Active surveillance in a cohort of men with prostate cancer; McGill University Experience

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I. Abbreviations

AS – Active Surveillance
BPH – Benign Prostatic Hyperplasia
CI – Confidence interval
CZ – Central Zone
ERSPC – European Randomized Study of Screening for Prostate Cancer
GS – Gleason's Score
HAT – Hemiablation Therapy
IQR – Interquartile Range
PCa – Prostate Cancer
PE – Physical Exam
PSA – Prostate Specific Antigen
PSAD – PSA Density
PZ – Peripheral Zone
RCT – Randomized Control Trial
RP – Radical Prostatectomy
RR – Relative Risk
RT – Radiotherapy
SD – Standard Deviation
TZ – Transitional Zone
PZ – Periphral Zone
DCE – Dynamic contrast-enhanced MRI
DWI – Diffusion-weighted MRI
T2WI – T2-weighted images
PI-RADSv_2 – Prostate Imaging Reporting and Data System version 2
UFD – Unfavorable disease

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III. Abstract

Introduction: Active surveillance (AS) is commonly recommended for men with localized low-intermediate–risk prostate cancer (PCa). The aims of our study were to evaluate clinical and pathological factors that influence the risk for disease progression in a cohort of patients with low-intermediate risk PCa under AS and to assess the probability that patients with PCa would develop unfavorable disease features (UDF) while under AS for the purpose of evaluating whether immediate hemiablation therapy (HAT) could bring clinical benefit to selected patients.

Methods: We studied a total of 300 patients diagnosed between 1992 and 2012 with prostate adenocarcinoma with favorable parameters or who refused treatment and were managed with AS. Of those, 155 patients with at least 1 repeat biopsy and no progression criteria at the time of the diagnosis were included for statistical analyses. Patients were followed every 3–6 months for prostate-specific antigen (PSA) measurement and physical examination (PE). Patients were offered repeat prostatic biopsy every year. Disease progression was defined as the presence of one or more of the following criteria: ≥3 positive cores, >50% of cancer in at least 1 core, and a predominant Gleason pattern of ≥4. In our cohort of AS patients, 157 were diagnosed with unilateral PCa with ≥1 repeated biopsy. Using five different definitions of UDF, patients' data were used to simulate the theoretical outcome if these patients were managed by immediate unilateral HAT or remained on AS.

Results: For the 155 patients, the mean age (SD) at diagnosis was 67 (7) years; median follow-up was 5.4 years (interquartile range [IQR], 3.6–9.5 years). Of these, 67 patients, 25 patients, 6 patients, and 2 patients had 2, 3, 4, and 5 repeat biopsies, respectively. At

baseline, 11 (7%) patients had a Gleason score (GS) of 3+4, while the remaining 144 (93%) patients had a GS of ≤6. A total of 50 (32.3%) patients showed disease progression on repeat biopsies, with a median progression-free survival time of 7 years. The rate of disease progression decreased after the second repeat biopsy. The 5-year overall survival rate was 100%. Having a PSA density (PSAD) of >0.15, >1 positive core, and GS >6 at the time of the diagnosis was associated with a significantly higher rate of disease progression on univariate analysis (P<0.05), while a maximum percentage of cancer in any core of >10% showed a trend toward significance for a higher progression rate (P=0.054). On multivariate analysis, only the presence of PSAD>0.15 remained significant for a higher progression rate (P<0.05). Of 155 patients, 5 (3.2%) subsequently received radiotherapy, 13 (8.4%) received hormonal therapy, and 13 (8.4%) underwent radical prostatectomy.

Of the 157 patients who had unilateral PCa, 144 (92%) had a Gleason score (GS) of ≤6. Using the whole range of definition for **UDF**, 10 to 47% of patients developed UDF while under AS. Using baseline GS, maximum percentage of cancer on any core, and PSAD, we found significant trends for higher development of **UDF** for patients under AS.

Conclusion: AS is a suitable management option for patients with clinically low-risk PCa. A PSAD of >0.15 ng/ml/cc is an important predictor for disease progression. The majority of our patients did not develop UDF while under AS and our study thus suggests that careful patient selection for focal therapy should be performed to avoid subjecting patients to unnecessary treatment.

IV. Resume

Introduction: La surveillance active (SA) est généralement recommandée pour les hommes atteints d'un cancer localisé de la prostate (CaP) à faible risque. Les objectifs de notre étude étaient d'évaluer les facteurs cliniques et pathologiques qui influencent le risque de progression dans une cohorte de patients atteints d'un CaP à risque faible ou intermédiaire sous surveillance active (SA) et d'évaluer la probabilité de développer les caractéristiques d'une maladie défavorables (CMD) sous SA. Le but étant de prédire si une thérapie par hémiablation (THA) immédiate pourrait apporter un bénéfice clinique aux patients sélectionnés.

Méthodes: Nous avons étudié un total de 300 patients diagnostiqués entre 1992 et 2012 avec un adénocarcinome de la prostate de faible risque ou qui ont refusé un traitement et ont qui ont opté pour une SA. De ces patients, 155 avec au moins 1 biopsie lors du suivi ont été inclus dans les analyses statistiques. Les patients ont été suivis chaque 3-6 mois avec une mesure de l'antigène prostatique spécifique (APS) et un toucher rectal (TR). Une biopsie de contrôle annuelle a été recommandée aux patients. La progression de la maladie a été définie par la présence d'un ou plusieurs des critères suivants: ≥3 biopsies positives, > 50% de cancer dans au moins une biopsie, et un grade de Gleason prédominant ≥4. Dans notre cohorte de patients, 157 ont été diagnostiqués avec un cancer unilatéral de la prostate et ≥1 biopsie dans le suivi. Avec ses cinq définitions différentes de CMD, les données des patients ont été utilisées pour simuler les résultats potentiels obtenus suite à une THA unilatérale.

Résultats: L'âge moyen (DS) au moment du diagnostique était de 67 ans (7) avec un suivi médian de 5,4 ans (IQR 3,6 à 9,5 ans). Parmis ces patients, 67, 25, 6, et 2 patients ont subit deux, trois, quatre, et cinq biopsies, respectivement. Au départ, 11 (7%) patients avaient un score de Gleason (SG) de 3 + 4, tandis que 144 (93%) patients avaient un SG ≤ 6. Un total de 50 (32,3%) patients ont démontré une progression de leur maladie lors du suivi, avec un temps médian de survie sans progression de 7 ans. Le taux de progression de la maladie a diminué après la deuxième biopsie. Le taux de survie globale à 5 ans était de 100%. Ayant une densité de APS (dAPS) de > 0,15, >1 biopsie positive, et SG > 6 au moment du diagnostique étaient associés à un taux considérablement plus élevé de progression de la maladie sur une analyse univariée (P <0,05). Un pourcentage maximal de cancer dans une biopsie de > 10% a démontré une tendance significative associée à un taux de progression plus élevé (P = 0,054). En analyse multivariée, seule la présence d'une dAPS > 0,15 est demeurée significatif pour un taux plus élevé de progression (P <0,05). Dès 155 patients, 5 (3,2%) ont par la suite reçu une radiothérapie, 13 (8,4%) ont reçu un traitement hormonal, et 13 (8,4%) ont subi une prostatectomie radicale. Sur les 157 patients qui avaient un CaP unilatéral, 144 (92%) avaient un SG ≤6. L'utilisation de l'ensemble de la gamme des définitions des CMD, démontre que 10 à 47% des patients ont développé des CMD sous SA. L'utilisation du SG de base, le pourcentage maximum de cancer et la dAPS, démontrent des tendances significatives pour le développement de CMD pour les patients sous SA.

Conclusions: SA est une option thérapeutique appropriée pour les patients atteints d'un cancer de la prostate à faible risque. Une dAPS > 0,15 ng/ml/cc est un prédicteur important de la progression de la maladie. La majorité de nos patients n'ont pas

développés de CMD sous SA. Notre étude suggère donc qu'une sélection méticuleuse des patients pour un traitement focal doit être effectuée pour éviter de soumettre les patients à un traitement inutile.

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A- Review of literature

A-1 Prostate

The “prostate” is a Greek word which means “the one who stand for”, “protector” or “guardian”. (1) It produces a milky slightly alkaline secretion, which contributes about 30% of semen.

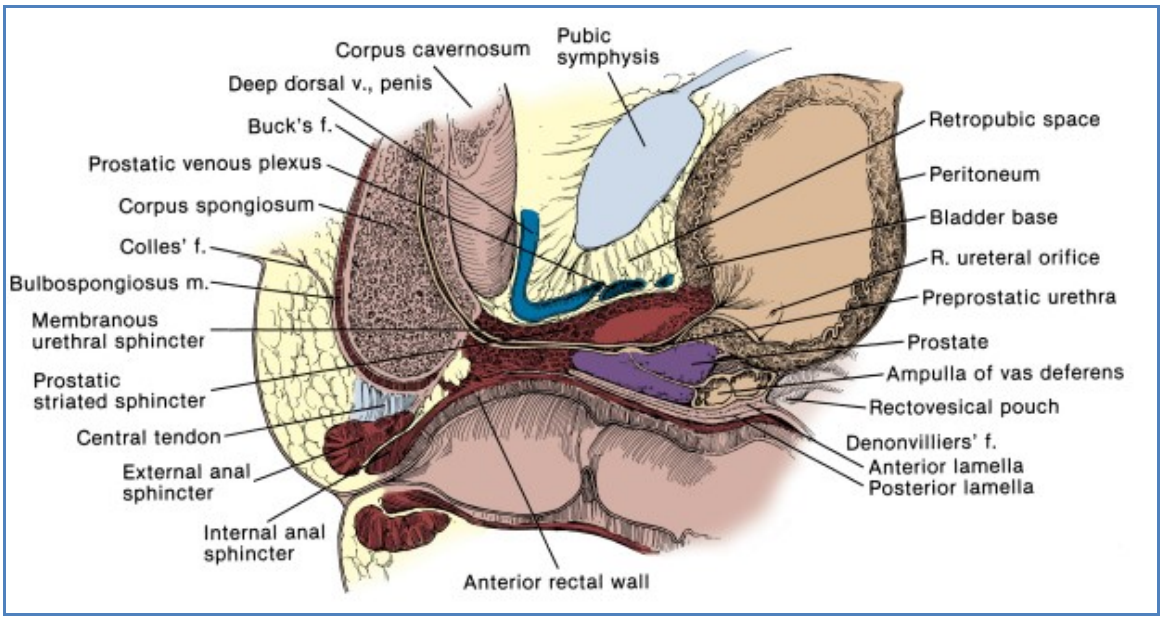
The prostate anatomy: (2)

The prostate is a pyramidal-shaped, fibromuscular and glandular organ which surrounds the prostatic urethra. The prostate relation with the surrounding structures is summarized in the Table 1.

