MRI-targeted Transrectal Ultrasound Fusion Prostate Biopsies: A Comparative Study of Cancer Detection Rates in Transperineal versus Transrectal Approach

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April 2023

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science in Experimental Surgery

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B. English Abstract

Background: Prostate biopsies are the main exam in prostate cancer diagnosis. The high rate of infectious complications in transrectal approach and the relative safety of transperineal approach is now well established. However, the difference in cancer detection rates between the two approaches is still under investigation.

Methods: In a single institution in Montreal-Quebec Canada, we compared two retrospective cohorts of patients undergoing MRI guided (MR) transrectal ultrasound (TRUS) fusion transperineal (TP) biopsies versus MR TRUS fusion transrectal (TR) biopsies between January 2020 and July 2022. All the patients had previous mpMRI and underwent either targeted or targeted plus systematic biopsies. We compared the cancer detection rates of the two approaches, as well as the differential detection of anterior lesions, as well as the difference in detection for initial, repeat biopsy and active surveillance setting, and the contribution of systematic biopsies.

Results: A better cancer detection rates in the transperineal arm is demonstrated in the per-lesion analysis, especially in the anterior lesions, and PI-RADS 4 lesions. Patients undergoing repeat biopsy showed no more benefit with TP biopsy. Detection rates by PI-RADS score are similar to the literature. The added value of systematic biopsies is visible in TR biopsies, making the overall detection rates in both routes similar when accounting for both targeted and systematic biopsies.

Conclusion: It seems that TP biopsy is more efficient in cancer detection especially in the anterior lesions. More solid data from randomized comparative trials is expected. Switching to TP route is supported so far by its safety profile.

C. French Abstract

Introduction: Les biopsies de la prostate sont l'examen principal pour le diagnostic du cancer de la prostate. Le taux élevé de complications infectieuses avec l'approche transrectale et la sécurité relative de l'approche transpérinéale est maintenant bien établie. Cependant, la différence dans les taux de détection du cancer entre les deux approches nécessite plus d'investigation.

Méthodes: Dans une seule institution à Montréal-Québec Canada, nous avons comparé deux cohortes rétrospectives de patients subissant des biopsies de fusion transpérinéales (TP) sous échographie transrectale (TRUS) guidée par IRM versus des biopsies transrectales (TR) entre Janvier 2020 et Juillet 2022. Tous les patients avaient subi une IRM multiparamétrique antérieurement et ont subi soit des biopsies ciblées soit des biopsies systématiques en plus des biopsies ciblées. Nous avons comparé les taux de détection du cancer des deux approches, ainsi que la détection différentielle des lésions antérieures, et la différence de détection pour la biopsie initiale, la biopsie de répétition et la surveillance active.

Résultats : Un meilleur taux de détection du cancer est démontré dans le bras transpérinéal dans l'analyse par lésion, en particulier dans les lésions antérieures et les lésions PI-RADS 4. Les patients subissant une biopsie de répétition n'ont pas montré un avantage supplémentaire de la biopsie transpérinéale. Les taux de détection par score PI-RADS sont similaires à la littérature. La valeur ajoutée des biopsies systématiques est visible surtout dans les biopsies TR, rendant les taux de détection globaux dans les deux voies similaires lorsqu'on tient compte des biopsies ciblées et systématiques.

Conclusion : Il semble que la biopsie TP soit plus efficace dans la détection du cancer, en particulier dans les lésions antérieures. Des données plus solides issues d'essais comparatifs randomisés sont attendues. Le passage à la voie TP est soutenu jusqu'à présent par son profil de sécurité.

D. Acknowledgments

I, Toufic HASSAN, would like to extend my sincerest gratitude and acknowledgement to all those who have contributed to the successful completion of my thesis.

I would like to express my appreciation for the assistance given by Drs Victor MCPHERSON, Maurice ANIDJAR and Rafael SANCHEZ-SALAS, in the design of this study, the analysis of data, and the preparation of the thesis. Their support and guidance have been invaluable, and I am grateful for the time and effort they have put into this project.

I would also like to acknowledge the supervision and advice given by my thesis supervisor Dr Victor MCPHERSON. His guidance and mentorship have provided me with the knowledge and skills necessary to complete this work, and I am truly grateful for the time and support he has given me. Dr Victor MCPHERSON will remain one of the most impressive surgeons and mentors I have worked with, whether in the surgical theatre or in the research field.

Finally, I would like to express my gratitude to all those who have supported me throughout my academic journey. I could not have completed this work without their encouragement, support, and belief in me. Especially, my wife Angelique, who gave birth to my wonderful baby girl Nina during my masters; I am thankful for her patience and continuous support for my academic work.

Thank you all, from the bottom of my heart.

E. Contributions of authors

I, Toufic HASSAN am the main author of this thesis. I have written every section of this thesis on my own.

Dr Victor MCPHERSON, my thesis supervisor, reviewed and advised me to correct any relevant expressions, and provided guidance throughout the redaction of this thesis.

F. List of figures tables and charts

G.List of abbreviations

ISUP: International Society of Urological Pathology.

mpMRI: Multiparametric magnetic resonance imaging

PI-RADS: Prostate Imaging Reporting and Data System

PSA: Prostate-specific antigen

TP: Transperineal

TR: Transrectal

TB: targeted biopsy

TRUS: Transrectal ultrasound

CsPCa: Clinically significant prostate cancer

CnsPCa: Clinically non-significant prostate cancer

H.Introduction

Prostate cancer is the leading cancer diagnosis in the male population. It is the second most common oncological cause of death. With around 1.4 million diagnoses around the world in 2020[1], the incidence of PCa differs widely among the geographical areas. This is due to multiple causes, biological, genetic, and lifestyle factors being influential, but also the patterns of screening, and the national/international recommendations concerning diagnosis and treatment.[2]

In the PSA era, a large number of patients at risk of prostate cancer are biopsied, with an estimation of one million biopsies a year in the united states.[3] Biopsy decision is based on several factors, including the level of PSA, the results of a digital rectal exam and suspicious MRI results. Other factors such as age and any potential co-morbidities should also be taken into consideration when deciding whether to perform a biopsy[4]. Many blood and urine biomarker assays were proposed to select men for biopsies or repeat biopsies, such as the 4K score, PHI, PCA3 and SelectMDX, with an uncertain and a non-cost-effective role.[5]

Recent studies have shown that MRI assessment can help avoid unnecessary biopsies of clinically insignificant cancers while increasing the chances of diagnosing CsPCa.[6–8] Evidence concerning the importance of MRI-guided biopsies has grown during the last decade, with "multiple pathways", from systematic biopsies to targeted biopsies, to combination of both, to the MR pathway. In the latter, MRI negativity is sufficient to abstain from performing a prostate biopsy in selected patients[9].

Historically, the most common prostate biopsy modality was the transrectal route. This technique was complicated by infections in up to 7%[10] of the cases depending on the studies, usually with a need of hospital stay, and leading sometimes to severe sepsis.[3] Antibioprophylaxis

was a necessity, but with the increased risk of emerging resistant germs, especially to fluoroquinolones, the European commission has decided against the use of Fluoroquinolones in 2018.[11]

The transperineal route was known since the early years of the last century. First attempts to biopsy the prostate transperineally date back to 1922[12]. This modality has progressed overtime with currently multiple biopsy systems offering Free-hand, Hands-free grids, fusion, or cognitive biopsies.

The recently published NORAPP study randomized patients undergoing TP biopsies to arms where patients were biopsied with or without prophylactic antibiotics. The study found no significant difference in infection rates, and thus antibiotics may be unnecessary during transperineal biopsy[13]. Additionally, the very low rate of infections has led to a change in the recent European guidelines that strongly recommends the use of transperineal route whenever technically possible[14].

The results of the NORAPP study and the subsequent recommendations has created a paradigm shift towards the use of transperineal biopsies. However, the studies comparing the detection rates between the TR and TP routes are still limited, and recently initiated randomized controlled studies are currently recruiting in France (PERFECT trial), in the UK (TRANSLATE trial) and the United States (ProBE-C trial).

In Quebec, the McGill University-Department of Urology at the Jewish General Hospital-in Montreal, was the first center to adopt the transperineal fusion MRI-guided biopsy as standard procedure for prostate cancer diagnosis. Since early 2020, this procedure was standardized, and the results have indicated that the TP route has promising future. With as little as 2 infections for

more than 300 patients, the need to have an oncological outcome study is necessary to generalize the use of TP route, sparing many patients the risk of infections due to the TR route.

In this study- a Master's thesis for the Experimental Surgery Department of McGill University- we will conduct a retrospective comparison of the TP versus TR MRI-Guided Fusion biopsies, performed at our center, and will compare their oncological detection. We hypothesized that the TP-TB will be non-inferior to the TR-TB in terms of prostate cancer detection. We also hypothesized that the anterior zones would benefit the most from this route, in addition to those having had the previously negative biopsy patients.

In the following section, we will review the existing literature concerning TP biopsies. We will subsequently describe our methodology and study design, as well as our results, and discuss them in the light of the current knowledge.

I. Review of literature

1. Prostate cancer, prostate biopsy, and MRI

Recently, the widespread utilization of prostate specific antigen (PSA) testing has caused a rise in the number of prostate biopsies conducted. It's estimated that up to one million biopsies take place each year just in the United States.[3] With the significant number of prostate biopsies carried out globally, much effort has been invested in finding the most precise way to perform the procedure with minimal risk of complications. Presently, the most prevalent method for performing a prostate biopsy is through a transrectal (TR) approach that is guided by ultrasound.[15]

The PROMIS study showed that triage of patients with mpMRI has the potential to prevent 27% of primary biopsies and diagnose 5% fewer cases of clinically insignificant prostate cancer.[16] The same study showed that targeting TRUS biopsies based on mpMRI findings could result in the detection of 18% more cases of clinically significant cancer compared to the traditional approach of systematic TRUS biopsy for all patients. By using mpMRI as a preliminary test before the first prostate biopsy, it may be possible to reduce the number of unnecessary biopsies by a quarter. This approach can also minimize over-diagnosis of clinically insignificant prostate cancer and enhance the detection of clinically significant cases.[16]

Three prospective multi-center trials evaluated MRI-targeted biopsy in biopsy-naive patients. In 2018, the PRECISION study compared the effectiveness of using mpMRI with or without targeted biopsy, compared to standard TRUS-guided systematic biopsy, for detecting prostate cancer in biopsy-naïve men with elevated PSA levels. The results showed that using MRI with targeted biopsy was superior to the standard approach in terms of diagnosing clinically

significant cancer. The MRI-targeted biopsy group had a higher rate of detection of clinically significant cancer (38%) compared to the systematic biopsy group (26%). Additionally, fewer men in the MRI-targeted biopsy group received a diagnosis of clinically insignificant cancer. The results suggested that using MRI for risk assessment before biopsy and targeted biopsy is a better option for biopsy naïve men at clinical risk for prostate cancer.[7]

In a subsequent prospective paired diagnostic study, done in 16 centers in France- the MRI-FIRST study[6]- the authors aimed to determine if using mpMRI before biopsy in biopsy-naive patients with prostate cancer would improve the detection of clinically significant prostate cancer. The patients underwent both systematic and targeted biopsy based on the results of their mpMRI. The results showed that there was no significant difference between systematic biopsy and targeted biopsy in detecting ISUP grade group 2 or higher prostate cancer. However, both techniques showed substantial added value; Clinically significant prostate cancer would have gone undetected in 5.2% of patients if systematic biopsy had not been performed, and in 7.6% of patients if MRI-targeted biopsy had not been performed. The authors concluded that, mpMRI prior to biopsy in biopsy-naïve patients has the potential to increase the detection of clinically significant prostate cancer, however, it does not appear to eliminate the necessity of a systematic biopsy.[6]

