The Role of MRI in Detecting Clinically Significant Prostate Cancer

The Manitoba Experience

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ABSTRACT

OBECTIVES: To examine magnetic resonance imaging-transrectal ultrasound (MRI-TRUS) fusion biopsies completed within Manitoba and evaluate their ability in detecting clinically significant prostate cancer.

PATIENTS & METHODS: 200 cases from October 2021 and May 2022 that met the inclusion criteria were reviewed. Clinical and pathologic information was collected for each case. The cancer detection rate (CDR) and clinically significant CDR were calculated for systematic and targeted prostate biopsy cores for patients that underwent MRIs at Health Sciences Centre (HSC) or St. Boniface General Hospital (SBGH). Clinically significant prostate cancer was set as all cancers with a Gleason score ≥4+3/Grade Group ≥3 or Gleason score 3+4/Grade Group 2 with cribriform and/or intraductal carcinoma present.

RESULTS: The overall CDR including both systematic and targeted biopsy cores was determined to be 75.0%, with an overall CDR for targeted biopsies of 70.5%. The targeted biopsy cores had an overall clinically significant CDR of 34.0%. Prostate cancer was detected in only the targeted biopsies in 38 of the 200 cases, with clinically significant prostate cancer detected in 12 of those cases compared to 9 cases that detected cancer in the systematic biopsies only, 3 of which were clinically significant. When stratified by MRI site, SBGH had a higher targeted biopsy CDR (76.1%) and clinically significant targeted biopsy CDR (35.1%) compared to HSC (59.1% and 31.8%). Nine of the 18 radical prostatectomies had no cancer detected in the systematic biopsies.

CONCLUSIONS: This study has established that MRI-TRUS fusion biopsies are effective in detecting additional clinically significant prostate adenocarcinomas in Manitoba.

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INTRODUCTION

As of 2020, Prostate cancer is the third most common malignancy worldwide, accounting for 7.3% of all cancers. It is the second most frequently occurring cancer in males and does not affect females. Prostate cancer accounts for 6.8% of all new cancers diagnosed in males, with almost 1.4 million new cases worldwide annually. It is the fifth most common cause of cancer deaths in men worldwide[1]. In the United States, 1 in 8 men will develop prostate cancer in their lifetime. Of these men, approximately 13% will succumb to the disease[2]. In Canada, prostate cancer is the leading cause of cancer in men, accounting for 1 in 5 newly diagnosed cancers. In 2022, the estimated number of prostate cancer cases in Canada was 24,600, of which 4,600 were estimated to be fatal[3]. It is projected that 750 men will have been diagnosed with prostate cancer in Manitoba in 2022, with 190 men succumbing to the disease. This is the lowest expected incidence rate in Canada[4].

The prostate is a walnut-shaped gland located within the male pelvis. It is just inferior to the urinary bladder, anterior to the rectum, and at the base of the penis. The prostate requires testosterone to function. Under normal conditions the prostate is 3cm long, with an average weight of 20 grams, and is comprised primarily of glandular tissue that produces approximately a third of the total seminal fluid. The portion of semen produced in the prostate provides nourishment for sperm and alkalinity, used to maintain a high pH[5]. The prostate surrounds the urethra and is comprised of four major zones: the peripheral zone (PZ), the central zone (CZ), the transition zone (TZ), and the anterior fibromuscular stroma (AFMS). Cancers of the prostate mainly occur in the PZ or TZ. The PZ contains 70-80% of the glandular tissue found within the prostate and thus 70-75% of cancers originate there. Twenty to thirty percent of prostate cancers originate in the TZ

which comprises approximately 5% of the glandular tissue in the prostate. Cancer within the CZ, which contains roughly 20% of the prostatic glandular tissue, is usually due to invasion of a PZ tumor into the CZ as primary CZ tumors are rare[6].

As the prostate is found within the pelvis of males, prostate cancer is one of the few cancers that only affects men[7]. However, it is important to be cognisant of the increasing number of people who identify as transgender or gender non-conforming, particularly those assigned male at birth when discussing prostate cancer. The 2021 Census of Population in Canada revealed that 100,815 of those 15 or older living in a private household identify as transgender or non-binary, which equates to 1 in 300 Canadians or 0.33% of the population in that age group. As acceptance and understanding of gender and sexual diversity has increased, more people have become comfortable openly recognizing and reporting their gender identity[8].

Overall, there have been 10 cases of prostate cancer reported in literature that have occurred in transgender women. Bertoncelli Tanaka *et al.* concluded that transgender women who are not on gender-affirming hormone therapy (GAHT) or who have not had gender-affirming surgery (GAS), and non-binary people who have not commenced GAHT or had GAS, are at the same risk of developing prostate cancer as the cis-male population. For transgender women who are on GAHT or who have had GAS, the incidence of prostate cancer is lower than cis-male in their age-matched population. As many transgender patients routinely face barriers to healthcare, resulting in 48% of transgender people delaying or avoiding medical interventions[7], healthcare professionals need to become better educated on the social, behavioural, physiological, and anatomical issues that transgender patients face[9]. Being able to discuss screening, diagnostic and treatment options for gender-at-birth cancer risks in a trans-sensitive manner should be a goal of healthcare professionals moving forward[7].

The incidence rates of prostate cancer vary greatly worldwide, from 6.3 to 84.4 per 100,000 men[1]. Areas with high or very high human development have the highest estimated prostate cancer rates. These include North America, Oceania, Northern Europe[10], Western Europe, the Caribbean and Southern Africa, with the Caribbean having the highest overall. The lowest incidence rates can be found in Asia and Northern Africa[1]. Overall, the incidence rates of prostate cancer in most countries are stabilizing, with a few countries experiencing a decrease in rates[10]. The exceptions to this trend can be found in China, Eastern Europe, and Sub-Saharan Africa where incidence rates continue to rise[1].

Underdiagnosis, disparities in healthcare access, and differences in prostate screening and diagnostic practices are the likely causes for the variation of prostate incidence rates between countries[11], with the latter contributing the most. In the late 1980s and early 1990s, in North America and Oceania, there was a rapid increase in the incidence of prostate cancer. This was due to the widespread introduction of prostate cancer screening, via prostate-specific antigen (PSA) testing, that allowed for the detection of prostate cancer in asymptomatic men. This sharp increase was followed by a sharp decline a few years later and is attributed to the decrease in latent cancers in the general population[1]. The reduction in the use of routine PSA testing, due to many high development countries no longer recommending population-based screening, has caused a further decline and stabilization in the incidence rates. Another possible explanation for recent stabilization or decline in rates is the shift that is taking place in some countries that favours monitoring PSA levels over more invasive diagnostic procedures such as prostate biopsies[10].

The mortality rates due to prostate cancer has been declining since the mid-1990s in North America, Oceania, and Northern and Western Europe because of advancements in treatment and detection[1]. Improvements in prostate surgery techniques, hormone and radiation therapies, and an

increase in access to these advancements have contributed to the decline in mortality rates in many countries. Outliers to this decline include several countries in Asia, South America, Eastern Europe (including many countries of the former Soviet Republic)[10], and Africa. Recently Thailand, Bulgaria, and Ukraine have moved to a more favourable trend[1].

The Caribbean, Sub-Saharan Africa, and Micronesia/Polynesia have the highest mortality rates[1], with Barbados and Trinidad and Tobago having sharp increases in recent years[10]. In many Sub-Saharan and Caribbean countries, prostate cancer is the leading cause of cancer death in men. Some of these countries have a high proportion of the population being of African ancestry, which have a higher risk of developing prostate cancer than other ethnic groups[1]. Additionally limited screening and detection methods in some of these countries, which can lead to more late-stage diagnoses, may be responsible for higher mortality rates. In countries with low incidence rates but high mortality rates, like in certain parts of Africa, lack of access to medical care and treatments can be another contributing factor[12].

In general, the incidence of developing prostate cancer increase as a man ages. In men under the age of 50 the likelihood of being diagnosed with prostate cancer is 1 in 350. Between the ages 50 and 59 that likelihood increases to 1 in 52. Once over the age of 65 the incidence is nearly 60 percent[12]. In Canada, the estimated lifetime risk of developing prostate cancer is 1 in 8[13]. The number of men diagnosed with prostate cancer, especially those with later stage disease who have a worse prognosis, is likely to increase in the next few years due of the COVID-19 pandemic, which has led to the delay of diagnosis, patient management, treatment, and research due to the diversion of resources[11].

Like most diseases, prostate cancer has several risk factors that increase the likelihood of development. They can be divided into unmodifiable and modifiable risk factors. As mentioned

previously, those of African ancestry, including African American, Caribbean, and Black men in Europe, have a higher risk in prostate cancer development compared to other racial and ethnic groups. Not only do they have the highest incidence of prostate cancer, but they are more likely to develop it earlier in life than in other groups[11] or develop a more aggressive form[12]. Many of these individuals possess chromosome 8q24, which is more susceptible to mutations, increasing their risk of developing prostate cancer[11,12]. Several studies have demonstrated that these men have a high rate of variation in the genes that supress tumors (i.e., EphB2) or that are in involved in cell apoptosis regulation (i.e., BCL2). Additionally, in the USA, African Americans are more likely to receive lower quality healthcare when compared to their white counterparts, making them less likely receive adequate healthcare including undergoing PSA screening[12].