Table 1: Description of the anatomical relations of the prostate with the surrounding structures.

Anatomical Relation	Description
Superiorly	It is continuous with the bladder neck where the urethra enters the upper aspect of the prostate.
Inferiorly	The apex of the prostate rests on the external sphincter.
Anteriorly	The pubic symphysis separated by the extraperitoneal fat of the space of Retzius or retropubic space. The prostatic plexus of veins. The puboprostatic ligament, near the apex of the prostate, passes forward to the pubis.
Posteriorly	The rectum separated by the fascia of Denonvilliers.
Laterally	The levator ani muscles.

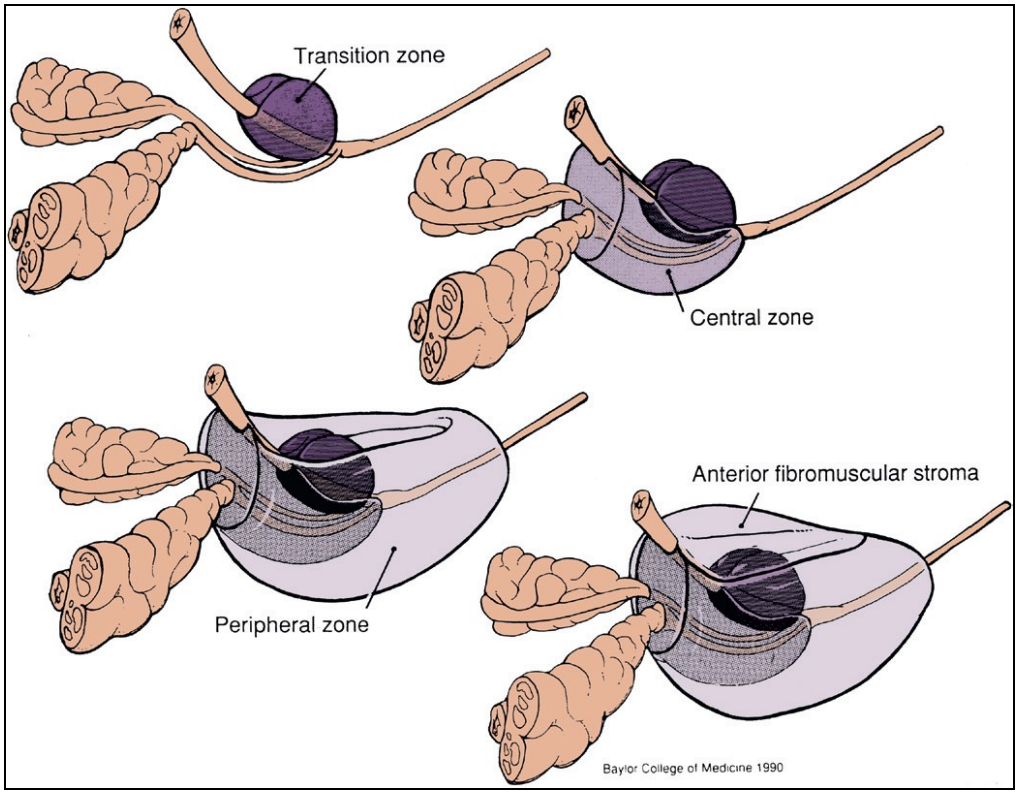
Figure1. The anatomy of the prostate.



Sagittal section through the prostatic and membranous urethra, demonstrating the midline relations of the pelvic structures. (From Hinman F Jr: Atlas of Urosurgical Anatomy. Philadelphia, WB Saunders, 1993, p 356.)

The glandular part of the prostate is divided into 3 zones; the transitional zone (TZ), the central zone (CZ) and the Peripheral zone (PZ). The TZ represents 5% of the glandular structure and commonly give raise Benign Prostatic Hyperplasia (BPH) and 20% of PCa occurs in this zone. The CZ represents 25% of the glandular structure and only less than 5% of PCa occurs in this zone. The PZ represents 70% of the glandular structure and 70% of PCa occurs in this zone.

Figure 2: The Anatomy of the glandular part of the prostate.



Zonal anatomy of the prostate as described by J.E. McNeal (Normal histology of the prostate. Am J Surg Pathol 1988;12:619–33). The transition zone surrounds the urethra proximal to the ejaculatory ducts. The central zone surrounds the ejaculatory ducts and projects under the bladder base. The peripheral zone constitutes the bulk of the apical, posterior, and lateral aspects of the prostate. The anterior fibromuscular stroma extends from the bladder neck to the striated urethral sphincter. (© 1990, Baylor College of Medicine.)

A-2: Prostate Cancer

A-2.1: Epidemiology

1) Internationally

Prostate cancer diseases have a great impact on men health worldwide. In the United States and many industrialized nations, prostate cancer is one of the most common cancers and is amongst the leading causes of cancer deaths (3). The incidence and mortality from prostate cancer is rising in developing countries but it is still less common than in industrialized countries (4). The geographical variations in the incidence and mortality from prostate cancer might be due to the combination of genetic and environmental factors as well as the improved reliability of cancer registries in reporting disease mortality(5).

2) In Canada

According to the Canadian cancer statistic (6), prostate cancer is the leading cancer diagnosed in men with 23,600 new cases diagnosed in 2014. The lifetime probability of developing prostate cancer is 1 in 8 men. The incidence of prostate cancer has two peaks followed by declines in 1993 and 2001 and both of them were at a periods of intensified prostate specific antigen (PSA) screening.

In term of cancer related death, prostate cancer is the third most common cause of death in men with 3,900 deaths in 2014. The mortality rate rose slowly from mid-1980s to the mid-1990s, when it began to decline. Between 2001 and 2009, the mortality rate declined significantly by 3.9% per year. This decline likely reflects improved treatment following the introduction of hormonal therapy for early and advanced-stage disease(7, 8)and advances in radiation therapy.(9)

Table 2: The most common cancer related incidence and mortality by sex in Canada according to the Canadian Cancer statistics 2014. (6)

Incidence		Mortality	
Males 96,200	Females 91,400	Male 39,400	Female 36,100
Protate 24.5%	Breast 26.1%	Lung 27.2%	Lung 26.3%
Lung 13.8%	Lung 13.3%	Colorectal 12.7%	Breast 13.9%
Colorectal 13.8%	Colorectal 11.6%	Prostate 10%	Colorectal 11.6%
Bladder 6.1%	Uterus 6.1%	Pancreas 5.5%	Pancreas 6%

A-2.2: Diagnosis

The suspicion of PCa diagnosis increases in patients with high PSA level and/or palpable lesion. Definitive diagnosis is made with pathological identification of adenocarcinoma by prostatic core biopsy examination. Patients with suspected cancer on DRE usually associated with more aggressive disease and thus it is strongly indicated to perform prostate biopsy.(10, 11)

PSA is a prostate specific kallikrein-like serine protease produced exclusively by the epithelial cells of the prostate but not cancer specific. Elevated level might be present in benign prostatic hyperplasia, prostatitis, and other nonmalignant cause as well. When compared to suspicious DRE and transrectal ultrasound finding as independent predictors, PSA level has better prediction of cancer diagnosis and the likelihood of having prostate cancer increases with higher values.(12)

A suspicious lesion in a gray-scale TRUS appears as a hypoechoic area but it is not adequately reliable.(13) The prostatic volume is calculated using one of the following formula; ellipse (anterio-posterior diameter x transverse diameter x longitudinal diameter

x π/6). Although this formula are based on geometric assumption and associated with inaccuracy, it is widely used in clinical basis.(14) The PSA density (PSAD) is calculated by dividing the PSA value by the prostate volume and used to adjust the PSA value to the prostate volume that help in better discrimination of PCa versus BPH.(15, 16) PSA kinetics, such as PSA doubling time (PSADT) and PSA velocity (PSAv), are also used in monitoring patients with PCa. PSADT is the time needed for the PSA value to double while the PSAv is the absolute increase in PSA value annually (ng/ml/year). (17, 18)

A baseline prostatic biopsy is needed to establish the diagnosis of PCa. Although a high PSA level can be associated with PCa, the first elevation of PSA level does not always implies the presence of cancer Before proceeding with more invasive investigation, a repeat value is often obtained under optimal conditions such as no ejaculation, urinary tract infection nor manipulations such as catheterizations or cystoscopy in the days preceding the PSA measurement. (19-21)

Prostatic Biopsy

Currently, US-guided biopsy is considered to be the standard of care. Repeated biopsy is indicated in the following circumstances; persistent high PSA value, rising PSA level, change in DRE which raise the suspicion of PCa, the presence of atypical small acinar proliferation (ASAP). Magnetic resonance imaging (MRI) may be considered if there is a doubt about the presence of PCa with negative biopsy result, followed by either TRUS or MRI-guided biopsies of the abnormal area.(22) Recent evaluation of Prostate Imaging Reporting and Data System version 2 (PI-RADSv_2) by Vargas et al and his group demonstrated 94–95 % correct identification of PCa foci ≥0.5 mL. The assessment was

limited for of GS ≥4+3 tumours ≤0.5 mL. Furthermore, DCE offered limited added value to T2WI and DWI.(23) The MRI features of PI-RADSv_2 are summarized in Table 3.(24)

Table 3: Summery of MRI features of PI-RADSv_2.(24)