In 2019, the 4M study, conducted by *Van Der Leest et al*[8], compared and evaluated the use of mpMRI and guided biopsy (MRGB) to traditional transrectal ultrasound-guided biopsy (TRUSGB) in biopsy-naive men with elevated PSA levels. 626 biopsy-naive patients were included in the study. All patients underwent pre-biopsy mpMRI and systematic TRUSGB, with men with suspicious lesions on mpMRI undergoing MRGB prior to TRUSGB. The results showed that the MRI pathway detected clinically significant prostate cancer (csPCa) in 25% of patients and insignificant prostate cancer in 14% of patients, while TRUSGB detected csPCa in 23% of

patients and insignificant PCa in 25% of patients. The MRI pathway allowed for biopsy avoidance in 49% of patients due to nonsuspicious mpMRI, and the number of biopsy cores taken was reduced from 7512 to 849 (-89%). The study concluded that in biopsy-naive men, the MRI pathway results in an identical detection rate of csPCa compared to the TRUSGB pathway and significantly fewer insignificant PCa cases.[8]

Finally, the Canadian study PRECISE published in 2021, is a prospective randomized clinical trial conducted in 5 Canadian academic health sciences centers which aimed to determine the effectiveness of Magnetic Resonance Imaging (MRI) with targeted biopsy versus systematic TRUS biopsy for the diagnosis of prostate cancer. The study included 453 biopsy-naive men with a clinical suspicion of prostate cancer. The results showed that MRI with targeted biopsy was noninferior to systematic TRUS biopsy in detecting ISUP grade group 2 or greater cancers, with a 5% difference (35% vs 30%). Adverse events were also found to be less common in the MRI-TB arm. The study concluded that MRI with targeted biopsy is a viable alternative to initial systematic biopsy in detecting prostate cancer[17].

2. History of transperineal approach

a. Early attempts

In 1922, Benjamin Barringer attempted the first transperineal prostate biopsy. With the use of screw tip needles, he executed multiple prostate punch biopsies at the Memorial Hospital in New York. This technique was of limited success, but still minimally invasive compared to an open perineal technique performed by Young in 1926.[12,18]

b. Minimally invasive techniques

Russell Ferguson, a urologist at Memorial Hospital in NY, developed a modified TP needle aspiration method in 1930, building on Barringer's work. The procedure involved administering local anesthesia to the perineum and prostate, then using a sterile glass syringe with a needle to acquire tissue from the suspected area of prostate cancer. The tissue sample was then transferred to a slide for analysis. The method had a 78-86% success rate in obtaining adequate prostate tissue, but its use declined in the 1940s due to unsatisfactory tissue for diagnosis and promising results for transurethral biopsy[19].

Kaufman later showed that needle biopsy, guided by concomitant digital rectal exam and Papanicolaou smear, was capable of diagnosing PCa with up to 86% accuracy. Kaufman's TP biopsy technique had advantages such as permanent tissue sampling, being performed in the office under local anesthesia, indication for certain palliative therapies, and allowing repeat biopsy. However, Kaufman emphasized that needle biopsy was not completely reliable and was inferior to open perineal biopsy.[20]

c. Imaging assistance

Transrectal ultrasound imaging has been used in the diagnosis of prostate cancer since 1965. The first use of TRUS-guided TP-Bx was in 1981, by Holm and Gammelgaard, which had satisfactory cancer detection with minimal complications[21]. Eight years later, TRUS-TR biopsy became established as the most common modality for biopsy, using the sextant technique for systematic sampling[12]. Over time, improvements in ultrasound technology and physician understanding have further facilitated TRUS-guided biopsy. In 2003, the use of a brachytherapy grid dividing the prostate into 24 zones was introduced to ensure precise systematic sampling via

the TP route [22]. The use of this grid for template mapping biopsies was found to have a 95% detection rate for lesions at least 0.125 cm3, proving non-inferior compared to TR PBx.[23]

3. Infectious complications and cost

The TR approach has significant limitations, including a growing risk of infection after the biopsy. Most prostate biopsies (97%) are done transrectally, which brings rectal bacteria into the sterile urinary tract with each needle pass. Despite using antimicrobial prophylaxis, the total risk of infections after transrectal biopsy, including urinary tract infections, prostatitis and sepsis is high, at around 7%, with 30,000 men requiring hospitalization each year in US.[24]

The incidence of sepsis following transrectal prostate biopsy is rising and ranges from 2% to 5% of cases. To determine the potential cost savings from reducing infection-related complications, a comprehensive literature review was conducted on the cost of post-prostate biopsy sepsis. The reporting of costs was found to be inconsistent, making interpretation difficult. Hospitalization duration varied from 1.1 to 14 days, with a percentage of patients admitted to the ICU ranging from 1.1% to 25%. The estimated cost of sepsis post-prostate biopsy, taking into account inflation, was found to range from $8,672 to $19,100. These findings highlight the significant cost of treating post-biopsy infections, and should be considered by payers and policymakers, particularly in value-based healthcare models.[25]

The recently published NORAPP trial was conducted in 2022. It included 553 patients undergoing TP-MRI fusion biopsies, and randomized patients to either cefuroxime -1.5 g IM or IV as antibiotic prophylaxis (AP)- or no antibiotic prophylaxis (NAP). Results showed that within two months after biopsy, there was one case of UTI in the AP group and three cases in the NAP

group, with no instances of sepsis or admission. This suggests that antibiotic prophylaxis may not be necessary in transperineal biopsy procedures.[13]

4. Anesthesia for transperineal biopsies

The common perception about transperineal biopsies is the historical need for general anesthesia. This obstacle has been tackled recently by many studies, and is no longer valid as a reason to abandon TP-Bx. With the risks of general anesthesia, its costs and programming burden on operative time, local anesthesia has been improved and has become the standard pain management for TP-Bx, reducing the burden on patients and providers.

Multiple approaches to the TP-Bx local pain relief have been described.

1) First, the subcutaneous perineal nerve block, described by *Smith et al* [26], in which local anesthesia (1% lidocaine with 1:200 000 adrenaline) is infiltrated into the subcutaneous layer of the perineal skin in a rectangular shape with a triangular extension above the anus. This technique is performed in bilateral segments on either side of the midline.

2) Second, the bilateral periprostatic nerve block (PPNB), described by *Iremashvili et al*.[27] involves inserting a 22-G spinal needle through the perineal skin 1.5-2.0 cm above the rectum at a 30 degree angle from the midline. With the help of TRUS guidance, local anesthesia is delivered to the vascular pedicle located at the base of the prostate.

3) Third, a pudendal nerve block can be performed on patients in lithotomy position. After locating the ischial tuberosity, a 23-G needle is passed through the skin to just under the ischial spine, where local anesthesia is then infiltrated. *Iremashvili et al*. conducted a randomized study to compare the effectiveness of PPNB and a combination of PPNB and pudendal nerve block in controlling pain during TP-Bx. The study found that the combined PPNB and pudendal nerve

block resulted in a statistically significant improvement in VAS pain scores compared to PPNB alone, both during the biopsy and 1 hour after. However, the pain scores associated with the pudendal nerve block were higher than those of PPNB, but the pudendal nerve block remained well tolerated by patients.[27]

4) Fourth, Periapical triangle block was described by *Kubo et al*[28]. The periapical triangle is defined as the region bounded by the levator ani, the rhabdosphincter, and the external anal sphincter muscle, which usually contains the pudendal nerve, the perineal nerve, and the prostatic plexus. TRUS guidance can be used to infiltrate the local anesthesia in this region. *Kubo et al*. evaluated this block to determine the tolerability of patients undergoing TP-Bx in conjunction with a TR-Bx. Pain scores were assessed at each stage. The results showed no significant difference in pain scores between the two biopsy procedures, with mean scores of 2.93 (1.97) and 2.67 (1.88), respectively ($P < 0.275$). They suggested that TP-Bx is well tolerated with a periapical triangle block.

5) Fifth, prostatic apex block is another technique proposed by *Smith et al*.[26] Aiming for high patient tolerability in an outpatient setting, this method involves administering local anesthesia under ultrasound guidance to the prostatic apex and pelvic floor, using about 35 mL of anesthesia with 1-2 mL injections in multiple spots. Pain levels were assessed during ultrasound probe insertion, local anesthesia infiltration, and biopsy procedure through a questionnaire. The average VAS score was 2.88 (1.28) during biopsy, with the most painful part being the local anesthesia infiltration, which had a mean VAS score of 3.29 (1.13).

Multiple studies compared these techniques and their impact on cancer detection. A study by *Cricco-Lizza et al*.[29] aimed to compare the diagnostic yield, complications, and costs of transperineal prostate biopsies performed with local anesthesia versus sedation. The data was

collected from 126 men who underwent transperineal MRI-targeted biopsy between October 2017 to February 2020. The results showed that the detection of clinically significant prostate cancer was similar for both local anesthesia and sedation, with a lower detection rate on targeted biopsies alone with local anesthesia. The complication rate was also similar for both groups and the median pain score was higher for local anesthesia compared to sedation. The procedure time was longer for local anesthesia and the costs were also higher for sedation. Overall, the results showed that transperineal biopsy with local anesthesia is safe and has comparable outcomes to sedation, with lower costs.[29]

In another study[30], *Wang et al*. described a novel perineal nerve block approach that was developed and validated for use during transperineal prostate biopsy. The anatomy of the perineal nerve was dissected on five cadaver specimens and the results were used to inform the development of the perineal nerve block. Ninety out of 115 patients were randomly assigned to receive periprostatic, periapical triangle, or branches of perineal nerve block during their biopsy procedure. The results showed that the branches of perineal nerve block was the most effective in reducing pain and had the fewest complications, including hematuria and urine retention. Overall, the study suggests that the branches of perineal nerve block is a safe and effective local anesthesia approach for transperineal prostate biopsy.[30]

A multicenter prospective study by *Giancarlo Marra et al*.[31] aiming to assess pain outcomes and factors influencing pain during transperineal fusion biopsies under local anesthesia was conducted on 1,008 men from 2016 to 2019. The results showed moderate pain during the biopsy, with a mean pain score of 3.1 on a 0-10 scale. Pain did not affect the detection of clinically significant prostate cancer. On multivariate analysis, age was found to be a protective factor for severe biopsy pain, while severe anxiety was a risk factor. Procedural time was also found to be

associated with an increased risk of experiencing severe biopsy pain. The study also found that using a numeric rating scale-based anxiety assessment could be used to identify patients at higher risk for experiencing severe pain.