Twenty percent of those with prostate cancer are likely to have a family history of the disease. This is thought to be due to similar genes, similar exposure to environmental carcinogens, and similar lifestyle habits[11,12]. Even so, only 5% to 15% of prostate cancer cases are because of inherited genetic background. To be considered an inherited case of prostate cancer, a gene mutation must be transmitted from one generation to the next and have at least three first-degree relatives affected. Prostate cancer can also be attributed as inherited when multiple generations of a family (2 or 3) or close relatives (father, brother, son, grandfather, uncle, or nephew) are affected. Genome-wide association studies have identified susceptibility in almost 170 loci, with several genes showing predisposition to prostate cancer including mutations in *HOXB13*, Lynch Syndrome genes *MLH1*, *MSH2*, *MSH6* and *PSM2*, *BRCA1*, *BRCA2*, *ATM*, *CHEK2*, *PALB2*[11], *HPC1*, *HPC2/ELAC2*, and *MSR1*. Additionally, men with mutations in *BRCA1* and *BRCA2* are more likely to have a clinically aggressive form of prostate cancer[12].

Modifiable risk factors include lifestyle, diet, and environment. Healthy lifestyle choices, including avoidance of alcohol and tobacco, and observance of public health measures like immunizations against cancer-causing infections, have shown to prevent 30 to 50% of cancers according to the World Health Organization (WHO)[11,14]. One of the easiest modifiable risk factors is changing one's physical activity levels. Those who exercise regularly have been found to have a significantly lower risk of developing prostate cancer and even lower PSA levels than their inactive counterparts. Obesity and high body mass index (BMI) have been linked to more aggressive prostate cancers with worse outcomes, which can be attributed to the alterations in the circulation of metabolic and sex steroid hormones within the bloodstream. When combined with physical inactivity, obesity leads to the development of reduced glucose uptake and insulin resistance, causing elevated levels of insulin within the bloodstream that promotes growth and proliferation[12].

With respect to diet, the dietary patterns found in the Western world are suspected to contribute to higher risk in prostate cancer development. There is a positive correlation between prostate cancer risk and dairy consumption[14], which could be due to a decrease in serum vitamin D levels because of higher levels of calcium, leading to less inhibition of cell proliferation and invasion. Additionally, dairy consumption per capita has been positively correlated to prostate cancer mortality, along with fat and meat consumption[11], however the correlation with fat and meat is a bit mixed[14]. When consuming fat, it is best to stick with unsaturated fatty acids like Omega-3 fats found in fish and vegetable oils, which are reported to reduce the risk of prostate cancer. Lastly diets involving tomatoes, cruciferous, and soybeans have shown in some studies to have an inverse association with prostate cancer development, with the lycopene found in tomatoes providing powerful antioxidant properties and cancer-preventative effects[11].

Finally, exposure to several environmental factors is known to cause an increase in the risk of developing cancer. Exposure to chlordecone, an insecticide, and other pesticides leads to a higher risk of prostate cancer in men with a family history of the disease. In 2014, a direct link between exposure to Bisphenol A (BPA), a harmful organic compound, and prostate cancer was found in *in vivo* and *in vitro* by two US research teams[12].

There have been several changes as recently as 2022 that have changed the classification of prostate cancers and their precursor lesions. Previously, the precursor lesion prostatic intraepithelial neoplasia (PIN) was thought to include both low-grade and high-grade PIN. This is no longer the case, with high-grade prostatic intraepithelial neoplasia (HGPIN) the only recognized PIN entity. Additionally, the histologic subtypes of HGPIN have been modified from four to three, and include micropapillary, flat, and tufted. Cribriform is no longer considered a subtype of HGPIN. Lesions previously classified as cribriform HGPIN are now referred as atypical intraductal proliferation (AIP), as they are more complex than HGPIN but do not quite meet the requirements for a diagnosis of intraductal carcinoma of the prostate (IDC-P)[15]. Other precursor lesions include atypical small acinar proliferation (ASAP), and possibly atypical adenomatous hyperplasia (adenosis), however there is no true consensus on whether adenosis is a precursor lesion or not[5].

Almost all prostate cancers are epithelial carcinomas. Epithelial carcinomas can be further sub-classified into glandular or squamous neoplasms of the prostate[15]. Most prostatic cancers are adenocarcinomas, accounting for over 99% of prostatic cancers[16]. Acinar adenocarcinoma, a glandular neoplasm, is the most common prostatic tumor. There are several recognized unusual histologic patterns within this type of carcinoma including atrophic adenocarcinoma, pseudohyperplastic adenocarcinoma, foamy gland adenocarcinoma, microcystic adenocarcinoma,

and mucinous (colloid) adenocarcinoma. Signet ring cell-like adenocarcinoma, pleomorphic giant cell adenocarcinoma, sarcomatoid carcinoma, and PIN-like carcinoma are newly recognized subtypes of acinar adenocarcinoma[15].

Intraductal carcinoma of the prostate is another glandular neoplasm. It was first recognized as a subtype of prostate cancer by the WHO in 2016. There are two distinct entities of IDC-P. A small minority of IDC-P lesions are "in situ" in nature, such as those that originate from the progression of a HGPIN precursor and can be seen as a possible precursor lesions. The remainder of IDC-P lesions are found later in tumor progression when high-grade invasive prostate cancer spreads to benign prostatic ducts. While considered a precursor lesion, IDC-P is very rare without the presence of concomitant invasive cancer, happening in only 0.06-0.26% of cases. In fact, IDC-P generally correlates with higher tumor grade, larger tumor volume, and greater chance of extraprostatic invasion, invasion of the seminal vesicles, and metastasis to the pelvic lymph nodes[15].

The last glandular neoplasm of the prostate is invasive ductal adenocarcinoma, which has large glands that a lined with tall columnar pseudostratified epithelium. It is more aggressive than acinar adenocarcinoma, with a greater risk of PSA reoccurrence and mortality. It is generally associated with a higher stage of prostate cancer[17]. A diagnosis of ductal adenocarcinoma can only be made on radical prostatectomy specimens with a minimum component of 50% ductal carcinoma. In its pure form, ductal adenocarcinoma is very rare and is mixed with acinar adenocarcinoma most of the time. This has led to the debate on whether it is its own distinct type of prostate cancer or if it is a subtype of acinar adenocarcinoma, which additional studies are needed to determine[15].

Prostate cancer either presents asymptomatically or symptomatically. Asymptomatic cases are identified during PSA screening. Prostate-specific antigen is a glycoprotein expressed by prostate cells, both benign and malignant. The screening tests the amount of PSA circulating in the blood, with a normal PSA level thought to be around 4 ng/ml[18,11]. Higher than normal PSA levels can be due to malignant prostate cells but can also be caused by many things including an enlarged prostate due to benign prostatic hypertrophy (BPH), prostatitis, and urinary tract infections. Unfortunately, PSA screening has some limitations. Approximately 1 in every 4 patients with a high PSA (over 4) will not have prostate cancer. Additionally, 15% of patients with prostate cancer will have a PSA less than 4[18].

At its onset, PSA screening was done in a population-based screening format, however guidelines have evolved year after year in many countries[1]. The Canadian Urological Association currently suggests that the screening only be offered to men who have a life expectancy over 10 years. Men electing to undergo PSA screening should be 50 years of age or older, or at least 45 years old if they have an increased risk of prostate cancer. The PSA screening interval should be tailored to each man individually based on their levels and should be discontinued as needed based on age, PSA levels, and general health. These recommendations aim to help diagnosis clinically significant prostate cancer while avoiding over-diagnosing and over-treating indolent cases[19].

In America, the US Preventative Services Task Force (USPSTF) recommendations for prostate cancer screening have changed periodically throughout the years, with the biggest change occurring in May of 2018. Due to a lack of sufficient evidence needed to assess the benefits and risks of prostate cancer screening, particularly in asymptomatic men under 75 years of age, the USPSTF did not make any recommendations with regards to prostate cancer screening in all men until May of 2012 when they recommended against PSA screening. This changed in 2018, with

the release of the most current recommendations. For men aged 55 to 69 years, the USPSTF recommends that the decision to screen or not be determined by each man. They should each discuss the risks and benefits of screening with their clinician and integrate their own personal values and preferences into their decision. For men 70 years and older, the USPSTF currently recommends against PSA-screening[20].