Score	Peripheral Zone (PZ) on T2WI
1	Uniform hyperintense signal intensity (normal)
2	Linear or wedge- shaped hypointensity or diffuse mild hypointensity, usually indistinct margin
3	Heterogeneous signal intensity or non- circumscribed, rounded, moderate hypointensity Includes others that do not qualify as 2, 4, or5
4	Circumscribed, homogenous moderate hypointense focus/ mass confined to prostate and <1.5 cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extra prostatic extension/invasive behavior
Score	Transition Zone (T) on T2WI
1	Homogeneous intermediate signal intensity (normal)
2	Circumscribed hypointense or heterogeneous encapsulated nodule(s) (BPH)
3	Heterogeneous signal intensity with obscured margins. Includes others that do not qualify as 2, 4, or 5
4	Lenticular or non- circumscribed, homogeneous, moderately hypointense, and <1.5 cm in greatest dimension
5	Same as 4, but ≥1.5cm in greatest dimension or definite extraprostatic
Score	Peripheral Zone (PZ) or Transition Zone (TZ) DWI
1	No abnormality (i.e., normal) on ADC and high b- value DWI
2	Indistinct hypointense on ADC
3	Focal mildly/moderately hypointense on ADC and isointense /mildly hyperintense on high b- value DWI.
4	Focal markedly hypontense on ADC and markedly hyperintense on high b- value DWI; <1.5cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior
Score	Peripheral Zone (PZ) or Transition Zone (TZ) for DCE
(-)	No early enhancement, or diffuse enhancement not corresponding to a focal finding on T2 and/or DWI or focal enhancement corresponding to a lesion demonstrating features of BPH on T2WI
(+)	Focal, and; earlier than or contemporaneously with enhancement of adjacent normal prostatic tissues, and; corresponds to suspicious finding on T2W and/or DWI

Peripheral Zone (PZ) overall PIRADSv$_2$			
DWI	T2WI	DCE	PI-RADSv$_2$
1	Any	Any	1
2	Any	Any	2
3	Any	(-)	3
3	Any	(+)	4
4	Any	Any	4
5	Any	Any	5
Transition Zone (TZ) overall PIRADSv$_2$			
T2WI	DWI	DCE	PI-RADSv$_2$
1	Any	Any	1
2	Any	Any	2
3	≤4	Any	3
3	5	Any	4
4	Any	Any	4
5	Any	Any	5
PI- RADSv$_2$ Assessment Categories			
1	Very low (clinically significant cancer is highly unlikely to be present		
2	Low (clinically significant cancer is unlikely to be present)		
3	Intermediate (the presence of clinically significant cancer is equivocal)		
4	High (clinically significant cancer is likely to be present)		
5	Very high (clinically significant cancer is highly likely to be present)		

The number of cores taken in prostate biopsy varies. Sextant biopsy has been abandoned. Currently, extended (10 ± 2 cores) biopsy is considered to be the gold standard method.(25) Some limitations encounter the use of transrectal sextant and extended biopsies. Such limitations include, inaccurate localization, understaging and undergrading of the disease, as well as missing significant PCa in up to 30% mainly in the anterior part of the prostate.(26-29) Saturation biopsy (>20 cores), can be done via transperineal approach as well, is associated with higher PCa detection 30 - 43%. In a study using Epstein's criteria of insignificant PCa, the authors demonstrated the specificity, sensitivity, and false negative rate of transrectal saturation biopsy to be 95.8%, 71.9% and 11.5%.(30) On the other hand, another 2 studies used Epstein's criteria

of insignificant PCa and D'Amico criteria for low risk disease and didn't showed significant difference between saturation and standard biopsies regarding cancer detection. (31, 32) Furthermore, both transrectal and transperineal approaches of saturation biopsies showed similar results.(33)

Transperineal template prostate mapping biopsy performed in lithotomy position using 5mm hole brachytherapy grids in which a systemic sampling of the entire prostate is achieved. This method is associated with higher cancer detection, higher rate of Gleason grade 4, and more precise three-dimensional representation of location, volume, and extent of the lesion. In addition, it helps in management planning strategy for focal therapy.(34-37) The utilization of many resources including anesthesia requirement, longer processing time, expense and higher comorbidities are considerable obstacles of this technique. (34, 35, 38)

Gleason Score:

Gleason's grading system is the most commonly used in histological analysis of prostatic biopsy.(39) It ranges from 1 to 5 based on histological finding of prostatic biopsy. Gleason's score is obtained by the sum of the predominant pattern, which occupies the largest area of the specimen under low-magnification, and the second most common patter; resulting in a score ranging from 2 to 10. Recently, a modification of Gleason's score replacing the secondary pattern by tertiary patter 5 in biopsy Gleason's score 3 + 4 or 4 + 3 to be 3 + 5 or 4 + 5 respectively.(40) Such modifications are based on results that suggest that tertiary pattern may affect prognosis.

According to the International Society of Urological Pathology Modified Gleason System (2005), Gleason's pattern has 5 grades.

Pattern 1:

- Circumscribed nodule of closely packed but separate, uniform, rounded to oval, medium-sized acini (larger gland than pattern 3).

Pattern 2:

- Like pattern 1, fairly circumscribed, yet at the edge of the tumor nodule there may be minimal infiltration.
- The glands are more loosely arranged and not quite as uniform as Gleason's pattern 1.

Pattern 3:

- Discrete glandular units.
- Typically smaller glands than seen in Gleason's pattern 1 or 2.
- Infiltrates in and amongst non-neoplastic prostate acini.
- Marked variation in size and shape.

Pattern 4:

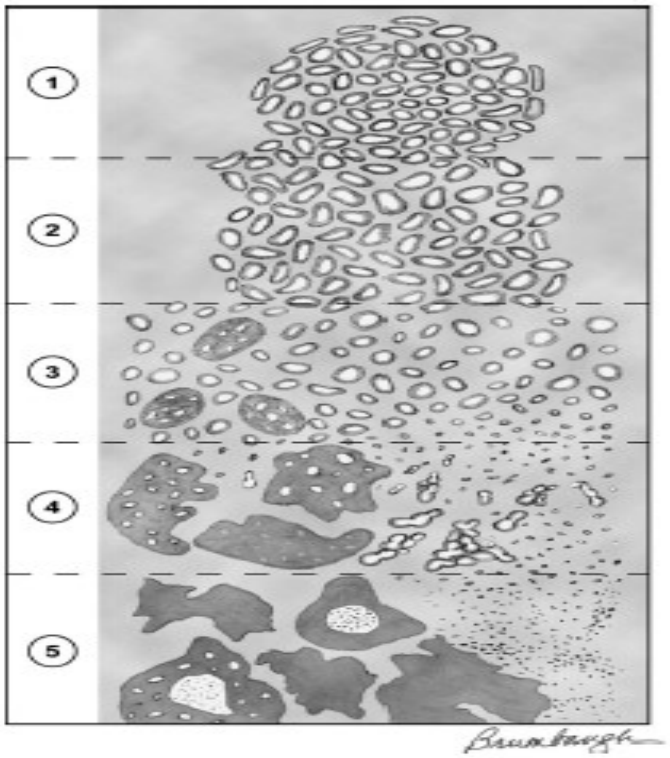
- Fused microacinar glands.
- Ill-defined, with poorly formed glandular lumina.
- Large cribriformed glands.
- Hypernephromatoid.

Pattern 5:

- No glandular differentiation composed of solid sheets, cords or single cells.

- Comedocarcinoma with central necrosis surrounded by papillary cribriform or solid mass.

Figure 4: Schematic diagram of modified Gleason's grading system.(40)



Risk Stratification

Pre-treatment risk stratification is helpful in guiding management decision, outcome reporting and data exchange, as well as in clinical trials design. Several parameters have been used to estimate PCa treatment outcomes; clinically (overall survival, disease-specific survival, disease-free survival, and metastasis-free survival), surgically (rate of extracapsular extension, seminal vesicle involvement and positive surgical margins and/or lymph nodes metastasis) and biochemically (PSA biochemical-free survival). There are different classification systems using the same factors to stratify the risk of localized (non-metastatic) PCa based on Tumor stage, histopathological feature (Gleason's score and tumor volume), and pre-treatment PSA level.

Table 4: Organizational pre-treatment prostate cancer risk stratification systems.

Classification System	**Low Risk**	**Intermediate Risk**	**High Risk**
Harvard(D'Amico) (41) **AUA (42)** **EUA (43, 44)**	T1-T2a GS ≤ 6 PSA ≤ 10	T2b GS = 7 PSA 10 - 20	≥ T2c GS 8- 10 PSA > 20
GURO* (45) **NICE* (46)**	T1-T2a GS ≤ 6 PSA ≤ 10	T2b GS = 7 PSA 10 - 20	≥ T3a GS 8- 10 PSA > 20
CAPSURE* (47)	T1-T2a GS ≤ 6 PSA ≤ 10	T2b GS = 7 PSA 10 - 20	T3-T4 GS 8- 10 PSA > 20
NCCN(48)	T1-T2a GS ≤ 6, PSA ≤ 10 Very low risk: <3 positive cores ≤ 50% cancer in each core PSAD<0.15ng/ml/gm	T2b or T2c GS = 7 PSA 10 - 20	T3a GS 8- 10 PSA > 20 Very High risk: T3b-T4
ESMO(49)	T1-T2a GS ≤ 6 PSA ≤ 10	Not High nor Low Risk	T3-T4 GS 8- 10 PSA > 20
AUA: American Urological Associated, EUA, European Urological Association. GURO: Genitourinary Radiation oncology, NICE: National Institute of Health and			

Clinical Excellence, CAPSURE: Cancer of the Prostate Strategic Urologic Research Endeavour, NCCN: National Comprehensive Cancer Network, ESMO: European Society of Medical Oncology.
T: T stage, GS: Gleason's Score, PSA: Prostate Specific Antigen. *Use of the 1997 TNM staging system (T2a Involve one lobe, T2b involve two lobes, no T2c category)

Adapted from Rodrigous et al.(50)

Table 5: TNM Clinical Staging Systems for Prostate Cancer.