A comprehensive study of different local anesthesia modalities was performed by *McGrath et al*. in this non-systematic review, they concluded that the available literature on the use of anesthetic techniques during TP-Bx is limited. According to the current research, PPNB alone seems to be less effective compared to other methods of prostatic nerve block. Other techniques may be used in clinical practice but have not been documented. More extensive studies are needed to evaluate the effectiveness of these prostatic nerve blocks in TP-Bx procedures. [32]

5. Studies comparing different approaches to prostate biopsy.

Data comparing the TR vs TP biopsy is available on this subject, especially high-level evidence. A systematic review and meta-analysis were done by *Tu et al* aiming to compare the diagnostic accuracy of magnetic resonance imaging (MRI)-targeted biopsy in the detection of clinically significant prostate cancer (csPCa) when performed via the transperineal (TP) or transrectal (TR) route. A systematic search of relevant databases was conducted up to April 2019. The results showed that TP MRI-targeted biopsy detected more csPCa, with a detection rate of 62.2% compared to 41.3% for the TR route. The overall diagnostic sensitivity of TP route was found to be better than TR route. Additionally, the TR approach missed more csPCa located at the anterior zone of the prostate. The study concluded that TP route performed better than TR route in MRI-targeted biopsy, especially in detecting csPCa located at the anterior prostate. However, more large prospective randomized studies were needed to compare the two approaches.[33]

Rai et al conducted a systematic review with the objective to compare the detection and complication rates of MRI-TRUSB and MRI-TPB. A literature search was conducted in several databases, and five studies were included in the qualitative analysis and two in the quantitative synthesis. The results showed that the detection rate of clinically significant prostate cancer (csPCa) was higher with MRI-TPB compared to MRI-TRUSB. The anterior csPCa detection rate was also higher with MRI-TPB. The overall cancer detection rates between the two methods were similar, but the complication rates were lower with MRI-TPB. However, the evidence for these findings was rated as "very low" certainty by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evaluation. In conclusion, while there is a lack of high-quality evidence comparing MRI-TRUSB and MRI-TPB, MRI-TPB appears to have higher detection rates for csPCa and anterior tumors, as well as lower complication rates.[34]

Meyer et al conducted a study to examine the impact of transperineal prostate biopsy on the incidence of prostate cancer upgrading in men with very low or low-risk prostate cancer undergoing active surveillance. They included 790 men. Results showed that 21.2% of men who underwent transperineal prostate biopsy were upgraded to grade group ≥2 compared to 14.7% of men who underwent transrectal biopsy. Transperineal prostate biopsy was also found to be significantly associated with upgrading to grade group ≥2 (OR 1.49, p=0.01). This study suggests that transperineal prostate biopsy leads to an increased likelihood of upgrading to clinically significant prostate cancer due to improved sampling of the anterior prostate[35].

In 2022, *Bajeot et al*[36] evaluated the efficacy of transperineal image-guided biopsies of the index target (TPER-IT) in the context of discordant findings between multiparametric magnetic resonance imaging (mpMRI) and transrectal image-guided biopsies of the prostate (TRUS-P). The study analyzed cases referred for suspicion or treatment of localized prostate cancer, and

discordant findings were characterized into three scenarios: type I-negative biopsies or ISUP grade 1 cancer in PI-RADS ≥4 index target (IT); type II-negative biopsies or ISUP grade 1 cancer in anterior IT; and type III-<3 mm stretch of cancer in PI-RADS ≥3 IT. Of the 558 patients who received TRUS-P, 132 (23.7%) had discordant findings and were reassessed with TPER-IT. The study found that TPER-IT biopsies resulted in more cancer tissue materials for analysis and better informed the presence and grade of cancer. As a result, a significant proportion of patients were reassigned from follow-up or active surveillance to surgery or intensity-modulated radiotherapy. Overall, the study recommends a multidisciplinary review of mpMRI and TRUS-P findings and reassessment TPER-IT in type I-II discordances. The results of the study suggest that transperineal biopsies are a valuable tool in cases where discordance exists between mpMRI and TR-Bx. It can help to better inform the presence and grade of cancer and lead to a significant impact on treatment recommendations.[36]

These studies suggest at least a non-inferiority of the transperineal route. However, most of the studies included in those reviews were of a retrospective nature, and prospective studies had multiple confounding factors, such as the difference in fusion methods (cognitive vs software), the biopsy scheme (targeted only, targeted and systematic), multicentric (pathology and MRI results may vary), and ultrasound probe handling (freehand vs holder).

One interesting and recent multicentric retrospective study by *Zattoni et al*, evaluated whether TP MRI-targeted prostate biopsy could improve the detection of clinically significant prostate cancer (csPCa) compared to TR biopsies. The study included 1,936 patients who underwent TR-TBx and 3,305 patients who underwent TP-TBx at 10 referral centers. The results showed that the rate of PCa and csPCa diagnosed was higher for TP-TBx compared to TR-TBx (64.0% vs 50%, $p < 0.01$ and 49% vs 35%, $p < 0.01$). Multivariable logistic regression analyses

adjusted for age, biopsy naïve/repeated biopsy, cT stage, Prostate Imaging–Reporting and Data System®, prostate volume, PSA, and number of biopsy cores targeted showed that TP-TBx was an independent predictor of PCa (odds ratio [OR] 1.37, 95% CI 1.08–1.72) and csPCa (1.19, 95% CI 1.12–1.50). When considering the approach according to the site of the index lesion, TP-TBx had a significantly higher likelihood than TR-TBx to detect csPCa in the apex and anterior zone. Overall, the study suggests that TP-TBx may be a more effective approach than TR-TBx for the detection of csPCa.

6. Templates of transperineal biopsy of the prostate

The Barzell technique[37], established by *Barzell and Whitmore* in 2003, is a systematic transperineal prostate biopsy method using a brachytherapy grid, designed to overcome random and uneven sampling of the prostate. The use of a grid with TRUS improves reproducibility and accuracy of prostate sampling, reducing human error and providing precise cancer localization. The fixed coordinates allow for accurate lesion mapping, leading to targeted therapy options. The transperineal approach also offers access to the antero-apical regions of the prostate. This template (Figure 1) involves dividing the prostate into eight sectors using transverse, sagittal, and coronal planes. The transverse plane separates the prostate into proximal (base) and distal (apex) halves, the sagittal plane splits each half into right and left lobes, and the coronal plane divides into anterior and posterior regions.

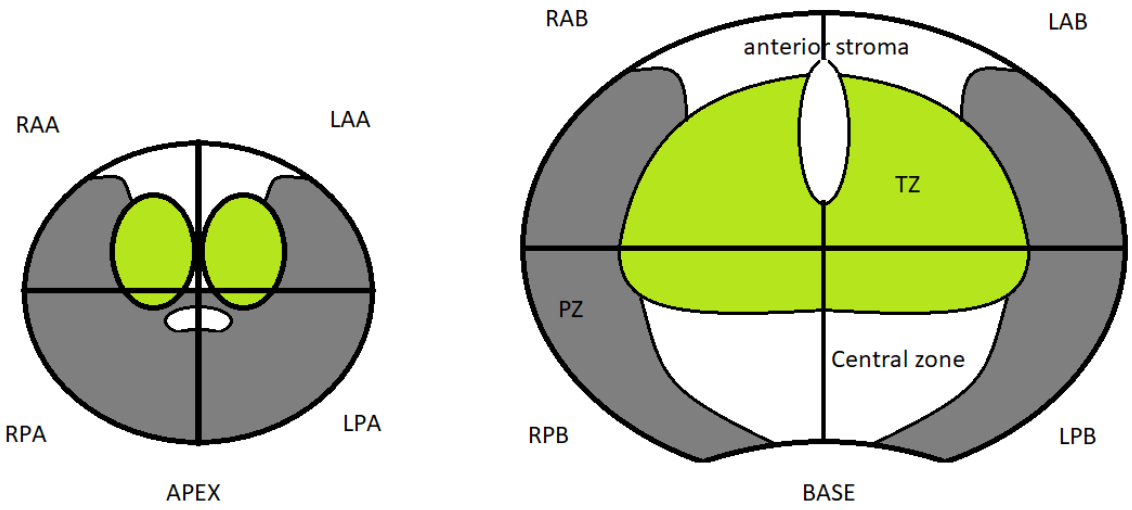

Figure 1: Barzell template, eight sectors: LAA, left anterior apex; LAB, left anterior base; LPA, left posterior apex; LPB, left posterior base; PZ, peripheral zone; RAA, right anterior apex; RAB, right anterior base; RPA, right posterior apex; RPB, right posterior base; TZ: transitional zone.

The researchers at University College London modified the Barzell template into 20 separate sectors (Figure 2) and called it the Modified Barzell (MB) template[38]. It consists of left and right halves, anterior and posterior sections, and an apex and base, adding two midline (central) regions and two extreme lateral regions. The biopsy samples are taken from medial to lateral sectors. Each side is labeled with parasagittal anterior apex and base, parasagittal posterior apex and base, medial anterior apex and base, medial posterior apex and base, and lateral sectors. This modification also enables the midline prostate to be sampled through the midline apex and midline base sectors. This method was validated in the PROMIS trial, with an overall cancer detection rates of 71%[16]. The high number of cores made this template a go-to for the prior negative biopsy

patients, with a high rate of urinary retention and prostate bleeding.[39]

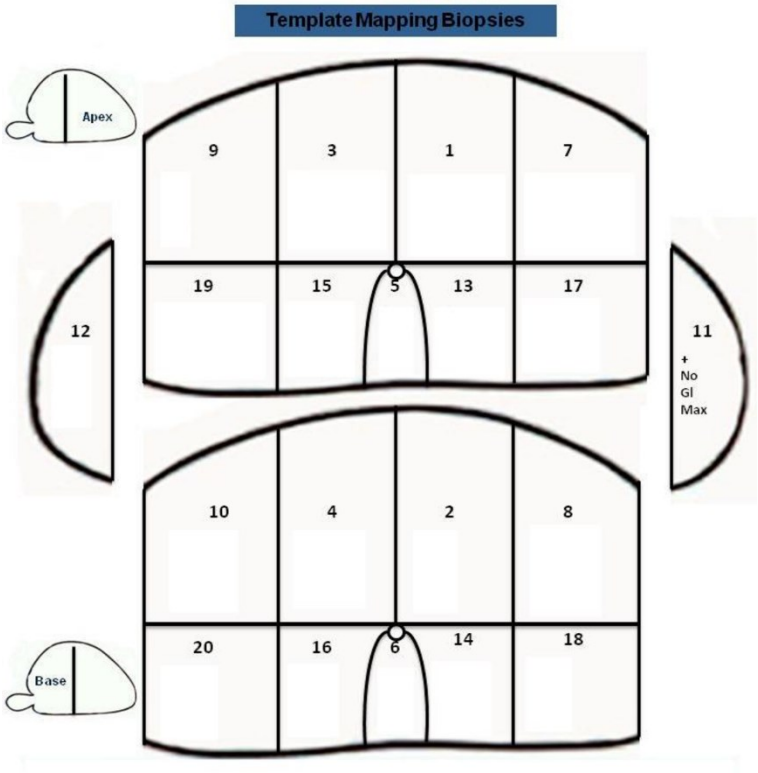

Figure 2: Template Mapping Histopathology Report – Modified 20 Barzell zones[40]

The Barzell technique is well-regarded for its accuracy and reliability, but its high tissue sampling makes it difficult to adopt widely. The Ginsburg consensus aimed to standardize TP systematic biopsies and encourage future studies and multi-center data collaboration by creating definitions and requirements for a prospective TP-Bx database. The panel had concerns about the limitations of the Barzell technique, including increased side effects and the added burden on pathology from processing more samples. As a result, they introduced the Ginsburg Biopsy Scheme (Figure 3) and suggested that it be used as the standard practice by clinicians moving forward.[41] The prostate was divided into three areas: the anterior zone, the apical (mid-sector) peripheral zone, and the posterior peripheral zone. Four to six cores should be taken from four

evenly spaced locations from medial to lateral in each of these zones, on both sides of the gland. For prostates that are longer than 4 cm or have a volume greater than 50 ml, an extra basal peripheral zone and posterior transition zones are added. In prostates that are smaller, with a volume of up to 30 ml, a total of 24 cores should be obtained, whereas larger prostates may require up to 38 cores.

