;3</td>
<td>14 (19.7)</td>
<td>25 (8.2)</td>
<td></td>
</tr>
<tr>
<td>Highest percent in a core</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>34 (47.7)</td>
<td>158 (54.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>37 (52.3)</td>
<td>131 (45.5)</td>
<td></td>
</tr>
<tr>
<td>Total number of patients with pathological re-classification on B2</td>
<td>19 (26.8%)</td>
<td>42 (13.8%)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Other parameters (n, %)

| PSA immediately before B2        |                                   |                                   |         |
| <4                               | 23 (32.4)                         | 115 (38.1)                        | 0.58    |
| 4-10                             | 46 (63.4)                         | 171 (56.0)                        |         |
| >10                              | 3 (4.2)                           | 16 (5.3)                          |         |
| Missing                           | 0                                 | 2                                 | 0.002   |

| Presence of HGPIN at B2           |                                   |                                   |         |
| Yes                              | 6 (8.5)                           | 18 (5.9)                          | 0.62    |
| No                               | 65 (91.5)                         | 284 (94.1)                        |         |
| Unknown                          | 0                                 | 2                                 | 0.77    |

| Presence of ASAP at B2            |                                   |                                   |         |
| Yes                              | 0                                 | 2                                 | 0.77    |
| No                               | 71 (100.0)                        | 300 (96.0)                        |         |
| Unknown                          | 0                                 | 2                                 | 0.77    |

| Presence of inflammation at B2    |                                   |                                   |         |
| Yes                              | 2                                 | 6                                 | 0.77    |
| No                               | 69 (97.2)                         | 296 (97.4)                        |         |
| Unknown                          | 0                                 | 2                                 | 0.77    |

| TRUS nodule present at B2         |                                   |                                   |         |
| Yes                              | 31 (43.3)                         | 55 (33.1)                         | 0.01    |
| No                               | 38 (56.7)                         | 109 (66.9)                        |         |
| Unknown                          | 1 (1.4)                           | 0                                 | 0.00    |

| Time between first and second biopsy ≤1 months | 39 (51.7) | 251 (82.0) | 0.06 |
| >1 months                          | 13 (18.3) | 53 (17.4)  |       |

Abbreviations: ASAP: atypical small acinar proliferation; HGPIN, high-grade prostatic intraepithelial neoplasia; TRUS, transrectal ultrasound.

We found a sensitivity analysis was performed only looking at men in our cohort who had 10–14 cores taken at B1. This confirmed external biopsy location as a significant predictor of re-classification at B2.

In the external B1 group (n = 71), only five biopsies were reported by external pathologists with uro-oncology expertise. Because of this low event rate, comparison within the external group was not oncology and general pathologists could not be performed. Internal pathology review of externally taken diagnostic biopsies was performed for 32/71 men. However, any increased Gleason grade on internal pathology review resulted in ineligibility for A5 and hence these men were not captured in our database for analysis. Changes in cancer volume at B1 from internal pathology review of external biopsy are shown in Table 4a with increase in percentage amount of core involved the most frequent change. In Table 4a, increases in grade and volume at B2, for men having external B1 with and without internal pathology review are compared. There was no difference between the two groups seen. A multivariate logistical regression model, (examining age, PSA, % core involvement, total number of cores taken and time between B1 and B2), to predict which men had internal pathology review did not yield any significant results (data not shown).

**DISCUSSION**

The relationship between having a B1 performed outside an academic high-volume center and future risk of re-classification is an important one to explore. Until adoption of A5 for low risk prostate cancer becomes commonplace, many patients are seen and managed at tertiary care centers. The proportion of men with external diagnostic biopsies has not been well reported in published A5 cohorts but is likely significant. Herein, we have demonstrated that patients with an externally taken B1 (18.9% of our cohort) were more likely to have pathological re-classification at their B2 (OR 3.05, 1.46–6.19, P = 0.002). Sub-analyses showed that external biopsy also predicted both grade (OR 3.06, 1.23–7.66, P = 0.002) and volume-related re-classification (OR 3.14, 1.44–6.63, P = 0.003), at the B2.

As we have previously shown, grade re-classification (GS ≥7) is the most relevant comparator as different A5 cohorts use varying volume criteria for eligibility. We found a greater frequency of grade re-classification in men with an external B1 compared with an internal B1 (19.7% versus 7.5%, P = 0.03), similar to a previous report (26% versus 16%).5 Berglund et al. examined repeat prostate biopsies in men with prostate cancer suitable for A5, all performed at outside referring centers, though without our restriction on total number of cores initially taken, and without comparison with an internal biopsy group or a multivariate analysis. In 104 men, the proportion of Gleason upgrading (18/104, 17.3%) found was similar to our findings (14/71, 19.7%). In men suitable for A5 who had immediate radical prostatectomy, the proportion of upgrading has been reported to be 31–56.0%.12

To our knowledge, this is the first time externally performed B1 has been found in a multivariate model, to demonstrate an increased risk of both grade and volume re-classification on B2 (Table 3). Furthermore, our data suggest that PSA, maximum % core involvement, and time between B1 and B2 were also significant predictors of re-classification on the B2 (Table 3). Although B2 is recommended within 12 months at our institution, a 24-month period was chosen for analysis to allow for patient or administrative delay in B2. Over 80% of the patients received their B2 within 18 months. Univariate analysis examining time intervals between B1 and B2 suggests a time >12 mo significantly increased risk of re-classification at B2 (Table 3). These results could be used to triage timing of B2 for men considering A5.

Biopsy operator is known to be an independent predictor of detecting prostate cancer at TRUSB.13 This could be due to differences in operator experience, case volume, nuances in technique and quality of equipment used. An end firing ultrasound probe configuration, compared with side firing, is also suggested to have an increased cancer detection rate.16 Differences in described visible TRUS nodules between internal and external biopsy groups (Tables 1 and 2) suggest variation in operator technique. However, although visible TRUS nodule status may be a surrogate for operator experience, on multivariate analysis it did not predict re-classification. Biopsy using different template schema can also account for differences in cancer found.17 However, we excluded men who had <10 cores at B1 from our analysis to diminish possible confounding by the use of outdated sextant biopsy templates.

Differences in pathological interpretation could also account for the discrepancy found between internal and external B1 groups. Our data examining frequency of high-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation...
### Table 1. Logistic regression examining predictors at baseline biopsy (B1) of re-classification at confirmatory biopsy (B2)

#### (a) Predictors of grade-related re-classification (GS ≥ 7) at B2

<table>
<thead>
<tr>
<th>Baseline variables from B1</th>
<th>OR of non-re-classified (N = 336) versus re-classified (N = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariable</td>
</tr>
<tr>
<td>Age (per 10-year increase)</td>
<td>1.92 (1.12–3.31)</td>
</tr>
<tr>
<td>Family history (yes versus no)</td>
<td>1.30 (0.61–2.78)</td>
</tr>
<tr>
<td>(unknown versus no)</td>
<td>0.61 (0.23–1.51)</td>
</tr>
<tr>
<td>Biopsy location (extravascular versus internal)</td>
<td>3.13 (1.54–6.33)</td>
</tr>
<tr>
<td>PSA ng mL⁻¹ (per 1-unit increase)</td>
<td>0.55 (0.13–2.40)</td>
</tr>
<tr>
<td>Prostate volume (ml) (per 1-unit increase)</td>
<td>1.13 (0.96–1.31)</td>
</tr>
<tr>
<td>Log(PSA density) (ng mL⁻¹·ml⁻¹) (for every 1-unit increase)</td>
<td>0.68 (0.96–1.00)</td>
</tr>
<tr>
<td>DRE palpable nodule (yes versus no)</td>
<td>2.64 (1.36–5.10)</td>
</tr>
<tr>
<td>TRUS nodule present (yes versus no)</td>
<td>1.38 (0.54–3.52)</td>
</tr>
<tr>
<td>Number of positive cores per positive core</td>
<td>1.07 (1.03–1.12)</td>
</tr>
<tr>
<td>Maximum % core involved (per 1-percentage increase)</td>
<td>0.93 (0.82–1.06)</td>
</tr>
<tr>
<td>Time between B1 and confirmatory biopsy (per 6-month increase)</td>
<td>1.57 (1.14–2.16)</td>
</tr>
</tbody>
</table>

#### Time between B1 and confirmatory biopsy

<table>
<thead>
<tr>
<th>Time</th>
<th>Reference</th>
<th>0-6 months</th>
<th>6–12 months</th>
<th>12–18 months</th>
<th>18–24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td></td>
<td></td>
<td>1.43 (0.48–4.28)</td>
<td>0.52</td>
<td>NA</td>
</tr>
<tr>
<td>6–12 months</td>
<td></td>
<td></td>
<td>2.41 (1.29–8.56)</td>
<td>0.02</td>
<td>NA</td>
</tr>
<tr>
<td>12–18 months</td>
<td></td>
<td></td>
<td>2.65 (0.97–7.84)</td>
<td>0.08</td>
<td>NA</td>
</tr>
<tr>
<td>18–24 months</td>
<td></td>
<td></td>
<td>1.16 (0.35–2.43)</td>
<td>0.09</td>
<td>C-statistics = 0.79</td>
</tr>
</tbody>
</table>

#### MRL (yes versus no)

| MRL (yes versus no) | 1.16 (0.35–2.43) | 0.09 |

#### (b) Predictors of volume-related re-classification (≥ 50% single core and positive core ≥ 3) at B2

<table>
<thead>
<tr>
<th>Baseline variables (first+versa)</th>
<th>OR of non-re-classified (N = 333) versus re-classified (N = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariable</td>
</tr>
<tr>
<td>Age (per 10-year increase)</td>
<td>1.43 (0.86–2.37)</td>
</tr>
<tr>
<td>Family history (yes versus no)</td>
<td>1.47 (0.68–3.18)</td>
</tr>
<tr>
<td>(unknown versus no)</td>
<td>1.25 (0.57–2.75)</td>
</tr>
<tr>
<td>Biopsy location (extravascular versus internal)</td>
<td>2.42 (1.29–4.89)</td>
</tr>
<tr>
<td>PSA (ng mL⁻¹) (per 1-unit increase)</td>
<td>0.51 (0.12–2.19)</td>
</tr>
<tr>
<td>Prostate volume (ml) (per 1-unit increase)</td>
<td>1.06 (0.91–1.23)</td>
</tr>
<tr>
<td>Log(PSA density) (ng mL⁻¹·ml⁻¹) (for every 1-unit increase)</td>
<td>0.98 (0.96–0.99)</td>
</tr>
<tr>
<td>DRE palpable nodule (yes versus no)</td>
<td>2.16 (1.57–4.50)</td>
</tr>
<tr>
<td>TRUS nodule present (yes versus no)</td>
<td>1.88 (0.81–4.37)</td>
</tr>
<tr>
<td>Number of positive cores (per positive core)</td>
<td>6.81 (0.29–1.73)</td>
</tr>
<tr>
<td>Gleason score (for every 1-unit increase)</td>
<td>Not used</td>
</tr>
<tr>
<td>Total number of cores (per core increase)</td>
<td>6.91 (0.79–1.03)</td>
</tr>
<tr>
<td>Time between B1 and confirmatory biopsy (per 6-month increase)</td>
<td>1.41 (1.04–1.91)</td>
</tr>
</tbody>
</table>

#### Time between B1 and confirmatory biopsy

<table>
<thead>
<tr>
<th>Time</th>
<th>Reference</th>
<th>0-6 months</th>
<th>6–12 months</th>
<th>12–18 months</th>
<th>18–24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td></td>
<td></td>
<td>1.38 (0.49–3.86)</td>
<td>0.54</td>
<td>NA</td>
</tr>
<tr>
<td>6–12 months</td>
<td></td>
<td></td>
<td>2.52 (0.88–4.57)</td>
<td>0.05</td>
<td>NA</td>
</tr>
<tr>
<td>12–18 months</td>
<td></td>
<td></td>
<td>2.85 (1.05–7.79)</td>
<td>0.04</td>
<td>NA</td>
</tr>
<tr>
<td>18–24 months</td>
<td></td>
<td></td>
<td>1.72 (0.87–3.41)</td>
<td>0.11</td>
<td>C-statistics = 0.69</td>
</tr>
</tbody>
</table>

#### MRL (yes versus no)

| MRL (yes versus no) | 1.72 (0.87–3.41) | 0.11 |

C-statistics = 0.69
H and L fit test = 0.31
Table 3. (Continued)

<table>
<thead>
<tr>
<th>Baseline variables (first-versus)</th>
<th>OR of non-re-classified (N = 374) versus re-classified (N = 51)</th>
<th>Univariable P-value</th>
<th>Multivariable P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10-year increase)</td>
<td>1.52 (0.99–2.35)</td>
<td>0.056</td>
<td>1.65 (1.02–2.73)</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(yes versus no)</td>
<td>1.78 (0.93–3.41)</td>
<td>0.08</td>
<td>Not used</td>
</tr>
<tr>
<td>(unknown versus no)</td>
<td>1.19 (0.59–2.35)</td>
<td>0.83</td>
<td>Not used</td>
</tr>
<tr>
<td>Biopsy location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(external versus internal)</td>
<td>2.28 (1.23–4.23)</td>
<td>0.009</td>
<td>2.96 (1.43–6.04)</td>
</tr>
<tr>
<td>DRE palpable nodule (yes versus no)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRUS nodule present (yes versus no)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Positive cores (per positive core)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum % involved (per 1 percentage increase)</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of cores taken (per core increase)</td>
<td>0.68 (0.26–0.99)</td>
<td>0.03</td>
<td>0.86 (0.77–0.99)</td>
</tr>
<tr>
<td>Time between B1 and confirmatory biopsy (per 6-month increase)</td>
<td>1.07 (1.03–1.12)</td>
<td>0.002</td>
<td>1.46 (1.09–1.96)</td>
</tr>
<tr>
<td>Time between B1 and biopsies confirmed biopsy</td>
<td>Reference</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>0–6 months</td>
<td>2.13 (0.86–5.27)</td>
<td>0.10</td>
<td>NA</td>
</tr>
<tr>
<td>6–12 months</td>
<td>3.91 (1.66–9.18)</td>
<td>0.001</td>
<td>NA</td>
</tr>
<tr>
<td>12–18 months</td>
<td>3.33 (1.31–8.45)</td>
<td>0.01</td>
<td>NA</td>
</tr>
<tr>
<td>MRI during AS (yes versus no)</td>
<td>1.83 (1.03–3.28)</td>
<td>0.043</td>
<td>2.17 (1.12–4.16)</td>
</tr>
</tbody>
</table>

Abbreviations: AS, active surveillances; SARI, 5 alpha reductase inhibitor; DRE, digital rectal examination; GS, Gleason sum; MRI, magnetic resonance imaging.
NA, not applicable. OR, odds ratio; TRUS, transrectal ultrasound.

reported suggest as such. At B1, both high-grade prostatic intraepithelial neoplasia (16.1% versus 7.6%) and atypical small acinar proliferation (5.1% versus 0.5%) were reported more frequently in the external B1 group. However, at B2, which was all reported internally, this difference disappeared (Table 2). Furthermore, when considering AS eligibility at prostate biopsy, there is recognized inter-observer variation for each of the pathological criteria. Challenges surrounding GS interpretation have been well documented, even among uropathologists. The agreement in reporting of GS 6 between 15 expert uropathologists and 337 members of the European Network of Uropathology was reported as 71.4% (58.2–89.3%). One of the greatest difficulties lies in reproducibly recognizing small amounts of Gleason pattern 4 in biopsies that otherwise contain only Gleason pattern 3. This is particularly true when the minor amount of Gleason pattern 4 consists of small glands with inconstant or absence of lumina. Another point of contention centers on the reporting of cribriform Gleason patterns 3 and 4. In a study investigating the accuracy of Gleason scores assigned to biopsy samples, there were less agreement in scoring (no change in AS status) in 12.1%. Thus, collaboration with dedicated uropathologists when managing patients considering AS is important.

The study had the limitations in terms of the patients' characteristics. The patients included in this study are from a single institution with retrospective analyses. Patient referral patterns differ geographically so our results may not be representative of other AS populations, though most published cohorts are from similar academic centers. There may be referral bias that we could not account for in our analysis. Our institution, like many others, does not have a fixed B2 requirement before starting AS. However, 80% of men had B2 within 18 mo of B1. All B2 were performed internally, 75% by a single operator, which decreased inter-operator variability and allowed consistent comparison with the baseline diagnostic TRUS/P8. All B2 biopsies were reported by one of four genitourinary pathologists whose pattern of practice includes pre-sign-out quality assurance reviews to confirm Gleason scores when B2 biopsies are found to have a small component of Gleason pattern 4 tumor that would result in re-classification. This may not be representative of practices at other institutions. We were unable to demonstrate that internal pathology review of external B1 altered re-classification at B2. However, this analysis was affected by selection bias as any men found unsuitable for AS by internal pathology review of external B1 were not captured in our AS database. Multiparametric magnetic resonance imaging was not performed routinely in our cohort though this has been reported as a useful tool to predict re-classification among men on AS. Finally, the relationship between long-term outcomes such as overall survival, cancer-specific survival and cancer-free survival, with pathological re-classification need to be explored further.

Our findings have implications for enrollment of patients in AS. The entity is on academic institutions accepting referrals for AS to investigate if the quality of biopsy in referred men is similar to those performed in-house. Although mandatory B2 and mandatory centralized pathology review are appealing solutions, they are not without patient morbidity and additional cost that require further study in AS populations.
Table 4. Men having external B1 with internal pathology review
(a) Changes at B1 as a result of internal pathology review (n = 33)\textsuperscript{a}

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of positive cores</strong></td>
<td></td>
</tr>
<tr>
<td>Increased $\geq$ 3$^a$</td>
<td>None by definition</td>
</tr>
<tr>
<td>Increased</td>
<td>6 (18.8)</td>
</tr>
<tr>
<td>Decreased</td>
<td>1 (3.1)</td>
</tr>
<tr>
<td>Same</td>
<td>25 (78.1)</td>
</tr>
<tr>
<td><strong>Highest % cancer percent in core</strong></td>
<td></td>
</tr>
<tr>
<td>Increased $\geq$ 50$^b$</td>
<td>None by definition</td>
</tr>
<tr>
<td>Increased</td>
<td>11 (34.4)</td>
</tr>
<tr>
<td>Decreased</td>
<td>7 (21.9)</td>
</tr>
<tr>
<td>Same</td>
<td>14 (43.8)</td>
</tr>
</tbody>
</table>

(b) For men with externally performed biopsy, comparison between those with and without internal B1 pathology review: changes in grade and volume parameters at B2

<table>
<thead>
<tr>
<th>External B1---no P internal pathology review</th>
<th>External B1---with P internal pathology review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gleason score (n)</td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>39</td>
</tr>
<tr>
<td>Decreased</td>
<td>17 (43.6)</td>
</tr>
<tr>
<td>Same</td>
<td>14 (35.9)</td>
</tr>
<tr>
<td>No cancer at B2</td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>17 (43.6)</td>
</tr>
<tr>
<td>Decreased</td>
<td>16 (41.0)</td>
</tr>
<tr>
<td>Same</td>
<td>6 (15.4)</td>
</tr>
<tr>
<td>Number of positive cores (4)</td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>22</td>
</tr>
<tr>
<td>Decreased</td>
<td>17 (43.6)</td>
</tr>
<tr>
<td>Same</td>
<td>14 (35.9)</td>
</tr>
<tr>
<td>Highest % cancer percent in core (n)</td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>11 (33.3)</td>
</tr>
<tr>
<td>Decreased</td>
<td>7 (21.9)</td>
</tr>
<tr>
<td>Same</td>
<td>12 (36.3)</td>
</tr>
<tr>
<td>Number of patients that re-classified pathologically</td>
<td>8 (24.2)</td>
</tr>
</tbody>
</table>

Abbreviations: A5, active surveillance; B1, baseline (or diagnostic) prostate biopsy; B2, second (or confirmatory) prostate biopsy. As only patients who were suitable for A5 were selected for analysis, by definition at baseline biopsy, there were no patients with pathological re-classification seen. Hence, any pathological re-classification from internal pathology review resulted in exclusion from A5 and our study.

CONCLUSION
In an academic centre managing men on A5, we have demonstrated that an external B1 was a predictor of re-classification at the B2. Location where initial biopsy was performed, along with age, PSA density and percentage of involved cores, should be considered carefully when triaging timing of the B2.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

REFERENCES
CHAPTER 7: Should follow-up biopsies for men on Active Surveillance for prostate cancer be restricted to limited templates?

Introduction and PDF
This chapter examines the prostate biopsy template used during AS. In particular, the aim was to investigate if prostate biopsy templates with fewer cores could be utilized during active surveillance (AS) for prostate cancer. Currently, our institution uses an AS protocol template (ASPT) consisting of 13-17 cores. We hypothesize in the setting of known cancer, sextant (6 cores) or standard extended (10-12 cores) templates, could be used with similar effect.
Should Follow-up Biopsies for Men on Active Surveillance for Prostate Cancer Be Restricted to Limited Templates?


OBJECTIVE
To investigate if prostate biopsy templates with fewer cores can be used during active surveillance (AS) for prostate cancer.

METHODS
At present, we use an AS protocol template (ASPT) consisting of 13-17 cores. We hypothesize in the setting of known cancer, sextant (6 cores) or standard extended (10-12 cores) templates, could be used with similar effect. We identified patients in our referral institution database (1997-2009) with entry prostate-specific antigen <10 ng/mL, stage ≤T2, Gleason sum ≤6, ≤3 cores positive for cancer, <50% of single core involved, and age ≤75 years (N = 272). Patients fulfilling standard criteria for pathologic reclassification (N = 94) at any follow-up biopsy were selected for evaluation. By mapping tumor location on the pathologic reclassification determining biopsy, hypothetical scenarios of sextant or standard extended templates (SET) were compared with our ASPT and examined for frequency of cancer detection and pathologic reclassification.

RESULTS
For the 94 patients analyzed, the median number of cores taken was 9.7 (6-22) at baseline and 15 (14-17) for the reclassification biopsy. The median time between baseline and the pathologic reclassification determining biopsy was 15.4 months. Analysis of subgroups showed that sextant template would identify 84% of cancers and 47.9% of the reclassification events, whereas SET detected 99% of cancers and 81.9% of patients who pathologically reclassified. When only considering Gleason sum ≥7-related progression events, SET found 16.2% less (n = 57) compared with ASPT (n = 68).