2009	**1997**	**1992**	**Description**
T_x	T_x	T_x	Primary tumour can not be assessed
T_0	T_0	T_0	No Evidence of Primary Tumour
T_1	T_1	T_1	Not palpable tumour – no evidence on imaging
T_{1a}	T_{1a}	T_{1a}	Tumour found in tissue at TUR; ≤ 5 % is cancerous tissue and GS < 7
T_{1b}	T_{1b}	T_{1b}	Tumour found in tissue at TUR; > 5 % is cancerous tissue and GS ≥7
T_{1c}	T_{1c}	T_{1c}	Tumour identified by prostatic needle biopsy due to elevated PSA
T_2	T_2	T_2	Palpable Tumour confined to the prostate
	T_{2a}		Tumour involves ≤ 1 lobe
T_{2a}		T_{2a}	Tumour involves ≤ ½ of one lobe by normal tissue on all sides
	T_{2b}		Tumour involves >1 lobe
T_{2b}		T_{2b}	Tumour involves > ½ of one lobe but not both sides
T_{2c}	None	T_{2c}	Tumour involves >1 lobe
T_3	T_3	T_3	Palpable tumour beyond prostate
T_{3a}	T_{3a}	T_{3a}	Unilateral Extracapsular extension
T_{3b}	T_{3b}	T_{3b}	Bilateral Extracapsular extension
T_{3c}	T_{3c}	T_{3c}	Tumour involves the seminal vesicle(s)
T_4	T_4	T_4	Tumour is fixed or invades adjacent structures (not seminal vesicles)
T_{4a}	T_{4a}	T_{4a}	Tumour invades bladder neck, external sphincter, and/or rectum

T_{4b}	T_{4b}	T_{4b}	Tumour invades levator muscle and/or fixed to pelvic wall
N_x	N_x	N_x	Regional lymph node involvement can not be assessed
N_0	N_0	N_0	No lymph node metastasis
N_1	N_+	N_+	Involvement of regional lymph nodes
None	N_1	N_1	Metastasis to single regional lymph node, ≤ 2 cm in diameter
None	N_2	N_2	Metastasis to single regional lymph node (> 2 but ≤ 5 cm in diameter) Metastasis to multiple regional lymph node; none > 5 cm in diameter
None	N_3	N_3	Metastasis to multiple regional lymph node > 5 cm in diameter
M_x	M_x	M_x	Distant metastasis can not be assessed
M_0	M_0	M_0	No evidence of distant metastasis
M_1	M_1	M_1	Distant metastasis
M_{1a}	M_{1a}	M_{1a}	Involvement of nonregional lymph node
M_{1b}	M_{1b}	M_{1b}	Involvement of bones
M_{1c}	M_{1c}	M_{1c}	Involvement of other distant sites

TNM, tumor-node-metastasis; TUR, transurethral resection.

A-3: Active surveillance

Conservative management of PCa includes active surveillance (AS) and watchful waiting (WW). In AS patients are followed up with serial PSAs and biopsies and offered treatment with curative intent when unfavorable disease features developed. On the other hand, WW patients are managed conservatively till they become symptomatic and palliative therapy is offered to them. AS is currently a recommended treatment option for low risk PC. The first reporting of AS was in 2002.(51, 52) Although AS series are maturating, there is no consensus on the eligibility criteria, surveillance protocols and no standardized definition of unfavorable disease (disease progression). (53-63)

A-3.1: Patient eligibility criteria

Patient selection for AS is based on clinical, pathological, and/or biochemical features.(53-63) Most studies included clinically localized disease i.e. ≤ cT2a N0 M0. Pathological selection criteria included GS of ≤ 3+3 but some studies also included low volume ≤ 3+4 (56, 57, 63). In regard to total positive cores some studies based their inclusion on the number of positive core with a cutoff of 2 or 3 positive cores while others based on the percentage of positive cores out of total number of cores taken with a cutoff 33 or 50%. Regarding to amount of cancer on individual cores, which is the length of cancer in the core divided by the total length of the core biopsy, most studies used 50% as a cutoff while other (58) were more strict and used 20% as a cutoff. Biochemically, most studies used PSA of 10 ng/ml as a cut off but some studies went up to 15ng/ml (56, 63)and some studies used PSAD in their inclusion criteria with a cutoff 0.15 or 0.2 ng/ml/gm (59, 60).

A-3.2: Surveillance protocols

The surveillance protocol consisted of serial visits with DREs, PSA, and repeat prostatic biopsies.(53-63) Generally, DRE and PSA are done every 3 - 6 months in the first 2 years. After the second year, both are performed every 6 to 12 months. The first repeat biopsy is usually done 9 to 18 months following the diagnostic biopsy. Some centers suggest to proceed with immediate repeat biopsy in order to confirm the elegibilty of patients to AS. Thereafter, repeat biopsies are performed every 1 to 3 years according to physician preference. The biopsy frequency can also be influenced by change in DRE or PSA values.

A-3.3: Definition of unfavorable disease (disease progression)

The definition of disease progression is an important concept. Progression can be identified based on biochemical, clinical, and/or pathological characteristics. (53-63) The biochemical features includes PSAv with a cutoff point of 0.75 – 1 ng/ml/year (53, 63), PSADT with a cutoff 2 – 3 years (53, 55, 56, 60), PSAD with a cutoff 0.15 ng/ml/gm (59), and total PSA with a cutoff 10 ng/ml(54, 59). Although some investigators included PSA parameters in their reclassification criteria, recent studies showed that they are not the most reliable tools in predicting disease progression. The clinical criterias of progression includes a change in DRE. The pathological features includes a change in GS with progression from Gleason 6 to 7 (3+4) in some studies while others (56, 63) used the presence of predominant pattern 4 (≥ 4+3) as a criteria of pathological progression, increase in tumor volume on any core greater than 20 to 50% (58, 59), or the total number of positive cores greater than 3 are also used as criteria for progression (54, 58-60, 63).

A-3.4: Outcome of Active Surveillance

In a recent review of literature (62, 64), the median follow up ranged from 1.4 – 6.8 years. (53-63) Around 30% of patients were reclassified or considered to have progression during AS; 13 -14 % is based on PSA parameters (56, 63), 7- 14% based on GS upgrading (54, 56, 59, 63), and 10 – 17 % based on cancer volume and/or number of positive cores (59, 63). The reported median time to treatment range up to 6.5 years. (59) Of the patients who will undergo treatment, 11 to 33% patients will receive treatment with curative intent at a median time to treatment of 1.3 – 2.2 years. (53-63) Of all patients treated, five – 17% of patients underwent radical prostatectomy (RP) with a median time to RP of 1.3 – 2.5 years. Fifty to 75% of patient had GS 7 or higher, less than 1% of patients had nodal metastasis at the time of RP and the reported positive surgical margin rates ranged from 18 – 25%. (53, 54, 56, 58-60, 63, 65, 66) Five to 20% of patients received radiotherapy (RT) with a median time to RT of 2.6 – 2.8 years. (53, 54, 56, 58, 59, 63) There are limited follow up reports after curative treatment. The difference in the biochemical-free survival (BFS) in patients treated with RP versus RT is controversial. Tosoian and his group found a higher BFS with RP while Klotz his group did not found significant difference in their cohort of treated patients. (56, 59) In term of survival, the reported cumulative cancer specific survival was almost 100% and the overall survival ranged between 79 – 100%.(62, 64)

A-4: Focal therapy

The role of focal therapy is tissue preservation with presumed less side effects and morbidities compared to radical treatment.(67-70) This treatment modality is still considered an experimental option. Several authors are investigating the feasibility and safety to introduce this modality as a valid treatment option for patients with localized prostate cancer.(71)

A-4.1: Patients selection

There is no agreement on the ideal candidate for focal therapy. In the initial feasibility series, focal therapy was offered mainly to patients with organ confined disease.(72-81) Currently, investigators tend to select patients with low-intermediate risk disease, unilateral disease and GS $\leq$ 4+3. Patients with very low risk disease are usually not included as they remain ideal candidate for AS. There is no consensus on the PSA cutoff to be used but usually a value of 20 ng/ml or lower is used.(81)

A-4.2: Disease localization

Accurate disease localization remains a significant limitation for focal therapy. Multiple imaging modalities have been proposed in order to ensure adequate and accurate localization. Although there is no agreement on a standard method to be used, many investigators used TRUS biopsy as the only method of disease localization (74, 76, 77, 79-85). Others attempted to increase accuracy with the addition of Doppler US (76, 81) and most recently multi-parametric MRI has been proposed as the most appropriate imaging technique (74, 79, 80, 82, 84, 85). Finally, transperineal template mapping biopsy (TTMP) with multiparametric MRI (mpMRI) has also been used to confirm tumor localization (70, 86, 87).