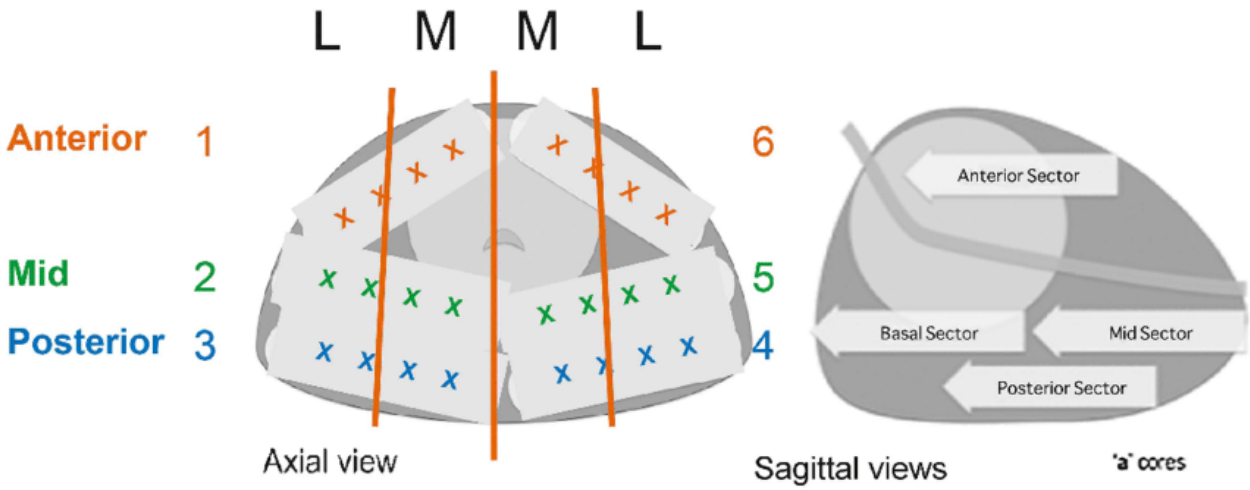

Figure 3: Ginsburg protocol template[42]

The Michigan Urological Surgery Improvement Collaborative (MUSIC TP) template (Figure 4) is another adaptation of the MB template. The template was created to minimize the total number of cores obtained during TP-Bx sampling, while still getting samples from the peripheral zone where prostate cancers are commonly found. It involves taking biopsies from six sectors in each lobe of the prostate, including the paramedian apex, paramedian base, posterior apex, posterior base, lateral, and anterior prostate. Each sector is biopsied once in each lobe, making it a 12-core biopsy and allowing for comparison to traditional 12-core transrectal biopsies.[43]

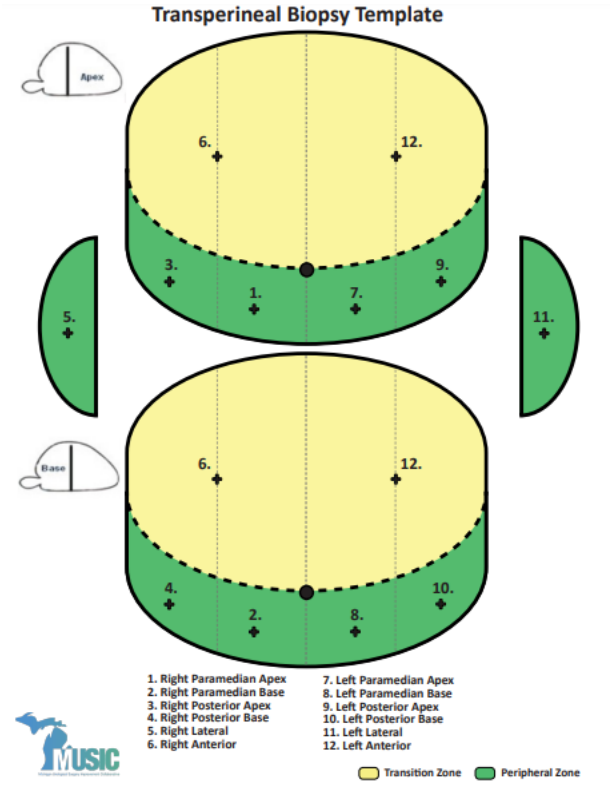

Figure 4: MUSIC Template for transperineal prostate biopsies[44]

The Dickinson 27 sectors template (Figure 5) is also one of the most used templates around the globe. During 2010 European consensus meeting, a 16-sector standard MRI prostate reporting system was established, with average axial sections at the prostate base and midgland divided into four regions (midlobar and lateral) at the apex and two regions at the base. The anterior sections are divided into two regions, with the anterior region starting 17mm from the prostate's posterior surface. A 10-core extended biopsy scheme is expected to sample the 10 posterior sectors. Another 27-sector standard MRI prostate reporting scheme was also established, with average axial sections at the prostate base, midgland, and apex divided into four regions (midlobar and lateral). The anterior prostate is divided into four midlobar and lateral regions and three anterior stroma regions. The anterior region starts 17mm from the prostate's posterior surface, and a 12-core extended biopsy scheme is expected to sample the 12 posterior sectors.[45]

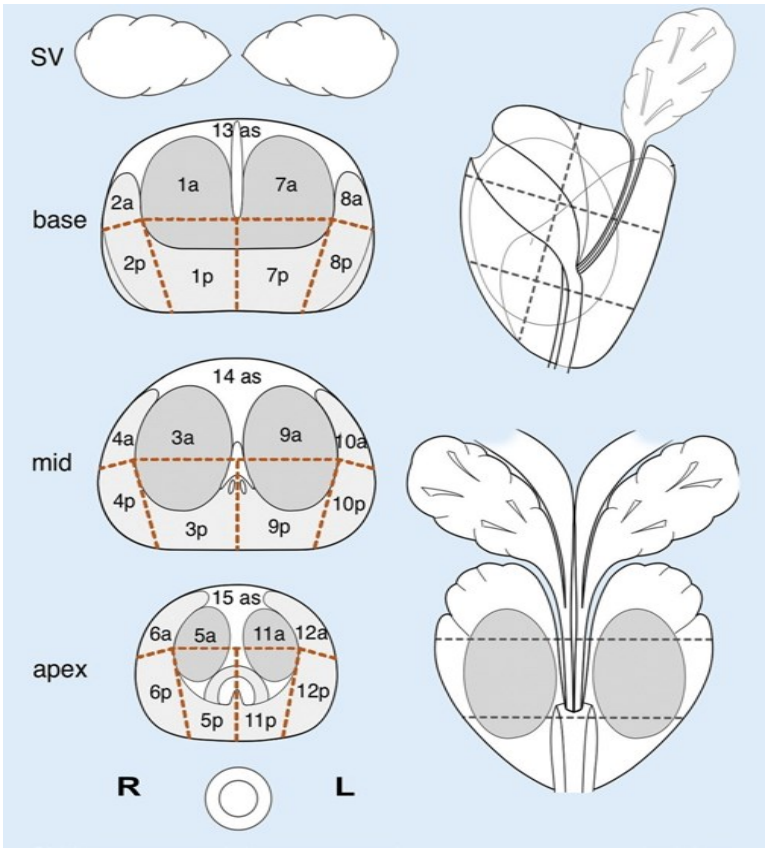

Figure 5: Dickinson prostate biopsy 27 regions template[45]

J. Methodology:

1. Description of a transperineal biopsy procedure at JGH.

a. Clinical assessment and preparation

As standard practice, patients are seen in out-patient setting where the indication of prostate biopsy in discussed and the patient is consented and informed about the procedure's steps. Care is taken to mention in the chart if the patient is on anticoagulants. Patient's history, especially PSA levels, PSA progression, MRI findings and previous biopsy results are also well mentioned. MRI can be done in-house at JGH radiology department or done in another imaging center utilizing either 1.5 or 3 Tesla MRI imaging platforms. In the case of outside imaging, the surgeons make sure to acquire the patient's imaging CD, which is necessary for fusion. After consenting the patient, a biopsy is scheduled as soon as possible, and a prescription for Cefixime 400 mg once orally to be taken at the morning of the procedure, as antibiotic prophylaxis, and a rectal enema, as well as urine analysis is given to the patient and the result is checked as soon as it is out.

The day of the procedure, the patient is again instructed regarding the steps of the procedure and informed about the possible complications in the immediate and short term. After the standard hygienic treatment of the procedure room, the patient is invited in, wearing nothing but his gown. Here he meets the surgeon, and the assistant (usually a fellow or senior resident). A confirmation checklist for patient's identity and procedure is done before the patient is placed on the procedure table. All these steps are aiming to minimize patient's stress and maximize patient's safety, confidence, and interaction with the treating personnel.

b. Pre-Biopsy planning with MRI preparation:

Using Koelis' ProMap Lite™ Application, the MRI images are imported from disc media. The prostate is manually contoured and is then segmented by the software, suspicious lesions are identified and marked, and segmented MRIs are transferred to the Koelis Trinity® prostate biopsy platform for precision 3D biopsy guidance.

c. Procedure

The patient is then asked to lie down on the examination table, the legs are separated, raised, and supported in a boot-style leg holder. The patient is now in lithotomy position. This position is exaggerated as much as tolerated by the patient. Care is taken in case of previous orthopedic surgery. The patient is then asked to lift his scrotum. A sterile preparation of the perineal area is performed by the surgeon, and a sterile drape is taped right below the scrotum and is used to separate the patient from the procedure area. A lubrication gel is then injected in the rectum.

The next phase is the superficial anesthesia. A specific mixture of 40 cc of normal saline, along with 36 cc of xylocaine 1% and 4 cc of sodium bicarbonate 8,4% is prepared by the nurse and the resulting 80 cc of anesthesia is divided into four 20cc syringes. Using one of the syringes, the 22-gauge needle is bent to 90° and inserted 1 cm above the anus, on the median raphe, directed to be parallel to the skin. Anesthesia is then injected in a radiating fashion to cover the area on both sides of the raphe, where the biopsy needles would be inserted later. The surgeon will go deeper with the next needle but will be proceeding with the same fashion.

Once the superficial anesthesia in injected, the ultrasound probe is then inserted gently in the rectum and the prostate in visualized on the KOELIS® fusion machine. We used a KOELIS®

Side-Fire Ultrasound Probe with Internal Motorized Array Model (K3DEL00) with a frequency of 4-9 MHz, and a field of view of 75 mm, linear lateral-fire. This ultrasound probe has a sweeping angle of 170°, and a shaft radius of 10 mm. It can be modeled in 2D B-mode, Color Doppler mode, Power Doppler mode, 3D B-mode.

The biopsies were done in a stabilized, Hands-free technique using KOELIS® light probe holder Steady Pro™. A "PERINE" Mini Grid –Guide for transperineal biopsy is then mounted on the probe to guide the needle placement. Deep anesthesia phase is then started. Using ultrasound live images, the 18-gauge needle is introduced and a periprostatic nerve block is done. Periprostatic nerve block was achieved by injecting 15 mL of 1% plain lidocaine posteriorly and bilaterally into the periprostatic fat, followed by additional lidocaine injections into the levator ani muscle complex and the space between the apex of the prostate gland, bathing the neurovascular bundles of the prostate capsule. The urethra, penile bulb, and minor perineal arteries visible in the midline are avoided, and the needle proceeds lateral to them in a para-sagittal route to the prostate. Intravascular injection can be avoided by aspirating carefully before injection. Then we let 5 minutes for the block to take effect.

During that time, the prostate is then scanned using the KOELIS® ultrasound technology, where a motorized sensor rotates the ultrasound array within the probe's housing, resulting in a 3D prostate scan recorded in less than 3 seconds. A 3D model of the prostate is generated after the Ultrasound contouring done by the surgeon and the previously segmented MRI is fused with the ultrasound image, creating a reference volume of the prostate that is displayed with MRI targets. The actual prostate biopsy can now take place using a Bard Magnum™ 18G x 20cm adapted biopsy needle.