Symptomatic cases are rare, with about 85% of prostate cancer cases identified during screening. The severity of the symptoms a person experiences can be due to the location of the cancer within the prostate or how advanced the cancer is. Prostate cancer can cause a multitude of urinary symptoms: needing to urinate frequently, difficulty with initiation of urination, weak or interrupted flow, painful urination, and hematuria. Erectile and ejaculatory symptoms are also possible, including difficulty with erections, painful ejaculation, and blood in the semen. Bone pain in the lower back, hips or upper thighs and swelling in the lower extremities are symptoms of advanced prostate cancer metastatic to bones. It is important to note that while these symptoms can be caused prostate cancer, they can also be due to many things, like BPH[21].

Decisive diagnosis of suspected prostate cancer cases is done via tissue sampling after abnormal screening. While PSA screening remains the hallmark screening procedure, digital rectal examination (DRE) is also utilized. A DRE involves as physician inserting a gloved finger into the patient's rectum to feel the prostate gland for any abnormalities[22]. The DRE is limited in its detection of prostate cancer, with most patients with abnormal PSA having normal DRE, though any irregularities or nodules felt during the examination is an indication for tissue sampling regardless of PSA levels[23].

Once an abnormal screening result is determined, a patient is sent for prostate biopsy. During the procedure a thin hollow needle is inserted into the prostate gland to collect small

samples of tissue[22]. The standard is a transrectal ultrasound (TRUS)-guided prostate biopsy that collects 12 samples of tissue, called cores, from various locations in the prostate[23]. To locate the prostate a TRUS is utilized, which is a probe inserted into the rectum of the patient. Within the rectum it emits sound waves that reach the prostate and creates echoes, and the echoes are read to create a black and white image of the prostate[22]. A prostate biopsy can consist of less than 12 cores or even up to 50 cores[23]. It is an invasive procedure that comes with a significant risk of infection from rectal commensal or other bacteria being introduced to the prostate via the needle. The cores are then sent for histological examination[11]. Recently magnetic resonance imaging (MRI) has been utilized during prostate biopsies in the form of MRI-TRUS fusion biopsies. For these biopsies, the man undergoes an MRI of the prostate. Any suspicious areas are given a Prostate Imaging Reporting and Data System (PI-RADS) score, and scores $\geq$3 are sampled during the biopsy. For this to happen the MRI images are contoured and then fused with the real-time TRUS images to guide the needle to the suspicious areas[24].

The cores are examined microscopically by a pathologist to determine if the samples are negative or positive for prostate cancer, which is based on the presence or absence of cancer cells in the samples[22]. Unfortunately, there is a significant risk of false-positives and false-negatives, with the false-negatives resulting from the needle missing a small lesion or the lesion appearing benign histologically, like in the early stages of prostate cancer. Despite this, prostate biopsies remain the best tool for diagnosing prostate cancer[11].

The grade and stage of prostate cancers has a direct impact on treatment, therapies, and prognosis. The Gleason grading system is the recommended system for determining histologic grade in all prostatic tissue specimens containing adenocarcinoma[16]. This grading system is based on the work of the Veterans Affairs Cooperative Research Group that included pathologist Dr.

Donald F. Gleason. The group conducted a study between 1959 and 1964 with a purpose of defining optimal treatment of prostate cancer. The study included 270 men with prostate cancer and at the conclusion of the study, a grading system for prostate cancer was created in 1966. The Gleason grading system uses the architectural patterns of prostate cancer to determine the histopathological grade[25].

Nine histological patterns of prostatic adenocarcinoma were initially observed but have evolved to the five current patterns after the combination of some patterns. These five histological patterns determine the Gleason grade, which is identified after the pathologist has examined the biopsy tissue samples under the microscope[25]. There are five Gleason patterns ranging from organized to disorganized. Patterns 1 and 2 contain single, separate glands that are round to oval and range from closely (pattern 1) to loosely packed with stromal separation (pattern 2). As of the 2014 International Society of Urological Pathology (ISUP) conference, grade patterns 1 and 2 are no longer used. Pattern 3 also contains single, separate glands, however these glands can be irregularly shaped and separated, and are infiltrative in nature. The hallmark of pattern 3 is the retention of stroma between all the glands, even the most minute amount, and for the most part they are well formed, relatively uniform glands. The keystone of pattern 4 is fused and poorly formed glands. These glands can present in multiple different patterns including small acinar structures, cribriform, intraductal carcinoma, and glomeruloid. Presence of cribriform or intraductal carcinoma must be explicitly stated[26]. Lastly, pattern 5 forms either masses or sheets of carcinoma with a few tiny glands or signet ring cells[27] or comedonecrosis[26].

The Gleason score was created after the observation that most prostate tumors had more than one histological pattern. The score incorporates the primary predominant pattern and the secondary less dominant pattern. The primary Gleason pattern is added with the secondary pattern

to give a Gleason score between 2 to 10. If there is no secondary pattern present, the primary pattern is doubled[24]. Additionally, if pattern 5 is present 5% or more, it must be designated as the secondary pattern, regardless of there being another secondary pattern[27]. Because Gleason scores 2 to 5 have disappeared from clinical practice, the current version of the Gleason grading system was endorsed at the 2014 ISUP conference[28] and adapted by the WHO in 2016[16]. Gleason scores are now grouped into five prognostic categories, called Grade Groups. The Grade Groups build on Dr. Gleason's original work and incorporate both the Gleason pattern and Gleason score into the final grading system, which is provided in Table 1[16,28].

While the Gleason Grade Group can be assigned based on histological data gathered from prostate biopsies alone, additional information is required to assign clinical and pathological stage classifications and thus the prognostic stage. The pathological stage is comprised of three components: the extent of the primary tumor (T), whether the cancer has metastasized to nearby lymph nodes (N), and whether the cancer has metastasized to other parts of the body (M). Each of these components is assigned a number to be give a pathological TNM classification (pTNM). The clinical stage classification only includes T. The determination of the clinical stage classification of the tumor (designated cT) based on several things including results of the DRE prostate biopsy, and any imaging. Imaging modalities include MRI, ultrasound, and computed tomography (CT), with the former the most valuable. The physician takes the information gathered during these tests, makes an educated estimate on the extent of the tumor, and assigns a cT stage. The breakdown of the clinical stage classification is provided in Table 2[30].

To determine the pathological stage a radical prostatectomy (RP) must be performed, however not every person with prostate cancer will receive one. Once the patient undergoes a RP, the T, N and M pathological categories can be assigned after histological examination. Regional

lymph nodes used for pN staging include the hypogastric, obturator, pelvic, periprostatic, sacral, presacral, lateral sacral, promontory, and internal and external iliac lymph nodes. A summary of the pathological stage classification can be found in Tables 3, 4, and 5[29]. Both the clinical and pathological stage classifications help to provide an overall prognostic stage, which helps to determine treatment options.

When determining the prognostic stage of a cancer based on the American Joint Committee on Cancer (AJCC) staging parameters, prostate cancer utilizes both traditional anatomic and non-anatomic features. In most cancers the T, N, and M stage classifications are combined to determine the prognostic stage. However, in addition to these anatomic features, prostate cancer also utilizes PSA levels and the Gleason Grade Group to determine prognosis. In prostate cancer there are 4 prognostic stage groups, which are divided into 9 substages according to the AJCC. Stage I consists of Grade Group 1 tumors with a PSA less than 10 ng/mL and the following stage classifications: cT1 N0 M0, cT2a N0 M0, and cT2 N0 M0. Stage IIA consists of Grade Group 1 tumors that are cT1 N0 M0, cT2a or pT2 N0 M0, and cT2b or cT2c N0 M0. In stage IIA the PSA levels are ≥10 to <20 ng/mL for cT1, cT2a and pT2 and <20 ng/mL for cT2b and cT2b. Stage IIB consists of Grade Group 2 tumors with a PSA <20 ng/mL and T1 or T2 N0 M0. Stage IIC includes Grade Group 3 or 4 tumors with a PSA <20 ng/mL and T1 or T2 N0 M0. Stage IIIA and IIIB include tumors with Grade Groups 1 to 4, with IIIA also including T1 or T2 N0 M0 and a PSA ≥20 ng/mL. Stage IIIB also includes T3 or T4 N0 M0 with and PSA level. Stage IIIC is Grade Group 5 tumors with T3 or T4 N0 M0 and any PSA level. Stage IVA includes any Grade Group, PSA level, and T, with N1 M0 and stage IVB is any grade group, PSA level, T and N, with M1. A summary of the stages is provided in Table 6[30].

Whether or not the tumor is confined to the prostate is important prognostically and, along with the Gleason Grade Group, helps to determine the treatment options available to each patient with prostate cancer. The National Comprehensive Cancer Network (NCCN) outlines a risk stratification schema for localized prostate cancer used to help determine the treatment modalities that a patient is eligible for, and it is summarized in Table 7. This schema, along with patient personal preferences, guides the patient towards the most appropriate treatment for them[31].