A-4.3: Available technology for focal therapy

Different modalities have been used in focal therapy. A brief technical description of each modality as follow:

1) Cryotherapy (CT)

In CT, cryoprobes are inserted into the prostate through the perineum under ultrasound guidance. Freezing of the prostatic tissue is achieved by theses probes, reaching a temperature of -40°C. Cell destruction results in coagulative necrosis usually after 2 freezing-thawing cycles. (88)

2) High intensity Focal Ultrasound (HIFU)

In HIFU, a transrectal probe is inserted and delivers high intensity ultrasonic waves under US guidance. Prostatic tissue destruction is achieved by both thermal waves reaching >56°C and mechanical ablation as well. (89)

3) Photothermal laser (PTL)

In PTL, laser probes are inserted though the perineum into the prostate. A direct thermal effect of these probes cause coagulative necrosis of the prostatic tissue. Thermal monitoring is maintained during the procedure by thermal sensors. (82, 90)

4) Photodynamic therapy (PDT)

In PDT, photosensitizer drug is injected intravenously. Laser fibers are inserted into the prostate through the perineum and deliver a specific wavelength of light activating the drug present in the tissue of the prostate. As a result, reactive oxygen radicals are produced leading to tissue damage and destruction. (80, 90)

5) Brachytherapy

In low dose-rate brachytherapy, small radioactive seeds are implanted in the prostatic tissue and release radiation to the surrounding tissue for the months to follow. Alternatively, high dose brachytherapy can also be used. In this instance a high dose of radiation is delivered in the prostatic gland in a single session. (91)

6) Radiofrequency ablation (RFA)

In RFA, a thermal damage to the prostatic tissue is achieved by high frequency current (480 kHz) generated by a needle advanced into the prostatic tissue. (73)

A-4.4: Oncological outcome

There is no clear definition of success and failure in focal therapy. Although there are no validated criteria measuring biochemical disease free (bDFS) survival after focal ablative therapy, the majority of investigators are using Phoenix and/or American Society for Therapeutic Radiology and Oncology (ASTRO) criteria. (92) These criteria are used in patients treated with radiotherapy. The mechanism of tissue damage caused by radiotherapy differ from ablative therapy in term of the remaining prostatic tissue, which still produce PSA, as well as the immediate ablative effect in focal therapy. These differences affect the behavior of PSA kinetics. A study suggested that the use of phoenix with PSAv <0.75ng/ml/year is better than using phoenix criteria alone in predicting a biopsy-proven failure after focal therapy. (85) In the current literature, the reported bDFS ranged between 38 – 95% depending on the duration of follow up, the criteria used to define bDFS, and the baseline risk stratification of the patients. (76-79, 83, 85, 93, 94)

Pathological findings post ablative therapy are variable. Significant cancer was reported in up to 17% of treated patients and insignificant cancer was identified in 4 - 50%.of patients. In series where the intent to treat was to destroy all tumor, the reported need for secondary focal treatments ranged from 0 to 34%. (67)

Most of the reported series have short-term follow-up, making impossible the adequate assessment of cancer specific and overall survival. Longer follow-up with well-designed randomized control trials (RCT) are essential to assess non inferiority of focal therapy compared to standard treatment modalities. Such trial would need time for patients' recruitment as well as long-term follow up duration. (95-105)

A-4.5: Side effects

Following focal therapy, the reported median length of hospital stay was 1 day with poor perioperative reporting. The reported incidence of urinary complications after focal therapy, using different modalities, is as follow: urinary retention from 0 – 17%, stricture from 0 – 5%, and urinary tract infection from 0 – 17%. The reported urinary functional outcome using validated questionnaires demonstrate 95 -100% pad-free continence rates and 83- 100% leak-free continence rates. In term of sexual outcome, 54-100% of patients reported erection sufficient for penetration, with or without the use of phosphodiesterase inhibitor medication. Regarding rectal toxicity, it was poorly reported with less than 1% reported fistula rate. (67)

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B- Aim of Thesis

1) To evaluate clinical and pathological factors which influence the risk for disease progression in a cohort of patients with low-intermediate risk PCa under AS.

2) To assess the probability of developing UDF in patients with clinical localized PCa under AS as a guide to estimate the benefit of immediate hemi-ablation therapy (HAT).

C- Manuscript 1:Factors Influencing Disease Progression of Prostate Cancer under Active Surveillance: A McGill University Health Center Cohort

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Key words: Prostate cancer, adenocarcinoma, active surveillance, biopsy, risk factor.

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C-1: Abstract

Objective: To evaluate the clinical and pathological factors influencing the risk of disease progression in a cohort of patients with low–intermediate risk prostate cancer under active surveillance (AS).

Patients and Methods: We studied 300 patients diagnosed between 1992 and 2012 with prostate adenocarcinoma with favourable parameters or who refused treatment and were managed with AS. Of those, 155 patients with at least one repeat biopsy and no progression criteria at the time of the diagnosis were included for statistical analyses. Patients were followed every 3–6 months for prostate-specific antigen (PSA) measurement and physical examination. Patients were offered repeat prostatic biopsy every year. Disease progression was defined as the presence of one or more of the following criteria: ≥ 3 positive cores, > 50% of cancer in at least one core, and a predominant Gleason pattern of 4.

Results: For the 155 patients, the mean (SD) age at diagnosis was 67 (7) years; the median (interquartile range) follow-up was 5.4 (3.6–9.5) years. Of these, 67, 25, six, and two patients had two, three, four, and five repeat biopsies, respectively. At baseline, 11 (7%) patients had a Gleason score of 3+ 4, while the remaining 144 (93%) patients had a Gleason score of ≤ 6. In all, 50 (32.3%) patients had disease progression on repeat biopsies, with a median progression-free survival time of 7 years. The rate of disease progression decreased after the second repeat biopsy. The 5-year overall survival rate was

100%. Having a PSA density (PSAD) of > 0.15 ng/mL/mL, > 1 positive core, and Gleason score > 6 at the time of the diagnosis was associated with a significantly higher rate of disease progression on univariate analysis (P <0.05), while a maximum percentage of cancer in any core of > 10% showed a trend toward significance for a higher progression rate (P = 0.054). On multivariate analysis, only the presence of a PSAD of > 0.15 ng/mL/mL remained significant for a higher progression rate (P < 0.05). Of the 155 patients, five (3.2%) subsequently received radiotherapy, 13 (8.4%) received hormonal therapy, and 13 (8.4%) underwent radical prostatectomy.

Conclusion: AS is a suitable management option for patients with clinically low-risk prostate cancer. A PSAD of > 0.15 ng/mL/mL is an important predictor for disease progression.

C-2: Introduction

Prostate cancer is the most common cancer among men, with 26 600 expected new cases diagnosed in Canada in 2013 and the third-most common cause of cancer-related death in Canadian men. (1) Autopsy reports suggest that half of men aged > 50 years may already harbour some form of prostate cancer. (2,3) Using PSA for early detection of prostate cancer and performing more prostatic core biopsies can increase the likelihood of detecting clinically insignificant disease. (4) The slow growth rate and low likelihood of disease progression in patients with low-risk or very-low-risk prostate cancer has led to the adoption of active surveillance (AS) as a valid management option for this patient population. (5) Despite this practice, overtreatment of newly diagnosed prostate cancer has led to the adoption of a grade ‘D’ recommendation by the USA

Preventive Services Task Force (USPSTF), recommending against PSA-based screening for prostate cancer in men of all age groups for updated data in 2012. (6–9)

AS is a reasonable management option for patients with low-risk or very-low-risk prostate cancer. This approach is also being offered to select patients with intermediate-risk disease. (10–12) Although patients under AS are monitored closely until disease progression is observed and then offered treatment with curative intent, there is no consensus on the AS protocol and definition of disease progression. (13–21) The goal of the present study was to evaluate the role of clinical and pathological factors in predicting disease progression.

C-3: Patients and Methods

After approval from the Institutional Review Board, we performed a retrospective chart review of patients diagnosed with prostate adenocarcinoma between 1992 and 2012 at the McGill University Health Center. Patients included in this cohort elected to be managed by AS because either the pathological findings on prostatic biopsies were suggestive of insignificant prostate cancer or they refused treatment. As previously described (20), our AS protocol consisted of clinical evaluation with DRE, PSA level measurement every 3–6 months, serial TRUS, and prostatic biopsy. The first repeat biopsy was taken 12–18 months after the initial diagnosis; subsequent biopsies were taken every 1–3 years according to the preference of the treating physician.

Prostatic biopsies taken in our patient population included 6–16 cores based on the time period of the biopsy and the physician's preference. All biopsies were reviewed by two genitourinary pathologists (L.R.B. and F.B.) to standardize reports according to

changes in the Gleason grading system observed over time. The pathological findings included the Gleason score, the percentage of cancer on individual core(s), and the number of positive cores.We defined disease progression as the presence of one or more of the following criteria on repeat biopsies: > 50% of cancer in any involved core, Gleason score ≥ 4+ 3, and ≥ 3 positive biopsy cores. Time to disease progression was defined as the time between diagnostic biopsy and repeat biopsy with documented pathological progression or last follow-up in censored patients, with censoring of those who were lost to follow-up, had withdrawn from the study, or had died by the time of the last biopsy. The baseline PSA level was defined as the PSA level performed within 6 months of diagnosis. The baseline PSA density (PSAD) was calculated by dividing the baseline PSA level by the baseline prostatic volume measured on ultrasound.

From our cohort of patients under AS, 155 patients had at least one repeat biopsy and met the study's inclusion criteria (< 3 positive cores, Gleason score ≤ 3+ 4, and < 50% of cancer on any involved biopsy core) and thus were included in our analysis.

Statistical analysis was performed using SPSS Statistics version 20.0 software® . Kaplan–Meier curves were used to estimate the progression-free survival and overall survival. Univariate and multivariate Cox proportional hazard analyses were used to assess the effect of clinical, biochemical, and pathological factors on the rate of disease progression. A $P < 0.05$ was considered to indicate statistical significance.

C-4: Results

The baseline clinical, biochemical, and pathological characteristics are described in Table 1. At the time of diagnosis, the mean (SD) age of our patients was 67 (7) years.

The baseline PSA level of our cohort was ≤ 10 ng/mL in 140 (90.4%) patients. Only 11 (7%) patients had a Gleason score of 3+ 4; the remaining patients had a Gleason score of 6. The percentage of cancer in any involved core was ≤ 20% in the vast majority of our patients (86%). The median (interquartile range) follow-up duration was 5.4 (3.6–9.5) years. None of our patients died during the study period, thus the cancer-specific and overall survival rates were 100%.

In all, 50 (32%) patients developed disease progression (Fig. 1). Disease progression was confirmed most commonly by the presence of ≥ 3 positive cores; 13 of 50 (26%) patients progressed based on upgrading, and 14 of 50 (32%) patients progressed by having > 50% maximum cancer percentage in any core (Table 2). Figure 2 shows the likelihood of disease progression at each repeat biopsy. There was a decrease in the rate of disease progression with repeat biopsy, from 21.9% at the first repeat biopsy, taken at a median time of 1.2 years after diagnostic biopsy, to only 8% at the third repeat biopsy, taken at a median time of 4.6 years after diagnosis (Fig. 2).