During the biopsy of the prostate, an updated 3D ultrasound is acquired with each pass of the biopsy needle, and the location of each biopsy core is transferred to the reference volume, allowing KOELIS Trinity® to build a precise 3D map of the biopsy procedure. According to indication, patients can have target-only biopsies or target plus systematic biopsies.

Following the biopsy, the 3D map can be reviewed on the Trinity workstation. This map can guide subsequent biopsies and aid in future treatments such as prostate focal treatment.

2. Description of a transrectal biopsy procedure at JGH.

a. Preparation

The transrectal prostate biopsy patients are prepared in the same fashion at our center. The consent visit in out-patient setting, as well as the MRI imaging disc preparation are performed identically to TP approach. However, the patients undergoing TR biopsies do not get an enema and are given Ciprofloxacin 500 mg daily for three days beginning the day before biopsy, and a single dose of 80mg of Tobramycin IM pre-procedure on the day of the biopsy.

b. Pre-Biopsy planning with MRI preparation:

This is done in the same fashion as the TP biopsies. Using the Koelis' ProMap Lite™ application, we import the MRI images from disc media. The prostate is manually contoured and is then segmented by the software, suspicious lesions are identified and marked, and segmented MRIs are transferred to the Koelis Trinity® prostate biopsy platform for precision 3D biopsy guidance.

c. Procedure

After the patient enters the procedure room, and the checklist is completed, he is asked to lie on his left side on the table. The patient will be asked to flex his hips and knees into fetal position and to place his buttock as close as possible to the edge of the table. After the injection of the content of one xylocaine gel tube in the rectum, the ultrasound probe is inserted gently.

The KOELIS 3D End-Fire Transrectal Ultrasound Probe with Internal Motorized Array is utilized to perform live imaging. This probe acquires whole-prostate 3D ultrasound images using an internal motorized array that allows for a prostate scan in less than three seconds, without the need for a manual sweep. This feature improves prostate visualization and reduces patient discomfort during transrectal prostate biopsy due to a reduction in necessary time and probe movement.

The K3DEC00-2 probe, which was used is specifically designed for prostate applications and operates at a frequency of 4-9 MHz. It has a field of view of 146° with a convex end-fire and a sweeping angle of 90°. The probe's radius of curvature is 10mm, allowing for excellent image quality and visualization of the prostate. The imaging modes available with the probe include 2D B-mode, Color Doppler mode, Power Doppler mode, and 3D B-mode.

The procedure begins with three offset 3D ultrasound scans using the probe, which produces a 3D model of the prostate. Biopsy guidance is then facilitated by fusing the previously segmented MRI to ultrasound images, which displays a reference volume of the prostate with MRI targets.

First the surgeon performs a peri-prostatic bloc using one syringe of 10 cc of xylocaine 1%, then he proceeds with the targeted biopsies using a Bard Magnum™ 18G x 20cm adapted

biopsy needle, on a re-usable metallic guide. During the biopsy, an updated 3D ultrasound is acquired with each pass of the biopsy needle, and the location of each biopsy core is transferred to the reference volume.

Finally, the KOELIS Trinity® system builds a precise 3D map of the biopsy procedure using a process called 3D cartography, which enables to accurately target areas of concern and optimize patient outcomes. The TR biopsies are done with a Free-Hand technique, meaning that the probe is held by the surgeon, without the aid of a stabilizing mechanical holder.

When the targeted biopsies are done, the surgeon proceeds to perform the systematic biopsies with 12 posterior and 2 anterior (3A,9A) cores according to the Dickinson template, and all the cores are labelled and sent in formalin for anatomopathological analysis.

3. Research design

a. Study design

This study is a retrospective cohort study that compares the diagnostic efficacy of TP and TR biopsies for detecting prostate cancer. The study used chart review to gather data on patients who underwent a biopsy for prostate cancer between January 2020 and July 2022 at the Jewish General Hospital in Montreal.

b. Inclusion/ exclusion criteria

Among all the transperineal MRI-fusion TRUS guided prostate biopsy patients between January 2020 and July 2022, we included:

- Biopsy naïve patients,

- Active surveillance patients: History of prostate cancer and diagnostic biopsy whether transperineal or transrectal was preceded by a multiparametric MRI of the prostate;
- Patients with prior negative biopsy: Previously negative biopsy with high clinical suspicion of prostate cancer and/or a PiRADS 3-4-5 lesion on MRI;
- Patient having had a multiparametric prostatic MRI with 3 sequences (T2, diffusion, perfusion) interpreted by a local radiologist or a trained radiologist in a regional center with at least one PI-RADS 3-4-5 lesion on MRI;
- Patients eligible for prostate, transperineal and transrectal biopsies, targeted and systematic;

We excluded all the patients who have had acute prostatitis within the last 3 months, are unfit to undergo prostate biopsy under local anesthesia, have had prior definitive therapy for prostate cancer such as radiation therapy or partial gland ablation, have no MRI, a negative MRI or lesions with a PI-RADS score less than 3, have a dermatological disease preventing perineal access, rectal amputation, are presenting with a urinary tract infection, or are on anticoagulant treatment at an effective oral dose that has not been stopped for a sufficient period of time pre-procedure.

c. The outcomes:

Primary endpoint is to compare the efficacy of the targeted biopsy routes (TP vs TR) in terms of detection of clinically significant cancers, which is defined as: Number of patients (or percentage) diagnosed with International Society of Urological Pathology cancer grade ≥ 2 on targeted biopsies. We will perform a per-lesion analysis -defined as: statistical analysis taking into account each lesion identified on MRI and biopsied by the surgeon as a separate case- and a per-

patient analysis -defined as: statistical analysis taking into account the highest PI-RADS score of a patient's biopsied lesions.

Multiple secondary endpoints were aimed in our study. First, the detection of any ISUP grade prostate cancer on targeted or systematic biopsies. Second, the detection rates per prostate zone divided into anterior (PZ, TZ, and AFMS), and posterior (PZ). Third, the contribution to detection rates of the additional systematic biopsies. Lastly, compare the number of positive cores, length of cancer involvement and percentage of highest Gleason score.

d. The statistical approach

Descriptive statistics: Descriptive statistics will be used to summarize the patient demographics, biopsy characteristics, and MRI findings. Continuous variables, such as age, prostate volume, and tumor size on MRI, will be summarized using means and standard deviations or medians and interquartile ranges, as appropriate. Categorical variables, such as biopsy approach, biopsy results, and PIRADS score on MRI, will be summarized using numbers and percentages.

Univariate analysis: Univariate analysis will be used to compare the detection rates of clinically significant cancer by PiRADS groups; and by tumor locations between the transrectal and transperineal biopsy groups; a global analysis on all patients will be performed and also subgroup analysis on specific sub-populations (biopsy-naïve, active surveillance, repeat biopsy). Chi-square tests or Fisher's exact tests will be used for categorical variables, and t-tests or Wilcoxon rank-sum tests will be used for continuous variables, as appropriate.

Multivariate analysis: Multivariate analysis will be used to adjust for potential confounding variables, such as age, PSA level, prostate volume, percentage of core positive, PIRADS score on MRI, and tumor size on MRI. A logistic regression model will be used to estimate the adjusted

ORs and 95% CIs for the association between biopsy approach and biopsy results, while adjusting for potential confounders.

Subgroup analysis: Subgroup analysis will be performed to evaluate the added value of systematic biopsies. Patients will be analyzed in two times: first by counting the targeted biopsies only and then by adding the systematic biopsies. The detection rates of clinically significant cancer will be compared between these two groups using the same statistical methods described above.

Sensitivity analysis: Sensitivity analysis will be performed to evaluate the robustness of the results to different assumptions and modeling strategies. This will include varying the definition of clinically significant cancer, adjusting for different sets of confounders, and using different statistical models.

Statistical significance: A p-value of less than 0.05 will be considered statistically significant. All statistical analyses will be performed using R STUDIO® statistical software.

4. Material used for statistics, referencing, and writing the thesis.

In this study, R Studio® version 4.2.2 was used for statistical analysis. R Studio® is a popular integrated development environment (IDE) for the R programming language, which allows for efficient data analysis and visualization. The statistical analysis in this study was performed using various R packages, which provided the necessary tools for data cleaning, exploratory analysis, and regression modeling.

All statistical analyses were performed in R Studio® , and the code used for analysis was documented using R® Markdown to ensure reproducibility. The datasets were imported into R Studio® and cleaned using various data manipulation functions. Exploratory analysis was

performed using various visualization techniques, including scatter plots, box plots, and histograms. Regression models were developed using packages and model assumptions were checked using diagnostic plots. The use of R Studio® allowed for efficient and accurate statistical analysis of the data.

For referencing, Zotero® was used as the primary citation and reference manager to collect and organize research sources. Zotero® allowed for efficient management of citations and automatic generation of in-text citations and bibliographies in the Vancouver superscript citation style. All research sources were imported into Zotero®, either manually or using the browser extension, and were organized into collections based on topic and relevance. In-text citations and bibliographies were generated using the Vancouver superscript citation style, which was chosen to meet the requirements of this study. The use of Zotero® allowed for easy and accurate management of citations and ensured consistency in formatting throughout the manuscript.

Microsoft Word® was used as the primary software for writing and editing the thesis. Word® is a popular word processing software that provides necessary tools for document formatting, styling, and editing. The document was structured using the default settings, with headings and subheadings formatted using the provided styles in line with the requirements of McGill University thesis guidelines. The final version of the document was reviewed and edited for clarity, grammar, and spelling.

5. Data collection strategy

After ethical committee agreement, a full list of patients biopsied transperineally and transrectally from January 2020 till July 2022, was generated. Patient charts are examined and all information regarding patient history, MRI result and biopsy consent, teaching, and technical

details is extracted. The inclusion/exclusion criteria were then applied, and the final eligible patients were identified.

A computerized databank was gathered using the information in the charts, after patients were anonymized. Both databases of transperineal and transrectal biopsies were then combined, and the data was examined for inconsistency and data integrity as well as missing data points.

Data gathered included patients epidemiological and clinical variables. Age, PSA, previous biopsy results, mpMRI results: prostate size, number of lesions, PiRADS score, size, location; pathology results including total number of cores, number of targeted cores, number of systematic cores, ISUP grade and Gleason score of targeted or systematic biopsies, number of positive cores of the targets and the systematic biopsies, and percentage of tumor invasion on biopsy core.

6. Ethical committee approval

The Research Ethics Board of the CIUSSS West-Central Montreal Board (Federalwide Assurance Number: 0796) is designated by the province (MSSS) and follows the published guidelines of the TCPS 2 - Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (2018), in compliance with the "Cadre de référence ministériel pour la recherche avec des participants humains" (MSSS, 2020) , and the membership requirements for Research Ethics Board defined in Part C Division 5 of the Food and Drugs Regulations; and acts in conformity with standards set forth in the United States Code of Federal Regulations governing human subjects research, and functions in a manner consistent with internationally accepted principles of good clinical practice.

The Medical/Biomedical REC of CIUSSS West-Central Montreal REB had the necessary scientific expertise and carried out the scientific evaluation of the project. The Committee rendered a positive evaluation of the project (2023-3629).

K. Results

1. Patients characteristics

From January 2020 until July 2022, a total of 323 patients, and 307 patients were biopsied using the TP route and the TR route respectively. After the eligibility criteria were applied, the number of patients remaining was 251 and 191 respectively. Table one lists the general demographics and patients characteristics of the two prostate biopsy groups.

In total 442 patients were included for analysis, with 251 patients undergoing transperineal biopsy and 191 patients undergoing transrectal biopsy. The patients undergoing transperineal biopsy were younger compared to those undergoing transrectal biopsy (65.6 vs. 67.9, $p<0.01$, Table 1). There were no significant differences observed between the two groups with respect to prostate volume (55.9 vs 58.4), PSA levels (9.5 vs 8.9), PSA density (0.2 vs 0.19), and diameter of lesions on MRI (12.09 vs 12.72).