CONCLUSION
When monitoring patients on AS, a 13-17 core template detects more pathologic reclassification than standard sextant (18.1%) or extended (52.1%) biopsy templates. UROLOGY 82: 405-409, 2013. © 2013 Elsevier Inc.
performed AS, still use TRUSPB to monitor most of their patients.

Published AS series have traditionally baser their biopsy schema on a standard 10-12 core extended peripheral zone biopsy. The only report from Johns Hopkins, since 2009, discusses routine biopsy outside the peripheral zone. At our institution for biopsy during AS, we have routinely been using a 13-17 core template (Fig. 1) modeled on Bahaid et al’s study to minimize undersampling from the initial biopsy. In this study, we examine a cohort of patients who had pathologic reclassification on biopsy during AS. We compare the hypothetical effects of using standard template schema with fewer cores (sextant and extended) with our AS protocol biopsy template when assessing the outcomes of cancer detection and pathologic reclassification.

MATERIALS AND METHODS

Patients were identified from our single institution prospectively maintained database of AS (1997-2009). Our inclusion criteria for this study consisted of baseline PSA <10, Gleason sum (GS) ≤6, stage cT2, ≤3 cores positive for cancer, <50% of single core involved, and age ≤75 years. From this group (n = 272), 94 patients fulfilled criteria for pathologic reclassification at any follow-up biopsy and were selected for evaluation. Pathologic reclassification was defined as the presence of GS 7, number of positive cores ≥4 or single core cancer involvement >50%, or both.

Baseline and repeat TRUSPBs for patients on AS were taken in a standard manner at our institution, using an endfire probe (C9-5 ICT, Philips, Bothwell, WA) under local anesthesia. A single operator (A.T.) performed most of the biopsies (75%). Biopsy location and involvement were systematically captured and entered into the database along with other clinical-pathologic variables. For biopsies on AS, an AS protocol template (ASPT), modeled on Bahaid et al’s study, of 13-17 cores was taken. The ASPT samples lateral and medial peripheral zones (PZ), transition zone, and midline at the base of the prostate (Fig. 1). Extra cores of suspicious areas outside this systematic area may be taken. In comparison, a sextant schema (6 cores) samples the PZ (medial) and extended schema (10-12 cores) includes lateral and medial PZ cores (Fig. 1). Biopsy cores were grouped and labeled by the region sampled (eg right lateral peripheral zone) rather than individually. Positive core location was mapped from all biopsies during AS. Thus, for the pathologic reclassification determining biopsy, we were able to compare hypothetical scenarios of sextant or standard extended templates (SET) with the ASPT we typically use. The outcomes measured were the ability to detect cancer and pathologic reclassification.

Differences between groups were determined using the Chi-squared test. Logistical regression was performed using SAS statistical software version 9.1 (Cary, NC) to identify predictors of patients that might be suitable for sextant or SET biopsy schema. All statistical tests were 2 sided with P < 0.05 considered to be statistically significant.

RESULTS

The baseline characteristics for the 94 patients analyzed are shown in Table 1. The median number of cores taken by each biopsy was baseline 9.7 (6-22), biopsy 15 (14-17), and at reclassification 15 (14-17). The median time between baseline and the pathologic reclassification determining biopsy was 15.4 months (8.9-27.8), and the median number of biopsies performed was 3 (range 2-6). Of the 94 patients, 44 (46.5%) were reclassified on the second (confirmatory) biopsy, 35 (37.2%) on the third, 12 (23.8%) on fourth, and 3 (3.2%) on fifth or subsequent biopsies. Patients were reclassified with 1 (56.4%), 2 (28.7%), and all 3 criteria (14.9%) respectively.

The comparisons between different biopsy template schema in detection of cancer and detection of pathologic reclassification are shown in Table 2. For pathologic reclassification, the ASPT detected 18.1% and 52.1% more cases than SET and sextant, respectively.

Table 1. Patient characteristics at diagnosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients (N)</td>
<td>94</td>
</tr>
<tr>
<td>Age (y)</td>
<td>Median (IQR) 66.2 (61.2-69.7)</td>
</tr>
<tr>
<td>Family history of prostate cancer N (%)</td>
<td>Yes: 19 (20.2), No: 46 (48.9)</td>
</tr>
<tr>
<td>DRE node palpable: N (%)</td>
<td>Yes (cT2): 29 (30.9), No (cT1): 55 (58.5)</td>
</tr>
<tr>
<td>PSA ng/mL</td>
<td>Median (IQR) 5.1 (3.0-6.8)</td>
</tr>
<tr>
<td>Prostate volume (mL) N (%)</td>
<td>Median (IQR) 44.4 (33.0-64.0)</td>
</tr>
<tr>
<td>PSA density (ng/mL/mL) N (%)</td>
<td>Median (IQR) 0.11 (0.07-0.16)</td>
</tr>
</tbody>
</table>

Fig. 1. Different biopsy templates. Sextant standard extended active surveillance protocol at our institution. (Color version available online.)

UROLOGY 82 (2), 2013
Table 2. Comparisons between different biopsy templates in cancer yield and detection of pathologic reclassification

<table>
<thead>
<tr>
<th>Template</th>
<th>Proportion of Patients With Cancer Detected</th>
<th>Proportion of Patients With Reclassification Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sextant</td>
<td>84%</td>
<td>47.9%</td>
</tr>
<tr>
<td>Standard</td>
<td>99%</td>
<td>81.9%</td>
</tr>
<tr>
<td>extended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS protocol</td>
<td>100% (by definition)</td>
<td>100% (by definition)</td>
</tr>
</tbody>
</table>

AS, active surveillance.

To account for the effect of increasing total number of cores taken with the ASPT, subgroup analysis of only grade-related (GS ≥7) reclassification events was performed. Table 3 shows total reclassification events, separated into grade and volume criteria, and all differences between groups were statistically significant. ASPT detected more grade reclassified patients (n = 69) than sextant (n = 33, 48.5%; P = .001) or SET (n = 57, 83.8%; P < .001) templates.

Univariate analysis to identify predictors of patients that could be biopsied using schemas with fewer cores (sexant and SET) was performed. Parameters examined included baseline PSA, PSA density, age, prostate volume, number of positive cores at baseline biopsy, 5-alpha reductase inhibitor use, PSA before progression biopsy, and time between initial and reclassification biopsies. No predictors of patients suitable for biopsy schema with fewer cores were found.

COMMENT

As AS cohorts mature, and the evidence for over-diagnosis and overtreatment mounts, methods for optimizing the observation of patients when on AS will become more germane. PSA velocity has inconsistently identified progression or lack of progression on AS. Thus, repeat biopsy continues to be a necessary component of AS follow-up. When rebiopsy patients on AS, our institution has routinely been using a 13-17 core template (Fig. 1). With detailed biopsy cancer location data, we reviewed our results to consider if fewer biopsy cores could be taken, using routine extended or even sextant biopsy templates, without jeopardizing the detection of cancer or pathologic reclassification.

Our AS biopsy template (100% by definition) resulted in more reclassification than extended (81.9%) or sextant (47.9%) biopsy templates (Table 2). Of all reclassification events, 53.5% (n = 50) occurred after the second biopsy, so our results are not simply a confirmatory biopsy phenomenon. It is clear that a sextant biopsy remains an inferior and inadequate method for sampling the prostate gland, even in the context of a known diagnosis of cancer. Interestingly, the SET found cancer in 99% of men with cancer but would have missed reclassification in 18.1% of men. As the definition for reclassification on cancer volume varies between institutions (eg maximum number of positive cores allowed, maximum 50% single core involved), we also examined patients who were reclassified with grade-related events (GS ≥7 or volume criteria, or both; Table 3). The advantage of ASPT was upheld when compared with sextant (n = 33 vs 68; 48.5%) and SET (n = 57 vs 68; 83.8%). These findings are significant, given that the published AS series reports results derived from standard extended biopsy templates. The SunnybrookToronto (Klotz) and PRIAS cohorts report increasing number of biopsies with prostate volume but only John Hopkins Hospital, since 2009, discusses biopsy outside the routine peripheral zone. Hence, rebiopsy using the template we described could considerably increase the proportions of patients reclassifying when on AS.

The evidence for biopsy schema on AS has been extrapolated from the diagnostic biopsy era with very little evidence directly arising from AS cohorts. The idea of using sextant biopsy for AS to minimize morbidity is not without consideration. A prospective randomized trial found no difference in cancer detection comparing 6 to 12 biopsy cores, although this was in the diagnostic biopsy setting. However, subsequent systematic review concluded an extended 12-core template that detected 31% more cancer than sextant with similar adverse event rates, and this remained without changing philosophy. This review also assessed taking >12 cores added no significant benefit, with schemes taking >18 cores more likely to be associated with more adverse events. Other studies have suggested the number of cores taken should be increased in men with larger glands. With the help of work already performed to fine-tune the subtleties of diagnostic biopsy, we should also examine how to best optimize rebiopsy for our patients on AS.

The shortcomings of TRUS/PB have motivated the exploration of alternatives. Use of contrast enhanced transrectal ultrasound, might improve diagnostic accuracy of prostate biopsy over standard ultrasound. Transperineal saturation biopsy for AS rebiopsy, which by using a grid, more accurately maps the location of cancer found with improved access to the transition and anterior zones. The proportion of reclassification using this technique is reported as high as 41%-85%, and many of these cancers found are in the anterior zone. Although the infection rate is decreased, concern over detection of insignificant cancers, an increased rate of urinary retention, and the possibility of increased fibrosis impacting on radical prostatectomy, issues surrounding necessity of general anesthetic, and time required for the procedure have limited the widespread uptake. The use of mp-MRI to predict reclassification among men on AS is promising and the use of image guided prostate biopsy, such as office based magnetic resonance ultrasound fusion devices, shows exciting potential. In comparison to random systematic biopsies, MRI-guided targeted biopsies are reported to increase detection of cancer, in particular higher Gleason grade disease. However, centers with expertise in performing and interpreting mp-MRI are still limited and their techniques described are still undergoing evaluation.
Table 3. Reclassification events by grade and volume criteria

<table>
<thead>
<tr>
<th>Reclassification Criteria</th>
<th>Sextant (6 core Bx)</th>
<th>Extended/SET (10-12 core Bx)</th>
<th>AS Protocol (13-17 core Bx)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade only</td>
<td>28</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Volume only</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Grade and volume</td>
<td>11</td>
<td>22</td>
<td>34</td>
</tr>
<tr>
<td>Total reclassification events (%)</td>
<td>48 (51.1)</td>
<td>77 (11.9)</td>
<td>94 (100.0)*</td>
</tr>
<tr>
<td>Total grade-related reclassification events (%)</td>
<td>33 (48.5)</td>
<td>57 (83.8)</td>
<td>68 (100.0)*</td>
</tr>
</tbody>
</table>

SET, standard extended template; other abbreviation as in Table 2.

Grades criteria = Gleason score ≥7.
Volume criteria = number of PCGears ≥2, maximal core length involvement ≥50%.
* P values for comparison of overall reclassification: extended/SET vs sextant (P = .001); AS protocol vs sextant (P = .008); AS protocol vs extended/SET (P = .04).
† P values for grade-related reclassification: extended/SET vs sextant (P = .001); AS protocol vs sextant (P < .001); AS protocol vs extended (P < .001).
‡ Men who reclassified with a combination of grade and volume criteria.
§ Total includes patients who reclassified by both grade only, and grade and volume criteria.

Hence, simpler and more generalizable strategies using standard TRUSFB still warrant exploration.

The impetus to improve rebiopsy on AS comes from the growing evidence that prostate biopsy is associated with increasing morbidity. Population-based studies have shown increased incidence of infectious complications associated with prostate biopsy. Several factors including diabetes, prostate enlargement, chronic obstructive pulmonary disease, and hospitalization the month before biopsy have been suggested to increase the risk of complications after prostate biopsy. At present, increasing the number of cores taken at biopsy does not appear to increase septic complications. In the only randomized trial examining whether an increase in total number of biopsy cores results in increased morbidity, Naughton et al compared 6 vs 12 cores in the initial diagnostic biopsy setting. In the 12-core group, there were no significant differences in urinary symptoms, fever, or hospitalization. Furthermore, subgroup analysis from a large Canadian study examining patients undergoing initial or repeat (usually more cores) biopsies, did not show any difference in hospitalization.3

Although our study is one of the initial reports examining the impact of rebiopsy template and core location on reclassification, it has its limitations. Our biopsy data are collected prospectively; however, the analysis is post-hoc and thus, retrospective. Ideally, this should be investigated in a randomized study with comparison between different biopsy templates. The use of hypothetical scenarios might not reflect real life situations, as it is recognized that freehand TRUSFB is associated with geometric variability. However, strength in consistency comes from the fact that most biopsies, baseline and repeat, were taken by a single operator. The pathology was read by 1 of 4 genitourinary pathologists and reported using a standardized synoptic format. Timing of rebiopsies was at the discretion of the individual urologist, and hence our cohort may not be representative of other AS populations with strict confirmatory and rebiopsy policies. However, patients in general had a confirmatory biopsy within 6-12 months of diagnosis and then repeat biopsies at 1- to 2-year intervals. Follow-up of our cohort is still relatively short and with longer time, we might be able to identify characteristics in a subgroup of patients on AS that are truly destined to never reclassify. For this group, we could consider longer intervals between biopsies and perhaps using fewer cores. Lastly, the significance of missing pathologic reclassification by using a different template on long-term outcomes, such as overall survival and cancer-specific survival for patients remains to be fully delineated.

It is clear that strategies for monitoring men on AS require further investigation. There has been significant work to date investigating the roles of imaging, saturation biopsy templates, and biomarkers on predicting pathologic reclassification for patients on AS. However, for the time being, routine repeat biopsy remains a critical part of AS follow-up and our data suggest that the standard 10-12 core extended systematic biopsy is less effective than a 13-17 core schema in detecting pathologic reclassification.

CONCLUSION

For men on AS for low risk prostate cancer, a 13-17 core template prostate biopsy results in more pathologic reclassification than sextant or extended biopsy templates. Our findings are contrary to the concern that increasing the number of biopsy cores taken would result in more insignificant cancers being found. Until better predictors for tailoring biopsy templates or improvements in imaging to accurately localize tumors are established, we suggest a more extensive template for rebiopsy on AS.

References

5. UROLOGY 82 (2), 2013


CHAPTER 8: Regular transition zone biopsy during Active Surveillance may improve detecting pathological progression.

Introduction and PDF

In chapter 8, the findings from chapter 7 are explored in more depth. The active surveillance biopsy template used at Princess Margaret Cancer Centre (PMCC) was found to identify more cancer and pathological progression than traditional “standard extended template” and “sextant template”. Thus fewer cores during AS follow-up biopsy is not recommended.

The main difference in the PMCC AS biopsy template to standard extended template is that transition zone (TZ) biopsies were taken. In this chapter, specific examination of detection of cancer, and progression of cancer in the TZ is analyzed over the course of multiple biopsies during AS. Of particular interest is the outcome “exclusive-TZ progression” as this is where disease progression only occurred in the TZ and hence if the TZ had not been biopsied, these men would have been falsely re-assured.
Regular Transition Zone Biopsy during Active Surveillance for Prostate Cancer May Improve Detection of Pathological Progression

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Abbreviations and Acronyms

- AS = active surveillance
- B1 = diagnostic (first or baseline) biopsy
- B2 = confirmatory (second) biopsy
- BS+ = biopsy 5 or greater
- GS = Gleason sum
- MRI = magnetic resonance imaging
- PSA = prostate specific antigen
- PZ = prostate peripheral zone
- TPTMGB = transperineal template guided mapping biopsy
- TRUSGB = transrectal ultrasound guided prostate biopsy
- TZ = prostate transition zone

Purpose: We investigated the frequency of cancer and pathological progression in transition zone biopsies in men undergoing multiple biopsies while on active surveillance.

Materials and Methods: Eligibility criteria of the active surveillance prostate cancer database (1997 to 2012) at our tertiary center includes prostate specific antigen 10 ng/ml or less, cT2 or less, no Gleason grade 4 or 5, 3 or fewer positive cores, no core with greater than 50% involvement, patient age 75 years or less and 1 or more biopsies after initial diagnostic biopsy. We excluded from analysis men with fewer than 10 cores at diagnostic biopsy and/or confirmatory biopsy greater than 24 months after diagnostic biopsy. Multiparametric magnetic resonance imaging was performed selectively to investigate incongruity between prostate specific antigen and biopsy findings. Pathological progression was defined by grade and/or volume (greater than 50% of core involved). Transition zone progression was subdivided into exclusively transition zone and combined transition zone (transition and peripheral zones). A multivariate Cox proportional hazards model was used to determine predictors of transition zone progression.

Results: A total of 392 men were considered in analysis. Median followup was 45.5 months. At each biopsy during active surveillance (confirmatory biopsy to biopsy 5+) there were transition zone positive cores in 18.6% to 26.7% of cases, all transition zone progression in 5.9% to 11.1% and exclusively transition zone progression in 2.7% to 6.7%. Volume related progression was noted more frequently than grade related progression (24 vs 9 cases). Predictors of only transition zone progression were the maximum percent in a single core (HR 1.69, 95% CI 1.30–2.17, p = 0.002) and cancer on magnetic resonance imaging (HR 3.19, 95% CI 1.23–8.27, p = 0.02).

Conclusions: Across multiple active surveillance biopsies 2.7% to 6.7% of men had only transition zone progression. We recommend that transition zone biopsy be considered in all men at confirmatory biopsy. Positive magnetic resonance imaging findings or a high percent of core involvement may subsequently be useful to identify patients at risk.

Key Words: prostate, prostatic neoplasms, neoplasm progression, biopsy, magnetic resonance imaging
The conventional biopsy template reported in AS cohorts is the standard extended template, which only samples the PZ. Prostate cancer is located in the PZ in 70% to 85% of cases with the remaining cancers located in the TZ. A review of established AS cohorts showed that only 1 recent series mentioned routine sampling of the TZ. Since 2001 at our institution, the TZ has been routinely sampled during AS rebiopsy using a template modeled on that of Babaian et al. The TZ is easily accessible by standard TRUSPB. However, the TZ is not routinely sampled because evidence from diagnostic biopsies suggests that the yield of TZ cancer detection is low and, thus, this is best performed in the setting of prior negative TRUSPB. The situation is different in men on AS. Having already been diagnosed with cancer, consideration of unsampled regions such as the TZ, which could potentially harbor significant cancer, necessitates a shift in the diagnostic focus of TRUSPB.

Radical prostatectomy series suggest that the incidence of TZ tumors is 24% to 29%, of which 11.6% to 17.8% are the index (largest) tumor. Multifocality with concomitant TZ tumors is common (65% to 85% of cases). While TZ tumors are often associated with higher serum PSA and can have a large volume, they often have a lower Gleason score, lower rates of extraprostatic extension and seminal vesicle invasion, and less risk of positive surgical margins than PZ tumors of similar volume. When present, positive surgical margins often involve the bladder neck and anterior fibromuscular zones.

In a cohort of men on AS who underwent routine prostate rebiopsy we investigated the impact of routine TZ biopsy by examining the amount of cancer and adverse pathology findings in the TZ.

METHODS

Patients were identified from our tertiary referral center AS database from 1997 to 2012 at Princess Margaret Cancer Center. Institutional ethics review board approval was obtained. Eligibility criteria included PSA less than 10 ng/ml, clinical stage cT2 or less, GS 6 or less, 3 or fewer positive cores, no single core greater than 50% involved, age 75 years or less and 1 or more prostatic rebiopsies after diagnosis (622 patients). Men with a total of fewer than 10 cores at B1 (459) and/or B2 more than 24 months after B1 (181) were excluded from analysis since these groups were outside currently acceptable standards for AS. Thus, 392 men were included in study.

TRUSPBs were taken in a standard manner using a C9-5 ICT end fire probe (Philips®) with the patient under local anesthesia. A single operator (AT) performed 75% of the biopsies. Collected biopsy cores were labeled by the region sampled (eg left medial PZ). Cancer location was captured systematically together with other clinical pathological variables. For B1 a standard extended template of 10 to 12 cores was used that sampled only the PZ. For subsequent rebiopsies we used an AS protocol template of 13 to 17 cores modeled on that of Babaian et al. Some diagnostic biopsies were performed elsewhere but all followup biopsies were done in house. The AS protocol template samples the lateral and medial PZ, the TZ and the midline at the prostate base (see figure). TZ biopsies were directed at the thickest part of the prostate in the immediate paraurethral region. Operator discretion was used to decide whether 1 or 2 TZ cores from each side were taken for a total of 3 or 4 TZ cores. In addition to this systematic schema, extra cores of areas suspicious on ultrasound may have been obtained.

Followup of patients on AS at our institution consists of PSA measurement and digital rectal examination every 3 months for 2 years and every 6 months thereafter if stable. We have no mandatory immediate confirmatory biopsy policy but it is recommended to patients within 12 months of B1 with rebiopsy every 1 to 3 years until the patient is 80 years old or refuses active treatment. Biopsy for cause is allowed at treating urologist discretion, often triggered by increasing PSA or abnormal digital rectal examination. Multiparametric MRI was done selectively to examine for anterior tumors when PSA and biopsy findings differed.

By submitting biopsy cores from each location in a separate container that was labeled accordingly men with TZ cancer and TZ pathological progression could be identified at each AS biopsy. For TZ cancer pathological progression was defined as findings of GS 7 or greater (grade) and/or greater than 50% of a single core involved (volume) on subsequent AS biopsy. Core involvement by cancer was estimated visually. For cores with discontinuous cancer foci core involvement was reported as the percent of total core length occupied by cancer. Benign prostate parenchyma between cancer foci was not included when determining the extent of core involvement. More than 3 positive cores were not used as a measure of volume progression because it was thought that increasing the total number of cores taken by biopsying the TZ would increase...
the likelihood of finding cancer and, thus, overestimate the reporting of progression.