The baseline characteristics of PSAD > 0.15 ng/mL/mL, > 1 positive core, and Gleason score 3+ 4 were all associated with a higher risk of disease progression on univariate analysis (Table 3). Patients with a cancer percentage in any core of > 10% had a trend toward higher progression rate (P = 0.054). In all, 20 of 44 (46%) patients with a PSAD of > 0.15 ng/mL/mL had disease progression, while 21 of 95 (22%) patients with a PSAD of ≤ 0.15 ng/mL/mL progressed during follow-up. In all, 20 of 45 (44%) patients with > 1 positive core had disease progression, while 30 of 110 (27%) patients with 1

positive core biopsy progressed during follow-up. Six of 11 (55%) patients with a Gleason score of 3+ 4 had disease progression, while 44 of 144 (31%) patients with a Gleason score of ≤ 6 progressed during follow-up. In all, 19 of 55 (36%) patients with a maximum percentage of cancer in any core of > 10% had disease progression, while 27 of 95 (28%) patients with a maximum percentage of cancer in any core of ≤ 10% progressed during follow-up. On multivariate analysis, only a baseline PSAD of > 0.15 ng/mL/mL was an independent predictor of disease progression after adjusting for patients' age, number of positive cores, maximum cancer percentage in any core, total number of cores and Gleason score. Ultimately, 31 of the 155 patients received treatment with curative intent, while some elected to remain on AS despite documentation of disease progression. Of these, 16 (52%) were treated because of disease progression, with three and seven patients receiving radiotherapy and hormonal therapy respectively, and six patients undergoing radical prostatectomy; the remaining 15 patients received treatment based on the patient's or physician's preference (Table 4).

C-5: Discussion

The vast majority of the present patients were considered to have low-risk prostate cancer based on pathological findings on biopsy, and most (> 90%) had a PSA level of ≤ 10 ng/mL. Although Cooperberg et al. (22) found that patients with prostate cancer of intermediate risk could be candidates for AS and are not necessarily likely to progress, fewer than 15% of our present patients had a Gleason score of 3+ 4 and/or a PSA level of > 10 ng/mL. One-third of our patients progressed during the follow-up period. This finding is consistent with the reported rate of disease progression in other series. (13–20) The median progression-free survival of our cohort was 7.32 years, and

61% of patients were free of disease progression at 5 years, supporting the role of AS in this patient population.

The definition of disease progression in the present patient cohort was based on pathological findings observed on repeat prostatic biopsy.Most of the present patients progressed based on the number of positive biopsy cores. This finding might either reflect the development of new foci of cancer or represent missed cancers on previous biopsies. Upgrading was noticed in only 13 (26% of progressors and 8% of overall cohort) patients. The use of multi-parametric MRI (mpMRI) may reduce the risk of underestimating the tumour volume. We recently started using mpMRI in evaluating our patients under AS, but our experience remains too limited to draw any conclusions. Margel et al. (23) found that MRI may reveal missed significant lesions in up to 22% of patients and that biopsy of these areas helped to reclassify up to 18% of patients. MRI might also be helpful in assessing patients' eligibility for AS, as an MRI score of ≤ 2 was associated with a high (0.96–1.0) negative predictive value, whereas a score of 5 for tumour upgrading had a high sensitivity (0.87–0.98). (24) Although we most probably underestimated tumour volume in a certain percentage of the present patients with our biopsy strategy and the absence of mpMRI during our initial patient evaluation, the favourable outcome of our patient cohort supports the use of AS as a suitable management option.

It is interesting to note the decrease in the rate of disease progression after the second repeat biopsy. The risk of progression decreased from 20.9% to 8% and 0% on the second, third, and fourth repeat biopsy, respectively. This finding is consistent with

our previous study and another study reporting that most patients who progressed were detected in the first 2 years after diagnosis. (20,21) This result should bring reassurance to patients who reach their third repeat biopsy without evidence of disease progression, suggesting a very low risk of progression and a limited role for repeat biopsies over the next few years. On the other hand, the present data suggest a role for a regular biopsy protocol in patients under AS within the first 2–3 years of diagnosis.

Many studies have evaluated the association between various factors and disease progression. Tseng et al. (25) found that having a higher percentage of free over total PSA and higher percentage of core involvement at the time of diagnosis was associated with a higher rate of disease progression in the first AS biopsy, whereas having higher PSAD and the presence of prostate cancer at the first repeat AS biopsy was associated with higher risk of progression. Iremashvili et al. (26) found that African-American race, higher number of positive cores, and higher PSAD at the time of diagnosis were each associated with a higher risk of disease progression. These authors also noted in a subsequent study that using the total number of positive cores in both diagnostic and repeat biopsies correlates with the risk of disease progression. (27) Kotb et al. (28) also noted the association between PSAD and disease progression, as found in our previous study. The Prostate cancer Research International: Active Surveillance (PRIAS) trial showed that the baseline characteristics of patient's age, PSAD, and number of positive cores were important predictors for disease progression. (19) In the present study, we found that the number of positive cores was associated with a higher risk of disease progression on univariate analysis but not on multivariate analysis. This contradiction

might support the need of using combined number of positive cores in both diagnostic and initial AS biopsies, as patients with only one positive core in diagnostic biopsy and negative initial AS biopsy appeared to have the lowest risk of disease progression, whereas those with two positive cores on both biopsies have the highest risk. (27) We could not reproduce these findings (data not shown), and we attribute this shortcoming mainly to our small patient population.

In the present study, AS had a negative effect on neither cancer-specific nor overall survival. None of our 155 patients died during the AS period. Even when the survival analysis was performed on our entire cohort of patients under AS, including patients with more extensive disease (N = 300), the 10-year cancer-specific and overall survival rate was 99% and 98%, respectively. Klotz et al. (29) reported that the hazard ratio for non-prostate to prostate cancer mortality was 18.6 and the 10-year actuarial cancer-specific survival rate was 97%. Furthermore, studies comparing watchful waiting with radical prostatectomy did not find a significant difference in survival. (30,31) A large proportion of patients with favourable-risk prostate cancer are still being offered immediate intervention, which might be due to the patient's and/or the physician's preference. (5) It is clear that better patient counselling about the risks and benefits of each management option might improve the acceptance of AS in patients with prostate cancer.

In conclusion, AS is a safe management option for patients diagnosed with low-risk prostate cancer. Baseline PSAD appears to be a useful predictor for disease

progression. A close follow-up is recommended in the first 2–3 years of the AS protocol and the AS protocol can be tailored according to the risk of disease progression. Further prospective studies with larger patient cohorts and long-term follow-up are recommended to validate the present findings.

Table 1. Baseline Clinical, Biochemical, and Pathological Characteristics.

Clinical characteristics.	
Number of Patients	155
Mean (SD) Age, years	67 (7)
Median (IQR) follow0up duration , years	5.4 (3.6-9.5)
N (%):	
PSA ng/ml ≤4 4.1-10 10.1-20 ≥20.1 Unknown Prostate Volume, ml ≤ 40 >40 Unknown PSA Density, ng/ml/ml ≤ 0.15 >0.15 Unknown	 28(18.1) 112(72.3) 12(7.7) 1(0.6) 2(1.3) 61 (39.4) 79(51) 15 (9.7) 95(61.3) 44(28.4) 16 (10.3)
Pathological characteristics, N(%)	
Number of biopsy cores ≤6 7-10 >10 Gleason Score ≤6 3+4 Number of positive biopsy cores	 46(30) 74(47) 35(23) 144(93) 11(7)

1	111(72)
≥2	44(28)
Maximum percentage of cancer in any core	
≤ 10	95(61)
11-20	38 (25)
>20	17(11)
Unknown	5 (3)

Table 2: Number of patients who developed disease progression, based on different criteria.

Progression criterion/ criteria	N (%)
> 50% cancer alone	3 (6)
GS ≥ 4+3 alone	4 (8)
≥ 3 positive cores alone	26 (52)
GS ≥ 4+3 & ≥ 3 positive cores	6 (12)
> 50% cancer & ≥ 3 positive cores	8 (16)
All 3 criteria	3 (6)
Total	50 (100)

Table 3. Effect of baseline factors on rate of disease progression.

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age at diagnosis*	1.0 (0.99 - 1.1)	0.1	1.0 (0.97-1.1)	0.4
Positive Cores >1	1.9 (1.1- 3.4)	0.02	1.8 (0.9-3.7)	0.08
PSA Density > 0.15ng/ml/ml	2.6 (1.4 – 5.0)	0.003	2.7 (1.4 – 5.3	0.005
Prostate Volume ≤ 40 ml	1.6 (0.9 – 2.9)	0.1		
Percentage of Cancer >10	1.8 (0.99 -3.2)	0.05	1.1 (0.5-2.3)	0.8
Total cores ≤ 10	1.3 (0.6 - 2.7)	0.5	1.7 (0.8-3.7)	0.2
Gleason's Score >6	3.7 (1.52 - 8.9)	0.004	3.3 (1.0 - 11)	0.05
PSA >10 ng/ml	1.8 (0.7 – 4.2)	0.2		

HR: hazard ratio; *: Continuous variable. PSA and prostate volume were not included in the multivariate analysis because PSA density was included.

Table 4. Treatment methods selected during the AS period.