For patients determined to have clinically localized disease that is NCCN very low or low risk, active surveillance is the standard treatment option[31]. Active surveillance involves serial monitoring a patient's prostate cancer and treating only if there is evidence of cancer progression. It requires regular follow-ups with the doctor and for the patient to be on top of their care. Each country has their own surveillance protocol[32]. In Ontario, Canada the recommended protocol for low-risk prostate cancer (Gleason score $\leq$6, PSA < 10 and $\leq$ stage T2A) is as follows: a PSA test every 3 to 6 months, a DRE every year, and a 12 to 14 core confirmatory TRUS biopsy (including anterior directed cores) within 6 to 12 months, with serial biopsy a minimum of every 3 to 5 years after. In the case where the patient's clinical findings do not correlate with the pathological findings, a multiparametric MRI may be included in the protocol[33].

Active surveillance has many advantages, including avoidance of surgery and radiotherapy, along with their side effects[32], preservation of erectile function, decreased costs of treatment, and sustainment of quality of life and normal activities. Unfortunately, it can lead to the possibility of cancer metastases prior to discovery, missed opportunity for curative therapy, more complex therapy with worse side effects for larger and more aggressive tumors, less chance of preserved potency after therapy, more medical appointments and follow-ups, and increased anxiety by patients and family. Nonetheless, active surveillance remains the best option for those who are

low risk, or who have a short life expectancy[22]. Active surveillance is also an option for those with favourable intermediate risk disease but comes with a higher risk of metastasis than definitive therapy. It should not be offered to those with unfavourable intermediate risk disease, cribriform histology or intraductal cancer on biopsy[31].

If those with low-risk disease have a high probability of cancer progression, the doctor may offer definitive therapy in the form of radiation therapy or a radical prostatectomy. The most common forms of radiotherapy are external beam radiotherapy and brachytherapy[31]. External beam targets the prostate tissue with strong X-ray beams. It allows for high dose radiation to the prostate with less effect on surrounding tissues. Brachytherapy involves the direct placement of radioactive therapy into the prostate gland. This is achieved using seeds, injections, or wires under the guidance of TRUS, and can deliver low or high dose radiotherapy. The implantation of radioactive seeds in the prostate tissue is considered low dose brachytherapy, which loses its radioactivity gradually[22]. It is traditionally utilized to treat slow-growing early-stage prostate cancer that has a low risk of recurrence after treatment[34]. High dose brachytherapy comes with a significant risk of leakage into surrounding organs[22] and is generally utilized in the treatment of fast-growing early-stage prostate cancer that has a high risk of spreading[34].

External beam radiotherapy is a treatment option for those with NCCN intermediate, high, and very high-risk prostate cancer. It can be delivered stand alone or combined with other treatment options. Although external beam can be successful alone, particularly for intermediate risk, when it is combined with hormonal therapy, in the form of androgen deprivation therapy (ADT), a more robust response to treatment is noted. Long term ADT is generally recommended in high and very high-risk cancer and lasts 18 to 36 months[31]. Androgen deprivation therapy involves the blockage of the production of testosterone and other male hormones to prevent them

from supplying prostate cancer cells. It can be achieved with a bilateral orchiectomy or medical castration, which utilizes luteinizing hormone-releasing hormone analogs or antagonists[22]. ADT is the primary option for those who do not qualify for definitive therapy, like those with limited life expectancy, and have local symptoms. It is also utilized as adjuvant therapy, along with radiotherapy, after a radical prostatectomy with adverse pathologic features[31].

A radical prostatectomy removes the prostate gland via open or laparoscopic/minimally invasive techniques and can be robotically assisted. It requires small incisions to be made in either the retropubic space or peritoneum. Those under the age of 65 or who have a life expectancy over 10 years have better cancer control benefits from a prostatectomy than older patients. Unfortunately, a RP comes with the risk of two significant complications: urinary incontinence, and erectile dysfunction. These complications are due to damage to the urinary sphincter and penile nerves, and depend on the extent of the prostate cancer, expertise of the surgeon, and the type of surgical technique used. Older patients are more likely to experience these complications than younger[35].

Those with low-risk disease who undergo a RP have the option of a retroperitoneal lymph node dissection (RLND), but it is not required. Intermediate and high-risk patients undergoing a RP will also undergo a RLND, with high-risk patients without fixation to adjacent organs/tissues undergoing an extended RLND. Positive lymph nodes from a RLND are an indication for more aggressive therapy in the form of radiation therapy or ADT[31].

Determination of treatment for patients with clinically locally advanced disease who are classified as very high risk by the NCCN determination of treatment is a bit more difficult. The there is no optimal treatment for those who are Grade Group 5. Options include external beam

radiotherapy with long term ADT which may be combined with brachytherapy, or a RP with extended RLND in younger individuals[31].

For younger individuals who undergo a RP, PSA levels should be monitored post-surgery as it can provide important information. If the patients PSA does not fall to undetectable levels or rises, it can be an indication that there is residual or recurrent carcinoma. The recent RADIALS-RT trial demonstrated that there is no optimal time for adjuvant radiotherapy for patients with localized prostate cancer that have an increased risk of relapse. In five years after prostatectomy, there was no difference in cancer reoccurrence between men who underwent radiotherapy after surgery compared to men who underwent salvage radiotherapy after cancer relapse. Delaying radiotherapy until cancer recurrence allows men with localized prostate cancer to who do not have a reoccurrence of their cancer to be spared some of the side-effects of radiotherapy, which include urinary leakage and narrowing of the urethra[36].

Watchful waiting can be utilized for patients in this risk group if they have a life expectancy of 5 years or less[31], have serious co-morbidities, or if the risks of surgery or radiotherapy outweigh the benefits. It can also be used by patients who do not want to undergo definitive therapy. These patients undergo treatment to control the cancer and manage any symptoms they may develop but does not aim at curing the cancer[32]. Those with clinical lymph node involvement will usually be treated with radiotherapy and ADT, unless they are younger with minimal regional lymph node involvement, in which case they may be offered a RP in combination with adjuvant therapy. If metastasis is present the standard treatment is ADT, which may be combined with chemotherapy in some cases[31].

The overall prognosis for prostate cancer is quite good, with a moderate increase since the 1990s. In Canada the five-year net survival is high (≥94%) among patients who are diagnosed

before the age of 75. In contrast, the five-year net survival for those diagnosed at the age of 85 or older is only 52%. The overall predicted survival rate for prostate cancer in Canada, regardless of age and stage, is 97% at one year, 94% at three years, 91% at 5 years, and 88% at 10 years[13]. A study from 2014 by Schröder *et al.* compared the rate ratios of prostate cancer mortality at 9, 11 and 13 years. They determined that while the rate ratio at 9 years, 0.85, was not statistically significant, this was not the case at 11 and 13 years, whose rate ratios of 0.78 and 0.79 were found to be statistically significant[37]. When broken down by stage, localized cancer has an almost 100% five-year relative survival in Canada, and locally advanced is over 95%. Unfortunately, prostate cancer is not immune to the prognosis of metastatic cancer, with only a 30% five-year relative survival in cases that metastasize to other organs in the body[38].

With a good prognosis for localized and locally advanced prostate cancer, attention is moving towards ways to diagnosis clinically significant prostate cancer while reducing the number of patients that undergo invasive biopsy procedures. One such way is with the emerging use of MRI technology. Through a series of steps, a PI-RADS score is assigned to any suspicious areas within the prostate. This information is utilized during MRI-US fusion biopsies to target specific areas of the prostate in patients that qualify for biopsies[24,6]. The data regarding MRI with high PI-RADS scores is still evolving and its ability to detect clinically significant prostate cancer better than traditional systemic biopsy protocols remains uncertain.

The aim of this study is to determine whether the use of MRI directed PI-RADS scores in Manitoba can detect clinically significant prostate cancer better than systematic biopsies. This will be achieved using data collected from three regional hospitals. Scoring accuracy between two regional MRI sites will also be analysed. The findings will be compared and contrasted to those of recently published literature.

LITERATURE REVIEW

The first version of Prostate Imaging Reporting and Data System (PI-RADS) was created in 2012 by the European Society of Urogenital Radiology (ESUR) to enable radiologists to use a universal system for performing, interpreting, and reporting prostate multiparametric (mp)MRI. The system was used to identify any potential tumors, stratify a patient's risk, and help guide image-guided prostate biopsies. Version 1 (v1) used anatomic T_2-weighted imaging (T2WI), diffusion weighted imaging (DWI), dynamic contrast-enhanced MRI (DCE-MRI), and MR spectroscopy (MRS) to assess possible lesions, which were graded on a 5-point scale. While a meta-analysis of 14 studies showed good diagnostic accuracy of prostate cancer detection using PI-RADS v1, it had a major limitation. The scoring of the system was complex and lacked specific recommendations to derive an overall lesion score from the individual scores of a lesion obtained from individual imaging sequences[39].