Men with disease progression in TZ biopsies were subdivided into 2 groups (only TZ and combined TZ progression, respectively). Combined TZ progression indicated progression in TZ and PZ biopsies. If no TZ biopsy was taken, disease was considered to have progressed based on PZ biopsy. Exclusively TZ progression was noted in TZ biopsies. Thus, if the TZ had not been biopsied, these men would have been falsely reassured. The term grade related progression was used to describe grade only progression (GS 7 or greater), and grade and volume progression (GS 7 or greater and greater than 50% involvement of a single core). Volume related progression was used to describe volume only (greater than 50% involvement of a single core), and volume and grade progression.

Differences between groups were determined using ANOVA or the chi-square test. Important clinical and pathological variables were first analyzed using univariate analysis. Multivariate models were built using Cox proportional hazards with the forward stepwise regression technique. Men were censored if they progressed, elected treatment without progression or were lost to followup. All statistical tests were 2-sided with p < 0.05 considered statistically significant. SAS® version 9.1 was used for all analyses.

RESULTS
The supplementary table (http://jurology.com/) lists the characteristics of the 392 men in the study dichotomized by positive and negative TZ biopsies. Median followup after B1 was 45.5 months (IQR 31.2–66.0). Comparing these 2 groups at B1 revealed that men with cancer in TZ biopsies had a smaller prostate volume, higher PSA density and more positive cores. During AS more men with positive TZ biopsies underwent MRI but fewer were on a 5z-reductase inhibitor.

For each rebiopsy during AS the frequency of cancer and progression was documented in the entire cohort and in those with TZ disease (table 1). The denominator for calculated percents was the total number of men at that particular biopsy point, eg 392 at B2. Of the men 11.9% to 20.5% had pathological progression at each biopsy (B2 to B5+).

The proportion of men with positive cores in TZ biopsies (18.6% to 26.7%) and with TZ progression (5.9% to 11.1%) was consistent at each biopsy. The proportion of men with only TZ progression in each biopsy was 2.7% to 6.7%. Approximately 40% to 60% of cases of TZ progression occurred at B2 with the remainder distributed across subsequent biopsies (biopsy 3 or greater).

Table 2 shows TZ progression subcategorized by progression type (Gleason grade and/or a volume of greater than 50% of the core involved) and location (combined TZ/PZ or only TZ). A total of 47 men had pathological progression in TZ biopsies, including 31 (66.0%) exclusively in the TZ. TZ grade related progression developed in 18 men, including only in the TZ in 7. In these 7 cases GS was 3 + 4 in 6 and 4 + 3 in 1. In men with only TZ progression volume related progression was more common than grade progression (22 vs 7) while 2 had volume plus grade progression.

Multivariate analysis using Cox proportional hazards regression was done to identify predictors of TZ cancer, all TZ progressions and only TZ progression. Table 3 lists significant variables. Maximum percent of a single core involved was statistically significant for predicting exclusively TZ progression (HR 1.09, 95% CI 1.03–1.05, p = 0.002) and positive TZ biopsy cores (HR 1.03, 95% CI 1.00–1.05, p = 0.02). A MRI diagnosis of cancer was statistically significant for predicting exclusively TZ progression (HR 3.19, 95% CI 1.23–8.27, p = 0.02) and combined (TZ and PZ) progression (HR 1.76, 95% CI 1.07–2.89, p = 0.03). The total number of rebiopsies after B2 was associated with a lower risk of TZ cancer (HR 0.60, 0.47–0.77, p<0.001), all TZ progression (HR 0.52, 0.35–0.80, p<0.001) and only TZ progression (HR 0.59, 0.38–0.92, p = 0.02).

DISCUSSION
Routine transition zone biopsy in our cohort detected cancer and progression with remarkable regularity. During the course of 4 biopsies (B2 to B5+) during AS 18.6% to 26.7% of men at each biopsy had cancer detected in TZ biopsies (table 2). The

**Table 1.** TZ cancer and progression relative to entire cohort

<table>
<thead>
<tr>
<th></th>
<th>No. B2 (%)</th>
<th>No. Biopsy 3 (%)</th>
<th>No. Biopsy 4 (%)</th>
<th>No. Biopsy 5+ (%)</th>
<th>Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>392</td>
<td>315</td>
<td>76</td>
<td>27</td>
<td>510</td>
</tr>
<tr>
<td>Ca</td>
<td>225</td>
<td>194</td>
<td>67</td>
<td>21</td>
<td>307</td>
</tr>
<tr>
<td><strong>Pathological progression</strong></td>
<td>86 (17.9)</td>
<td>44 (20.5)</td>
<td>11 (14.7)</td>
<td>3 (11.1)</td>
<td>127</td>
</tr>
<tr>
<td><strong>TZ disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca</td>
<td>50 (25.3)</td>
<td>28 (22.0)</td>
<td>8 (10.6)</td>
<td>4 (26.7)</td>
<td>100</td>
</tr>
<tr>
<td><strong>Progression, any TZ status</strong></td>
<td>23 (5.9)</td>
<td>15 (6.9)</td>
<td>6 (8.0)</td>
<td>3 (11.1)</td>
<td>47</td>
</tr>
<tr>
<td>TZ + TZ progression</td>
<td>16 (3.9)</td>
<td>4 (1.9)</td>
<td>1 (3.0)</td>
<td>1 (6.7)</td>
<td>16</td>
</tr>
<tr>
<td><strong>TZ progression, no TZ progression</strong></td>
<td>12 (3.0)</td>
<td>11 (5.1)</td>
<td>5 (8.7)</td>
<td>2 (2.7)</td>
<td>21</td>
</tr>
</tbody>
</table>

*GS 7 or greater and/or greater than 50% of single core involved.*
Table 2. TZ progression types

<table>
<thead>
<tr>
<th>Prostate Zone</th>
<th>No. Progression</th>
<th>Grade Only</th>
<th>Vol Only</th>
<th>Grade + Vol</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>B2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All TZ</td>
<td>9</td>
<td>11</td>
<td>3</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>TZ + PZ pos</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>10</td>
<td>19</td>
</tr>
<tr>
<td>TZ pos, PZ neg</td>
<td>3</td>
<td>10</td>
<td>0</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Biopsy 3:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All TZ</td>
<td>6</td>
<td>8</td>
<td>1</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>TZ + PZ pos</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>TZ pos, PZ neg</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Biopsy 4:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All TZ</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>TZ + PZ pos</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>TZ pos, PZ neg</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Biopsy 5+:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All TZ</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>TZ + PZ pos</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>TZ pos, PZ neg</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Totox</td>
<td>All TZ</td>
<td>18</td>
<td>24</td>
<td>5</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>TZ + PZ pos</td>
<td>11</td>
<td>2</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>TZ pos, PZ neg</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>11</td>
</tr>
</tbody>
</table>

*GS 7 or greater
† Greater than 50% of single core involved

incidence of progression in the TZ biopsy was 5.9% to 11.1%. This incidence represented 2.7% to 6.7% of cases when considering exclusively TZ progression. To our knowledge this consistent rate of positive TZ biopsies during AS has not been reported previously. Furthermore, whether considering combined TZ progression or only TZ progression more than half of these events occurred after B2.

In our cohort men with exclusively TZ progression formed the subgroup of greatest interest. Without TZ biopsy these cases would not have been found to progress. Of the 31 men with exclusively TZ progression 22 had volume only progression (table 3). This suggests that the TZ harbors cancer nodules of significant size that are not detected by standard PZ biopsy. This observation is reinforced by our multivariate analysis, which showed that a higher maximum percent of core involvement at B1 predicted TZ cancer and exclusively TZ progression.

Comparing data on the extent of core involvement among published AS cohorts is challenging due to variations in reporting methods. At our institution the percent of core involvement is reported using a visual estimate based on the amount of cancer in a given core. Unlike groups at other institutions we do not include intervening benign parenchyma in our determination of the percent of core involvement when cores are discontinuously involved by cancer. At different institutions there are varying definitions of what represents progression during AS. PRIAS (Prostate Cancer Research International: Active Surveillance Study) does not consider the percent of core involvement when assessing AS eligibility. We previously suggested that grade related progression during AS be reported independently of total progression to aid in standardization because the significance of pure volume related progression remains to be elucidated.

Our findings differ from those of a previous study of AS TZ biopsy by RiChard et al. They concluded that routine TZ biopsy during AS rarely provides unique evidence of disease progression. Methodological differences in that study include AS eligibility (PSA less than 15 ng/ml and GS 7 microfoci accepted), definition of progression (more than 2 positive cores) and timing of TZ biopsy (TZ also biopsied at B1). RiChard et al noted only 1 case (1.2%) of exclusively TZ progression, which was grade related, and no case of volume related progression despite the stricter volume criteria. Thus, the frequency of only TZ progression (7.9% vs 1.2%) differed between the 2 series. The most likely explanation for our diverse findings is our larger sample size (622 vs 96 patients) and our longer follow up, which was not reported by RiChard et al.

Routine TZ sampling means an increased total number of cores taken with each round of biopsies, which has several implications. Data on transperineal saturation template biopsy suggest that more cores may increase the probability of finding cancer. In this study we did not use the number of positive cores as a criterion for progression. Thus, our results likely underestimate the total number of men in our cohort with progression. Increasing the number of biopsy cores could also potentially increase the risk of pain and sepsis. A randomized trial showed that increasing the number of biopsy cores from 6 to 12 was not associated with increased pain scores, fever or hospitalization, although significant increases in hematochezia and hematopsia were noted. Population based data
suggested an increase in hospitalization due to TRUS biopsy but this was likely secondary to an increase in the number of biopsies.

The incidence of detecting exclusively TZ cancer on transrectal ultrasound guided TZ biopsy in the diagnostic setting was previously reported to be 1.5% to 13%. TPTMBs systematically sample the TZ. In a cohort of 539 men undergoing prostate TPTMB a median of 11 TZ cores was taken. The incidence of TZ cancer was 24.1% (19 cases), similar to our results of 18.6% to 26.3% across B2 to B5+, although we only obtained 2 to 4 TZ cores. Comparing the number of exclusively TZ tumors found is difficult. With TPTMB a median total of 58 cores was taken so that only 1.1% of tumors were exclusively TZ. TPTMB allows better access to the anterior and api cal portion of the prostate and it is associated with a decreased risk of sepsis. However, because it requires anesthesia and more time to perform, most urologists and radiologists still perform TRUS biopsy and, thus, the potential benefit of our findings.

Advances in prostate multiparametric MRI have been described enthusiastically. We found that cancer on MRI predicted combined progression (PZ plus TZ) and exclusively TZ progression but only in a select patient group. T2-weighted images reveal zonal anatomy well but with increasing age benign prostatic hypertrophy arising from the TZ causes heterogeneous signal intensity, making differentiation from cancer difficult. Multiparametric techniques such as magnetic resonance spectroscopy can assist in differentiating benign prostatic hypertrophy from cancer but magnetic resonance identification of TZ cancer remains more challenging, particularly for smaller tumors. Current reports of prostate multiparametric MRI arise from academic centers with limited generalizability to many urologists. Thus, we must continue to explore methods of improving TRUS biopsy in parallel with other techniques.

Our study has limitations. Although reported followup is relatively short considering the long natural history of prostate cancer, to our knowledge it represents the longest followup of men who underwent repeat TZ biopsy. Since our results differ from those previously published, further study is required to determine whether they are reproducible. Although the location of positive cores was carefully documented, this was limited by the interpretation of the biopsy operator who labeled each biopsy. The division between TZ and PZ may not be apparent in all prostates and biopsy cores may unintentionally traverse the 2 zones, particularly in smaller glands. Because prostate cancer grows in an irregular manner, it is difficult to differentiate between an exclusively TZ tumor growing into the PZ or vice versa. This is highlighted by studies reporting that 40% to 88.9% of men with positive TZ cores at biopsy had no TZ cancer upon examination of the radical prostatectomy specimen. Assigning a zone of origin based on histological morphology is extremely difficult since current methods are limited by lack of specificity. The long-term significance of pathological progression, particularly volume related progression in the TZ, remains to be elucidated with longer followup.

**CONCLUSIONS**

By adding 2 to 4 TZ biopsy cores at each AS biopsy we found that 2.7% to 6.7% of men had only TZ progression (greater than 50% of a single core and/or GS 7 or greater disease). Our findings suggest that TZ biopsy could be considered at confirmatory biopsy in all men. For subsequent biopsies guidance from positive MRI findings or a high percent of core involvement may be useful.

**REFERENCES**


Chapter 9: A Negative Confirmatory Biopsy Among Men on Active Surveillance for Prostate Cancer Does Not Protect them from Histological Grade Progression

Introduction and PDF

Here in chapter 9, the significance of absence of cancer at the confirmatory biopsy (B2) was explored. The concept of the confirmatory biopsy arose from the need to check that men referred to an academic centre for active surveillance (AS), truly were suitable. It was suggested by the group at Memorial Sloan Kettering Cancer Centre that the confirmatory biopsy if performed within 3mo, finds 27% of men to be upgraded and/or upstaged and no longer suitable for AS(158). Furthermore, a positive confirmatory biopsy was predictive of pathological progression (90).

Conversely, it is well documented that a proportion of men will have no cancer found at the confirmatory biopsy, reported to be 21-52% in the literature. This group of men is an easily identifiable group that might have a reduced risk of pathological progression. If so, their intensity of follow-up might be reduced by decreasing frequency of re-biopsy. Hence the prognostic implications of no cancer at confirmatory biopsy warrant further investigation.
A Negative Confirmatory Biopsy Among Men on Active Surveillance for Prostate Cancer Does Not Protect Them from Histologic Grade Progression

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a Division of Urologic Oncology, Princess Margaret Cancer Centre, Toronto, Canada; b Department of Medicine, University Health Network, Toronto, Canada; c Department of Radiology, University Health Network, Toronto, Canada; d Department of Pathology, University Health Network, Toronto, Canada

Abstract

Background: Many men (21–52%) are reported to have no cancer on the second, also known as the confirmatory, biopsy (B2) for prostate cancer active surveillance (AS). If these men had a reduced risk of pathologic progression, particularly grade related, the intensity of their follow-up could be decreased.

Objective: To investigate if men with no cancer on B2 are less likely to undergo subsequent pathologic progression.

Design, setting, and participants: Men were identified from our tertiary care centre AS prostate cancer database (1995–2012). Eligibility criteria were prostate-specific antigen (PSA) ≤10, CT2 or lower, no Gleason grade 4 or 5, three or fewer positive cores, and no core >50% involved. Only patients with three or more biopsies were selected and then dichotomized on cancer status (yes or no) at B2.

Intervention: AS.

Outcome measurements and statistical analysis: Pathologic progression was defined as grade (advancement in Gleason score) and/or volume (more than three positive cores, >50% core involved). Progression-free survival was compared. Predictors of progression were investigated using a Cox proportional hazards model.

Results and limitations: Of the 286 patients remaining on AS after B1, 149 (52%) had no cancer and 137 (48%) had cancer. The median follow-up after B2 was 41 mo (interquartile range [IQR]: 26.5–61.9). Progression-free survival at 5 yr was 85.2% versus 67.3% for negative B2 versus cancer on B2, respectively (p = 0.002). Men with no cancer at B2 had a 53% reduction in risk of subsequent progression (hazard ratio [HR]: 0.47; 95% confidence interval [CI], 0.29–0.77; p = 0.003). Subanalysis showed prognostic indicators of volume-related progression were absence of cancer (HR: 0.36; 95% CI, 0.20–0.62; p = 0.0006) and PSA density (HR: 1.79; 95% CI, 1.12–2.80; p = 0.01). The only predictor of grade-related progression was age (HR: 1.05; 95% CI, 1.00–1.10; p = 0.04). Retrospective analysis was the major limitation of the study.

Conclusions: Absence of cancer on B2 is associated with a significantly decreased risk of volume-related but not grade-related progression. This must be considered when counseling men on AS.

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1. Introduction

As active surveillance (AS) for low-risk prostate cancer gains acceptance, we require improvements in risk assessment to counsel individual patients regarding prognosis [1,2]. Currently, patients undergo repeat prostate biopsies to monitor for progression and account for sampling error, although the frequency of rebiopsy reported in the literature ranges from yearly [3] to every 3–4 yr [4]. Stratification to guide intensity of follow-up would be desirable to avoid biopsy-related morbidity [5,6] without compromising the detection of significant progression.

An easily identifiable group where frequency of rebiopsy might be reduced is men with absence of cancer on their confirmatory, or second, AS biopsy (B2). A review of published AS cohorts found this ranged from 21% to 52% [1]. This phenomenon most likely arises both from selecting men with low-volume disease and the inherent sampling error associated with transrectal ultrasound-guided prostate biopsy (TRUSPB) [7]. The absence of cancer on prostate biopsy is comforting for both patient and physician, and intuitively it would suggest a lower risk of progression.

We investigated the prognostic significance of a negative confirmatory AS biopsy on pathologic progression in an AS cohort. Because absence of cancer is likely a surrogate marker for extremely low-volume disease, we also examined potential predictors of grade- and volume-defined progression.

2. Patients and methods

Patients were identified from the AS database at Princess Margaret Cancer Centre (PMCC) between 1995 and 2012. This is a prospectively maintained database approved by the research ethics board. Eligibility criteria were patients with prostate-specific antigen (PSA) ≤10, clinical stage T2a or lower, no Gleason grade 4 or 5, three or fewer positive cores (PCore) involved, and no core >50% involved at the diagnostic biopsy.

For the purposes of this study, we defined the first (baseline, diagnostic) TRUSPB as biopsy 1 (B1) and the second biopsy (confirmatory, first AS or repeat biopsy) as biopsy 2 (B2). Patients who did not receive a third (B3) or subsequent biopsy, because of either stopping AS after B2 or having insufficient follow-up to reach B3, were excluded (Fig. 1). Thus patients who progressed (or were reclassified) at B2 and ceased AS were excluded from this study. The remaining patients who continued with AS (n = 286) were dichotomized on the basis of cancer status (yes or no) from B2. The primary outcome analyzed was pathologic progression, occurring at any biopsy, after B2. Pathologic progression was defined as an increase in Gleason score (GS) ≥7 (grade-related progression) and/or volume-related progression (Pcore more than three or single core maximum involvement >50%).

Three genitourinary radiologists performed TRUSPB, and a single operator (A.T.) performed the majority (75%). A standard extended 10- to 12-core template schema was used for initial biopsy, with a 13- to 17-core Bahian schema [8] performed for repeat biopsies after 2001. All biopsies taken at PMCC were read by one of four dedicated genitourinary pathologists, and synoptic reporting was used. Although a standardized follow-up protocol is not used at PMCC, patients are generally reviewed with PSA and digital rectal examination (DRE) every 3 mo for 2 yr and then every 6 mo if stable. A confirmatory biopsy is recommended to patients within 12 mo of initial diagnostic biopsy and then every 1–3 yr until the patient reaches 80 yr of age or declines active treatment. Earlier biopsy is triggered by either a rising PSA or an abnormal DRE at the treating physician’s discretion. Magnetic resonance imaging (MRI) was performed selectively, often if there was a discrepancy between PSA and biopsy findings, to examine for an anterior tumor [9].

Differences between groups were determined by the independent t test or the chi-square test. Univariate and multivariate Cox proportional hazards regression were used to examine absence of cancer and other standard clinical parameters for predictors for progression.

Subanalyses for predictors of both grade-related and volume-related progression were also performed. Grade-related progression was defined as men with grade-only and grade-and-volume progression. Volume-related progression included men with volume-only and volume-and-grade progression. Important clinical and pathologic variables for the Cox regression analysis were selected and univariate analysis performed to identify significant variables. The number of covariates for the multivariable model was selected to avoid overfitting and multicollinearity check performed for PSA, prostate volume, and PSAD density (PSAD), with PSA carried forward into the multivariable Kaplan-Meier method and comparisons made by the log-rank test.

Survival time began at the date of B2, and patients were censored at the time of progression biopsy, time of treatment, or date of last follow-up. Logistic regression was performed to identify predictors at baseline for absence of cancer on B2 and the model assessed with the C-statistic and Hosmer-Lemeshow goodness-of-fit test. All statistical tests were two sided with p < 0.05 considered statistically significant. SAS statistical software v8.1 (Cary, NC, USA) was used for all analyses.

3. Results

Of the total 286 patients remaining on AS after B2 and available for analysis, 149 (52%) had no cancer and 137 (48%) had cancer. The overall median follow-up after B2 was 41 mo (interquartile range [IQR]: 26.5–61.9). For both groups, there was no difference between the median number of TRUSPBs performed after B2 and the time interval from B2 to subsequent biopsies. Table 1 shows a comparison of characteristics at the time of B2 between the no-cancer and cancer groups. Significant differences noted between the groups were age, PSA, and prostate volume, although PSAD was similar. Approximately 60% of men in
Table 1 – Characteristics of patients at the second biopsy dichotomized into no-cancer and cancer groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>No cancer on B2</th>
<th>Cancer on B2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, total no. (%)</td>
<td>140 (52)</td>
<td>137 (48)</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>61.8 (57.8–66.2)</td>
<td>65.0 (58.3–70.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Family history of prostate cancer, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (22.2)</td>
<td>33 (24.1)</td>
<td>0.84</td>
</tr>
<tr>
<td>No</td>
<td>77 (51.3)</td>
<td>72 (53.8)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>30 (20.2)</td>
<td>32 (23.8)</td>
<td></td>
</tr>
<tr>
<td>DRE, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>5 (3.4)</td>
<td>1 (0.7)</td>
<td>0.24</td>
</tr>
<tr>
<td>Positive</td>
<td>130 (93.3)</td>
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<td></td>
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<td>Unknown</td>
<td>5 (3.4)</td>
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<td>Discrete palpable, n (%)</td>
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<td></td>
</tr>
<tr>
<td>Yes (C72)</td>
<td>17 (11.4)</td>
<td>17 (12.4)</td>
<td>0.79</td>
</tr>
<tr>
<td>No (C71)</td>
<td>132 (88.6)</td>
<td>120 (87.6)</td>
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</tr>
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<td>PSA, nm/L</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>5.0 (2.9–6.9)</td>
<td>4.0 (2.5–5.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Prostate volume, ml, n</td>
<td>140</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>45.5 (26.9–63.7)</td>
<td>41.0 (33.0–50.5)</td>
<td>0.006</td>
</tr>
<tr>
<td>PSA density, PSA/prostate volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>138</td>
<td>134</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.09 (0.06–0.13)</td>
<td>0.09 (0.06–0.14)</td>
<td>0.43</td>
</tr>
<tr>
<td>Cores taken at B2, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n &lt; 10</td>
<td>144</td>
<td>137</td>
<td></td>
</tr>
<tr>
<td>10–12</td>
<td>15 (10.5)</td>
<td>15 (11.0)</td>
<td></td>
</tr>
<tr>
<td>&gt;12</td>
<td>122 (85.3)</td>
<td>113 (82.4)</td>
<td></td>
</tr>
<tr>
<td>TRUS nodule seen, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>98 (65.8)</td>
<td>99 (72.3)</td>
<td>0.22</td>
</tr>
<tr>
<td>Yes</td>
<td>51 (34.2)</td>
<td>37 (27.0)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Highest percentage core of involved positive cores, n</td>
<td>137</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>NA</td>
<td>5.0 (5.0–10.0)</td>
<td></td>
</tr>
<tr>
<td>If cancer, nx of PCorr, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>140 (100)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>NA</td>
<td>67 (48.0)</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>NA</td>
<td>56 (40.9)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>NA</td>
<td>14 (10.2)</td>
<td></td>
</tr>
</tbody>
</table>

| Year of B2 (%)                              |                 |              |         |
| Before 2005                                 | 26 (17.5)       | 22 (16.1)    | 0.75    |
| 2005 or later                               | 123 (82.6)      | 115 (83.9)   |         |
| Time between B1 and B2 (%)                  |                 |              |         |
| ≤12 mo                                      | 95 (63.8)       | 82 (59.0)    | 0.76    |
| 12–24 mo                                    | 39 (26.2)       | 41 (28.0)    |         |
| >24 mo                                      | 15 (10.1)       | 14 (10.2)    |         |

B1 = first, or diagnostic; prostate biopsy; B2 = second, or confirmatory (or first active surveillance [AS]); prostate biopsy; DRE = digital rectal examination; IQR = interquartile range; NA = not applicable; PCorr = positive core; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

* Patients with cancer who still satisfy A2 eligibility criteria.