The majority of patients undergoing transperineal and transrectal biopsies were for diagnostic purposes (74.5% and 90.05% respectively, Table 1). The total number of lesions identified was higher in the transperineal biopsy group (327 lesions) compared to the transrectal biopsy group (238 lesions). There were twice as many PIRADS 3 lesions in the TP group, but there were no significant differences observed in the PIRADS 4 or 5 lesions. There were no differences in the location of the lesions between the two groups: anterior lesions were about 34% of the TP group lesions, and about 29% of the TR group ($p=0.22$).

However, patients undergoing TP biopsy had a significantly lower total number of biopsy cores compared to those undergoing TR biopsy (7.5 vs. 19, $p<0.01$), and a significantly lower

number of systematic biopsy cores compared to those undergoing transrectal biopsy (2.25 vs. 13.79, p<0.01). In the TR population, more patients underwent systematic biopsies than in the TP group (92.3% vs 29.5%).

Table 1: Patients' characteristics

		TP		TR		P-
Number of patients		251		191		-
Age		65.6		67.9		<0.01
Volume		55.9		58.4		0.46
PSA		9.5		8.9		0.27
PSA density		0.2		0.19		0.86
Indication						
	Diagnostic	187	(74.5)	172	(90.0)	-
	Active surveillance	64	(25.5)	19	(9.9)	-
Total number of lesions		327		238		-
Location						
	Anterior	112	(34.2)	70	(29.4)	0.22
	Posterior	215	(65.7)	168	(70.6)	
Diameter of lesion in mm		12.09		12.72		0.22
PI-RADS score						
	3	69	(21.1)	25	(10.5)	0.02
	4	190	(58.1)	166	(69.7)	-
	5	68	(20.8)	46	(19.3)	-
Total number of cores		7.5		19		<0.01
Number of targeted cores		4.5		4.3		0.06
Number undergoing systematic biopsies		74	(29.5)	177	(92.7)	<0.01
Number of systematic biopsy cores		2.25		13.79		<0.01

2. Primary outcome

a. Per-lesion analysis

The table 2 shows the number of cancers diagnosed through TP and TR biopsies, classified into benign, clinically non-significant (CnsPCa), and clinically significant (CsPCa) prostate cancer.

The results indicate that the TP biopsy method diagnosed a higher number and percentage of prostate cancers (183; 55.9%) compared to the TR method (108; 45.3%). Additionally, the TP method diagnosed more clinically significant lesions (144; 44%) compared to the TR method (81; 34%). The Pearson chi-square test was used to determine if there was a statistically significant association between the biopsy modality and detection of clinically significant and non-significant prostate cancer lesions. The test showed a statistically significant difference in favor of the TP route with a p-value of 0.035.

Table 2: Global cancer detection rates (per-lesion analysis)

MODALITY	BENIGN	CNSPCA	CSPCA	TOTAL LESIONS
TR	130 (54.6)	27 (11.3)	81 (34.0)	238
TP	144 (44.0)	39 (11.9)	144 (44.0)	327
				p=0.035

b. Per-patient analysis

In this analysis showed in table 3, the results of patients diagnosed through TP and TR biopsies, classified again into benign, clinically non-significant (CnsPCa), and clinically significant (CsPCa) prostate cancer.

The results indicate that the TP biopsy method diagnosed a higher number and percentage of patients with prostate cancer (146; 58.2%) compared to the transrectal method (94; 49.2%). Additionally, the transperineal method diagnosed more clinically significant lesions (121; 48.2%) compared to the transrectal method (74; 38%). However, the Pearson chi-square test did not determine a statistically significant association between the biopsy modality and detection of clinically significant and non-significant prostate cancer lesions. The test showed a non-statistically significant difference with a p-value of 0.126.

Table 3: Global cancer detection rates (per-patient analysis)

MODALITY	BENIGN	CNSPCA	CSPCA	TOTAL PATIENTS
TR	97 (50.8)	20 (10.5)	74 (38.7)	191
TP	105 (41.8)	25 (9.9)	121 (48.2)	251
				p=0.126

3. Secondary outcomes

a. Any ISUP Cancer detection

i. per-lesion

The comparison of overall cancer detection rates between TP and TR approach (Table 4) showed that there is a statistically significant (p=0.012) better detection in TP arm. Fifty-six percent of the targeted lesions showed prostate cancer on the histopathological analysis, versus 45.4% in the TR arm.

Table 4:Any cancer detection per-lesion

MODALITY	BENIGN	PCA	TOTAL LESIONS
TR	130 (54.6)	108 (45.4)	238
TP	144 (44.0)	183 (56.0)	327
			p=0.012

ii. per-patient

The comparison of overall cancer detection rates between TP and TR approach (Table 5) in a per-patient analysis did not show a statistically significant advantage of the TP arm despite the higher detection percentages of 58.2% versus 49.2% in the TR arm (p=0.06).

Table 5: Any cancer detection per-patient

MODALITY	BENIGN		PCA		TOTAL LESIONS
TR	97	(50.8)	94	(49.2)	191
TP	105	(41.8)	146	(58.2)	251
					p=0.06

b. Sub analysis: per PI-RADS

i. *Per lesion analysis*

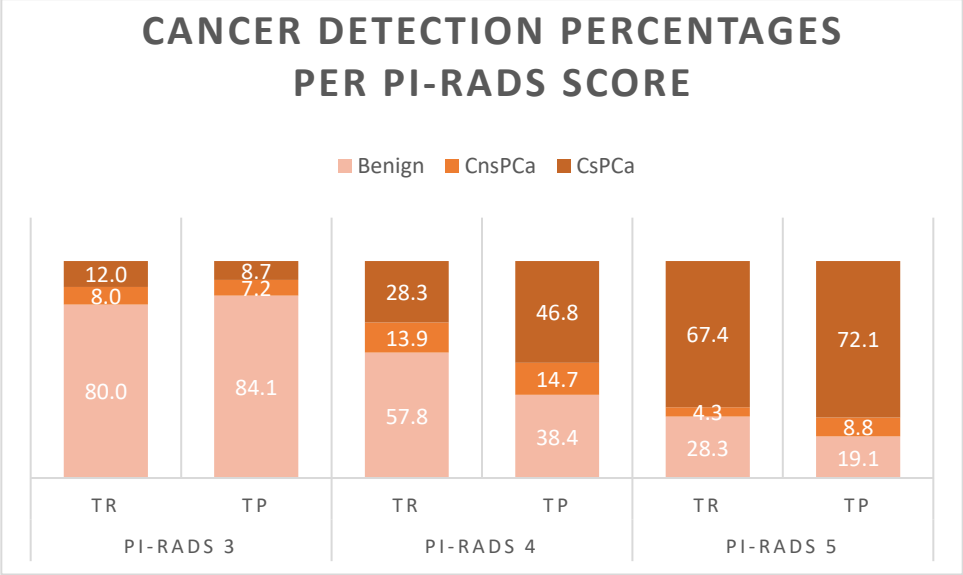

Chart 1:Cancer detection percentages per PI-RADS score

When stratifying lesions according to their respective PI-RADS score (Chart 1), TP biopsies showed a higher detection rate of CsPCa if the lesions were PI-RADS 4 or 5. For example, in PI-RADS 4, 46.8% of the lesions had CsPCa, whereas it was only 28.3% in TR biopsies. In PI-RADS 5, the detection rates were higher in TP vs TR (72.1% vs 67.4%). This difference is statistically significant in PI-RADS 4 subgroup with a p-value <0.0001, but not in PI-RADS 5 where p=0.43. In PI-RADS 3, both populations had similar detection rates (p=0.81). The occurrence of low counts in PI-RADS 3 and 5 made the Fisher exact test necessary to test the

difference and calculate the p-value in those sub-strata, while for PI-RADS 4, we used the Pearson test because its conditions were satisfied. (Table 6).

Table 6: Cancer detection stratified by PI-RADS score.

	MODALITY	BENIGN	CNSPCA	CSPCA	p-value
PI-RADS 3	TR	20	2	3	*(fisher)*
	TP	58	5	6	0.812
PI-RADS 4	TR	96	23	47	
	TP	73	28	89	<0.001
PI-RADS 5	TR	13	2	31	*(fisher)*
	TP	13	6	49	0.426

ii. Per patient analysis

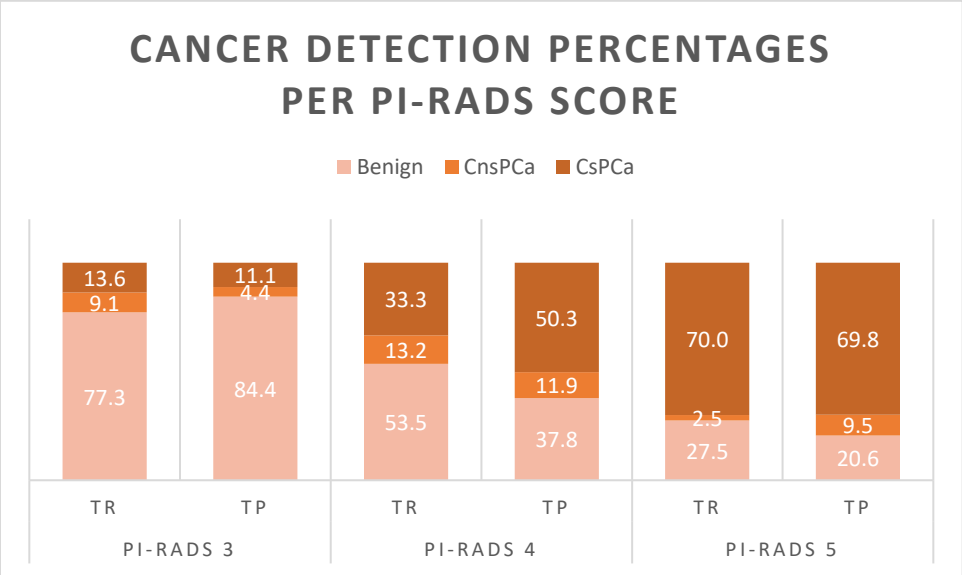

Chart 2:Cancer detection percentages per PI-RADS score

When stratifying patients according to their respective index lesion PI-RADS score (Chart 2), TP biopsies showed a higher detection rate of CsPCa if the lesions were only PI-RADS 4 where 50.3% of the patients had CsPCa, this was only 33.3% in TR biopsies. This difference is statistically significant with a p-value of 0.01. In PI-RADS 3 and 5, the detection rates were similar

in TP vs TR. The occurrence of low counts in PI-RADS 3 and 5 made the Fisher exact test necessary to test the difference and calculate the p-value in those sub-strata, while for PI-RADS 4, we used the Pearson test because its conditions were satisfied. (Table 7).