Treatment	N (%)	Median (range) time to treatment, years	Median (range) follow-up after treatment, years
Radiotherapy	5 (3.2)	1.9 (1.1– 6.1)	3.3 (1.14 – 6.2)
Hormonal	13 (8.4)	6.2 (1.2-9.6)	3.4 (0 – 11.1)
Prostatectomy	13 (8.4)	1.8 (1.2 – 6.4)	2.4 (0 – 10.4)

Figure 1. Kaplan-Meier curve of progression-free survival

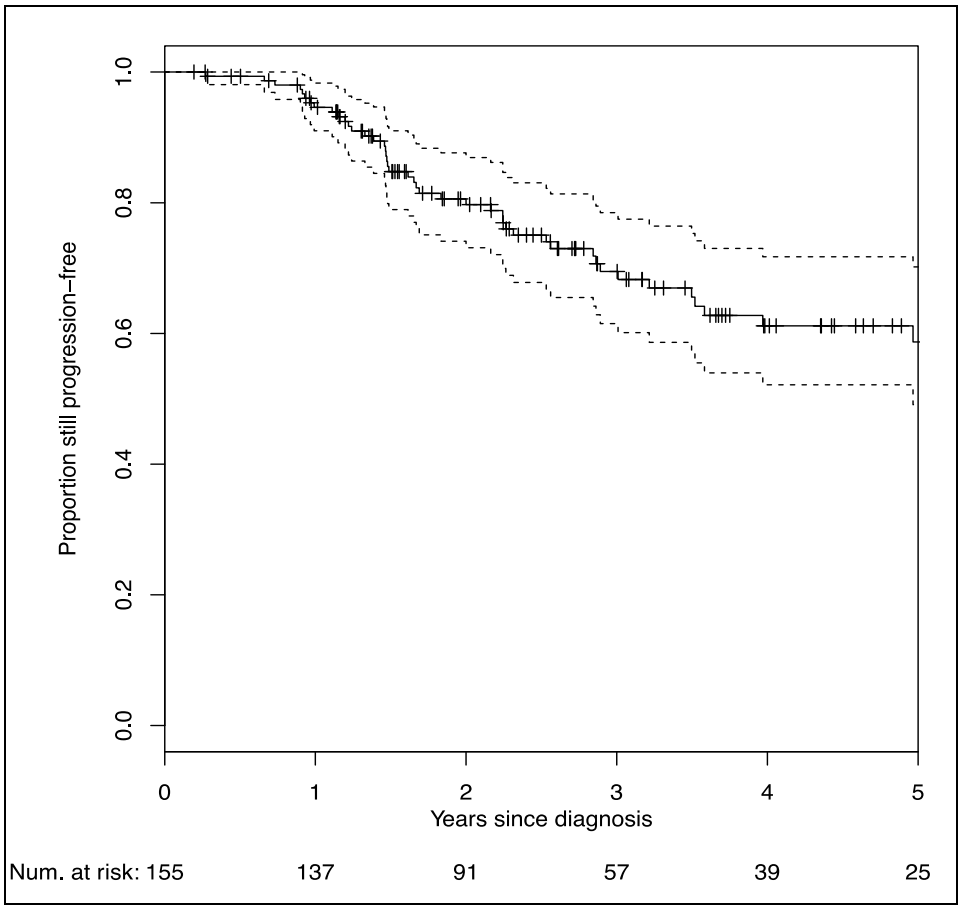
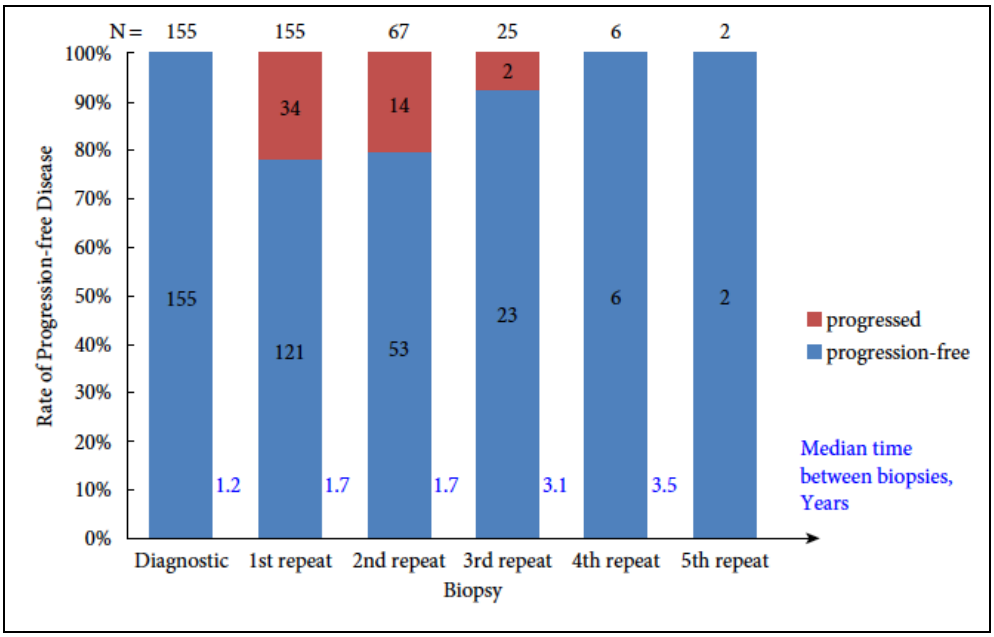


Figure 2. Rate of disease progression on each repeat biopsy.



C-6: References

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D- Manuscript 2: Outcome of Repeated Prostatic Biopsy during active Surveillance: Implications for Focal Therapy

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D-1: Abstract

Introduction: Active surveillance (AS) is commonly recommended for men with localized low-intermediate-risk prostate cancer (PCa). The aim of our study was to assess the probability that patients with PCa would develop unfavorable disease features (UDF) while under AS for the purpose of evaluating whether immediate hemiablation therapy (HAT) could bring clinical benefit to selected patients.

Methods: In our cohort of AS patients, 157 were diagnosed with unilateral PCa. Using five different definitions of UDF, patients' data were used to simulate the theoretical outcome whether these patients were managed by immediate unilateral HAT or remained on AS.

Results: The mean age at the time of diagnosis was 67 years (range 47–81). The median follow-up was 5.4 years [interquartile range (IQR) 3.4–8]. Baseline characteristics included a median PSA value of 5.5 ng/ml (IQR 4.5–7), median number of biopsy taken of 10 (IQR 6–10), and maximum cancer percentage on any core of 10 (IQR 5–20). Of the 157 patients, 144 (92 %) had a Gleason score (GS) of ≤6. Using the whole range of definition for UDF, 10–47 % of patients developed UDF while under AS. Using baseline GS, maximum percentage of cancer on any core, and PSA density, we found significant trends for higher development of UDF for patients under AS.

Conclusion: The majority of our patients did not develop UDF while under AS. Our study, thus, suggests that careful patient selection for focal therapy should be performed to avoid subjecting patients to unnecessary treatment.

D-2: Introduction

Since its introduction in the 1980s, prostate-specific antigen (PSA) evaluation has led to a significant reduction in mortality associated with prostate cancer (PCa) [1]. In fact, nearly 50 % of newly diagnosed patients have low-risk PCa, and PSA values have been used to detect stage-specific disease progression. But concerns with overdiagnosis and overtreatment have led the US Preventive Services Task Force to recommend against PSA screening [2]. It is unclear whether this recommendation will lead to the detection of more advanced disease in newly diagnosed patients [3, 4]. On the other hand, to avoid overtreatment, therapy may be offered only to patients selected by disease risk stratifications and the presence of comorbidities.

Active surveillance (AS) is currently recommended as a valid management option for patients with low-risk and selected intermediate-risk PCa. Patients managed with this approach are followed closely and offered active treatment with curative intent once progression is identified [5–12]. Active surveillance is safe in well-selected patients, given the long time to progression in the majority of patients with low-risk disease [13, 14] and the reported high cancer-specific survival rate at 5 and 10 years (>95 % each) [5–7, 10, 12]. Several studies are currently evaluating the role of focal therapy in patients with PCa [15–17]. Using different source of energy, focal therapy can treat selected areas of the prostate [18, 19] while minimizing damage to surrounding structures such as the bladder neck, rectum, external urinary sphincter, and neurovascular bundles [17, 20]. It is estimated that nearly one-third of men with localized PCa have unilateral disease and could be considered candidates for hemiablation therapy (HAT) [21–23]. The aim of our study was to assess the probability that patients with low-risk PCa would develop

unfavorable disease features (UDF) while under AS for the purpose of estimating the benefit of immediate HAT.

D-3: Methods

Our cohort included 300 patients diagnosed with an adenocarcinoma of the prostate between 1992 and 2012 who were managed by AS because either their pathological findings were suggestive of insignificant PCa or the patients refused definitive therapy. Patients were followed with clinical evaluation including digital rectal examination (DRE) and PSA measurements every 3–6 months and serial transrectal ultrasound (TRUS) guided prostate biopsies. The first repeat biopsy was performed 12–18 months following initial diagnosis, and subsequent repeat biopsies were performed every 1–3 years based on the treating physician's preference. Prostate biopsy included 6–16 cores according to the period when the biopsies were performed and physician's preference. All biopsies were reviewed by one of two genitourinary pathologists (with author initials LRB and FB) to standardize reports according to Gleason score (GS) changes. The pathological findings included GS, the percentage of cancer on the involved cores, the number of positive cores, and the location within the prostate. Our AS cohort included 300 patients, of whom 194 patients had at least one repeat biopsy. This study comprises patients with PCa with unilateral involvement of the prostate (unilateral disease: UD) based on initial prostate biopsy (N = 157).

Five different definitions of unfavorable disease (UDF) were used in this study (Table 1). Time to UDF was defined as the period between diagnostic biopsy and the first repeat biopsy with documented UDF. Kaplan–Meier analysis was used to assess the

probability of developing UDF while under AS. To assess the probability of having UDF in the contralateral half of the prostate during follow-up, we created a model using the consecutive pathologic biopsy results, assuming that those patients would have had immediate HAT on the side of positive biopsy at the time of diagnosis. Statistical analysis was done using R software®.

D-3: Results

The mean age of our 157 patients with UD was 67 years (range 47–81), with a median baseline PSA value of 5.3 ng/ ml (IQR 4.3–7). The majority of patients (92 %) had a baseline GS of ≤6, the median maximum cancer percentage on any core was 10 % (IQR 5–20), and 73 % of patients had a single positive biopsy core. The median follow-up duration was 5.4 years (IQR 3.4–8). Half of the patients had >1 repeat biopsy (Table 2a, b).

The 3- and 5-year risk of developing UDF varied from 9 to 67 % based on the definition used (Table 3). The majority of patients had disease progression on the ipsilateral prostate, with only 1–12 % of patients progressing on the contralateral prostate during the period of observation.