Both groups had their B2 performed ≤12 mo after B1, and 92.5% of men had ≥10 cores taken at B2. There were 19 patients excluded from analysis who stopped AS after B2 without pathologic progression and thus never had B3. Of these men, 17 elected to have active treatment without pathologic progression, and 2 had their B3 within 3 mo of B2. Table 2 shows pathologic progression and important related variables. The number of men with pathologic progression differed significantly between the no-cancer and cancer groups (23.5% vs 40.1%, respectively; p = 0.002). When examining for differences in type of progression, men with cancer at B2 were more likely to have volume-related progression than those without (29.2% vs 12%; p = 0.0003). The frequency of grade-related progression for both groups was similar (no cancer 17.5% and cancer 23.4%; p = 0.12) with most having a GS 3 + 4.

The probability of remaining free of pathologic progression, stratified by cancer status at B2, is shown in Figure 2a. Median time to progression was 32.5 mo (IQR: 19.9–56.9 mo) for the no-cancer group and 26.9 mo (IQR: 17.5–37.3 mo) for the cancer group (log-rank p = 0.002). The probability of remaining free of pathologic progression at 5 yr, stratified by cancer status on B2, was 85.2% (no cancer) and 67.3% (cancer) (p = 0.003). Kaplan-Meier survival curves for both grade-related and volume-related progression, stratified by cancer status at B2, are shown in Figure 2b and 2c. A significant difference between groups is seen with volume-related progression-free survival (p < 0.001) but not with grade-related progression (p = 0.07).

Univariate and multivariate Cox regression analysis for predictors of progression at B3 or subsequent biopsies is
Table 2 – Men with pathologic progression after the second biopsy

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>No cancer on B2</th>
<th>Cancer on B2</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall follow-up, mo</td>
<td>149</td>
<td>137</td>
<td>0.08</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>44.5 (29.2–63.1)</td>
<td>36.7 (24.4–59.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total subsequent pathologic progression events, n (%)</td>
<td>35 (23.5)</td>
<td>55 (40.2)</td>
<td></td>
</tr>
<tr>
<td>Type of pathologic progression, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade only (GS = 7)</td>
<td>17 (11.6)</td>
<td>15 (11.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Volume only (&gt; 3 Core; &gt;50% single core involved)</td>
<td>9 (6.0)</td>
<td>23 (16.8)</td>
<td></td>
</tr>
<tr>
<td>Both grade and volume</td>
<td>9 (6.0)</td>
<td>17 (12.4)</td>
<td></td>
</tr>
<tr>
<td>Total volume-related progression, n (%)</td>
<td>18 (12.1)</td>
<td>40 (29.2)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Total grade-related progression, n (%)</td>
<td>26 (17.5)</td>
<td>32 (23.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>GS 3 + 4</td>
<td>19 (13.1)</td>
<td>26 (18.3)</td>
<td></td>
</tr>
<tr>
<td>GS 4 + 3</td>
<td>3 (1.5)</td>
<td>3 (0.4)</td>
<td></td>
</tr>
<tr>
<td>GS ≥ 4 + 4</td>
<td>4 (1.5)</td>
<td>4 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Biopsy number at which grade progression occurred, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st biopsy</td>
<td>14 (12.0)</td>
<td>13 (10.5)</td>
<td>0.82</td>
</tr>
<tr>
<td>2nd biopsy</td>
<td>6 (23.1)</td>
<td>13 (40.0)</td>
<td></td>
</tr>
<tr>
<td>3rd biopsy</td>
<td>3 (11.5)</td>
<td>5 (15.6)</td>
<td></td>
</tr>
<tr>
<td>4th biopsy</td>
<td>2 (7.7)</td>
<td>1 (3.1)</td>
<td></td>
</tr>
<tr>
<td>7th biopsy</td>
<td>1 (3.8)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>MRI status post B2, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI performed with cancer reported</td>
<td>25 (16.7)</td>
<td>20 (14.3)</td>
<td>0.57</td>
</tr>
<tr>
<td>MRI performed with no cancer reported</td>
<td>15 (10.1)</td>
<td>19 (13.6)</td>
<td></td>
</tr>
<tr>
<td>MRI not performed</td>
<td>107 (73.2)</td>
<td>98 (71.5)</td>
<td></td>
</tr>
<tr>
<td>k-ARI use, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>59 (41.6)</td>
<td>44 (32.1)</td>
<td>0.19</td>
</tr>
<tr>
<td>No</td>
<td>90 (60.4)</td>
<td>93 (67.9)</td>
<td></td>
</tr>
<tr>
<td>Time to progression, mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>32.5 (19.9–56.9)</td>
<td>26.9 (17.5–37.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>No. of biopsies performed after B2 MedScan (IQR)</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>0.15</td>
</tr>
<tr>
<td>Time interval between B2 and subsequent biopsy, mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2–B3 (n = 285)</td>
<td>10.4 (12.0–25.6)</td>
<td>20.8 (13.8–27.8)</td>
<td>0.86</td>
</tr>
<tr>
<td>B2–B4 (n = 133)</td>
<td>10.4 (30.2–50.4)</td>
<td>39.5 (28.9–53.8)</td>
<td>0.71</td>
</tr>
<tr>
<td>B2–B5 (n = 44)</td>
<td>58.3 (46.0–57.8)</td>
<td>62.5 (50.9–71.3)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

5-ARI = 5α-reductase inhibitor; B2 = second active surveillance (AS) biopsy (or confirmatory biopsy); GS = Gleason score; IQR = interquartile range; MRI = magnetic resonance imaging; k-ARI = positive core.

As shown in Table 3. On multivariate analysis, no cancer at B2 was associated with a 53% reduction in risk of progression (hazard ratio [HR]: 0.47 [0.29–0.77]; p = 0.003). In addition, increasing age (HR: 1.05 per year [1.01–1.09]; p = 0.01), PSA (HR: 1.49 per unit increase [1.02–2.18]; p = 0.04), and MRI reporting cancer (HR: 1.74 [1.00–3.01]; p = 0.04) were also independent predictors of progression.

Subanalyses examining for predictors of volume-related (n = 58) and grade-related (n = 58) progression were performed. Prognostic variables for volume-related progression were cancer status at B2 (HR: 2.78; 95% confidence interval [CI], 1.61–5.0; p = 0.006) and increasing PSA (HR: 1.79; 95% CI, 1.12–2.88; p = 0.01). The only predictor of grade-related progression was increasing age (HR: 1.05; 95% CI, 1.00–1.10; p = 0.04) with cancer status at B2 not significant (HR: 0.77; 95% CI, 0.41–1.46; p = 0.43). Higher volume of disease (i.e., the number of positive cores and the maximum percentage of core involved) did not predict for grade progression.

Because cancer status at B2 was prognostic for pathologic progression, multivariate logistic regression to identify predictive variables at baseline biopsy was performed. Significant predictive variables for the presence of cancer at B2 were age (odds ratio [OR]: 1.06 per year; p = 0.02) and increased maximum percentage of core involved (OR: 1.47 per unit increase; p = 0.04) (C statistic: 0.71; Hosmer-Lemeshow goodness-of-fit test: 0.75). The number of positive cores was only significant on univariate analysis (1 vs 3; p = 0.03).

In our cohort, 36% of men (n = 103) used a 5α-reductase inhibitor (5-ARI) during AS. Only one man was exposed to 5-ARI prior to beginning AS with the remainder exposed during AS. Because 5-ARI use may affect the natural history of prostate cancer [10], a sensitivity analysis, repeating the Cox model for predictors of progression, was performed with these patients excluded. Significant predictors of pathologic progression (age, PSA, absence of cancer at B2) remained the same (data not shown).

4. Discussion

Although AS is gaining traction [11], the field desperately needs more information for counseling patients on the risk of progression. Repeat prostate biopsies are currently used to monitor for progression because the utility of PSA kinetics is inconsistent [4,12,13] and MRI remains investigational [14]. We examined the significance of a negative second AS biopsy (B2). The primary outcome measured was
pathologic progression, subclassified into grade- and volume-related progression.

Our findings demonstrated that absence of cancer on B2 was associated with a 54% decreased risk of subsequent pathologic progression (HR: 0.46; p = 0.002), with a significant difference in 5-yr progression-free survival after B2 (Fig. 2) between the no-cancer and cancer groups (85.2% vs 67.3%; log-rank p = 0.002). Cancer status at B2 was reported previously as a predictor of progression [15–17]. Al-Otaibi et al. [15] suggested a difference in the 5-yr actuarial progression-free probability of B2% (negative B2) compared with 50% (positive B2), although this cohort was small (n = 92) with only 50 men having two or more AS biopsies. Both Adamy et al. [17] and Tseng et al. [16] found on multivariate analysis that cancer status at B2 was a predictor of progression.

Previous studies on AS have not differentiated between grade- and volume-related progression. We found a significant difference in volume-related progression between the no-cancer and cancer groups (12.1% vs 29.2%; p = 0.0003), whereas grade-related progression was similar (17.5% vs 23.4%; p = 0.12). Cancer status at B2 and increased
Table 3 – Predictors of pathologic progression after the second biopsy: Cox regression model, univariate and multivariate

<table>
<thead>
<tr>
<th>Variables at B2</th>
<th>HR of nonprogressed (n=196) vs progressed (n = 90)</th>
<th>p value</th>
<th>Univariable</th>
<th>p value</th>
<th>Multivariable</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per year</td>
<td>1.06 (1.00–1.09)</td>
<td>0.001</td>
<td>1.06 (1.01–1.09)</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs no</td>
<td>0.99 (0.59–1.66)</td>
<td>0.97</td>
<td>Not used</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown vs no</td>
<td>0.83 (0.47–1.46)</td>
<td>0.62</td>
<td>Not used</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA, ng/ml, per 1-U increase</td>
<td>0.99 (0.90–1.07)</td>
<td>0.92</td>
<td>Not used</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate volume, ml, per 1-ml increase</td>
<td>0.58 (0.38–0.90)</td>
<td>0.01</td>
<td>Not used</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adj. PSA density, per 1-U increase</td>
<td>1.52 (1.08–2.14)</td>
<td>0.01</td>
<td>1.40 (1.02–1.81)</td>
<td>0.041</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRE palpable nodule</td>
<td>1.16 (0.66–2.04)</td>
<td>0.58</td>
<td>1.12 (0.65–2.04)</td>
<td>0.72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs no</td>
<td>0.72 (0.45–1.15)</td>
<td>0.17</td>
<td>Not used</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRUS nodule seen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer present</td>
<td>0.51 (0.33–0.78)</td>
<td>0.002</td>
<td>0.47 (0.29–0.77)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No vs yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive core</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 vs 3</td>
<td>0.26 (0.11–0.58)</td>
<td>0.001</td>
<td>Not used</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 vs 3</td>
<td>0.44 (0.19–1.61)</td>
<td>0.06</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 vs 3</td>
<td>0.51 (0.21–1.21)</td>
<td>0.13</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum percentage of single core, per 1% increase</td>
<td>Not used</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. cores taken, per 1-core increase</td>
<td>0.96 (0.99–1.02)</td>
<td>0.23</td>
<td>0.96 (0.96–1.03)</td>
<td>0.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-ARI use</td>
<td>0.72 (0.40–1.32)</td>
<td>0.14</td>
<td>Not used</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs no</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time between B2 and B3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time B2-B3 (n = 285)</td>
<td>0.99 (0.98–1.01)</td>
<td>0.44</td>
<td>Not used</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time B2-B3 (n = 130)</td>
<td>0.98 (0.96–0.99)</td>
<td>0.04</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time B2-B3 (n = 48)</td>
<td>0.99 (0.97–1.02)</td>
<td>0.39</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time between B1 and B2, mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;24</td>
<td>1.45 (0.77–2.71)</td>
<td>0.25</td>
<td>1.02 (0.56–2.05)</td>
<td>0.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI performed, dx = cancer</td>
<td>1.49 (0.90–2.48)</td>
<td>0.11</td>
<td>1.74 (1.06–3.01)</td>
<td>0.049</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI performed, dx ≠ no cancer</td>
<td>0.95 (0.49–1.86)</td>
<td>0.86</td>
<td>1.67 (0.52–2.20)</td>
<td>0.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI not performed</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. biopsies performed after B2, per 1-U increase</td>
<td>0.74 (0.54–0.93)</td>
<td>0.013</td>
<td>0.84 (0.64–1.10)</td>
<td>0.21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5-ARI = 5α-reductase inhibitor; AS = active surveillance; B2 = second AS biopsy (or confirmatory biopsy); B3 = third AS biopsy; DRE = digital rectal examination; dx = diagnostic; HR = hazard ratio; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

PSAD predicted volume-related progression; increasing age predicted grade-related progression. Because men with no cancer at B2 represent one end of the spectrum of low-volume disease, it is not surprising that they are less likely to progress on volume criteria. Importantly, grade-related progression still occurred in the no-cancer group (17.5%), so biopsy cannot be completely abandoned. The differences in grade- and volume-related progression found in our study have implications for the reporting of pathologic progression in AS. Institutional variations in volume-related eligibility parameters mean the definitions of progression will also differ [19–21]. We suggest that grade-related progression should be reported independently of total progression because GS 6 remains the most consistent inclusion criteria used across institutions [3,4,17–19].

The understanding of volume progression as a trigger for treatment in AS is poor and reflected in the uncertainty seen in various guidelines. Currently, only the National Institutes of Health (NIH) consensus statement specifically includes volume by stating, “increased extent of disease (more biopsy tissues involved with cancer)” [11]. The European Association of Urology (EAU) guidelines list “Gleason score ≥7, patient anxiety, and PSA doubling time” [22]. The National Comprehensive Cancer Network states, “change in risk group strongly implies disease progression” [23]. The National Institute for Health and Clinical Excellence suggests “rise in PSA or adverse findings on biopsy” [24].

Other than cancer status at B2, significant predictors of pathologic progression identified were increasing age, PSAD, and cancer seen on MRI (Table 3). Age, the only predictor of grade-related progression, is a well-established risk factor for high-grade prostate cancer [25]. PSA and PSAD were reported previously as predictors of progression [16,17] and time to active treatment [16,26]. Both the EAU and NIH guidelines recommend the use of PSAD to guide triggering treatment [11,22].

The role of multiparametric MRI to select patients for AS [27] and predict high-risk disease or progression [14] is still under investigation. Most published series are retrospective, and expertise currently remains restricted to certain centers, limiting generalizability. Our results regarding MRI predicting progression should be interpreted cautiously because MRI was used selectively, usually to investigate for anterior tumors when there was a discordance between PSA and biopsy findings [9]. There may be a role for MRI to increase sensitivity of biopsy in low-volume disease and guide timing of rebiopsy, although the costs of MRI would need to be balanced against the morbidity of TRUSB. An
alternative technique to MRI for the detection of anterior tumors is transperineal template-guided mapping prostate biopsy (TTMB).

Evaluation of TTMB to diagnose prostate cancer, in the setting of previous negative TRUS biopsy, found cancer detection rates of 34.4–55.5%. With increasing previous negative biopsies, cancer was identified more frequently in the anterior part of the prostate [28].

Although our analysis is limited by length of follow-up, the median follow-up (41 mo; IQR: 26.5–61.9) is comparable with published contemporary series [3,4,17,19–21]. With short follow-up in a disease having a long natural history, it is difficult to ascertain the relationship between pathologic progression and longer-term outcomes. However, pathologic progression is important because it often triggers treatment with its associated morbidity. By restricting our cohort to having three or more AS biopsies, generalizability is limited to men who are on AS for longer periods of time. Although our institution has a guide to rebiopsy every 1–3 yr, there is variation in follow-up intensity reflected in the timing of surveillance biopsies. In our cohort, 25% of men had B2 12–24 mo after B1, with a further 10% >24 mo. This may differ with other AS series. However, analyses showed that the total number of biopsies performed and the time from B2 to subsequent biopsies was similar between the two groups (Table 2). An important point to recognize is that the timing of the diagnosis of progression is limited by the timing of prostate biopsies. Part of our cohort has been used for previous studies examining the effect of 5-AR1 on progression in men on AS [10,29]. However, it should be noted that both previous studies included men who progressed at B2, unlike the current cohort under investigation, and hence the risk and time point of progression is different. In our cohort, 82.3% had >12 cores taken at B2. Occasionally, a Babalasian template may consist of fewer than 13–17 cores because in smaller glands the peripheral and transition zones are sampled in a single needle firing. However, undersampling is possible but was balanced between our groups. Our cohort spanned a change in GS grading (2005). However, the total number of patients affected by this time period was relatively small (before 2005, n = 48 [16.8%]) and was evenly distributed between our two groups (Table 1). Biopsy specimens were evaluated by four dedicated genitourinary pathologists, and even in a high-volume center with a centralized review of difficult cases, interobserver variation may still be present.

5. Conclusions

At our institution, absence of cancer at B2 was a significant protective factor for pathologic progression, decreasing its risk by 53%. However, our subanalyses suggest further investigation is required because cancer status at B2 and PSAD were found to be prognostic factors for volume-related progression, whereas only increasing age predicted grade-related progression. Thus subsequent biopsy in men with negative B2 cannot be completely abandoned or delayed at present, and clinicians should avoid being overly reassured by the absence of cancer at B2. As AS cohorts mature, the long-term significance of both grade- and volume-related progression will emerge.

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Author contributions: Antonio Finelli had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.urology.2013.04.038.

References


Discussion:

Summary of clinical implications with clinical recommendations:

In this thesis on active surveillance for prostate cancer, the selection process for inclusion, re-biopsy template schema and predictors for pathological progression were examined. A summary of the clinical implications and subsequent recommendations is given below.

1. **Selection of men for AS:**

Chapter 4:

Predictive models designed to assist with selection of men for AS showed only moderate performance when externally validated using a combined Australian, Canadian and United Kingdom cohort.

- Clinical recommendation:
  - These models should be used with caution as uninformed use could cause false reassurance.

Chapter 5:

Biopsy Gleason 3+4, when compared to 3+3, increases the risk of adverse pathology being present at radical prostatectomy for less stringent selection criteria.

- Clinical recommendation:
  - Active surveillance for biopsy 3+4 should be reserved for highly motivated men who satisfy a stricter AS inclusion protocol such as PRIAS.
Chapter 6:

Patients having initial diagnostic biopsy performed externally prior to referral to an academic centre were more likely to have adverse pathological features and re-classify on subsequent confirmatory biopsy.

- Clinical recommendation:
  - Quality of prostate biopsy, regardless of where it is performed, is essential to optimize determination of suitability for AS.

2. **Choice of template schema for re-biopsy of men on AS**

Chapter 7:

The AS protocol template used at PMCC detected more significant cancers than the standard extended template.

Chapter 8:

Transition zone cancers are identified regularly (14.3-16.6%) with transition zone biopsies and approximately 1/3 of these will be significant tumours.

- Clinical recommendation:
  - A template incorporating transition zone biopsies should be utilized for re-biopsy during AS.

3. **Counseling patients on the significance of a negative confirmatory biopsy**

Chapter 9:

A negative confirmatory biopsy significantly reduced the risk of volume-related progression but not grade-related progression.

- Clinical recommendation:
Men with a negative confirmatory biopsy should be counseled that regular re-biopsy is still required to monitor for grade-related progression.

**Thesis Limitations**

A number of general limitations must be acknowledged regarding this thesis.

- **Retrospective analysis, observational studies:**

  All analysis performed in this thesis was performed retrospectively, even though data at Princess Margaret Hospital was collected prospectively. Without randomization of patients and control groups, unexplained confounders could potentially influence the findings reported. Most of the literature on AS consists of similar single armed prospective cohort studies. The only trial that contains comparison arms is the ProtecT study. This is a randomized trial where AS is compared to radical prostatectomy and conformal radiotherapy (Lane et al., 2010) and patients are still accruing.

  In the pooled collaborative data examined in Chapter 4, retrospective analysis meant the data collected was dependent on individual centres protocols. Thus, differences in data collected limited our analysis. An example of this was the variable “tumour volume present in biopsy cores”. In some centres, this was recorded as millimetres of cancer whereas
others used percentage of core involved. Furthermore, as the data were
from a surgical cohort rather than an AS database, unforeseen biases in
patient selection such as age, co-morbidities, family history, patient
anxiety for intervention, findings on imaging or institutional bias, will be present.

In the subsequent chapters examining the PMCC AS database, data fields
were defined prospectively and data collected in a standardized manner.