Table 7: Cancer detection stratified by PI-RADS score (per-patient analysis)

	MODALITY	BENIGN	CNSPCA	CSPCA	p-value
PI-RADS 3	TR	17	2	3	*(fisher)*
	TP	38	2	5	0.7
PI-RADS 4	TR	69	17	43	
	TP	54	17	72	0.014
PI-RADS 5	TR	11	1	28	*(fisher)*
	TP	13	6	44	0.32

We conducted a comparison of the mean of prostate volumes in both populations of PI-RADS 4 patients. The average prostate size for PI-RADS 4 patients in the TR and TP arms were 60.0 and 54.3, respectively. The Student t-test mean comparison was performed and there was no statistically significant difference between the populations, p=0.22. The same comparison was performed for the size of lesion on MRI in the per-lesion sub group of PI-RADS 4, the average lesion size was higher in the TR arm with an average lesion size in the TR and TP arms of 11.21 mm and 10.16 mm respectively (p=0.01).

c. Sub analysis: per location

In this analysis we sub stratified the lesions into anterior (including anterior horns of the Peripheral zone, transitional zone, and anterior fibromuscular stroma) and posterior lesions (posterior peripheral zone). One hundred and twelve anterior lesions were biopsied in the TP arm, whereas 70 anterior lesions were biopsied in the TR arm. In the TP arm, 62.5% of the anterior lesions were CsPCa, while this percentage was lower in the TR arm with only 34.2% of CsPCa.

the overall (any ISUP) cancer detection rates were 74.1% and 42.8% in the TP and TR arms respectively. A Pearson test showed that the difference in detection of CsPCa is statistically significant with a p-value<0.001, in favor of the TP arm (Table 8).

Table 8:Detection rates of prostate cancer in anterior lesions

MODALITY	BENIGN	CNSPCA	CSPCA	TOTAL ANTERIOR
TR	40 (57.1)	6 (8.6)	24 (34.2)	70
TP	29 (25.9)	13 (11.6)	70 (62.5)	112
				p<0.0001

We tested the distribution of the anterior lesions per PI-RADS score, to check for a difference between TP and TR arms. This is shown in the Chart 3 . Both TP and TR arms had similar distribution among the PI-RADS scores, no statistical difference was shown (p=0.19).

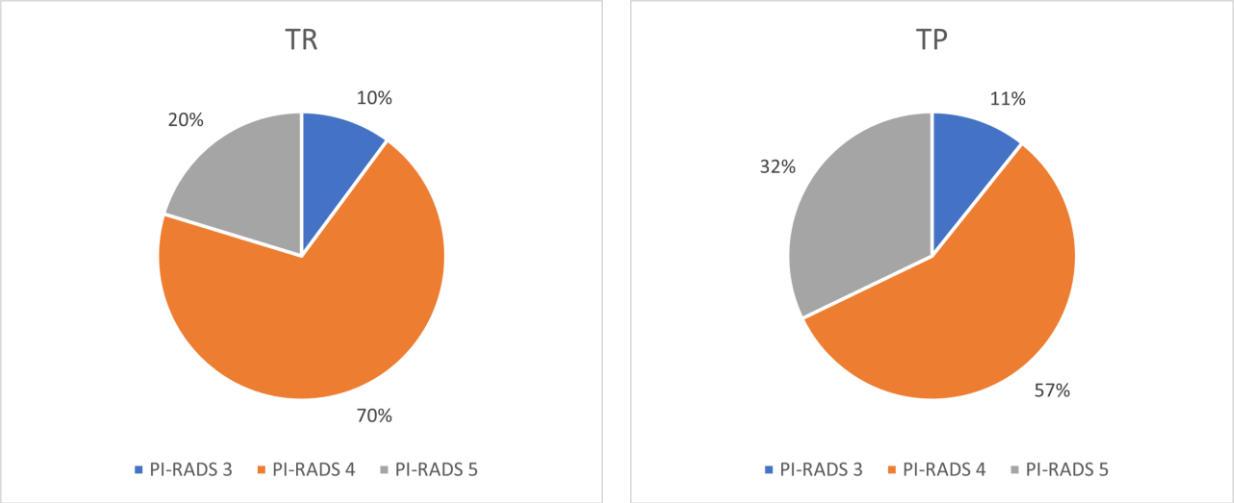

Chart 3: distribution of anterior lesions by PI-RADS score

In this sub-analysis, the mean tumor size on MRI of the anterior lesions was 13 mm and 13.9 mm in TP and TR arms respectively. The average number of targeted biopsy cores taken from the anterior lesions was 5.3 and 4.7 in the TP and TR arms, respectively. Neither the size of the

anterior lesions, nor the number of targeted biopsy cores has shown a statistically significant difference with p-value of 0.5 and 0.1 respectively.

d. Sub analysis: per indication

In this analysis we stratified the patients according to their indication. We divided the patients first into diagnostic and active surveillance. We then sub-divided the diagnostic group into biopsy naïve and repeat biopsy, as shown in the charts below.

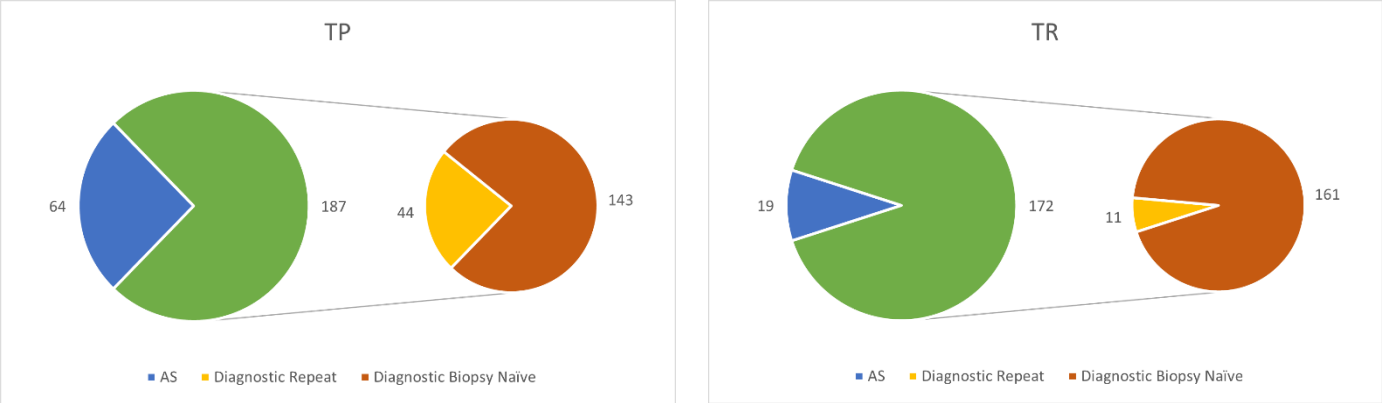

Chart 4: distribution of patients by indication

i. *Biopsy naïve:*

In the TP arm, 143 patients were biopsy naïve, while the TR arm had 161 patients. There was a higher detection of CsPCa in the TP arm with 51.7% versus 39.1% in the TR arm. This difference was not statistically significant on Pearson test, with a p-value of 0.07.

Table 9: cancer detection in biopsy naive patients

MODALITY	BENIGN	CNSPCA	CSPCA	TOTAL
TR	82 (50.9)	16 (9.9)	63 (39.1)	161
TP	55 (38.5)	14 (9.8)	74 (51.7)	143
				p=0.07

ii. *Repeat biopsy:*

In this subgroup, the low number of patients undergoing repeat biopsy in the TR arm underpowers the statistical analysis. We have summarized the detection rates in the Table 10.

Table 10:Cancer detection rates in the repeat biopsy setting

MODALITY	BENIGN	CNSPCA	CSPCA	TOTAL
TR	7 (63.6)	0 (0.0)	4 (36.4)	11
TP	28 (63.6)	3 (6.8)	13 (23.6)	44
				p=0.9

iii. *Active surveillance:*

In the TP arm, 64 patients were biopsied as part of an active surveillance protocol, while only 19 patients in TR arm. In the TP arm, 51.6% of the AS patients were diagnosed with CsPCa, versus 36.8% in the TR. The detection rates in TP arm were higher but the statistical analysis wasn't powered enough to demonstrate a statistically significant difference in terms of CsPCa or PCa detection between the two sub-groups, mainly because of the small numbers in the TR arm.

Table 11: Detection rates of cancer in the active surveillance population

MODALITY	BENIGN	CNSPCA	CSPCA	TOTAL
TR	8 (42.1)	4 (21.1)	7 (36.8)	19
TP	22 (34.3)	9 (14.1)	33 (51.6)	64
				p=0.5

e. Impact of systematic biopsies:

The percentage of patients undergoing systematic biopsies was significantly higher in the TR population (92.7% vs 29.5%).

A comparison of the cancer detection rates between TP and TR arms, when accounting for systematic biopsies is showed in the Table 12. This table shows the results of targeted and

systematic biopsies for both arms with the highest ISUP grade is taken into consideration. TP biopsies detected overall more CsPCa than TR (51.6% vs 36.8%), but this difference is not statistically significant (p=0.1)

Table 12: Cancer detection rates including systematic biopsies

MODALITY	BENIGN		CNSPCA		CSPCA		TOTAL
TR	70	(36.6)	31	(21.1)	90	(36.8)	191
TP	103	(34.3)	24	(14.1)	124	(51.6)	251
							p=0.1

The table below shows the impact of the systematic biopsies on the final ISUP grade.

Table 13: impact of systematic biopsies on final ISUP grade

MODALITY	DOWNGRADE		SAME GRADE		UPGRADE		TOTAL
TR	25	(13.1)	120	(62.8)	46	(24.1)	191
TP	127	(50.1)	117	(46.6)	7	(2.8)	251

The TR arm had more upgrading due to the systematic biopsies (46 occasions, 24.1% of the patients). This upgrading was from benign to clinically significant or non-significant cancer on 27 occasions, from clinically non-significant to clinically significant on 5 occasions and upgrading within the clinically significant grades in 14 occasions. These results are shown in Chart 5.

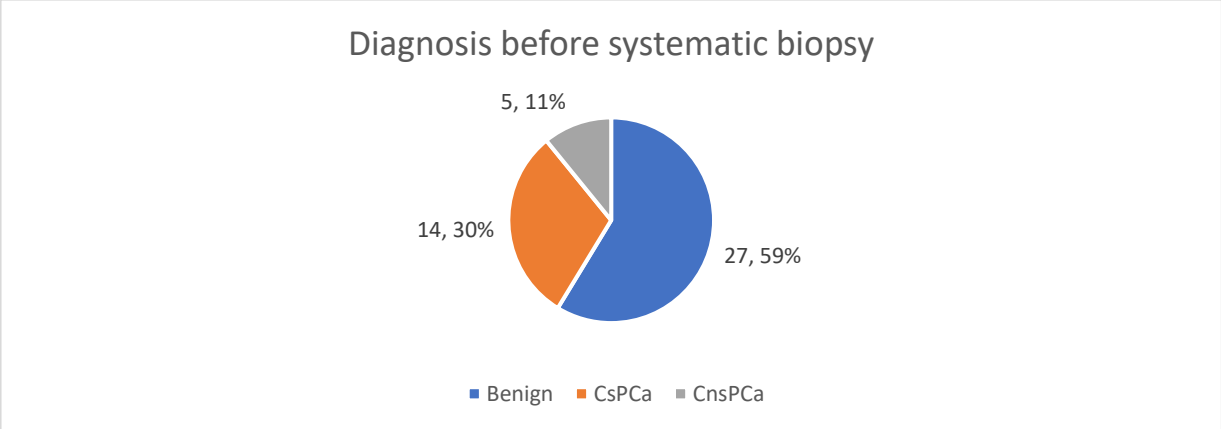

Chart 5:Original diagnosis in patients who were upgraded by systematic biopsy.

L. Discussion

Recent interest in TP biopsies has been encouraged by the safety profile of this prostate technique and the recent data proving its low rate of infections and sepsis. These findings have made the use of antibioprophylaxis obsolete in this setting. Ongoing studies are evaluating the oncologic detection of this method, with many randomized clinical trials recruiting in the US, UK, Australia and France.

This work represents the first study comparing TP and TR biopsy detection rates in Quebec. Although it is a single institution study, the number of patients included in both arms was sufficient for a robust statistical analysis. Both arms were performed concurrently, and pathology reports were generated by the same pathologists, which reduces the bias due to multiple examiners.