To combat these issues, the second version (v2) of PI-RADs was developed in 2015 through the combined effort of the ESUR, the American College of Radiology (ACR), and the AdMeTech Foundation. The goal for PI-RADS v2 was to decrease interpretation and exam performance variability between clinicians and optimize communication between disciplines. Further changes were made between PI-RADS v2 and v2.1. A summary of the key changes is provided in Table 8. The second version also included assessment categories to aid clinicians in decision-making regarding patient management that included specific recommendations[39]. There are 5 categories based on the likelihood of clinically significant cancer being present, ranging from very low to very high[6]. A PI-RADS score of 1 indicates clinically significant cancer is highly

unlikely to be present, unlikely to be present in PI-RADS 2, equivocally present in PI-RADS 3, likely to be present in PI-RADS 4, and highly likely to be present in PI-RADS 5[39,6].

There are 3 important technical specifications used to assign a PI-RADS score: the magnetic field strength, an endorectal coil (ERC), and computer-aided evaluation (CAE) technology. The preferred magnetic field strength for prostate MRI is 3 Tesla (T), which has an increased signal-to-noise ratio (SNR) compared to 1.5T. However, 1.5T is acceptable when a patient has an implanted device that: a) can only undergo a 1.5T MRI or b) the device can undergo a 3T MRI, but the location of the device could compromise image quality like in the case of bilateral hip prothesis. It is not recommended that the magnetic strength of the MRI be less than 1.5T[6].

The use of ERC, when integrated with external phase array coils and regardless of the magnetic strength, increases the SNR in the prostate. In fact, a 1.5T MRI with ERC is comparable in image quality as a 3T MRI without ERC, which is helpful in the instances where a patient cannot undergo a 3T MRI. While the use of ERC is preferred, it's use can lead to increased costs and examination time, deformation of the prostate gland, introduction of artifacts, and more reluctance from patients to undergo an MRI due to decreased comfort. Additionally, ERCs with inflatable balloons can distort the DWI due to the possible introduction of local magnetic field inhomogeneity, thus solid, rigid ERCs that do not need to be inflated and decrease gland distortion are preferred. If the utilization of ERCs is not possible, satisfactory results are still possible at 1.5T and 3T[6].

While the use of CAE technology is not required, the utilization of a specialized software or dedicated workstation may have many benefits. Computer-aided technology could provide quantitative pharmacodynamic data, enhance lesion detection, aid radiologists who are less

experienced at interpreting mpMRIs, and help with the integration of MRI data for use during MR targeted biopsies. In short, CAE technology may improve all aspects of the MRI of the prostate, from display and analysis to interpretation, reporting, and communication[6].

The biggest factors in determining the PI-RADS score are T2W and DWI, and their importance is determined by the location of the suspicious area. If the suspicious area is in the transition zone (TZ), the T2W the primary determining sequence and weighted higher than DWI. If the area is in the peripheral zone (PZ), the opposite is true with the DWI being the primary determining sequence. Because of this, identification of the zonal location of the suspicious area is of absolute importance. A summary of PI-RADS scoring of TZ and PZ suspicious areas are in Tables 9 and 10. Problems arise when assigning PI-RADS scores in the interface between the central zone (CZ) and PZ at the base of the prostate and the interface of the anterior zone of the PZ with the TZ and anterior fibromuscular stroma (AFMS)[6].

T_2-weighted images are used to determine prostatic zone anatomy, and assess any abnormalities found within the prostate. It can also be used to evaluate if the suspicious areas have invaded the seminal vesicles, involved any nearby lymph nodes, or extended beyond the prostate borders. A minimum of two planes are required to obtain the images, with the axial plane being one of them. They are obtained using 2D rapid acquisition with relaxation enhancement (RACE) pulse sequences, with the 2 most common being fast-spin-echo (FSE) and turbo-spin-echo (TSE). Assessment for T2W score is different for the PZ and the TZ, and the breakdown for each can be found in Tables 11 and 12. Additionally, T_1-weighted (T1W) images should be obtained to determine the outline of the prostate gland and presence or absence of hemorrhage in the prostate[6].

Diffusion-weighted imaging is based on the random motion of water molecules[6], specifically it's diffusion. Since the actual diffusion coefficient of water is not measured by MRI,

an apparent diffusion coefficient (ADC) is calculated to quantify the diffusion of water in tissues. The inability for water diffusion to occur in tissues is inversely related to tissue cellularity and the intactness of cell membranes[40]. An ADC map and high b-value images should be included in the DWI. An ADC map displays the ADC values for each voxel of an image, with areas with restricted diffusion, like clinically significant cancers, appearing hypointense on gray-scale ADC maps. Unfortunately, benign prostatic findings, including BPH, can also appear hypointense, making differentiation between them and carcinoma difficult[6].

High b-value images require a b-value of at least 1400 sec/mm^2. At lower b-values, normal prostatic parenchyma can sometimes have very high signal intensity that can make it difficult to distinguish the normal from the abnormal, like prostate cancer. High b-values are utilized to improve accuracy and minimize T2W and perfusion effects. Unfortunately, higher b-values can lead to a decrease of the SNR and an increase in image distortion and artifact susceptibility[41]. The optimum high b-value should be determined based on magnetic field strength, software, and manufacturer. Because of this, there is no optimal high b-value to utilize PI-RADS, only the minimum. When assessing the DWI score for both the TZ and PZ, the signal intensity of a suspicious area should be visually compared to the average signal of "normal" tissue of that zone. A breakdown of DWI score assessment can be found in Table 13[6].

When a low molecular weight gadolinium-based contrast agent (GBCA) is utilized, the collection of rapid T1W gradient echo scans before, during and after its administration, called dynamic contrast-enhanced (DCE) MRI, can be used to help detect small significant cancers. This is because prostate cancers often exhibit early enhancement when compared to normal prostate tissue. Positive enhancement in a suspicious area typically occurs within 10 seconds of the injected GBCA reaching the femoral arteries. A positive DCE MRI lesion has focal enhancement that

enhances earlier than adjacent normal prostate tissue and corresponds to T2W and/or DWI findings. Compared to surrounding prostate tissue, a negative lesion does not enhance early or has diffuse multifocal enhancement that do not correspond to T2W and/or DWI findings or has focal enhancement corresponding to a finding of BPH on T2W. Overall DCE MRI is an essential component of PI-RADS assessment, but it remains secondary to T2W and DWI. Additionally, the presence of a positive DCE lesion does not definitively indicate clinically significant prostate cancer, just as a negative DCE lesion does not exclude the possibility of clinically significant prostate cancer being present[6].

There are three types of targeted prostate biopsies that utilize MRI technology: direct MRI-guided (in-bore) biopsy, cognitive fusion biopsy, and MRI-TRUS fusion biopsy. In a direct MRI-guided biopsy, the prostate biopsies are obtained in the MRI after initial mpMRI images are analysed and suspicious areas are identified. A nonmagnetic needle device is inserted into the rectum where T2W FSE MRI images determine the location of the needle in relation to the prostate gland and suspicious area(s). Once the correct position is obtained, the targeted biopsy of the suspicious area(s) in the prostate is completed. Detection of clinically significant cancers using this technique varies with Overduin *et al.* reporting a detection rate of 81-93%[42], while Hoeks *et al.* showed a cancer detection rate (CDR) of 41% in the biopsies obtained and 87% of those biopsies having clinically significant cancer. When direct MRI-guided biopsies are compared to traditional TRUS biopsies, Quentin *et al.* demonstrated that these biopsies had a higher cancer involvement per core while requiring significantly less cores to be obtained. Unfortunately, this technique is expensive with the need for MRI-compatible biopsy equipment, and time consuming, using a significant portion of valuable MRI time that could be used for other diagnostic tests. Additionally, it can be difficult to schedule due to the coordination between urology, radiology,

and anesthesiology needed[43], and the prone position the patient is required to maintain for the length of the procedure can be quite uncomfortable[42]. For these reasons, this MRI biopsy technique is not as common as the other two[42,43].

Cognitive fusion prostate biopsy is the simplest and cheapest technique of the three due to the lack of specialized software[42]. A mpMRI of the prostate is completed on a patient, and if any suspicious areas are identified, a TRUS biopsy is done utilizing the data collected during the MRI. In a cognitive fusion biopsy, the operator uses anatomical landmarks of the prostate seen on US and references the mpMRI scan to manually target these suspicious areas[43]. The technique largely depends on the experience[42] and technical abilities of the operator and has reduced accuracy at detecting small lesions. While Puech *et al.* found no significant differences in CDRs between cognitive fusion and MRI-TRUS fusion biopsies[43], Cool *et al.* found that cognitive fusion biopsies only detected 50% of clinically significant cancers that were detected by the MRI-TRUS fusion biopsies within their study[42].