- **Generalizability:**

Studies reported in chapters 5-8 are derived from the AS database at PMCC.
Characteristics of this single institution data set may not be generalizable to
other centres. In particular, one dedicated ultrasound operator performed 75%
of the TRUSPB. The biopsy template used, as defined in chapters 6 and 7, differs
from most other institutions and may detect higher rates of pathological
progression. Also, the pathology was reviewed by 1 of 4 dedicated genito-urinary
pathologists using synoptic reporting, who also utilize pre-sign-out quality
assurance reviews for difficult cases. The effect of inter-observer variation in
pathology reporting was reviewed in chapter 5 and certainly could be present
between different institutions.

Our institution has a guide for confirmatory biopsy at 6-12 months and then to
re-biopsy every 1-3 years. However our results showed variation in timing of
surveillance biopsies reflecting different follow-up intensity of patients. As such,
the influence of “for cause” biopsies may influence our results compared to institutions who have protocols for immediate confirmatory biopsy (Adamy et al., 2011) or yearly annual re-biopsies (Tosoian et al., 2015). This is an important point to recognize as the diagnosis of pathological progression is limited by the timing of when prostate biopsies are performed. It is important to note, that the terms pathological “progression” and “re-classification” have been used somewhat interchangeably in the thesis to describe the findings of worse pathology at succeeding biopsy. Given that pathological upgrading is only determined at prostate biopsy, it is not possible to establish if this is an effect of previous biopsy under-sampling (disease was present but not diagnosed), advancement of disease present at previous biopsy, or even development of new more aggressive disease.

Much of the data derived in this thesis is from Toronto, Canada. Hence the conclusions drawn may not be applicable to standard practice in Australia. It should be noted that local geographical practice patterns are influenced local factors. Transperineal prostate biopsy in Australia is utilized more due to concerns regarding resistant bacteria related to our proximity to South East Asia, but also because of relatively easier access to operating theatres and the general anaesthetic required. MRI prostate, whilst not reimbursed by the Australia government, is offered by providers at a much more affordable cost in Australia than other countries and hence the uptake here is relatively high. There is less distinction between “academic” and “community” centres in Australia compared to North America, however, there are recognized discrepancies in health between “metropolitan” and “rural” areas here (Strong et al., 1998).
• **Length of follow-up:**

Although our analysis of the PMCC AS database is limited by length of follow up, the median follow-up (41 months, IQR 26.5-61.9) is comparable to published contemporary series (Adamy et al., 2011; van den Bergh et al., 2007; Soloway et al., 2010; Tosoian et al., 2015). Updates from Sunnybrook Toronto, the earliest reported AS cohort, have a median follow-up time of 6.4 years but 206 of their 993 patients have been followed for more than 10 years.

As prostate cancer is a disease known to have a long natural history, outcomes such as treatment failure, cancer specific survival and overall survival for men who embark on AS require longer follow-up. For many of the studies in this thesis, a surrogate end-point of pathological progression has been used. The relationship between pathological progression and longer-term outcomes remains to be established. Having pathological features of advanced disease on biopsy may not necessarily translate to poorer outcomes after surgery. However, we believe pathological progression is an important medium term outcome to document as it often signifies a failure of AS, and triggers radical treatment with its associated morbidity. From natural history studies, there is evidence to suggest that men with higher Gleason score face increased risk of death from prostate cancer when managed conservatively (Albertsen, P.C. et al., 2009; Popiolek et al., 2013). Furthermore, in the Sunnybrook AS cohort, of the 28 men (2.8%) who developed metastasis, 26 of these men either had Gleason 3+4 at diagnosis or were upgraded to ≥ 3+4 disease before developing metastasis (Klotz et al., 2015).
During follow-up, our cohort spanned a change in Gleason score grading (2005). However, the total number of patients affected by this time period was relatively small (<2005, n=48, 16.8%).

**Future directions for AS:**

**Standardization of patient selection and triggers for treatment**

This thesis has utilized selection criteria for AS based on our institution's preference. As noted in Table 2-1, there is institutional variation in stringency of these criteria, which affects both selection and decision to proceed to active treatment. Pathological re-classification from repeat biopsy has served as an able short-term surrogate for harder survival endpoints. Work from this thesis included as Chapter 8 has been at the forefront in distinguishing between grade and volume progression that may assist in standardization of defining progression whilst on AS. Time will eventually tell if this delineation bears clinical impact on the longer term, hard end points.

Data from longer follow-up of AS cohorts with concrete end points such as biochemical recurrence after treatment, metastatic disease and prostate cancer specific mortality is emerging. In the Sunnybrook AS cohort (Klotz et al., 2015), the 10 and 15 year CSS rates were 98% and 94% respectively. In total, there were 15 deaths from prostate cancer among 993 patients (1.5%). In comparison, the series from John Hopkins (Tosoian et al., 2015) published a 99.9% 10 year CSS rate, with only 2 prostate cancer deaths, albeit with overall shorter follow-up.
John Hopkins also had fewer metastatic events (0.3% versus 2.8%). Compared to Sunnybrook, John Hopkins entry criteria to AS are much stricter requiring additional conditions such as PSA density <0.15ng/ml, ≤2 positive biopsy cores, and maximum of 50% involvement of any biopsy core with cancer, to be satisfied. Furthermore, patients had more regular surveillance biopsies (interval between biopsies 1 year versus Sunnybrook 3-4 years). Whilst it appears that the manner in which John Hopkins conducts AS results in less cancer specific mortality and metastasis, the trade-offs of fewer men being eligible for AS (and hence more undergoing radical treatment with the morbidity associated with this) and the risks associated with more frequent biopsy must be considered.

The allowable volume of Gleason 3+3 disease remains unclear. The permissible number of positive cores ranges from 2 to any (Table 2-1). The evidence from which this variable was derived may be obsolete. AS inclusion criteria were developed from a definition of insignificant prostate cancer being ≤ 0.5ml (Stamey et al., 1993; Epstein et al., 1994). During that time, tumour volume was an important prognostic marker. In the modern PSA-screening era tumours are detected earlier and are thus smaller. Subsequent radical prostatectomy studies have suggested final tumour volume is inferior to pathological grade, stage and margin status in predicting biochemical recurrence (Epstein, 2011; Wolters et al., 2010). The 0.5ml “significant” threshold was re-evaluated Wolters et al by examining tumour threshold volume in an organ-confined, no Gleason 4-5, modern prostate cancer cohort(Wolters et al., 2011). The findings from this study suggested an index tumour volume of 1.3ml, and total tumour volume of 2.5ml be considered. The other issue with allowable numbers of positive cores is
that for surveillance biopsy, the total number biopsy cores taken, has been increased in many centres. This is in response to minimize the error missing significant cancer because of under-sampling. As we discussed in Chapters 6 and 7, this sampling bias will influence the number of positive cores found.

There have been some reports on the feasibility of AS in men with Gleason 3+4 disease (intermediate risk). The University of California San Francisco (USCSF) reported outcomes for a group of strongly motivated men with “intermediate risk” prostate cancer, who after informed consent accepted the risks of “off-label” AS (Cooperberg et al., 2011). Their definition of intermediate risk was Gleason score 7 or Cancer of Prostate Risk Assessment (CAPRA) score 3 to 5. With short follow-up (median 51mo, range 14-140mo), they reported no difference when comparing low to intermediate risk groups on AS, for progression-free survival, no PSADT ≤2 years, and no active treatment. In the updated Sunnybrook cohort, with median follow-up of 6.4 years, including 250 patients followed-up for >10 years, Gleason score was predictive of overall survival(Klotz et al., 2015). However this is not surprising given their selection criteria allowing Gleason 3+4 in older men having more co-morbidities. More significantly, metastatic disease developed in 2.8% (n=28) of the cohort, and only 2 of these patients were not upgraded to Gleason ≥ 7 before developing metastases. Thus presence of Gleason 4 disease likely signifies a gain in biological behaviour with ability to metastasize. When considering AS for intermediate risk disease for men without competing comorbidities, the risk of death from prostate cancer is likely to outweigh death from other causes so radical treatment should be the recommended standard of care.
Grayscale ultrasound, performed transrectally, has been the imaging of choice to guide prostate biopsy for nearly 25 years (Hodge, McNeal and Stamey, 1989). However, it has low sensitivity in visualizing prostate cancer and thus its use has been limited to guiding the biopsy needle into zones of the prostate rather than targeting specific lesions of suspected cancer. Improvements to grayscale ultrasound using power Doppler sonography (Zalesky et al., 2008) have not been consistently demonstrated.

Utilization of MRI to aid management of prostate cancer has recently rapidly disseminated. This is due to significant improvements in prostate MRI techniques. Initial prostate MRI relied on morphologic and signal changes present on T1- and T2-weighted images and thus had poor sensitivity and specificity for detecting prostate cancer (Johnston et al., 2013). Prostate MRI now utilizes a multiparametric approach, in which two or more functional sequences complement the morphologic information provided by T2-weighted imaging. Stronger magnetic fields of 3.0 Tesla (T) MRI systems give better definition and provide a higher signal-to-noise ratio compared with 1.5T systems. To augment the signal of a 1.5T system, an endorectal coil (ERC) was placed adjacent to the prostate. Understandably, the discomfort of having an ERC was a barrier to some patients when considering having a prostate MRI.

Current guidelines from the European Society of Urogenital Radiology (ESUR) recommend utilizing multiparametric MRI (mp-MRI) (Barentsz et al., 2012) to investigate for prostate cancer. The components of the mp-MRI approach are T2
weighted imaging (T2WI); diffusion weighted imaging (DWI); dynamic contrast enhanced imaging (DCEI) and MR spectroscopic imaging (MRSI) (Gupta et al., 2013). High resolution T2WI provides the best assessment of the prostate gland’s anatomy, margins and differentiation between peripheral and transition zones. On T2WI sequences, prostate cancer typically appears as a hypointense low signal (dark) lesion in the peripheral zone. DWI distinguishes cancer from normal glandular tissue by evaluating differences in functional tissue microstructure. Tumours with higher cellular density and complex microstructure restrict how freely water protons can move in space, and are thus described as having “restricted diffusion” on DWI. Reports also propose the ADC (apparent diffusion coefficient) map, produced from the DWI sequencing, can be used to further classify foci based on degree of histopathological aggressiveness (Gleason score at biopsy or surgery) (Vargas et al., 2011; Woodfield et al., 2010). The DCEI sequence utilizes tumour angiogenesis, which leads to detectable vascular differences such as increased blood flow, microvascular density and capillary leakiness. Prostate MRSI examines the relative concentrations of metabolites in the prostate, in particular choline (increased concentration in prostate cancer) and citrate (reduced in prostate cancer). Most described protocols utilize T2WI with at least 2 functional MRI techniques as this has been shown to provide better characterization than T2WI with one functional technique. DWI and MRSI add specificity to lesion characterization whilst DCE has high sensitivity in cancer detection. As MRSI is both technically challenging and time-consuming, DWI is preferred in nearly all mp-MRI standard protocols.
Suspicious lesions seen on MRI still require prostate biopsy for confirmation of cancer and grade of disease. The simplest, and most common method of MRI guidance of prostate biopsy is the “cognitive-fusion” method. This involves the biopsy operator reviewing the MRI to assess location of the lesion, and then using standard transrectal ultrasound to aim the needle towards this suspicious region. Biopsies taken “in-bore” (within the MRI tube), use MRI to guide biopsy needle placement into the lesion. In-bore biopsies are likely the most accurate however they are slower to perform and expensive because of limited MRI magnet time. MRI-TRUS fusion technology involves using software to digitally overlay MR images to real time ultrasound. Specialized equipment and training is required but enables biopsies to be taken in the operating theatre, or even an office-outpatient setting.

Results demonstrating each of these MRI guided biopsy techniques all suggest more accurate sampling of lesions and improved detection of cancer over standard systematic TRUSPB (Sonn et al., 2013; Yerram et al., 2012; Pokorny et al., 2014). Studies have also investigated the issue of only taking targeted cores versus target cores and systematic sampling. The issues with only taking targeted cores involving balancing the benefit of reduction in over-detection of insignificant cancers, and the risk of missing a significant cancer not seen on MRI. In a study where men with PI-RADS 3-5 lesions on mp-MRI had MRI-guided biopsy followed by blinded 12 core TRUS-guided biopsy, and men with PI-RADS 1-2 lesions had 12 core TRUS-guided biopsy only, TRUS-guided biopsy detected intermediate/high grade cancer in only 15/223 (6.7%) men (Pokorny et al., 2014). Of these, 5/15 were not diagnosed at MRI and 10/15 were missed on MR-
guided biopsy. The authors definition of intermediate/high risk cancer was conservative and included Gleason 3+3 disease involving more than 2 positive cores, and any core >6mm involved. Thus, the number of Gleason ≥7 disease cases missed is even smaller. The other benefit of avoiding systematic biopsies is reducing detection of low-grade cancers. MpMRI/MR-guided biopsy detected 6 cases compared to 47 cases with systematic biopsy of low-risk prostate cancer. When comparing MR guided biopsy to transperineal prostate biopsy using a 20 zone “Barzell” template (Barzell et al., 2012), the amount of clinically significant cancer detected appears similar (57% vs. 62%), with less clinically insignificant cancer found (9% vs. 17%)(Kasivisvanathan et al., 2013). These authors suggest that MR guided biopsy can find the same amount of significant cancer as transperineal, with fewer biopsy cores required.

For men on active surveillance, mp-MRI is being increasingly used. Its primary role is to help identify any significant cancers that were missed on previous (non-MR guided) TRUSPB. There is hope that with its high negative predictive value, it may at some point be able to replace, or decrease the frequency, of serial prostate biopsy. The main region of many tumours missed with standard TRUSPB is the anterior zone (Lawrentschuk et al., 2010; Lemaitre et al., 2009). At the confirmatory biopsy, there is increasing evidence that prostate MRI can be helpful in selecting men that will upgrade (Margel et al., 2012; Vargas et al., 2012). In men where prostate mp-MRI demonstrates absence or only low suspicion lesions, the risk of pathological upgrading is thought to be low (Yerram et al., 2012).
Currently, the main limitations for prostate mp-MRI are cost, availability and expertise. In Australia, urologists are in consultation with the Medical Services Advisory Committee in regards to a rebate through Medicare for diagnostic mpMRI prostate scans, and MR-guided biopsy procedures (Medical Services Advisory Committee, Department of Health, Australia, 2015). It is highly likely that in the future, prostate mp-MRI will be increasingly utilized to aid selection for eligibility and monitor for disease progression in men considering AS.

**Transperineal template biopsy**

The development of transperineal prostate biopsy (TPPB) offers an additional approach to improving standard TRUSPB. To decrease the likelihood of under-sampling, and hence under-detection of prostate cancer, more biopsy cores are taken. A brachytherapy seed type template is used to better “map” location of biopsy needles. The median number of cores taken using this technique varies from 18 (Furuno et al., 2004) to over 50 (Taira et al., 2010; Patel et al., 2011), in what is known as a systematic “saturation” biopsy. An accepted advantage of TPPB is better access and sampling of the anterior zone, particularly for larger prostates. A further benefit of TPPB is a lower rate of infection as the biopsy is not performed through the rectum.

For men having TPPB in the setting of previous negative biopsy and persistently elevated PSA, cancers detection rate has been described as high as 51.6% (Taira et al., 2010). In the AS setting, performing TPPB as the second, or confirmatory biopsy, 31-85% had increase of Gleason grade and/or volume (Ayres et al., 2012;
Barzell et al., 2012), though this does depend on what definition of re-classification is used. This is more than when TRUSPB is used for confirmatory biopsy (17.6-22%)(Wong et al., 2014; Barzell et al., 2012) and hence TPTB has been proposed as a method of minimizing risk of undersampling from TRUSPB.

Widespread uptake of TPTB worldwide has been slow. This is likely because of longer times required to perform TPTB compared to TRUSPB, with requirement of either general or regional anaesthesia. There are also concerns with increased rate of post-biopsy urinary retention, and the possibility of increased fibrosis impacting on radical prostatectomy. Furthermore, the issue of over-diagnosis of insignificant cancers remains an important concern. In Australia, concerns regarding fluoroquinolone resistant E.Coli (Grummet et al., 2014), and easier access to operating theatres particularly in the private setting, has led to greater acceptance and utilization of TPTB.

**Biomarkers**

For active surveillance, the ability to distinguish between indolent and aggressive prostate cancer is priceless. Current cohort based selection criteria, based on Epstein pathological criteria, are effective but imperfect. There has been much research directed at exploring newer biomarkers from serum, urine and biopsy tissue that might advance our ability to better identify patients with more aggressive disease. A summary is presented below.

*Serum and Urinary markers:*
**Prostate Health Index (PHI)**

The Prostate Health Index is a formula that combines total PSA, free PSA and p2PSA into a single score to predict clinically significant prostate cancer (PHI=([-2]proPSA / free PSA) x √PSA.) It’s original utilization was to aid detection of prostate cancer for men in the total PSA range 4-10ng/ml by improving on the specificity of PSA or %fPSA alone (Catalona et al., 2011).

There has also been evidence to suggest that PHI may improve prediction of pathological progression of prostate cancer in men on AS. Tosoian et al. (Tosoian et al., 2012) looked at an active surveillance cohort of 167 patients who underwent yearly re-biopsy. Pathological upgrading was defined as finding (Gleason>7, ≥3 positive cores; >50% involvement). PHI was shown to predict which men progress on re-biopsy at a median follow-up of 4.3 years. In another study, Hirama et al. looked at 118 active surveillance patients. The reclassification rate on the 1-year biopsy was 37%. The only independent predictive factors on multivariate logistic regression analysis for pathological upgrading were baseline %p2PSA and PHI (Hirama et al., 2014).

Whilst these studies show great promise for a test that is easily performed and relatively affordable, further validation in larger cohorts is required. Appropriate thresholds values for clinical use, and the role of longitudinal PHI testing in AS cohorts remain to be elucidated.

**4Kscore® Test/ four-kallikrein panel**
Another test which utilizes PSA is the 4Kscore® Test (OPKO Lab, Nashville, TN). 4Kscore incorporates a panel of four kallikrein protein biomarkers (total PSA, free PSA, intact PSA, and human kallikrein-related peptidase 2) and other clinical information in an algorithm that provides a percent risk for a high-grade (Gleason score ≥ 7) cancer on biopsy. As prostate cancer becomes more undifferentiated it is thought that levels of these kallikreins increase. The 4Kscore has been extensively investigated in the initial diagnostic setting with studies consistent showing an AUC 0.82-0.90 to predict Gleason score ≥7 (Punnen et al).

**Prostate Cancer Antigen 3 (PCA3)**

PCA3 is a noncoding mRNA that is significantly overexpressed in prostate cancer tissue and collected in the urine post digital rectal examination (DRE). Much of research on PCA3 has demonstrated its high specificity for prostate cancer, and aiding clinicians to decide if patients should have initial diagnostic prostate cancer.

Utilization of PCA3 in the Canary Prostate Active Surveillance Study cohort (n=387) was examined by Lin et al. (Lin et al., 2013). PCA3 levels sequentially increased with both higher volume of disease and higher Gleason score on re-biopsy. However, in receiver operator curve (ROC) analysis, comparison of AUC for the prediction of Gleason ≥ 7 at study entry was 0.68 for PSA alone, 0.66 for PCA3 combined with TMPRSS2-ERG, and 0.70 for all 3 combined. Thus the addition of PCA3 to PSA was not found to be statistically or clinically significant
over PSA alone. Similarly, Tosoian et al. (Tosoian et al., 2010) looked at PCA3 in an active surveillance cohort of 294 patients. They found the mean PCA3 score were similar in those with and without progression (PCA3 60 vs. 51 p=0.131).

Other authors have found a low PCA3 to correlate with tumour volume <0.5ml, a definition of "insignificant cancer" (Ploussard et al., 2011; Nakanishi et al., 2008). These studies were not performed in AS cohorts, but rather men who were suitable for AS but underwent upfront radical prostatectomy. PCA3 thresholds of <25 have been suggested as having best diagnostic accuracy to predict small tumour volume. However, in Ploussard et al's group of already low risk cancer, only 28% of men had PCA3 scores < 25.

PCA3 may be able to assist prediction of small tumours (<0.5ml) but does not appear useful for men already diagnosed with prostate cancer to differentiate presence of more aggressive disease.

**Genetic Features:**

**Oncotype DX Genomic Prostate Score (GPS)**

Oncotype DX Genomic Prostate Score (GPS) test (Genomic Health, Redwood City, California, USA) is a gene expression signature test that can be performed on prostate biopsy tissue. Using an identified 17-gene panel, gene expression is quantified using reverse-transcriptase polymerase chain reaction (PCR) and a genomic progression score from 0 to 100 is derived. Work has been performed
to validate this panel’s role in risk stratifying men who are suitable for active surveillance.

In developing the GPS, a total of 727 genes were first identified from the literature. A two-step evaluation process was performed using first radical prostatectomy specimens and then prostate biopsies from low-intermediate patients to develop the final 17-gene panel. External validation showed GPS on biopsy tissue for men eligible for AS, was a significant predictor on multivariate analysis of pathologic stage and grade at prostatectomy. The odds ratio (OR) for each 20-point increase in GPS to predict high-grade and/or non-organ-confined disease was consistently ~2.0, even when adjusting for biopsy Gleason score, PSA, age, clinical stage and NCCN risk group (Klein et al., 2014).

Cullen et al. (Cullen et al., 2014) further examined utilization of GPS in men suitable for AS on biopsy according to NCCN low-intermediate risk prostate cancer who then had radical prostatectomy. In multivariate analysis to predict adverse pathology at radical prostatectomy and biochemical recurrence post radical prostatectomy, GPS score and NCCN risk group were both significant factors. In ROC analysis for adverse pathology, GPS improved the AUC of NCCN group alone (AUC 0.63 to 0.72).

As the GPS is performed on prostate biopsy tissue, it is still beholden to the problems of sampling error. Also, as it was derived from localized prostate cancer specimens rather than metastatic, it is best utilized in organ-confined disease.
**Prolaris Cell Cycle Progression Score**

Cell cycle progression can be used to predict aggressiveness of disease on histopathology. Prolaris (Myriad Genetics, Salt Lake City, Utah, USA) provides a quantitative measure of RNA expression of 46 genes, generating a cell cycle progression (CCP) score. Genes analysed include 31 cell cycle progression and 15 housekeeping genes. The test can be performed on formalin-fixed paraffin embedded tissue, i.e. standard prostate needle biopsy and radical prostatectomy specimens, using RNA extraction and gene amplification techniques.