We assumed that the 157 patients would receive HAT at the time of diagnosis and assessed the probability that they would develop UDF in the untreated half of the prostate on the follow-up biopsy. Only 18 (12 %) patients had contralateral positive biopsy, with >20 % cancer on any core during the follow-up period, corresponding to a 12 % risk of developing UDF in the untreated half of the prostate at 3 and 5 years. Two

(1 %) patients were found to have cancer, involving >50 % of the contralateral biopsy core during follow-up, corresponding to a 1 % risk at 3 and 5 years. Overall, the 5-year risk of contralateral prostate cancer progression varied between 7 and 17 % (Table 4).

D-5: Discussion

In this study, we used our AS cohort to quantify the potential benefit of hemiablation therapy in patients with low-risk or intermediate-risk PCa with unilateral disease. When we used less rigorous definitions (1 and 4) of UDF, we observed that more than 40 % of our patients would develop UDF, compared with only 10–17 % using stricter definitions, i.e., definitions 2, 3, and 5. By defining disease progression as the occurrence of predominant Gleason pattern 4, or >50 % cancer on any core, then, 17 % of patients were found to develop UDF during the follow-up period (Fig. 1). Therefore, 83 % of patients would receive unnecessary therapy at the time of diagnosis should hemiablation be proposed to them.

During AS, up to 36 % of patients developed UDF ipsilaterally, up to 7 % of patients developed UDF contralaterally, and up to 5 % of patients developed UDF bilaterally (Table 3). Those patients who developed UDF either ipsilaterally or contralaterally could be candidates for HAT. Patients who developed bilateral UDF might be candidates

for modified HAT, such as hockey stick [24, 25], whole gland ablation, or radical treatment.

When we assumed that HAT was performed on all patients at the time of diagnosis, we observed that 1–15 % of our patients would develop treatment failure contralaterally based on the definition used. Although this suggests relatively good cancer

control, patients still remain at risk of developing disease recurrence in the treated area as reported by Bahn et al. [26]. In fact, when routine post-therapy biopsies are performed, prostate cancer can be detected in up to 17 % of patients in the treated areas [26–29]. Biopsy-proven residual cancer in treated areas was reported to be between 1.5 and 3.9 % in cryotherapy series [24, 30–32], whereas the use of high-intensity focal ultrasound (HIFU) was associated with the presence of any cancer in the treated areas up to 23 % [25, 27, 28]. Lindner et al. [29] found that 50 % of patients had residual cancer after focal photothermal laser (PTL) therapy and, more specifically, 33 % of patients had residual cancer in the treated areas. It is important to note that in some of these series, biopsy was not routinely performed in all patients and therefore could have led to either an underestimation or overestimation of the real percentage of patients with residual cancer.

The different source of energy proposed for focal therapy is overall associated with limited toxicity. In cryoablation series—post-therapy urine retention was found in 1 % of patients; urinary continence in terms of patients being pad free was 96–100 % and leak free was 96.4 %; erectile function was preserved in 58–86 %; and rectal toxicity was negligible, with rectourethral fistula reported in only 1 patient (0.1 %) [24, 26, 30, 32]. In HIFU series—the reported post-therapy urine retention was 2.4–8 %; urethral stricture was 0–5 %; urinary tract infection (UTI) was 0–16 %; urinary continence in terms of patients being pad free was 95–100 % and leak free was 85–100 %; erectile function was preserved in 86– 95 %; and rectal toxicity was reported in only 1 patient (2.4 %) with suspected rectourethral fistula [20, 25, 27, 28]. In a series using PTL—the reported post-therapy urine retention was 0 %; urethral stricture was 0 %; UTI was 0 %; urinary continence in terms of patients being pad free and leak free was 100 % in both cases;

erectile function was preserved in 100 % of patients; and rectal toxicity was found in 25 % of patients, with perineal pain [29].

The eligibility criteria used in the published focal therapy studies varied [20, 24–32]. Treatment was offered mainly to patients with low-intermediate risk, with only a small percentage of patients having high-risk disease. Most of the series selected patients with unilateral disease were with a PSA below 20 ng/ml. In addition, most patients had a GS of 3 + 3 as a cutoff, whereas other series used up to 4 + 3.

Active surveillance and focal therapy could be considered as complementary therapeutic strategies. This means that patients with unfavorable features at the time of diagnosis should probably be considered for definitive therapy or alternatively focal therapy. On the other hand, patients with favorable features should be enrolled on active surveillance protocols and considered for focal or definitive therapy only if unfavorable features develop. Challenges facing AS management are in part related to the ability of TRUS biopsy to accurately stage cancerous lesions. Similarly, focal therapy is limited by the same challenge, as well as the demand for accurate lesion localization [33–35]. Multiparametric MRI (mpMRI) has recently been added to the AS protocol due to promising results in detecting clinically significant lesions, allowing for visualization of target lesions prior to therapy [36]. However, the expertise is not widely available to accurately interpret the imaging results. Template-guided transperineal mapping biopsy (TMB) is associated with better localization and tumor detection, but is more invasive than TRUS biopsy, requires general anesthesia, and is associated with higher morbidity, thus consuming more health care resources than standard biopsy [37]. Furthermore, the definition of clinically significant disease used by this technique needs validation [38].

In conclusion, in our study, most men with low-risk PCa did not develop UDF while on AS during the follow-up period and would have been spared the potential negative consequences of immediate HAT. An accurate definition of clinically significant prostate cancer requiring treatment will be essential to properly assess the clinical benefit of HAT.

Table 1: Five different definitions used to define unfavorable disease (UDF)

Definition	Histologic criteria
1	>20% cancer in any core
2	>50% cancer in any core
3	Predominant Gleason pattern of 4
4	>20% cancer in any core or predominant Gleason pattern 4
5	>50% cancer in any core or predominant Gleason pattern 4

Table 2: Patient baseline (a) clinical and biochemical characteristics; (b) pathological characteristics.

(a) Clinical and biochemical characteristics	
Number of patients	157
Mean age, years	67 (SD 6)
FU duration, y (median, 25^{th}–75^{th} percentile)	5.4 (3.4–8)
PSA, n (%)	
≤4	29 (19)
4.1–10	108 (69)
10.1–20	12 (8)
Unknown	8 (5)
Prostate volume, median (IQR)	42 (33–62)
PSA density, n (%)	
≤0.15	83 (29)
>0.15	37 (24)
Unknown	37 (24)
Pathological findings at diagnostic biopsy	n (%)
(b) Pathological characteristics	
No. of cores	
≤6	40 (25)
7–10	80 (51)
>10	37 (24)
Gleason's score	
≤6	144 (92)
3+4	9 (5)
>4+3	4 (3)
No. of positive cores	
1	114 (73)
2	28 (18)
≥3	15 (9)
Maximum percentage of cancer on any core	
≤20%	125 (80)
21–50%	20 (12)
>50%	9 (6)
Unknown	3 (2)

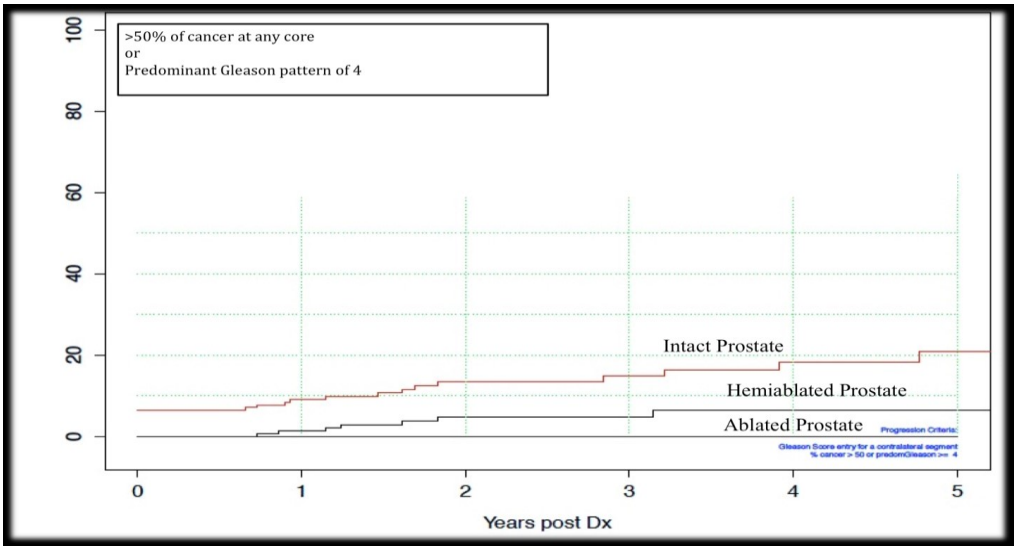
Table 3: The probability of developing UDF while the patients remained under AS

Definition	Developed UDF n (%)	3-year risk (%)	5-year risk (%)	Developed UDF ipsilaterally n (%)	Developed UDF contralaterally n (%)	Developed UDF bilaterally n (%)
1	70 (45)	42	50	52 (33)	11 (7)	7 (5)
2	15 (10)	9	11	14 (9)	1 (1)	0 (0)
3	20 (13)	10	20	16 (10)	1 (1)	3 (2)
4	74 (47)	45	62	57 (36)	11 (7)	6 (4)
5	25 (17)	15	21	21 (13)	2 (2)	2 (2)

Table 4: The probability of developing UDF if the patients would receive HAT

Definition	Would develop UDF n (%)	3-year risk (%)	5-year risk (%)
1	21 (12)	12	12
2	2 (1)	1	1
3	8 (5)	5	7
4	24 (15)	15	17
5	9 (6)	5	7

Figure 1: Probability for disease progression according to definition 5 for UDF.



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Conflict of interest: The authors declare that they have no conflict of interest.

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E: Summary

We conducted two epidemiological analyses using our Active Surveillance Database. We used our database to with two different inclusion criteria for each study, respectively. The first project evaluates the risk factors of development disease progression. PSAD was the independent predictor of disease progression in patients with prostate cancer under active surveillance. The second study shows that with using widely used definition of UFD, only 17% of patients developed UFD. Several limitations encounter our studies. One of these limitations is the lack of consistence definitions of disease progression and UFD. Furthermore, we did not used real focal therapy but we simulate focal therapy using pathological results as well as the limitation of disease localization by extended core biopsy. Further evaluation is necessary to compare active surveillance with focal therapy using a large cohort RTC.