The MRI-TRUS fusion biopsy integrates the data obtained from the mpMRI to a US using specialized software[43]. It is typically used in three scenarios: a) patients with a high suspicion of prostate cancer but previous negative biopsies, b) patients with voluminous prostates where systematic biopsies are discouraged, and c) patients who are on active surveillance. Like all the techniques, the patient undergoes a mpMRI of the prostate and any suspicious areas are given a PI-RADS score. If the decision is made to undergo a prostate biopsy after the results of the mpMRI, the MRI images are transferred to specific software to analyse and process them. The identified suspicious areas are labelled on the prostate sector map, and the radiologist segments the contour of the possible lesions, as well as the contour of the entire prostate. The software then

generates a three-dimensional (3D) image of the prostate gland and the segmented possible lesions. The 3D image is uploaded to the fusion biopsy system[42].

Ultrasound images are acquired just prior to the biopsy and are fused with the MRI image. Most of the fusion biopsy systems reconstruct the 2D images obtained during a TRUS into a 3D image to allow this fusion to take place. The suspicious areas labelled on the MRI prostate sector map are mapped onto the 3D TRUS images. The data and images produced are utilized to target the specific areas in the prostate that have been given a PI-RADS score for needle core biopsy. Because these targeted biopsies can miss up to 23% of the clinically significant prostate cancer that are detected by systematic biopsies, routine systematic biopsy cores are also obtained[42].

There are several challenges faced during MRI-TRUS fusion biopsies. It is of most importance to consider the difference in orientation and geometry between the MRI and TRUS images when the fusion takes place to obtain the most accurate fusion possible. Images are acquired during the MRI with the patient in a supine position whereas the patient is in a lateral recumbent position during the TRUS. Because of these differences in position, the orientation of the prostate gland will be rotationally and translationally different between the two images. Additionally, the pressure exerted by the TRUS probe can cause geometric differences between the MRI and TRUS images due to the compressive forces it places on the gland. Differing levels of bladder distention at the time of both procedures can also cause differences in geometry[42].

The most common MRI fusion biopsy systems are Artemis (Eigen, USA), UroNav (Invivo, USA), Urostation (Koelis, France), and BioJet (D&K Technologies, Germany)[43], and all four can be used transrectally or transperineally[42]. Artemis converts the 2D MRI image into 3D to superimpose on the TRUS images utilizing ProFuse multimodality fusion software which allows for better targeting of PI-RADS lesions. A study performed in 2013 by Sonn *et al.* found that

targeted needle core biopsies completed using the Artemis system detected Gleason ≥7 lesions more frequently than systematic core biopsies (36% vs. 24%), and 38% of those Gleason ≥7 lesions were only detected in the targeted biopsy cores[43]. Additionally, they found the system had an overall CDR of 34% and a clinically significant CDR of 25%[44]. The Artemis system has an increased CDR when compared to systemic and cognitive fusion biopsies, and more informative diagnoses when compared to the latter[43].

The UroNav fusion biopsy system uses DynaCAD fusion software[42] and electromagnetic guidance to target lesions identified on MRI. It was developed by the National Institute of Health with collaboration with Philips Healthcare and has a low false-negative rate. In 2015, Siddiqui *et al.* found that the UroNav had a 30% increase in high-risk prostate cancer identification with 17% fewer low-risk cancers identified when compared to the standard TRUS biopsy[43]. They also found that the system had an overall prostate CDR of 46%, with a 37.5% detection rate of clinically significant cancer[44]. When used transperineally, Kosarek *et al.* in 2018 found that the UroNav system had a clinically significant prostate CDR of 59.4% and an overall detection rate of 81.3%[43].

A 2018 study by Sathianathen *et al.*, utilizing the UroNav system, stratified the study group participants into biopsy naïve, previous negative TRUS biopsy, and those on active surveillance, as well as their respective PI-RADS scores. They found that overall CDRs for PI-RADS 1-2, 3, 4, and 5 were 7.7%, 29.7%, 42.4%, and 82.4%, with clinically significant prostate CDRs of 0.0%, 8.9%, 21.4%, and 62.7% respectively. These results demonstrate the correlation between PI-RADS scores and the likelihood of diagnosis of clinically significant cancer. Additionally, they discovered that participants with a previously negative TRUS biopsy and PI-ADS score of 3 or 4 had lower CDRs compared to those who were biopsy naïve or on active surveillance. This information could demonstrate a benefit of undergoing an MRI-TRUS fusion biopsy over the

standard TRUS biopsy as their first biopsy procedure in biopsy naïve participants[45]. As with most fusion biopsy systems, with more experience, detection of clinically significant prostate cancer improves[43].

Urostation is distinct from the previously mentioned fusion biopsy systems because it utilizes a 3D probe for TRUS image acquisition and McDraw fusion software[42]. It utilizes real-time 3D TRUS images and 3D MRI-TRUS fusion guidance that allows the urologist to collect the correct biopsies through US probe manipulation. In 2012 Ukimura *et al.* tested the Urostation system and found that 84% of the targeted biopsies detected prostate cancer. Additionally, a study by Mozer *et al.* in 2015 looked at 152 patients with elevated PSA and found that when compared to the standard needle core biopsy protocol, the Urostation detected more clinically significant prostate cancer[43]. In the Mozer *et al.* study, the Urostation had an overall CDR of 53.9% and a clinically significant prostate CDR of 43.4%[44].

The BioJet fusion biopsy system works in a similar fashion to the Artemis system except for one main difference; the angle-sensing position encoders in Artemis track the movement of a mechanised arm, whereas the BioJet encoders track the movement of a stepper[42]. In 2015, studies by Shoji *et al.* and Borkowetz *et al.* not only reported on the overall CDRs using the BioJet system, 31.8% and 44.1% respectively, but also included the breakdown of clinically significant prostate CDRs based on the PI-RADS score of the possible lesions that were targeted for biopsy. Shoji *et al.* demonstrated clinically significant CDRs of 13.3% for PI-RADS 3, 33.3% for PI-RADS 4, and 88.9% for PI-RADS 5, while Borkowetz *et al.* found a clinically significant CDR of 35.7%, with 24.2% for PI-RADS 3 and 41.6% for PI-RADS 4[44].

Using the BioJet system, a recent study by Benelli *et al.* in 2020 showed similar results to the studies that came before them, with an overall CDR and clinically significant CDR of 49.0%

and 34.3%. The study stratified patients into biopsy naïve, previous negative systematic biopsy, those on active surveillance and those with a previous ASAP or HGPIN, as well as their PI-RADS score. Similar results were also found during the PI-RADS score breakdown, with overall CDRs of 33.7%, 58.4%, and 84.4% for PI-RADS 3, 4, and 5 and clinically significant CDRs of 17.2%, 44.9%, and 73.4% for the respective PI-RADS scores. This again demonstrates the correlation between PI-RADS score and diagnosis of clinically significant prostate cancer. Other important data from the Benelli *et al.* study shows that without the MRI targeted biopsy 49.3% of the detected prostate cancers would have been missed, all the cancers that the targeted biopsy missed (9.6%) were considered Gleason score 6 tumors, and 43.6% of those on active surveillance had their tumors upgraded to clinically significant, with 9 of the 17 upgraded lesions being detected on the MRI targeted biopsy only. Additionally, the study demonstrates the benefit of undergoing an MRI-TRUS fusion biopsy while on active surveillance and affirms the idea that biopsy naïve patients could benefit from undergoing an MRI-TRUS fusion biopsy as their first biopsy procedure, with a 34.8% clinically significant CDR among the biopsy naïve participants[44].

OBJECTIVES

The primary objective of this study is to examine MRI-TRUS fusion biopsies completed within Manitoba and evaluate their ability in detecting clinically significant prostate cancer. This will be assessed in five different ways.

Firstly, we will look at the overall ability of MRI-TRUS fusion biopsies to detect prostate cancer by identifying the overall CDR of the targeted biopsies. This will be further stratified by the specific PI-RADS scores.

Secondly, we will determine the overall CDR of clinically significant cancer in the MRI-TRUS fusion biopsies. Again, these results will be stratified by their assigned PI-RADS scores.

Thirdly, we will identify the number of cases where prostate cancer is found only in targeted or systematic biopsies. If prostate cancer is found in both, we will analyze the number of cases where the cancer detected in the targeted biopsies was higher than the systematic biopsies.

Fourthly, the previously mentioned results will be stratified by the hospital in which the MRI took place.

Lastly, we will look at the cases that underwent radical prostatectomy and compare the highest Gleason scores at time of biopsy (systematic or targeted) with the Gleason scores of the corresponding prostatectomy.