Whilst Prolaris has not been formally evaluated in the AS setting, it is included in the review because of its promising potential. The CCP score from needle biopsy has been demonstrated to predict death from prostate cancer. In a cohort of conservatively managed needle biopsy men, 349 had a CCP score performed. On multivariate analysis CCP, Gleason score >7 and PSA were all predictors for prostate cancer mortality (Cuzick et al., 2012). Other work has shown the CCP score, when used on radical prostatectomy and TURP specimens, was statistically significant in predicting biochemical recurrence post radical prostatectomy, and prostate cancer mortality post TURP (Cuzick et al., 2011). Cooperberg et al. (Cooperberg et al., 2013) externally validated the CCP in a radical prostatectomy cohort and confirmed its ability to predict recurrence.

Currently, the role of Prolaris in predicting prognosis for active surveillance patients is under investigation. Markers that predict recurrence after surgery may not be the same as those that predict progression under active surveillance.
Furthermore, prostate cancer mortality occurs rarely in AS cohorts so large sample sizes may be required to fully evaluate an appropriate threshold in CCP for benefit in this group of low risk patients.

**TMPRSS2-ERG**

TMPRSS2 is an androgen-regulated gene. ERG is a member of the ETS transcription factor genes identified in prostate cancer patients. The fusion of the two, TMPRSS2:ERG, is a frequent event (40-78%) in prostate cancer. It is rarely found in men without prostate cancer and has a 97% specificity and 96% sensitivity for presence of prostate cancer (Salagierski and Schalken, 2012).

Berg et al. (Berg et al., 2014) recently looked at 265 patients on AS and used ERG immuno-histochemical staining on paraffin-embedded formalin-fixed biopsies. ERG-positive patients have significantly higher incidence of overall progression (HR: 2.45; p<0.0001), histopathological progression (HR: 3.06; p < 0.0001) compared to ERG-negative patients on multivariate analysis. Whelan et al (Whelan et al., 2014) examined biomarkers expressed prostatic secretion (EPS) and found a model using serum PSA and Type III and IV TMPRSS2-ERG mRNAs could detect upstaging in an NCCN AS group, prior to surgery.

The paper discussed above by Lin et al. (Lin et al., 2013) looking at the Canary Prostate Active Surveillance study examined TMPRSS2:ERG, in addition to PCA3. The results for TMPRSS2:ERG were similar to PCA3 in that although higher levels
correlated with volume of disease on biopsy it was not superior to PSA alone in predicting grade of disease on ROC analysis.

Research into TMPRSS2-ERG fusion to predict presence of more aggressive disease in AS cohorts shows mixed results and hence is not used in standard practice. Whilst promising, the results demonstrated by Berg and Whelan still requires validation.

MicroRNAs – miR-19, 345 and 519c-5p

MicroRNAs are small single stranded non-coding RNAs involved in the post-transcriptional regulation of gene expression. As such they can have both oncogenic and tumour suppressive effects, and dysregulated miR expression have been implicated in progression of a number of tumour types (Nair, Maeda and Ioannidis, 2012). Previous investigations in a small cohort of patients have established that the profile of miRs detectable in serum differs significantly in patients with clinically localized prostate cancer compared to healthy donors, which for a number individual miRs demonstrating a positive or negative correlation with increasing tumour risk (Moltzahn et al., 2011).

To extend these findings, Wang and colleagues profiled the expression of 672 individual miRs by quantitative RT-PCR in the serum of patients who were eligible for active surveillance based on the UCSF exclusion rule, but who underwent immediate prostatectomy (Wang et al., 2014). Using pathological upgrading to Gleason score > 7 as the endpoint, they identified that the
expression of 3 miRs (miR-19, miR-345 and miR-519c-5p) were significantly altered in patients harbouring higher grade disease, and improved the accuracy of multivariable prediction models including standard clinical and pathological parameters. Although promising, independent validation in a larger clinical cohort is required.

**Histopathological markers:**

**Immunohistochemistry:**

Ki67 is a nuclear protein providing an estimate of cell proliferation, present during active phases of the cell cycle. The fraction of Ki67 positive tumour cells is reported as a labelling index (LI), and has been best examined in prostate, brain and breast cancers.

In a small study of 28 patients (19 cases (PSA <4), 9 positive controls), Nagao et al. (Nagao et al., 2011) stained needle biopsy specimens for Ki67, p53, bcl-2, BUBR1, PTEN and E-Cadherin. There was significant correlation between high positive Ki67 and BUBR1 with high Gleason score (p=<0.01). The sensitivity and specificity of Ki67 and BUBR1 staining in discriminating the prostate cancer cases classified as clinically insignificant according to the Epstein criteria were 62.5 and 84.2%, or 57.1 and 100%, respectively.

Jhavar et al (Jhavar et al., 2009) used tissue microarrays constructed from 60 patients on active surveillance for prostate cancer to assess Ki67 and other immuno-histochemical markers. Ki67 LI was found to be an independent determinant of progression to radical treatment (p=0.03). However, Ki67 has
significant intra/inter-observer variability and is subject to sampling error and thus remains investigational.

Severi et al (11) assessed whether a panel of biomarkers (AZGP1, MUC1, NKX3.1, p53 and PTEN) detected using immunohistochemistry staining, could predict death from prostate cancer for men with localised disease (n=315). Expression of MUC1 and p53 was associated with increased prostate cancer specific mortality (p=0.02 and 0.005 respectively), whilst AZGP1 expression was associated with decreased prostate cancer specific mortality (p=0.04). The study concluded that a panel of markers (AZGP1, MUC1 and p53) might help guide treatment decisions by assisting in the determination of prostatic adenocarcinoma aggressiveness.

**Nuclear morphology**

The prognostic value of nuclear morphometric features to predict which patients in an expectant management program for prostate cancer, would require treatment, was examined by Makarov et al. (Makarov et al., 2007; Isharwal et al., 2010). Adding morphometric descriptors (e.g. nuclear size, shape, DNA content) to traditional clinic-pathological variables improved the accuracy of predicting which patients would develop an unfavourable biopsy (AUC 0.68 to 0.88). However the sample size was small (n=75), overall follow up was short and further validation is still required.

From prostate biopsies in the same active surveillance cohort, DNA content was further examined in, both benign-adjacent and cancer-tissue, by Isharwal et al.
(Isharwal et al., 2010). Abnormal DNA content may represent chromosomal alterations and reflect later-stage changes of genetic instability in tumour cells. Of the DNA variance factors measured, excess optical density in benign prostatic areas was a significant predictor for unfavourable biopsy conversion.

**Other Potential biomarker Sources**

**Circulating Tumour Cells**

Cells shed by primary and metastatic tumours into the vasculature can be detected in the circulation. As CTC counts are low even in patients with high tumour burdens, techniques that enrich for this rare cell based on cell surface antigen immunoreactivity or physical characteristics (size, density, deformatability) must be employed (Miyamoto, Sequist and Lee, 2014). In patients with metastatic castration resistant prostate cancer, CTC counts >4 /7.5 ml of blood prior to systemic therapy predict significantly shorter overall survival compared to lower counts, and patients with high CTCs which fail to fall with cytotoxic agents demonstrate early treatment resistance (Goodman et al., 2009). The detection of CTCs in localized prostate cancer using the CellSearch system (FDA approved system of combined positive and negative selection using 5 cell surface antigens) is much less frequent, and not significantly different to cancer-free controls (Davis et al., 2008). However other groups using less-stringent immune-based isolation techniques or RT-PCR have been reported detectable CTCs in up to four-fifths of patients with localized disease, with at least one group demonstrating fewer detectable CTCs in patients with indolent cancer by the Epstein pathological definition (Murray et al., 2014; Fizazi et al.,
However considerable work must be done on standardization and validation of these assays before they can be reliably applied in the low risk setting.

**Summary of genetic and histopathological markers:**

PHI and Oncotype DX currently hold greatest potential benefit to aid selection of men for AS. Prospective longitudinal evaluation and vigorous validation of these markers in larger AS cohorts, alongside improvements in imaging and biopsy, is required.

**Secondary chemoprevention**

Active surveillance represents an opportunity for “secondary chemoprevention”. Unlike primary prevention, where the intent is to prevent cancer from occurring, secondary prevention involves prevention of disease progression. Interest in secondary chemoprevention stems from prior investigation of 5 alpha -reductase inhibitors for primary prevention of prostate cancer. In 2 large randomized control trials, the Prostate Cancer Prevention Trial (PCPT, n=18 882) (Thompson et al., 2003) and the Reduction by Dutasteride of Prostate Cancer Events Trial (REDUCE, n=6729)(Andriole et al., 2010), 5ARIs were shown to significantly reduce the relative risk of prostate cancer detected on biopsy by ~25% (22.8% and 24.8% respectively) over 4 and 7 year follow-up respectively. Despite this high level evidence, widespread usage of 5ARIs for cancer prevention has not occurred because of the concerns of increased high-grade prostate cancer (Gleason 7-10) in the 5ARI arm of PCPT. The absolute increase, whilst
statistically significant, was very small (PCPT, 6.4% vs 5.1%, p=0.005). In the REDUCE trial, when high-grade cancer was defined as Gleason 8-10, the results were not statistically significant. However, the trial was likely underpowered to detect a difference as there were 12 of these patients in the 5ARI arm compared to 1 in the placebo arm. Proponents for primary chemoprevention attribute this association between 5ARI and high grade prostate cancer to sampling or detection bias resulting from decreased prostate volume whilst on 5ARI. There have been several attempts performing post randomization analyses to clarify any causation between 5ARIs and high risk prostate cancer but as expected with post-hoc analyses, clarity remains elusive(Cohen et al., 2007; Lucia et al., 2007; Redman et al., 2008).

Secondary prevention of prostate cancer, to prevent progression of disease in men on active surveillance, using 5ARI has also been investigated. The reduction by dutasteride of clinical progression events in expectant management (REDEEM) trial, was a randomized control trial comparing Dutasteride to placebo for men on AS (n=302) (Fleshner et al., 2012). A composite end point of pathological (worsening biopsy findings) and/or therapeutic (proceeded to treatment) progression was used. Thus men whose disease did not worsen, but had treatment for anxiety, cloud the definition of progression. At the 3-year close of study time point, fewer men in the Dutasteride arm reached this composite end point (38% versus 48%, HR 0.62, 95% C.I. 0.43-0.89, p=0.009). The study was not powered to examine pathological progression alone, and investigators and patients were not blinded to PSA results. Retrospective analysis examining effect of 5ARI on pathological progression has been performed using the the
PMCC AS database (Finelli et al., 2011). This showed “no-5ARI use” to be associated with pathological progression (HR 2.91, 95% C.I. 1.5-5.6). A subsequent time-dependent covariate analysis was performed, taking into account periods on and off 5ARI, with similar results (Wong, Fleshner and Finelli, 2013). For many men on AS, 5ARI might also improve any bothersome lower urinary tract symptoms. Off setting this however are the concerns regarding possible increased risk of high-grade cancer and potential side effects from 5ARIs. In particular, sexual side effects such as decreased libido and erectile dysfunction are counteract the purpose of AS, that is to preserve quality of life.

Other areas of interest for secondary chemoprevention include investigation of the roles of statins (Murtola et al., 2007), folate (Figueiredo et al., 2009), anti-inflammatories (Katz et al., 2010) and metformin (Fleshner and Bhindi, 2014).

Quality of life

A chief goal of AS is maintenance of quality of life (QoL), achieved by avoiding the side effects associated with radical treatment. It has been suggested that a potential “harm” of AS is the psychological distress caused by living with a cancer diagnosis.

Using various different validated scores to assess depression, anxiety and decisional conflict, van den Bergh and colleagues found men in the PRIAS study reported mainly favourable levels of anxiety and distress (van den Bergh et al., 2010). A more recent systematic review reported on 10 studies with quantitative
health related quality of life (HR-QoL) outcomes for men on AS (Bellardita et al., 2015). Despite 15 different measures being used to assess various facets of HR-QoL and psychological dimensions, high overall HR-QoL scores were reported. When evaluated against comparison groups, such as non-AS population and men undergoing radical treatment, no major differences were found. There were also low frequency of anxiety found (5 studies), and low levels of “decisional conflict”. The decisional conflict scale aims to elicit patients’ uncertainty in making a health related decision, and in one study, authors found men who elected AS in their cohort had less decision conflict than a cohort of men who elected to have radical treatment. They systemic review noted that the quality of the 10 studies had significant limitations. In particular, most were small, had short follow-up, were lacking in an appropriate (randomised) control group, and all did not have HRQoL assessment of the men prior to commencing AS.

Erectile function and lower urinary tract function are important aspects of HRQoL that should be monitored during AS. In a study by Jeldres et al (Jeldres et al., 2015), men suitable for AS at biopsy had HRQoL prospectively monitored, and those going on to have radical prostatectomy compared to those remaining on AS over 3 years. For HRQoL associated with sexual and urinary symptoms, men in the RP cohort reported significantly lower scores when compared to those on AS. These results are similar to a trial comparing radical prostatectomy to watchful waiting (Steineck et al., 2002). Here, men undergoing radical prostatectomy had more erectile dysfunction (80% vs. 45%) and more urinary leakage (49% vs. 21%) but less urinary obstruction (28% vs. 44%). However, the
Conclusion:

Active surveillance utilization is increasing globally due to recognition of the low mortality associated with appropriate selection of patients. The body of this thesis has focused on refining conventional prostate biopsy to select and monitor patients. Advancements in imaging with mpMRI have been rapidly adopted but biomarkers, due to concerns with cost and incremental improvement, remain at the periphery of every day practice in Australia. To achieve the ultimate aim of ensuring “perfect patient selection” in AS, a combination of techniques will be required. However, with any cancer diagnosis, tissue from prostate biopsy will continue to play a vital role.
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### Appendix A: List of variables

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>5ARI</td>
<td>5 alpha reductase inhibitor</td>
</tr>
<tr>
<td>AS</td>
<td>active surveillance</td>
</tr>
<tr>
<td>AUC</td>
<td>area under curve</td>
</tr>
<tr>
<td>B1</td>
<td>baseline, or diagnostic prostate biopsy</td>
</tr>
<tr>
<td>B2</td>
<td>confirmatory, or 1st prostate re-biopsy after B1</td>
</tr>
<tr>
<td>CAPRA-S</td>
<td>the Cancer of the Prostate Risk Assessment Post-Surgical - SCORE</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>cT</td>
<td>clinical stage of prostate cancer, from DRE.</td>
</tr>
<tr>
<td>DRE</td>
<td>digital rectal examination</td>
</tr>
<tr>
<td>EPE</td>
<td>extra-prostatic extension</td>
</tr>
<tr>
<td>FHx</td>
<td>family history</td>
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<tr>
<td>GS</td>
<td>Gleason score</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>PCore</td>
<td>positive cores (from prostate biopsy)</td>
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<tr>
<td>PRIAS</td>
<td>European Prostate Cancer Research International: Active Surveillance Study</td>
</tr>
<tr>
<td>PSA</td>
<td>prostate specific antigen</td>
</tr>
<tr>
<td>PSAD</td>
<td>prostate specific antigen density</td>
</tr>
<tr>
<td>PSA-DT</td>
<td>prostate specific antigen doubling time</td>
</tr>
<tr>
<td>PSM</td>
<td>positive surgical margin (from radical prostatectomy)</td>
</tr>
<tr>
<td>pT</td>
<td>pathological stage of prostate cancer, from pathology review of specimen.</td>
</tr>
<tr>
<td>PZ</td>
<td>peripheral zone (of prostate)</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver-operating curve</td>
</tr>
<tr>
<td>SET</td>
<td>standard extended template (prostate biopsy)</td>
</tr>
<tr>
<td>SVI</td>
<td>seminal vesicle invasion</td>
</tr>
<tr>
<td>TRUS</td>
<td>trans rectal ultrasound</td>
</tr>
<tr>
<td>TZ</td>
<td>transition zone (of prostate)</td>
</tr>
</tbody>
</table>
Appendix B: Co-authored manuscripts related to the thesis

- Impact of 5-Alpha Reductase Inhibitors on Men Followed by Active Surveillance for Prostate Cancer: A Time-dependent Covariate Reanalysis.
- Active surveillance in patients with a PSA >10ng/ml.
- An unusual general surgical presentation of advanced prostate cancer – a case for PSA testing in the unwell elderly man.
- An Increase in Gleason 6 Tumor Volume While on Active Surveillance Portends a Greater Risk of Grade Reclassification with Further Followup
Letters to the Editor NOT referring to a recent journal article

Impact of 5-Alpha Reductase Inhibitors on Men Followed by Active Surveillance for Prostate Cancer: A Time-dependent Covariate Reanalysis

We previously reported that lack of 5α-reductase inhibitor (5-ARI) use in a cohort of 288 men on active surveillance (AS) for prostate cancer was associated with pathologic progression (hazard ratio [HR]: 2.91; confidence interval [CI]: 1.5–5.6; p = 0.002) on retrospective analysis [1].

In a subsequent editorial, this work was heavily criticized for not using a time-dependent covariate analysis [2]. A time-dependent covariate analysis is used to account for time while on AS but not on a 5-ARI and to diminish the likelihood of overestimating the benefit. The work by Ross et al. [3] was referenced as “set the record straight.” They found that 5-ARI use, when treated as a time-dependent covariate, did not significantly alter biopsy reclassification.

It should be noted that only 8% of the cohort (47 of 587) studied by Ross et al. initiated 5-ARI use, whereas 24.3% of our cohort (70 of 288) did. Ross et al. performed analyses defining reclassification as either biopsy upgrading or increased tumor extent. However, they had only eight men with pathologic progression in their 5-ARI–exposed sample, four of which experienced grade-related progression and five of which had progression by volume. Hence, their cohort was somewhat underpowered to set the record straight.

We report a reanalysis of our same cohort for the time period of the previously published work [1], using a Cox proportional hazards model with time-dependent covariate analysis. Then the time when men were not on a 5-ARI during AS was analyzed as part of the non-5-ARI group. This reanalysis found that lack of 5-ARI use continued to be associated with pathologic progression (HR: 4.55; CI: 1.61–12.5; p = 0.004). Other significant predictors remained the same as in our previous analysis: age (per year; HR: 1.05; CI: 1.02–1.08; p = 0.003) and baseline prostate-specific antigen (per unit; HR: 1.10; CI: 0.99–1.21; p = 0.05).

To account for differences in prostate volume at baseline between 5-ARI and non-5-ARI groups (median: 61 ml vs 41 ml; p < 0.0001), sensitivity analyses were performed restricting men in the non-5-ARI group to those with larger glands (prostate volume > 40 ml). We found lack of 5-ARI use was still predictive of progression (HR: 3.87; CI: 1.37–10.8; p = 0.01).

Our reanalysis supports the protective role of 5-ARIs in preventing progression while on AS. Longer follow-up of these men should shed light on pathologic progression, risk of high-grade cancer, and treatment-related outcomes.

Conflicts of interest: The authors have nothing to disclose.

Acknowledgments: The authors would like to acknowledge the assistance of Nararsan Tilimbhia with data analysis and Dr. Robert Scowery with data entry.

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Letter to the Editor


I am happy to see that this team has used a time-dependent covariate analysis in reevaluating their observational study on the effect of 5α-reductase inhibitors (5-ARIs) on pathologic progression in men on active surveillance [1]. Although their reanalysis supports their original conclusions, the findings are still quite different from the results of the randomized trial on the subject [2].

In the REDEEM study, at 18 mo there was only a slight decrease in pathologic progression in men receiving dutasteride compared to the control group (28% vs 35%), and at 36 mo there was no effect [2]. In contrast, Ficrelli et al. found that the effect of 5-ARIs persisted and increased with time [2]. Thus there must be some other factor that needs to be considered. I suggest that it may be ascertainment bias.

Patients underwent protocol biopsies at specific times in the REDEEM study (18 mo and 36 mo) [2] and every year in the study by Ross et al. [3]. In contrast, in addition to protocol biopsies (12 mo and then every 2–3 yr) in the study by Ficrelli et al. [2], biopsies were also performed earlier if prostate-specific antigen (PSA) velocity was rapid or at the discretion of the caring physician. In this nonrandomized retrospective nonblinded study, it is easy to imagine that both patients and physicians could be lured into a false sense of security by low levels of PSA and PSA velocity in patients taking finasteride. Thus reluctance to perform a biopsy may explain the results. This confounding factor limits the ability of the authors to conclude that 5-ARIs provide a protective effect in this setting.

Conflicts of interest: The author has nothing to disclose.

References


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Active surveillance in patients with a PSA >10 ng/mL

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Published online October 22, 2014.

Abstract

Introduction: The use of prostate-specific antigen (PSA) in active surveillance (AS) for prostate cancer is controversial. Some consider it an unreliable marker and others as sufficient evidence to exclude patients from AS. We analyzed our cohort of AS patients with a PSA over 10 ng/mL.

Methods: We included patients who had clinical stage T1c-T2a Gleason 6 disease, and 93 positive cores with ≥50% core involvement at diagnostic biopsy and ≥2 local biopsies. Patients were divided into 3 groups: (1) those with baseline PSA >10 ng/mL, (2) those with a PSA rise >10 ng/mL during follow-up, and (3) those with a PSA <10 ng/mL throughout AS. Adverse histology was defined as biopsy parameters exceeding the entry criteria limits. We further compared this cohort to a concurrent institutional cohort with equal biopsy parameters treated with immediate radical prostatectomy.

Results: Our cohort included 608 patients with a median follow-up of 46.2 months. In total, 82 patients had a baseline PSA >10 ng/mL and 157 had a PSA rise >10 ng/mL during surveillance. No difference in adverse histology incidence was detected between groups (p = 0.3). Patients with a PSA >10 ng/mL were older and had higher prostate volumes. Hazard ratios for groups with a PSA >10 were protective against adverse histology. Larger prostate volume and minimal core involvement appear as factors related to this successful selection of patients to be treated with AS.