The demographics of both of our study arms were homogenous. PSA, PSA density, prostate volume, lesion size, frequency of PI-RADS scores 4 and 5 , and number of targeted cores were similar between TP and TR arms. On the other hand, the TP group was younger, and had more PI-RADS 3 lesions. The homogeneity in many of the possible confounding factors is a strength of our study.

Many studies have shown no difference in cancer detection rates in systematic biopsies between TP and TR route[46]. However, these were retrospective studies, and displayed at least a non-inferiority in detection rates between TP and TR targeted biopsies. In the systematic review by *Rai et al*[34], the included retrospective study had a lower number of patients in both arms compared to our study. The same review shows a common bias in these retrospective studies which is the heterogeneity of imaging fusion methods used.

Among the multiple retrospective studies comparing TP versus TR biopsies, one study by *Tewes et al* in 2017 is worth noting, because it compared two cohorts of patients undergoing software fusion biopsies, in contrast to the myriad of studies comparing different fusion methods. In their study[47] software fusion was used in both arms, while the other studies had either cognitive or software fusion for TP or TR arms. However, this study suffered from a small study arm sizes compared to our study, with only 75 in the TR arm and 79 in TP arm versus 191 and 251 patients respectively.

In our study, we performed per-lesion and per-patient analyses, which permits a more accurate estimation of detection rates, and a better understanding of the impact of location and PI-RADS score. As hypothesized, the per-lesion analysis showed that TP biopsies perform better in detecting CsPCa than TR biopsies. This superiority is reflected also in the subgroup analysis by PI-RADS score. While the PI-RADS 3 and 5 lesions did not show any statistically significant difference despite the higher detection rate of CsPCa in PI-RADS 5, PI-RADS 4 lesions showed a significant difference in detection rates (46.8 % vs 28.3%). This can be explained by the fact that PI-RADS 3 lesions have low rate of CsPCa, so showing a difference in that sub-group might need a bigger population. As for PI-RADS 5 lesions, those are usually bigger lesions by definition (>1.5cm) and can be detectable by both methods without showing big detection rate differences. In a meta-analysis of 17 studies involving men with suspected or biopsy-proven PCa, the average PPVs for ISUP grade > 2 cancers of lesions with a PI-RADS score of 3, 4 and 5 were 16% (7–27%), 59% (39–78%), and 85% (73–94%), respectively, but with significant heterogeneity among studies. These numbers are congruent with the rates of detection we had in the TP arm but not with TR arm. This difference is probably due to the fact that our detection rates were calculated based on the targeted lesions only.

The same per-lesion analysis showed that overall cancer detection (CnsPCa and CsPCa) is also higher in TP arm, by contrast to the per-patient analysis where detection rates of any cancer was not statistically significant (p=0.06), although higher in the TP arm.

The per-patient analysis, which is the comparison of targeted biopsies, with the highest PI-RADS and ISUP grade detected taken into account, did not show a statistically significant difference in the overall study. In the subgroup study, a difference was shown again in the PI-RADS 4 subgroup. This advantage in the PI-RADS 4 subgroup in both per-lesion and per-patient is unlikely to be attributed to confounding factors as the subgroup comparison of the prostate size and location didn't show any statistical differences. Paradoxically, TR arm PI-RADS 4 lesions were larger than TP arm PI-RADS 4 lesions.

Regarding the lesion locations, there was a clear difference between TP and TR detection rates. In anterior lesions, the detection rate was almost double in the TP arm with 62% vs 34 % CsPCa identified. We have inspected the PI-RADS scores of the anterior lesions and found no difference between both arms. The lesions sizes were also similar and the number of biopsy cores taken from each lesion was not different in both arms. This suggests that the anterior location of tumor is more easily biopsied and detected via the TP route. This result is consistent with previous studies [34,46,47] suggesting higher detection rates with TP biopsies in the anterior lesions.

In regards to indication, this study failed to show differences between TP and TR in the repeat biopsy setting, mainly due to small numbers of patients in this sub-category. With only 11 patients in the TR arm vs 44 in the TP arm, the detection rates were not statistically different. The fourfold ratio between TP and TR repeat biopsy patients can be due to the fact that previously biopsied patients with clinical suspicion of PCa, would undergo another type of biopsy, in this

case TP biopsy since most of the centers already perform TR biopsies. The comparison in the biopsy naïve and active surveillance populations was also not statistically significant.

The role of systematic biopsied was also investigated in our study. We have found that the TR population had more systematic biopsies than the TP. This is due to the surgeon's preference and indication of systematic biopsies. While the TP arm patients were more selected according to the PRECISE criteria, the TR arm patients had almost always systematic biopsies in addition to targeted biopsies. This is visible in the low percentage of systematic biopsies done in the TP arm (29.5% vs 92.7%). Nonetheless, we performed statistical analysis using the highest ISUP grade in a per-patient analysis, combining the results of targeted and systematic biopsies, and showed a non-statistically significant (51 % vs 36 %, p=0.1) higher rates of detection in the TP arm.

We further evaluated the impact of systematic biopsies on the final ISUP grade. In TR arm, 24 % of the patients (46 patients) were upgraded after including the results of the systematic biopsies. Of these patients, 59% (27 patients) would have been diagnosed as benign on the targeted biopsies alone, which constitutes 14 % of all the TR arm (27/191). Targeted biopsies would have missed 14% of the patients in the TR arm, which is a bit higher than the numbers reported in 4M trial (5%)[6], the MRI-first trial (5.2%)[8], and the cochrane meta-analysis by *Drost et al* (4.3%)[9].

This study found a higher rate of cancer detection in TP biopsies in PI-RADS 4 lesions, and in anterior lesions. This is consistent to the previous studies[36,46]. It is important to note that in our TP series we performed all our TP biopsies under local anesthesia, and each modality was employed by a separate single surgeon. In contrast, the same TRUS-MRI fusion software and machine was employed which could help to reduce the operator variability but impairs the generalizability of the results.

An operator bias might be one of the limitations of our study. The skill and experience of the surgeon can play a major role in the differences observed between transperineal and transrectal biopsies. However, both of our surgeons have a high load of biopsy patients, and established experience in their respective techniques. Usually, to minimize operator bias, one approach is to standardize the biopsy procedure across all surgeons. This can be done by providing clear guidelines and training to ensure that all surgeons are following the same technique and approach. In our study, the procedure was standardized and the major differences in patient preparation and in the manipulations were due to the inherent difference of both techniques. Another approach is to have multiple surgeons perform the biopsies and compare their results to identify any variations in outcomes that may be due to operator bias. This might be a future perspective once the TP technique becomes more accessible and common among surgeons; in our study addressing a pioneering technique, that is not common among our surgeons, this wasn't a possibility.

In addition to standardizing the procedure and having multiple surgeons perform the biopsies, it is also important to monitor and track outcomes over time to identify any trends or patterns that may be indicative of operator bias. This can be done by analyzing data and identifying any correlations between outcomes and the surgeon performing the biopsy. Overall, minimizing operator bias requires a multi-faceted approach that includes standardizing the procedure, providing training and guidelines, and monitoring outcomes over time. By doing so, it is possible to improve the accuracy and reliability of biopsy results and ensure that differences observed are not due to operator bias.

A review by *Noureldin et al* discusses the effect of learning curve and experience on prostate biopsy routes[48]. TR biopsy remains a popular choice as it can be done in a clinic with local anesthesia and has a shorter learning curve compared to TP biopsy, which often requires sedation

or general anesthesia. However, they discuss that TR biopsy has several limitations including being operator-dependent and having difficulty reaching anterior lesions, which reduces cancer detection in those regions. In recent years, TP targeted biopsy under local anesthesia has been offered using a deep prostate block, which has been found to be safe and feasible for most patients. Studies comparing different biopsy techniques have shown that TP biopsy under local anesthesia has high cancer detection rates and is a viable option. Free hand techniques have also been introduced recently, which avoid the discomfort and complicated setup of the brachytherapy stepper typically used in TP biopsy and have shown competitive cancer detection rates and safety in office settings. In our center we used a hands-free TP biopsy technique with a special biopsy grid, smaller than the brachytherapy grid, consisting of a single column grid attached to the ultrasound probe. This setup is less complicated than the brachytherapy grid, and allows for an easier manipulation using a probe holder.

Data comparing the accuracy and safety of TR vs TP MRI-guided prostate biopsy is currently limited with several unanswered questions. First, some surgeons suggest that the use of a biopsy grid might impair the access to anterior part of larger prostates. In our experience, we have performed biopsies on prostate sizes ranging from 16 to 215 ml, and a simple manipulation of the ultrasound by changing the axis of insertion can help to avoid the pubic bone and allow access to the anterior part of the prostate. Another critique is that this technique involves multiple skin punctures while a free-hand technique can be done with fewer; Although this is accurate, the number of punctures is not predictive of higher infection rates in any current study.

Secondly, another historic discussion is the feasibility and reliability of performing TP biopsies under local vs general anesthesia. While some believe that biopsies performed under GA may result in a higher detection rate due to the patients' immobility and ability to tolerate pain

during extensive sampling of the gland, others have reported optimal detection rates even when using local anesthesia[28,31]. Our study has shown that very good detection rates may be obtained under local anesthesia.

Third, the optimal number of target and perilesional cores is still not clear, as well as the importance of targeting secondary lesions seen on multiparametric MRI. This is shown in the discrepancy between the per-lesion analysis and per-patient analysis. In this study, significant difference in the detection of CsPCa was demonstrated in the per lesion analysis, but not in the per-patient analysis were the difference was present but not statistically significant. This pushes us to consider every lesion on its own. This is perhaps especially pertinent with TP biopsy due to its higher targeted biopsy detection rate.

Will ongoing and future RCTs be able to properly solve all these questions? In the era of Big Data - which refers to extremely large and complex data sets that cannot be processed using traditional data processing tools, it involves the use of advanced technologies and techniques to extract insights, patterns, and correlations from these data sets- clinical research is being reshaped, and the big data population based clinical trials will compete with RCTs for the top spot in evidence levels. The current RCT models of superselective populations and small sample cohorts, will potentially become less utilized in guiding the clinical decision making for the entire population, as population studies can more effectively study outcomes which are affected by the general populations much broader heterogeneity. The beginning of the “big data era” is marking the use of enormous amounts of information, and perhaps a combination of both it and the classical RCT will be the optimal strategy which informs the field of prostate cancer diagnosis.

Another potentially paradigm shifting technology in medicine is artificial intelligence (AI). In our center, the use of a deep learning AI method to predict the clinical or demographical

parameters of a patient to predict for the best biopsy modality is one of the future projects on the horizon. The TP route has a significant learning curve, and additionally requires investment in new material that might be out of reach for small or remote centers. A self-learning AI model, defining features to be tested as criteria to determine the optimal biopsy route, could allow triage of patients with TP preferred profiles to be sent to centers with surgeons experienced in the technique.

M. Conclusion

This study is the first to describe the TP biopsy results in Quebec. Transperineal biopsy has shown better cancer detection rates than TR biopsy on a targeted biopsy per-lesion analysis. This superiority is present especially in PI-RADS 4 lesions, in both per-lesion and per patient analysis when accounting for targeted biopsies alone. Our study also showed better detection rates in anterior lesions. There was no significant difference between the techniques in the repeat biopsy setting. The systematic biopsies contributed significantly to the TR biopsy results, and upon accounting for these, the overall cancer detection rates were not statistically different. Overall, TP biopsies are an adequate alternative to TR biopsies with better detection rates in some specific settings. More solid evidence is expected from randomized controlled studies currently recruiting worldwide. A promising future project is to determine whether Artificial Intelligence and Big Data can be useful in patient triage and selection for TP biopsy.

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