PATIENTS & METHODS

The patient population for our study was comprised of all available prostate cancer cases meeting the inclusion criteria between October 2021 and May 2022. A total of 200 MRI guided cases were included in the study. Cases included were limited to male patients who underwent an MRI at one of two Winnipeg Regional Health Authority (WRHA) hospitals: Health Sciences Centre (HSC) or St. Boniface General Hospital (SBGH). Of the 200 cases: 66 cases underwent their MRI at HSC, and 134 cases underwent their MRI at SBGH. Following the MRI they underwent an MRI-TRUS fusion biopsy at the Dr. Ernest W. Ramsey Manitoba Prostate Centre with the histopathological analysis completed at one of three WRHA hospitals: HSC, SBGH, and Grace Hospital (GH). The histopathological analysis breakdown was as follows: 140 cases at HSC, 2 cases at SBGH, 58 cases at GH. From these 200 cases 18 underwent radical prostatectomy (RP) with histopathological analysis breakdown as follows: 1 case at HSC, 4 cases at SBGH, and 13 cases at GH.

Methodologies for obtaining pertinent cases was the same regardless of hospital site. A list of all prostate biopsy reports from July 2018 to May 2022 was obtained from the CoPath database at Shared Health Manitoba. The data was further stratified by a Laboratory Information System Analyst using the keywords “fusion”, “MRI” and “directed”. The surgical pathology reports were obtained for the 200 most recent cases as well as the corresponding prostate MRI reports. If the patient had undergone a RP at the time of data collection, the surgical pathology reports for the RP were also obtained.

Clinical information collected for each case included: pathology number, sign out month and year, age of patient, site of MRI, site of histopathological analysis, and site of RP. Collected radiologic information included: PI-RADs score(s) and the location of possible lesion(s). Collected pathologic data from the MRI-TRUS fusion biopsy included: presence or absence of prostate cancer in systematic and MRI targeted biopsy cores, Gleason score, Gleason Grade Group, and presence or absence of cribriform or intraductal carcinoma. Additional pathologic information collection for cases that underwent RP included: Gleason score, and Gleason Grade Group.

Patients at both hospital sites underwent an MRI in a 3T Siemens Verio scanner with a pelvic phased array coil. Patients at SBGH were explicitly instructed to follow a low residue diet leading up to their MRI to reduce bowel gas and stool in the rectum. The multiparametric MRI was conducted using a 3 Telsa magnet that included axial T1-weighted turbo spin echo images, tri-planar T2-weighted turbo spin echo images, axial diffusion imaging (including b-1400 [HSC] and b-1500 [St. Boniface] images and ADC map generation) and axial post-contrast imaging. Tables 14 and 15 outline the prostate MRI protocols for HSC (Craig Snell, email communication, August 2023) and SBGH (Iain Kirkpatrick, MD, email communication, June 2023).

All patients within the study underwent an MRI-TRUS fusion biopsy utilizing the bkFusion biopsy system. Targeted biopsy cores were collected based on information obtained during MRI in addition to undergoing a standard systematic biopsy. Radiologic PI-RADS lesion locations were matched up with corresponding targeted biopsy specimens for each case to undergo analysis. In cases with multiple PI-RADS lesions and only one targeted biopsy specimen with multiple cores, the specimen's Gleason Grade/score were assigned to the highest PI-RAD lesion. The remaining lesions in these cases were not analysed. Where a bilateral PI-RADS lesion was sampled separately on each side, the PI-RADS score was counted twice. If a PI-RADS lesion did not have

a corresponding targeted biopsy specimen, and thus was not sampled, the lesion was not included in data analysis.

Clinically significant prostate cancer for this study was set as all cancers with a Gleason score ≥4+3/Grade Group ≥3. Additionally, cases with Gleason score 3+4/Grade Group 2 with cribriform and/or intraductal carcinoma present were designated as clinically significant prostate cancer.

RESULTS

The study population was comprised of 200 cases. The average patient age was 67.7 years old (range 45-87 years).

Targeted biopsy cores based on PI-RADS scoring and location were collected for all cases. A minimum of 1 targeted core per location was obtained. For the corresponding systematic biopsy protocol, a minimum of 6 cores to a maximum of 12 cores were obtained for each case. One hundred and fifty cases were identified as having prostate cancer in either the targeted or systematic biopsy cores, for an overall CDR of 75.0%.

Prostate cancer was detected in the targeted biopsy cores in 141 of the 200 cases, giving an overall CDR for targeted biopsies of 70.5%. Each case had at least one suspicious area identified by MRI with the total number of suspicious areas equalling 269. Most of the patients, 143, had one area assigned a PI-RADS score (53.2%), 46 had 2 targeted areas (34.2%), 10 had 3 suspicious areas (11.1%), and 1 had 4 suspicious areas (1.5%). The distribution of PI-RADS score was: 1 lesion (0.4%) PI-RADS 1, 2 lesions (0.7%) PI-RADS 2, 70 lesions (26.0%) PI-RADS 3, 132 lesions (49.1%) PI-RADS 4, and 64 lesions (23.8%) PI-RADS 5. Cancer detection rates (CDR) for the specific PI-RADS score are as follows: 0% for PI-RADS 1 (0/1), 50.0% for PI-RADS 2 (1/2), 35.7% for PI-RADS 3 (25/70), 74.2% for PI-RADS 4 (98/132), and 84.4% for PI-RADS 5 (54/64), for an overall CDR for PI-RADS lesions of 66.2%.

Of the 141 cases where the targeted core biopsies detected prostate cancer, 68 detected clinically significant cancer, for an overall targeted biopsy clinically significant CDR of 34.0%. Seventy-five lesions sampled out of the 269 total lesions contained clinically significant prostate

cancer, giving an overall clinically significant CDR of 27.9% for the PI-RADS lesions. When comparing the number of cases and lesions that detected cancer with the number of cases and lesions that detected clinically significant cancer, the results are extremely statistically significant (P value less than 0.0001). The following percentages represent the clinically significant CDR for each PI-RADS score: 0% PI-RADS 1 (0/1), 50.0% PI-RADS 2 (1/2), 15.7% PI-RADS 3 (11/70), 26.5% PI-RADS 4 (35/132), and 43.8% PI-RADS 5 (28/64).

Prostate cancer was detected in only the targeted biopsies in 38 of the 200 cases, with clinically significant prostate cancer being detected in 12 of those cases. The breakdown of Gleason scores is as follows: 7 cases 3+3 (Grade Group 1), 20 cases 3+4 (Grade Group 2) with only 1 with cribriform, 7 cases 4+3 (Grade Group 3), 1 case 4+4 (Grade Group 4), and 3 cases 4+5/5+4 (Grade Group 5). In comparison, the systematic biopsies and not the targeted biopsies detected prostate cancer in 9 of the 200 cases. Of those 9 cases, the systematic biopsies detected clinically significant cancer in 3 of the cases.

There are 103 cases where cancer was found in both the systematic and targeted biopsies. Fifty-three of the 200 cases contained systematic and targeted biopsy cores with the same Gleason scores, 25 cases with clinically significant prostate cancer in both types of cores and 1 case with clinically significant cancer in the systematic cores only due to the presence of cribriform carcinoma. Twenty-seven cases had higher Gleason scores in the targeted biopsies, while 23 cases had higher Gleason scores in the systematic biopsies. Of the 27 higher Gleason score targeted biopsy cases, 23 showed clinically significant prostate cancer within the targeted cores. In comparison, only 6 of those cases had clinically significant prostate cancer in the systematic cores.

When stratified by MRI site, 42 cases at HSC out of 66 detected prostate cancer for an overall HSC CDR of 63.6%. In comparison, 108 of the 134 cases where the MRI was performed

at SBGH detected cancer, giving an overall SBGH CDR of 80.6%. Of these cases, 23 at HSC and 59 at SBGH detected clinically significant prostate cancer, making their overall clinically significant CDR 34.8% and 44.0% respectively. When analysing only the targeted biopsy cores, 39 of the 66 cases detected prostate cancer at HSC (CDR 59.1%), 21 of which were clinically significant (CDR 31.8%), and 102 of the 134 cases detected prostate cancer at SBGH (CDR 76.1%), 47 of which were clinically significant (CDR 35.1%). When comparing the number of cases at one site that detected cancer against the other, the results are considered statistically significant (P value equals 0.0144), including when comparing just the targeted biopsy cores (P value equals 0.0204). However, they are not statistically significant when you compare the clinically significant detected cancer (P value equals 0.2256 [all cases] and P value equals 0.7512 [targeted biopsy cores]).

In total, the HSC prostate MRI detected 91 suspicious areas with the following distribution of PI-RADS scores: 1 lesion PI-RADS 1, 1 lesion PI-RADS 2, 31 lesions PI-RADS 3, 36 lesions PI-RADS 4, and 22 lesions PI-RADS 5. Of those 91 suspicious areas determined at HSC, 50 detected prostate cancer for a lesion CDR of 54.9%. The following percentages represent the CDR each PI-RADS score: 0% (0/0) PI-RADS 1, 100% (1/1) PI-RADS 2, 29.0% (9/31) PI-RADS 3, 61.1% (22/36) PI-RADS 4, and 81.8% (18/22) PI-RADS 5. Twenty-six of the HSC lesions sampled during targeted biopsies detected clinically significant prostate cancer with the following clinically significant CDR breakdown for each PI-RADS score: 0% (0/0) PI-RADS 1, 100% (1/1) PI-RADS 2, 19.4% (6/31) PI-RADS 3, 33.3% (12/36) PI-RADS 4, and 31.8% (7/22) PI-RADS 5. The overall clinically significant CDR from the HSC lesions is 28.6% (26/91).