Conclusion: These results suggest that a strict cut-off PSA value for all AS patients is unwarranted and may result in overtreatment. Though lacking long-term data and validation, AS appears safe in select patients with a PSA >10 ng/mL and low volume Gleason 6 disease.

Introduction

The use of prostate-specific antigen (PSA) in active surveillance (AS) for prostate cancer is controversial. A PSA >10 ng/mL is used as an exclusion criterion in many of the large AS series. However, the evidence to support the use of a PSA threshold is limited. Data from the PIVOT (Prostate Cancer Intervention Versus Observation Trial) study suggests that localized cancer with a PSA ≤10 may not require treatment. While it is clear from nomograms that a higher PSA incurs a higher risk of high-grade cancer, it is unclear how applicable a threshold PSA of 10 ng/mL is in the selected AS population where the volume of biopsy-detected disease is by definition very low.

In clinical practice, the use of PSA as a threshold in surveillance varies widely. The largest AS series published to date had 13.1% of patients at onset of surveillance with a PSA >10 ng/mL, and 38% with a PSA value over 10 at a median of 6.1 years of follow-up. PSA density can reduce the bias of PSA values induced by prostate size. Measurements of PSA velocity or doubling time may also be used, but the absolute value of PSA can be a driver of both patient and physician anxiety to discontinue surveillance.

At our institution an elevated PSA has not been used as an absolute contraindication to AS. Therefore, we reviewed our experience with patients with an elevated PSA, both at entry and during surveillance for otherwise low-risk localized prostate cancer.

Methods

In previous publications we have strictly limited our analysis to men suitable for AS according to standard inclusion criteria. Thus, we examined men with clinical stage T1c–T2a, Gleason score ≤6, and 3 or fewer cores positive with no more than 50% of a core involved at initial diagnostic biopsy and PSA <10 ng/mL. We also included men who pursued AS with either a PSA >10 ng/mL at baseline or experienced a PSA rise over 10 ng/mL during follow-up. Only patients with 2 or more biopsies were included.

Data on all patients on AS at our institution were prospectively collected in a database (1995-2011); with most patients enrolled in recent years. Institutional ethics board
approval was obtained. Our institution does not have a strict follow-up protocol, but we generally recommended PSA and digital rectal exam every 3 months initially (first 2 years) and then every 6 months subsequently. Prostate re-biopsy was recommended within the first 12 months of diagnosis and then every 2 to 3 years. “For-cause” biopsy based on physician discretion was allowed. For prostate re-biopsy, the transition zone was sampled, in addition to the standard extended peripheral zone template.2

The two groups of men with PSA >10 (at baseline and rise during AS) were compared to the remainder of patients on AS meeting standard entry criteria (Gleason score ≤6, ≤3 positive cores and all cores with ≤50% involvement) who never had a PSA >10 ng/mL. The primary outcome was the incidence of adverse histology at subsequent biopsies. Adverse histology was defined as biopsy parameters exceeding the entry criteria limits.

In a supplemental analysis, we compared our patients on AS with a concurrent cohort of men who underwent upfront radical prostatectomy (RP) at the same institution with identical biopsy features prior to RP (i.e., cT1c–T2a, maximum Gleason score of 6, ≤3 cores positive and ≤50% of any core involvement) during the period from 2000 to 2012. These patients were grouped into cohorts of a PSA <10 ng/mL or ≥10 ng/mL based on the last PSA prior to RP.

All statistical calculations were performed using SAS v.9.2 (SAS Institute, Cary, NC). Student T-tests were used to compare means, and Chi-squared test to compare proportions. Univariate and multivariate cox regression analysis analyzed risk factors for adverse histology on repeat biopsies. Covariates were selected based on univariate values (p < 0.10), except for the 3 groups of patients studied included a priori. Given our prior results demonstrating that 5-alpha reductase inhibitors (5ARI) prolong the time to pathologic progression (here referred to as adverse histology),3 we planned a sensitivity analysis excluding men on 5ARIs to determine the robustness of our findings.

### Results

From our institutional AS database, 698 patients met the inclusion criteria; of these, 239 (34%) patients never had a PSA >10 ng/mL. Of the entire AS cohort, the mean age was 64.1 years, with a median follow-up of 46.2 months (interquartile range 29.6-66.6). Most had 2 to 3 biopsies on surveillance (Fig. 1). Excluded from the 698 analyzed patients were 17 patients with only 1 biopsy, 50 patients with baseline Gleason grade 4 disease and 40 patients with higher volume Gleason 6 disease on biopsy (≥4 cores or ≥50% core involvement).

There were 82 patients with a PSA over 10 ng/mL at the start of AS, and 157 patients had a PSA rise over 10 during surveillance. Among these 157 patients, a change to active treatment without adverse histology occurred in 20 (12.7%) patients. Table 1 shows baseline characteristics of all men with entry biopsy criteria treated with AS, and those who had immediate RP. Notably, while men with a baseline PSA >10 ng/mL on AS had larger prostates and were older, there were no significant differences in initial biopsy characteristics between groups.

Comparing the initial 698 patient cohort with the 559 patients with immediate RP and an elevated PSA >10 ng/mL, allowed us to assess the factors involved in patient selection for AS (Table 1). We found that men selected for AS were older and had larger prostates. On initial biopsy, they also had a lower mean percentage of maximal core involvement and a lower number of positive cores.

Table 2 summarizes the outcomes of AS by group. Rates of adverse histology on first repeat or subsequent biopsy did not significantly vary between groups. As expected, those with a baseline PSA >10 or a PSA rise >10 had a higher rate of treatment on AS (Table 2).

Using multivariate Cox regression analysis, higher age, number of positive cores and higher percentage of core involvement were risk factors for subsequent adverse histol-

![Fig. 1. Distribution of number of biopsies per patient (%) by group used for analyses.](image-url)
Table 1. Baseline characteristics of patients with low risk (Gleason ≤6, ≤3 cores, ≤50% involvement of any core, ≥T2a) who underwent AS or RP at a single institution

<table>
<thead>
<tr>
<th></th>
<th>Baseline PSA ≥10 (n = 698)</th>
<th>PSA rise &gt;10 (n = 157)</th>
<th>PSA ≥10 (n = 459)</th>
<th>p value</th>
<th>Comparison cohort treated with immediate RP (n = 559)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean, SD)</td>
<td>69.6 (6.0)</td>
<td>64.9 (7.2)</td>
<td>63.4 (7.5)</td>
<td>0.058</td>
<td>86.8 (8.2)</td>
<td>0.37</td>
</tr>
<tr>
<td>Median PSA (IQR)</td>
<td>12.4 (10.7-14.9)</td>
<td>6.7 (4.8-8.2)</td>
<td>4.7 (3.2-6.1)</td>
<td>0.0001</td>
<td>12.0 (11.2-17.1)</td>
<td>4.5</td>
</tr>
<tr>
<td>Median PSA, ng/mL (IQR)</td>
<td>0.18 (0.14-0.27)</td>
<td>0.12 (0.09-0.18)</td>
<td>0.09 (0.07-0.14)</td>
<td>0.0001</td>
<td>0.25 (0.13-0.35)</td>
<td>0.11</td>
</tr>
<tr>
<td>Median prostate volume, **ml (IQR)</td>
<td>54 (50-93)</td>
<td>47.5 (38.0-62.0)</td>
<td>42 (33.59)</td>
<td>0.0001</td>
<td>98.4 (37.67)</td>
<td>0.039</td>
</tr>
<tr>
<td>DRE palpable nodule (%)</td>
<td>14 (17.1)</td>
<td>24 (15.3)</td>
<td>76 (16.5)</td>
<td>0.95</td>
<td>138 (58)</td>
<td>0.54</td>
</tr>
<tr>
<td>Previous negative biopsy (%)</td>
<td>25 (20.3)</td>
<td>35 (22.3)</td>
<td>160 (21.8)</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Biopsy characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive cores (%)</td>
<td>1  (72.2)</td>
<td>113 (72.4)</td>
<td>318 (69.4)</td>
<td>0.75</td>
<td>2011</td>
<td>139</td>
</tr>
<tr>
<td></td>
<td>2  (48.6)</td>
<td>32 (64.4)</td>
<td>161 (65.8)</td>
<td></td>
<td>19 (31)</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>3  (58)</td>
<td>10 (6.4)</td>
<td>19 (8.8)</td>
<td></td>
<td>12 (24)</td>
<td></td>
</tr>
<tr>
<td>Maximum % core involvement, mean (SD)</td>
<td>5.0 (7.5)</td>
<td>7.1 (7.6)</td>
<td>6.0 (7.4)</td>
<td>0.56</td>
<td>5.0 (14.8)</td>
<td>0.15</td>
</tr>
<tr>
<td>TRUS hypoechoic nodule (%)</td>
<td>25 (20.3)</td>
<td>47 (22.3)</td>
<td>115 (25.3)</td>
<td>0.41</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AS: active surveillance; RP: radical prostatectomy; DRE: digital rectal exam; PSA: prostate specific antigen; PSAD: PSA density; IQR: interquartile range; TRUS: transrectal ultrasound. *Data available for 25 patients. **Prostate volume for patients treated with immediate RP: This is the core with the highest percentage of involvement of a given biopsy from a given patient. *The denominator for these numbers is not 698, but the number for which this information was available.

Table 2. Outcomes of patients on AS by group (n = 698)

<table>
<thead>
<tr>
<th></th>
<th>Baseline PSA ≥10 (n = 698)</th>
<th>PSA rise &gt;10 (n = 157)</th>
<th>PSA ≥10 (n = 459)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up months (IQR)</td>
<td>33.8 (20.4-59.1)</td>
<td>53.9 (34.9-87.4)</td>
<td>53.9 (31.9-62.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Median months to first repeat biopsy (IQR)</td>
<td>13.7 (6.6-24.1)</td>
<td>15.2 (7.6-28.4)</td>
<td>12.3 (6.1-20.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>AH at first repeated biopsy (%)</td>
<td>18 (21.7)</td>
<td>43 (27.6)</td>
<td>102 (22.3)</td>
<td>0.37</td>
</tr>
<tr>
<td>AH at subsequent biopsy (%)</td>
<td>9 (13.9)</td>
<td>26 (23.0)</td>
<td>68 (19.1)</td>
<td>0.32</td>
</tr>
<tr>
<td>Reason for AH Number of cores involved (%)</td>
<td>6 (10.0)</td>
<td>29 (18.6)</td>
<td>62 (33.5)</td>
<td>0.18</td>
</tr>
<tr>
<td>Gleason score (%)</td>
<td>12 (14.5)</td>
<td>33 (21.2)</td>
<td>70 (15.3)</td>
<td>0.20</td>
</tr>
<tr>
<td>% core involvement (%)</td>
<td>4 (4.8)</td>
<td>18 (10.3)</td>
<td>30 (6.6)</td>
<td>0.20</td>
</tr>
<tr>
<td>Number who underwent treatment (%)</td>
<td>32 (40.5)</td>
<td>65 (31.9)</td>
<td>135 (29.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Number started on SABR (%)</td>
<td>16 (19.3)</td>
<td>29 (18.6)</td>
<td>80 (17.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Prostate mpMRI Cancer</td>
<td>17 (20.7)</td>
<td>31 (19.8)</td>
<td>52 (11.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>No cancer</td>
<td>5 (6.1)</td>
<td>21 (13.4)</td>
<td>34 (7.4)</td>
<td></td>
</tr>
<tr>
<td>mpMRI AD</td>
<td>66 (73.2)</td>
<td>105 (66.9)</td>
<td>273 (61.3)</td>
<td></td>
</tr>
</tbody>
</table>

AS: active surveillance; PSA: prostate specific antigen; IQR: interquartile range; TRUS: transrectal ultrasound; AH: adverse histology; SABR: stereotactic ablation; mpMRI: multi-parametric magnetic resonance imaging.
A total of 228 (33%) patients in our cohort eventually underwent treatment; 103 of these patients underwent a RP. Among men with a PSA rise, the use of non-surgical treatment was higher (64% vs. 53% and 51% for men on AS with a PSA >10 at baseline and a PSA <10, respectively; p = 0.03). Table 4 details the final pathologic outcomes by group. Five men had a rise in PSA >10 ng/mL on surveillance and a high Gleason (≥8) disease at RP; however, no high-grade disease at RP was found among AS patients treated with RP who had a PSA >10 ng/mL at baseline. In the concurrent RP cohort of men treated with identical risk disease on biopsy, 63 (11.3%) had a PSA >10 ng/mL (Table 1). While the numbers were small, the final pathologic outcomes among those treated with immediate RP were more favourable compared to those progressing to RP from AS with an initial PSA >10, similar to our previously reported results.4

**Discussion**

AS is a treatment approach for low-risk localized prostate cancer; it is gaining widespread use as patients and physicians understand the burden of over-diagnosis and overtreatment. However, the detailed protocols for AS remain largely based on expert opinion. While PSA carries prognostic information, this series demonstrates that, with appro-
priate selection, some patients with an elevated PSA over 10 ng/mL may be safely followed on AS.

Our results are clinically relevant as many patients are recommended active treatment based on their PSA. One series reports that half of those who “progressed” did so because of a rising PSA. In that series PSA at diagnosis was only predictive of PSA progression, not grade or volume progression. Two series have now reported surveillance outcomes among intermediate-risk disease, though with short follow-up. Our results resemble those of Cooperberg and colleagues, where most patients appeared to be classified as intermediate risk due to an elevated PSA (median 10.3 ng/mL). Conversely, worse outcomes with intermediate-risk disease on AS was seen in the ERSPC cohort. In that cohort, most patients had a PSA <10 ng/mL (median 5.3 ng/mL). Taken together with our results, this suggests that patients with an elevated PSA over 10 ng/mL, as the only criterion for intermediate-risk classification may have equivalent outcomes to low-risk patients.

A PSA may be elevated for reasons other than adenocarcinoma, with the common causes being benign prostatic hypertrophy and prostatitis. Evidence that these patients are enriched in our cohort is suggested by the higher average prostate volume and a higher proportion of low grade prostatic biopsies in those with a PSA >10 ng/mL. The varied RP pathology and longer follow-up in the cohort of men with a PSA over 10 ng/mL highlights the heterogeneity of the group. The selection of patients likely accounts for the protective hazard ratios for subsequent adverse histology found among those on AS with a PSA >10 ng/mL.

In our series, PSA on multivariate analysis was not clearly predictive of future adverse histology, though we found, as previously reported, that PSA density carries prognostic significance. Though not significant, there was a trend for patients in our cohort with a PSA rising over 10 ng/mL on AS to have a higher Gleason score on follow-up biopsy (Table 2). Adverse histology in this group was also more common in those with a higher baseline PSA (Table 5). Further, a higher incidence of high-grade disease and positive margins at RP among those whose PSA rose over 10 ng/mL on surveillance (Table 4) confirms that PSA monitoring can still yield important information in identifying significant cancers.

Conversely, with our selection of patients, no patients who started AS with a PSA over 10 ng/mL had high-grade (Gleason ≥8) disease. This is consistent with prior publications, that for low-risk disease baseline PSA carries limited prognostic value, but is insufficient to discriminate whether surveillance is a safe strategy. Nomograms may allow for modest improvement on these limited test characteristics when the decision is made to pursue AS or immediate treatment.

To understand the patient selection which presumably caused the surprising finding that an elevated PSA was protective against future adverse histology among patients with a baseline PSA over 10 ng/mL, we examined a concurrent cohort of men with an elevated PSA >10 ng/mL who opted for upfront surgical treatment (Table 6). As well as the expected bias with younger men receiving more immediate treatment, this comparison yielded two considerations which may be useful in selecting patients for surveillance when the PSA is elevated. The enlarged prostate size suggests that benign prostatic hyperplasia (BPH) may be the main driver of the elevated PSA, thus creating a selection bias. Another possibility is that BPH itself may play a protective role in prostate cancer progression. Minimal volume of disease, as indicated in core involvement (i.e., <1 cores and low percentage of core involvement) also appeared as a selection factor; notably, it was also significantly protective of future histologic reclassification on multivariate analysis (Table 3).

The limitations of this study include a lack of long-term follow-up with definitive endpoints. Despite our efforts to compare the patients on AS with others concurrently treated with RP, we were not able to fully elucidate all selection factors present, such as comorbidity or a diagnosis of prostatitis. The generalizability is also limited by the non-standardized AS surveillance protocols and follow-up. Finally, as a relatively small series, non-significant results may make it difficult to adequately power.

<table>
<thead>
<tr>
<th>Table 5. Characteristics of men with a PSA rise &gt;10 ng/mL during surveillance stratified by initial PSA (n = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline PSA group (ng/mL)</strong></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
</tr>
<tr>
<td>Time to PSA &gt;10, median (IQR, months)</td>
</tr>
<tr>
<td>Adverse histology</td>
</tr>
<tr>
<td>Grade*</td>
</tr>
<tr>
<td>Volume**</td>
</tr>
<tr>
<td>PSAV, median (IQR), ng/mL/yr</td>
</tr>
</tbody>
</table>

SD: standard deviation; PSA: prostate-specific antigen; IQR: interquartile range; PSAV: PSA velocity. *Gleason ≥7 on surveillance biopsy. **Excluding 50% core involvement or more than 5 cores involved with cancer.
Table 6. Predictors of adverse histology on AS using logistic regression analysis (n = 698)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariable p value</th>
<th>Multivariable p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per decade)</td>
<td>1.57 (1.28-1.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSA category</td>
<td>Baseline PSA &gt;10</td>
<td>0.78 (0.47-1.29)</td>
</tr>
<tr>
<td>PSA rise &gt;10</td>
<td>1.36 (0.94-1.96)</td>
<td>0.10</td>
</tr>
<tr>
<td>PSA ≤10</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Baseline PSA mg/mL (per 1-unit increase)</td>
<td>1.02 (0.98-1.06)</td>
<td>0.34</td>
</tr>
<tr>
<td>Baseline prostate volume (per 1-unit increase)</td>
<td>0.98 (0.98-0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log (baseline PSAD) (per 1-unit increase)</td>
<td>1.06 (1.03-1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline DRE palpable nodule yes vs. no</td>
<td>1.56 (1.04-2.36)</td>
<td>0.03</td>
</tr>
<tr>
<td>Baseline TRUS nodule present yes vs. no</td>
<td>0.95 (0.51-1.74)</td>
<td>0.36</td>
</tr>
<tr>
<td>Baseline positive biopsy cores</td>
<td>2 vs. 1</td>
<td>1.81 (1.24-2.61)</td>
</tr>
<tr>
<td>3 vs. 1</td>
<td>3.09 (1.73-5.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline maximum % core involvement (per 10-unit increase)</td>
<td>1.76 (1.38-2.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline total number of cores taken (per 1-unit increase)</td>
<td>0.89 (0.88-0.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5AR use yes vs. no</td>
<td>0.57 (0.37-0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to confirmatory biopsy, months</td>
<td>1.02 (1.01-1.03)</td>
<td>0.002</td>
</tr>
<tr>
<td>Follow-up time, months</td>
<td>1.01 (1.00-1.01)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Conclusion

Data from this unique cohort suggests that a strict cut-off PSA value for all AS patients is unwarranted and may result in overtreatment. This study suggests that with appropriate patient selection, patients with very low volume Gleason 6 cancer and a PSA >10 mg/mL may be good candidates for AS. Further follow-up and definitive outcomes assessment are needed.

Competing Interests: D. Torres, Dr. Wong, N. Timmler, Dr. Tilki and Dr. Scher are not competing financial or personal interests. Dr. Finelli has participated in clinical trials in the past 2 years for Amgen, Astellas, Janssen and Ferring. Dr. Heideman is a member of the Advisory Board for Amgen, Janssen, Astellas and Eli Lilly. He has received honoraria from Amgen, Janssen, Astellas and Eli Lilly. He is not paid to participate in clinical trials for Amgen, Janssen, Medivation, Digi and Prostate Cancer Canada.

This paper has been peer-reviewed.

References


Unusual presentation of advanced prostate cancer masquerading as metastatic and obstructing rectosigmoid cancer

An 86-year-old man presented with a 1 week history of constipation, abdominal pain and distension and overflow fecal incontinence on a background of 4 weeks of anorexia. His past history included a total hip replacement, pharyngoesophageal diverticulum and an incarcerated right femoral hernia requiring resuture of 5 cm of ileum (aneurysm bowel). He had no past or family history of malignancy.

On examination, he appeared cachectic with a distended and tender abdomen. Digital rectal examination (DRE) revealed a rectal stricture 2 cm from the anal verge, which was too tight to pass.

Computed tomography (CT) scan of his abdomen and pelvis demonstrated extensive ascites, a 9 cm segment of mural thickening affecting the rectosigmoid colon (Fig. 1) with proximal dilatation of distal small intestine and large bowel consistent with developing large intestine obstruction (LIO). There was no evidence of perforation, ischemia or metastatic disease. Gastrografin enema confirmed a high grade fixed stenosis involving the proximal rectum and rectosigmoid junction (Fig. 2). A presumptive diagnosis of rectosigmoid carcinoma was made.

The patient underwent emergency laparotomy with biopsies taken via flexible sigmoidoscopy at the same time. The caecum was noted to be 15–16 cm in diameter, with areas of ischemia and perforation. There was extensive ascites, peritoneal metastases and omental caking present. He underwent caecal decompression followed by a caecostomy and caecotomy.

Histopathological examination of the caecostomy specimen showed ulceration, inflammation and multiple small foci of poorly differentiated adenocarcinoma in the serosa and subserosa (Fig. 3).

Similar histology was seen in the biopsy specimen obtained from the rectum. The tumour cells were stained strongly for cytokeratin (CK) AE1/AE3 and moderately for prostate specific antigen (PSA). This immunohistochemical staining profile is most consistent with prostate adenocarcinoma with a Gleason pattern 5 + 5 = 10. The tumour was negative with CK20, CK7, S100 and transcription factor 1. CK20 negativity suggests that it is not colorectal adenocarcinoma.

Post-operatively, the patient’s PSA was 154 ng/mL. There was no preoperative measurement to compare. Bone scan post-operatively showed no definite evidence to suggest osteoblastic metastatic disease. Bicalutamide was commenced. The patient’s post-operative course was complicated by myocardial infarction, atrial fibrillation, feeding issues and aspiration pneumonia. The patient died 22 days post-operatively from cardiac and malignancy-related causes.

This case represents a very rare presentation of prostate cancer masquerading as both obstructing and metastatic rectal cancer. Locally advanced prostate cancer with rectal infiltration is uncommon. Historical series have reported between 1 and 9% rectal involve-
ment, but these were from the pre-PSA era (1955–1978). Similarly, an autopsy series (1967–1995) suggesting peritoneal metastasis occurring in 7% of men with prostate cancer likely overestimates contemporary occurrence. Our patient presented acutely with LBO requiring emergent laparotomy and was subsequently diagnosed with both locally invasive prostate cancer and extensive peritoneal carcinomatosis. Due to delayed presentation, the need for emergency laparotomy and pre-existing co-morbidities, our patient died 22 days after surgery from cardiopulmonary and cancer-related causes.

Diagnosis of prostate cancer in this man was not considered because of the unusual clinical presentation. The abnormal DRE may have prompted PSA testing; however, the clinical picture was more in keeping with LBO secondary to a sepsis or colorectal lesion. Prostate cancer metastasis distally via the lymphatic and hematogenous routes is not commonly seeding to lymph nodes and bone. Peritoneal carcinomatosis rarely occurs in the absence of bone metastasis. In men with metastatic prostate cancer, visceral metastases, poor performance status and PSA > 5.5 arc poor prognostic factors.

There are no series describing outcomes of men with both locally obstructing prostate cancer and peritoneal carcinomatosis. In a review of men with rectal infiltration by prostate cancer, it was found that 51% presented with gastrointestinal symptoms without prior established diagnosis of prostate cancer. Patients with acute large bowel obstruction were usually managed by definitive colostomy and androgen deprivations. The median survival for the 96 patients reviewed was 15 months. Metastatic peritoneal carcinomatosis is usually reported in the context of castrate-resistant prostate cancer and response to doxetaxel chemotherapy has been reported (six patients, five responded, median survival from starting doxetaxel was 24.5 months).

Propenents of PSA screening would argue cases such as this, with advanced symptomatic disease at presentation, could be prevented. PSA screening remains contentious with a large number needed to screen and treat to prevent one death from prostate cancer. The Melbourne Consensus Statement is an example of a balanced approach to this controversial subject. Elderly men often have an elevated PSA, but a level >100 ng/ml, as in this patient, is diagnostic of widespread prostate cancer. As screening over the age of 75 is not recommended, rapid development of an aggressive cancer above this age, while uncommon, is possible. Watchful waiting, a management strategy to monitor patients not able to tolerate or accept the side effects of radical curative treatment, is often offered to more elderly patients, particularly those with shorter life expectancy. In this group of men, the decision to commence non-curative treatment is based on symptoms and disease progression. In this case, rising PSA may have prompted imaging to diagnose progression of disease, with initiation of palliative androgen deprivation to prevent presentation in extremis.

This unusual case of prostate cancer with both local invasion and rare peritoneal carcinomatosis highlights the need for consideration of unusual presentations of prostate cancer in elderly men.

References

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An Increase in Gleason 6 Tumor Volume While on Active Surveillance Portends a Greater Risk of Grade Reclassification with Further Followup

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Purpose: We evaluated the relative risk of later grade reclassification and outcomes of patients in whom high volume Gleason 6 prostate cancer develops while on active surveillance.

Materials and Methods: A prospectively maintained database was used to identify patients on active surveillance between 1998 and 2013. Tumor volume was assessed based on the number of positive cores and proportion of core involvement. The chi-square and Fisher exact tests were used for analysis as appropriate. The primary end point was the development of grade reclassification, defined as grade only and/or grade and volume at the event biopsy.

Results: A total of 555 men met the study inclusion criteria. Mean followup was 46 months. Overall 70 patients demonstrated an increase in tumor volume at or after biopsy 2. Compared to those men never experiencing volume or grade reclassification, prostate specific antigen at diagnosis was not significantly different (p=0.95), but median prostate volume was smaller in patients who demonstrated volume reclassification (p<0.001). The incidence of pure volume reclassification was 6.8%, 6.1% and 7.8% at biopsy 2, 3 and 4, respectively. Men with volume reclassification were more likely to experience later grade reclassification than those without at 33.3% vs 9.3%, respectively (p<0.0001).

Conclusions: While Gleason 6 prostate cancer has a favorable natural history, it appears that patients on active surveillance who experience volume reclassification are at substantially higher risk for grade reclassification. Thus, urologists should pay close attention to tumor core involvement, and monitoring should be adjusted accordingly for early volume reclassification in younger men and those in good health.

Key Words: prostatic neoplasms, tumor burden, neoplasm grading, biopsy, watchful waiting

While prostate cancer is the most common malignancy affecting men, approximately 80% of men with PCa ultimately die of other causes.1-3 A significant proportion of incident cases are classified as low risk PCa according to the D’Amico criteria and, thus, do not necessitate immediate radical treatment.4,5 To mitigate overtreatment of indolent PCa many institutions have adopted active surveillance programs.6 In recent years

Abbreviations and Acronyms

5αRI = 5α-reductase inhibitor
AS = active surveillance
B1 = diagnostic biopsy (biopsy 1)
B2 = confirmatory biopsy (biopsy 2)
B3 = biopsy 3 (from diagnostic)
B4 = biopsy 4
GS = Gleason score
PCA = prostate cancer
PSA = prostate specific antigen


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The corresponding author certifies that, when applicable, a statement has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval, principles of Helsinki Declaration were followed in line of ethical review board, institutional animal care and use committee approval, all human subjects provided written informed consent with guarantees of confidentiality, IRB approved protocol number, animal approved project number.

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AS has become a widely accepted management strategy for men with low grade, localized PCs, with strong support for its use from the practice guidelines of several national organizations. The safety of AS has been demonstrated by single institution series with intermediate followup. However, the long-term verdict for AS has not been well established. Current practice protocols combine clinical T-stage, PSA value, PSA density, Gleason score, number of positive cores and/or amount of malignancy per core to select patients for AS. While AS has by and large proven to be a good alternative for carefully selected men with low risk PCs, there is a lack of understanding concerning indicators of progression and what is considered clinically significant progression. As more men are placed on AS programs it becomes important to identify these indicators.

Commonly GS upgrading to 7/10 or greater on routine biopsy will trigger treatment in a patient on AS. Increasing PSA and tumor volume are also indicators that can prompt physicians to offer therapy. However, increasing tumor volume as a prompt for treatment is not well-defined. Currently only the National Institutes of Health consensus statement specifically includes volume as a factor, with “increased extent of disease (more biopsy tissue involved with cancer).” The European Association of Urology guidelines list “GS >7, patient anxiety and PSA doubling time” as indicators of progression and reasons to offer treatment. The National Comprehensive Cancer Network states, “change in risk group strongly implies disease progression,” and the National Institute for Health and Care Excellence suggests, “rise in PSA or adverse findings on biopsy” should trigger definitive treatment for men with PCs.

This lack of consensus stems in part from the variability of AS inclusion criteria. Some protocols specify the number of positive cores involved whereas others may only indicate a proportion of total cores. The definition of volume progression is further complicated by the contended prognostic value of tumor volume. A contemporary study showed that in men suitable for AS who underwent up-front RP, the number of positive cores at biopsy predicted the presence of higher grade and stage disease at final pathology. In this study we determine the association of increased tumor volume after diagnostic biopsy with the risk of later grade reclassification in men enrolled in an AS program.

METHODS
Men diagnosed with low risk PCs and started on AS were identified using the Princess Margaret Cancer Centre AS database (1998 to 2013). Approval from the institutional ethics review board was obtained. AS eligibility criteria were PSA 10 ng/ml or less, clinical stage cT2 or less, GS 6 or less, number of positive cores 3 or less, no single core more than 50% involved, age 75 years or less and at least 1 repeat prostate biopsy after diagnosis (confirmatory, B2). For the purposes of this study we defined the first (diagnostic) transrectal ultrasound guided prostate biopsy as biopsy 1 (B1) and the second biopsy (confirmatory) as biopsy 2 (B2). Patients undergo a confirmatory biopsy within 12 to 24 months of the initial biopsy, with repeat biopsy every 1 to 3 years until the patient reaches age greater than 75 years or declines definitive treatment.

Patients who did not meet the AS criteria, those who did not undergo a confirmatory biopsy (B2) or those who did not have sufficient followup to reach B2 were excluded from analysis. The remaining patients on AS (518) were grouped based on reclassification (yes or no) and type of reclassification (volume or grade reclassification) only at B2 or any subsequent biopsy. The primary outcome analyzed was grade rate of grade reclassification, occurring after B2 in patients who experienced antecedent tumor volume reclassification and chose to continue with AS. Volume reclassification (or an increase in tumor volume) was defined as more than 3 positive cores, or a single core with 50% or greater involvement (threshold volume for AS eligibility). Pathological grade reclassification was defined as GS greater than 3-3. Grade and volume reclassification was defined as both having occurred (GS 7 or greater, and greater than 50% single core involvement, or more than 3 positive cores).

Transrectal ultrasound guided prostate biopsies were taken according to standard practices using an end fire probe (C9-5 ICT, Philips, Bothell, Washington) with the patient under local anesthesia. Three genitourinary radiologists performed transrectal ultrasound guided prostate biopsies with a single operator performing 75% of them. Biopsy cores were collected and labeled by region sampled. Cancer location was captured systematically and entered into the database along with the percent involvement of each core. The number of positive cores was also entered with other clinical pathological variables. For B1 a template (10 to 12 cores) was used. For subsequent repeat biopsies an AS protocol template of 13 to 17 cores modeled on Babaian et al. was applied. Some diagnostic biopsies (B1) were performed elsewhere. However, all followup biopsies were performed in-house. The study end point was grade reclassification, whether grade only or grade plus volume at the event biopsy. Medical charts of patients who demonstrated volume reclassification were reviewed.

For analysis men were censored if they demonstrated reclassification, elected to have treatment without reclassification or were lost to followup. Descriptive statistics used means with SD or medians with IQR. Comparisons were done using the ANOVA for continuous variables, and the chi-square and Fisher exact tests for categorical variables. All statistical tests were 2-sided with p < 0.05 considered statistically significant. SAS® statistical software version 9.1 was used for all analyses.
RESULTS

Of 806 men in the AS database, 555 satisfied the inclusion criteria. However, 37 men sought definitive treatment before any type of reclassification and, thus, were excluded from analysis. Mean age of the remaining study cohort (618) was 63 years. Median PSA of the study cohort at diagnosis was 4.8 ng/ml (full range 3.3 to 6.4). When examining disease volume at B1, 70.5% had 1 core positive for cancer, 21.6% had 2 cores and 7.9% had 3 positive cores. Median followup on AS was 46 months (IQR 31–66) and median number of biopsies was 3 (IQR 2–4). Median time between B1 and B2 was 12 months (IQR 7–20); between B2 and B3, 20 months (IQR 13–27); between B3 and B4, 23 months (IQR 19–28); and between B4 and B5, 24 months (IQR 19–28).

A total of 70 (13.5%) men from our cohort experienced an increase in tumor volume at any time after B2. Of these 70 men, 98.5% had less than 33.3% maximum core involvement at diagnosis and PSA was less than 6 ng/ml in 75.7% of these men. Characteristics of men who did not experience an increase in tumor volume, those who experienced grade reclassification and those who had an increase in tumor volume at any biopsy after B1 are shown in supplementary table 1 (http://jurology.com). Overall, 26.1% of patients on AS had an increase in tumor grade vs 60.4% who did not demonstrate any type of reclassification.

The incidence of pure volume reclassification was 6.8% at B2, 7.3% at B3 and 8% at B4. Median followup for those with reclassification at B2 or at subsequent biopsy was 44 months (IQR 34–70). A comparison between men who experienced volume reclassification at any time on AS and those who did not demonstrated that at B1 the former group had a smaller prostate volume, no significant difference in PSA and were less likely to be taking a 5ARI. When men who experienced grade reclassification were compared to those who never experienced any type of reclassification and who had increased tumor volume, PSA at diagnosis was found to be significantly different (p=0.008, supplementary table 1, http://jurology.com).

We documented volume only, grade only and volume + grade reclassification for each biopsy during AS (table 1). There were 392 men who had 2 followup biopsies (ie 3 biopsies total), 124 who had 3 biopsies and 46 who had 4 or more followup biopsies. The figure demonstrates the reclassification proportions with each serial biopsy. More than 75% did not experience reclassification of any type with each subsequent biopsy. The proportion of men demonstrating volume reclassification with each subsequent biopsy increased among the total cohort, and among all those with previous reclassification and remaining on surveillance.

Table 2 summarizes the proportions of men with grade reclassification. The denominator for grade reclassification after volume reclassification is the number of men with reclassification based on volume but continued on AS (eg 21) and had at least 1 additional biopsy. The denominator for the grade reclassification group is the total number of men on AS at that particular biopsy point (eg B3, 281).

Among men who underwent further biopsies after demonstrating volume reclassification there was a positive trend between upgrading and further tumor volume increase. Time between biopsies was significantly different (p < 0.001) and there was no difference in biopsy frequency between the groups. Reclassification to GS 7 or greater at or after biopsy 3 was more common in men with than in those without an antecedent increase in tumor volume. However, the majority of men (7 of 11) who had disease upgraded to GS 7 after an increase in tumor volume experienced this at biopsy 3.

A chi-square comparison between patients with disease upgraded to GS 7 (at B3) with vs without

Table 1. Reclassification type documented by biopsy

<table>
<thead>
<tr>
<th>Diagnosic Biopsy</th>
<th>Confirmatory Biopsy</th>
<th>Biopsy 3</th>
<th>Biopsy 4</th>
<th>Biopsy 5+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. pts</td>
<td>836</td>
<td>555*</td>
<td>325</td>
<td>124</td>
</tr>
<tr>
<td>Reason excluded (No.)</td>
<td>B1 (n)</td>
<td>B1 (n)</td>
<td>B1 (n)</td>
<td>B1 (n)</td>
</tr>
<tr>
<td>Age older than 75 yrs (30)</td>
<td>35</td>
<td>66/30</td>
<td>26</td>
<td>9</td>
</tr>
<tr>
<td>Conformity biopsy after more than 40 mos (34)</td>
<td>35</td>
<td>66/30</td>
<td>26</td>
<td>9</td>
</tr>
<tr>
<td>Only 1 biopsy (34)</td>
<td>35</td>
<td>66/30</td>
<td>26</td>
<td>9</td>
</tr>
<tr>
<td>AS criteria violation (199)</td>
<td>35</td>
<td>66/30</td>
<td>26</td>
<td>9</td>
</tr>
</tbody>
</table>

No. (% of total) | reclassification type / % of those with reclassification:

- Grade only:
  - Not applicable: 35
  - 35 (5,6/30.6)
- Vol only:
  - Total excluded (25)
- Vol + grade:
  - Only biopsy 2 (119)
  - Total excluded (25)
- No reclassification:
  - Treatment (23)
  - Only biopsy 2 (119)
  - Total excluded (25)
- Median max followup (01): 12 (7–20)

* There were 555 patients who underwent a confirmatory biopsy. However, the rest of our analysis focuses on 518 men because 37 sought treatment before any type of reclassification.
Reclassification proportions (A) and proportions of reclassification types (B) with each serial biopsy. Note 555 patients underwent confirmatory biopsy. However, remaining analyses consider 518 men because 37 men sought treatment before any type of reclassification.

Volume reclassification (on previous biopsy) revealed a significant difference in proportions (33.3% vs 9.3%, respectively, p < 0.0001). Men who had volume reclassification at B2 and continued on surveillance with follow-up biopsies were significantly more likely to experience upgrading to GS 7 compared to men who had never experienced tumor volume increase. Of the 70 men from our study cohort who experienced volume reclassification at or after B2, 19 remained on AS and 3 transitioned to watchful waiting (of these 22 men 7 had reclassification on B2, 10 at B3 and 5 at B4). 2 died of other causes and 2 were lost to followup. The other 44 men who demonstrated an increase in tumor volume sought treatment (28 from B2, 11 from B3 and 5 from B4+).

Supplementary table 2 (http://urology.com/) describes the characteristics of men with volume reclassification (only) who subsequently sought treatment compared to those who demonstrated volume reclassification but did not pursue definitive treatment (42.4%). There was a significant difference between the 2 groups with regard to PSA at diagnosis and at treatment. A significantly higher proportion of patients who chose not to undergo definitive treatment were on 5ARI therapy. Radiation therapy was the most popular choice of treatment at 33.9% (23.7% of men opted for brachytherapy, 6.8% external beam therapy, 3.4% focal therapy) and 20.3% underwent RP.

**DISCUSSION**

Currently AS is a widely accepted initial treatment option for men with low risk PCa. However, a significant proportion of men with GS 6 disease will eventually have reclassification to GS 7 or greater PCa while under surveillance, regardless of protocol. Therefore, there is a need for better tools to identify predictors of reclassification in patients with low risk disease. Currently and accepting limitations, we rely mostly on repeat biopsy pathology, and to some extent PSA kinetics and magnetic resonance imaging.

In this study we demonstrate that patients who experience early tumor volume reclassification and choose to continue on AS are at significantly increased risk for grade reclassification. To our knowledge limited work has been done on the relative risk of grade reclassification with antecedent volume reclassification in a large AS cohort with

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### Table 2. Relative risk of grade increase with or without antecedent increase in tumor volume

<table>
<thead>
<tr>
<th>Biopsy 3</th>
<th>Biopsy 4</th>
<th>Biopsy 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>302</td>
<td>124</td>
</tr>
<tr>
<td>Grade reclassified after vol reclassification (on B2):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% (n/total No.)</td>
<td>33.3 (101/302)</td>
<td>20.0 (25/124)</td>
</tr>
<tr>
<td>95% CI</td>
<td>12.0–53.5</td>
<td>0.0–44.2</td>
</tr>
<tr>
<td>Mean mos B2 to current biopsy</td>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>Grade reclassified:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% (n/total No.)</td>
<td>9.3 (29/302)</td>
<td>3.5 (4/114)</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.0–13.8</td>
<td>0.1–6.5</td>
</tr>
<tr>
<td>Mean mos B2 to current biopsy</td>
<td>22</td>
<td>37</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Biopsy 4</th>
<th>Biopsy 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>124</td>
</tr>
<tr>
<td>Grade reclassified after vol reclassification (on B3):</td>
<td></td>
</tr>
<tr>
<td>% (n/total No.)</td>
<td>0 (0/124)</td>
</tr>
<tr>
<td>95% CI</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Grade reclassified:</td>
<td></td>
</tr>
<tr>
<td>% (n/total No.)</td>
<td>2.2 (6/124)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.1–6.4</td>
</tr>
<tr>
<td>Mean mos B2 to current biopsy</td>
<td>15</td>
</tr>
</tbody>
</table>

---

<table>
<thead>
<tr>
<th>Biopsy 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
</tr>
<tr>
<td>Grade reclassified after vol reclassification (on B4):</td>
</tr>
<tr>
<td>% (n/total No.)</td>
</tr>
<tr>
<td>95% CI</td>
</tr>
<tr>
<td>Mean mos B4 to 35</td>
</tr>
<tr>
<td>Grade reclassified:</td>
</tr>
<tr>
<td>% (n/total No.)</td>
</tr>
<tr>
<td>95% CI</td>
</tr>
</tbody>
</table>
intermediate to long-term followup. In our series 13.6% of men who were on AS experienced a significant increase in tumor volume and approximately 54% of these men experienced the tumor volume increase at B2, with an additional 31% (22 of 70) at B3. Thus, more than 85% of men who demonstrated volume reclassification did so within 18 months of initiating AS. Of the 70 men who experienced volume reclassification 69.9% went on to have active treatment, 27.4% remained on AS, 4.3% transitioned to watchful waiting, 2.9% were lost to followup and 2.9% died of other causes. Notably 11 of the 26 men (44%) who experienced volume reclassification and did not seek treatment went on to have GS 7 disease. Given that reclassification to GS 7 occurred after the confirmatory biopsy it is less likely to represent misclassification of the original disease and more likely reflects reclassification.

Previously Cary et al reported that 50% of patients who experienced an increase in threshold volume also had a concomitantly grade increase. They studied 959 men on AS (GS 6 or less, PSA 10 ng/ml or less, 83% or less of biopsy cores involved, 50% or less of any single core positive, and clinical stage T1 or T2a disease), with 39 (10%) men in their cohort demonstrating an increase in tumor volume, and 44 (11%) an increase in volume and grade. Thus, the findings of Pertemiet al as well as the results of the present study support the assertion that an increase in tumor volume is associated with an increase in cancer grade on early repeat biopsies.

In our cohort GS 7 disease developed by biopsy in 21.5% of men who had an increase in tumor volume.

We also examined potential factors influencing a patient's decision to undergo definitive treatment. In our cohort there was a significant difference in PSA at diagnosis between patients who chose to remain on AS and those going on to treatment, suggesting that PSA may be a driving factor when considering treatment. Also, a significantly higher proportion of men on 5ARI therapy chose to remain on AS. The lack of other clinical differences (with the exception of those mentioned) between the groups of men confirms our belief that barring volume reclassification the men did not differ significantly.

The limitations of this study include the retrospective nature of certain data elements as well as the relatively low number of patients with reclassification to GS 7 disease with an antecedent increase in tumor volume. Also, although the compared groups were similar, there may be inherent differences that were not measured. Lastly, the true risk over time may not be appreciated given that the median followup was 46 months for the entire cohort.

In conclusion, our study demonstrates that for patients on AS early increased tumor volume significantly increases the risk of grade reclassification. Of patients with a previous increase in tumor volume 42.9% went on to experience GS 7 disease vs only 13.8% of those without previous volume reclassification. Furthermore, men who had volume reclassified at B2 and went on to undergo subsequent biopsies were significantly more likely to experience upgrading to GS 7 than those who had never experienced tumor volume increase. Thus, it is reasonable to recommend that urologists pay closer attention to the extent of core involvement when interpreting pathology reports from biopsies. In light of recent findings suggesting a significant risk of PCa related mortality for GS 7 with active surveillance, once tumor volume increases it is important to monitor patients closely and advise them accordingly. Closer monitoring can include, but is not limited to, magnetic resonance imaging and a higher frequency of biopsies.

REFERENCES


Author/s:
Wong, Lih-Ming

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2016

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