The SBGH MRI detected 178 suspicious areas in the prostate. The breakdown of SBGH PI-RADS scores are as follows: 0 lesions PI-RADS 1, 1 lesion PI-RADS 2, 39 lesions PI-RADS

3, 96 lesions PI-RADS 4, and 42 lesions PI-RADS 5. One hundred and twenty-seven of the suspicious areas detected prostate cancer for a lesion CDR of 71.3% and had the following CDR breakdown: 0% (0/0) PI-RADS 1, 0% (0/1) PI-RADS 2, 38.5% (15/39) PI-RADS 3, 79.2% (76/96) PI-RADS 4, and 85.7% (36/42) PI-RADS 5. Clinically significant prostate cancer was found in 49 of the targeted lesions for an overall clinically significant CDR of 27.5% (49/178). The clinically significant PI-RADS CDR breakdown is as follows: 0% (0/0) PI-RADS 1, 0% (0/1) PI-RADS 2, 12.8% (5/39) PI-RADS 3, 24.0% (23/96) PI-RADS 4, and 50% (21/42) PI-RADS 5.

Cancer was detected in only the systematic biopsies in 3 cases at HSC and 6 cases at SBGH, with 1 at HSC and 2 at SBGH being clinically significant. In comparison, 9 cases at HSC and 29 cases at SBGH contained prostate cancer in only the targeted biopsies. Of these cases, 3 at HSC and 9 at SBGH were clinically significant.

Sixteen cases at HSC detected the same Gleason score for both the systematic and targeted biopsies, 7 of which were clinically significant in both core types. In addition to this, 9 cases at HSC had higher Gleason scores in the targeted biopsy, in comparison to 5 cases that had higher Gleason scores in the systematic biopsies. Of the 9 higher targeted biopsies, 7 were clinically significant, however 2 of those 9 cases also contained clinically significant systematic biopsies.

At SBGH, 37 cases had systematic and targeted biopsies cores with the same Gleason scores, 18 of which were clinically significant in both types of cores and 1 case with clinically significant prostate cancer in just the systematic biopsies because of cribriform carcinoma. Both the systematic and targets biopsy cores had 18 cases each where they had the higher Gleason scores compared to the other type. Of the 18 cases with higher Gleason scores in the targeted biopsy cores, 14 cases had clinically significant cancer in the targeted cores, of which 4 cases also had clinically significant prostate cancer in the systematic biopsies.

Of the 18 cases that underwent a radical prostatectomy at time of data collection, when comparing the highest Gleason scores of the targeted and systematic biopsies, 3 cases had a higher Gleason score within the systematic biopsies, 3 cases had the same Gleason scores between the systematic and targeted biopsies, and 12 had a higher Gleason score within the targeted biopsies. Furthermore, 9 of the 12 cases with higher Gleason scores in the targeted biopsies had no cancer detected in the systematic cores, meaning the radical prostatectomies were performed due to information collected solely from the targeted biopsies. When comparing the highest Gleason score from the biopsy cores with Gleason scores from the subsequent prostatectomies, 11 patients had the same highest Gleason scores in their biopsies and prostatectomies. Of the remaining 7 patients, 6 had lower Gleason scores in their prostatectomies compared to their biopsies, with only one patient with a higher Gleason score in their prostatectomy.

DISCUSSION

MRI-TRUS fusion biopsies have been popularized by manufacturers and clinicians as a means to increase detection of prostate cancer, particularly clinically significant prostate carcinoma. The system used in Manitoba, bkFusion, advertises an 84% positive detection rate for prostate cancer. It further states that the system has been proven to detect cancer in 84% of PI-RADS 3-5 lesions and up to 81% of Gleason Grade ≥2 carcinomas[46]. This was not found to be the case in our patient population. While the CDR for PI-RADS 5 lesions in our study was found to be 84.4%, when combined with PI-RADS 3 and 4 that CDR decreases to 66.5% (177/266), with PI-RADS 3 having a significantly lower CDR of 35.7%.

Within our study, the overall CDR for the targeted biopsy cases was determined to be 70.5% (141/200). When looking at the total number of PI-RADS lesions that CDR decreases slightly to 66.2%, since many of our cases had more than one PI-RADS lesion identified with multiple targeted cores biopsied. While this is lower than the stated positive detection rate advertised by bkFusion, these overall CDRs are higher than the previous studies mentioned in the literature review, with the exception of the Ukimura *et al.* Urostation study that had a CDR of 84% for targeted biopsies[43]. It is important to remember that our study includes PI-RADS 1-5 lesions, while the bkFusion system only advertises PI-RADS 3-5 lesions.

Our overall CDR of clinically significant prostate cancer was determined to be 34.0% (68/200 cases). This number decreases to 27.9% when factoring in the number of PI-RADS lesions sampled. This means that less than half of the targeted MRI-TRUS fusion biopsies detected clinically significant prostate cancer. This is significantly different than the previously mentioned

studies. The various fusion systems reviewed in literature had varying differences between their overall CDRs and clinically significant CDRs, but none with as large of a difference as our study. For example, the study by Sonn *et al.* in 2013 found that the Artemis fusion system had an overall CDR of 34% and a clinically significant CDR of 25%. The 2015 Mozer *et al.* study determined a 53.9% overall CDR and 43.4% clinically significant CDR for the Urostation fusion system. Two reviewed studies included the BioJet fusion system, the 2015 Borkowetz *et al.* study and the most recent study by Benelli *et al.* in 2020. Borkowetz *et al.* determined an overall CDR of 44.1% with a clinically significant CDR of 35.7%, while Benelli *et* al. found overall CDR of 49.0% and a clinically significant CDR of 34.3%[44]. These studies show little differences between overall CDR and clinically significant CDR compared to our results.

This difference in literature is largely accounted for by differences in definition of clinically significant prostate cancer. The studies involving the Artemis and Urostation fusion systems determined clinically significant prostate cancer to include cancer core length ≥4mm or Gleason score ≥3+4, the BioJet studies defined clinically significant prostate cancer according to the Epstein criteria, which included Gleason score ≥7, >2 positive cores, PSA density >0.15 and bilateral cancer[44]. For this study, clinically significant prostate cancer was set as all cancers with a Gleason score ≥4+3/Grade Group ≥3 and all cases with Gleason score 3+4/Grade Group 2 with cribriform and/or intraductal carcinoma present. Our definition is based on current provincial standards for active surveillance in Ontario[33]. In terms of local practice, many patients with Gleason score 3+4 with no cribriform component, and low volume pattern 4 are surveilled (RH Wightman, MD, oral communication, November 13, 2023). Including cases with Gleason score 3+4 without cribriform and/or intraductal carcinoma dramatically increases our clinically significant CDR to 63.0% (126/200 cases). This differing definition of clinically significant

prostate cancer brings our clinically significant much closer to the stated manufacturer detection rates.

In general, when looking at PI-RADS scores, targeted biopsy cores had an increased probability of detecting prostate cancer and clinically significant prostate cancer as the PI-RADS score increased, except for in the case of PI-RADS 2 lesions. These findings are consistent with the studies completed by Shoji *et al.*, Borkowetz *et al.*, and Benelli *et al* using the BioJet fusion biopsy system[44] and Sathianathen *et al.*, who utilized the UroNav system[45].

When examining cases based on the location of MRI, SBGH had a higher targeted CDR (76.1%) and clinically significant targeted CDR (35.1%) compared to HSC (59.1% and 31.8%). While the differences between the targeted clinically significant CDR was not statistically significant between the sites (P value equals 0.7512), the differences in targeted CDR between SBGH and HSC was determined to be significant (P value equals 0.0204). The SBGH CDR for each PI-RADS score is as follows: 0% (0/0) PI-RADS 1, 0% (0/1) PI-RADS 2, 38.5% (15/39) PI-RADS 3, 79.2% (76/96) PI-RADS 4, and 85.7% (36/42) PI-RADS 5. These CDRs for SBGH are higher than the corresponding PI-RADS score CDRs at HSC, which are as follows: 0% (0/0) PI-RADS 1, 100% (1/1) PI-RADS 2, 29.0% (9/31) PI-RADS 3, 61.1% (22/36) PI-RADS 4, and 81.8% (18/22) PI-RADS 5. The findings are reversed when comparing the clinically significant CDRs for each PI-RADS score, with HSC having higher clinically significant CDRs for each individual PI-RADS score, except for PI-RADS 5, compared to SBGH (0% vs. 0% PI-RADS 1, 100% vs. 0% PI-RADS 2, 19.4% vs. 12.8% PI-RADS 3, 33.3% vs. 24.0% PI-RADS 4, and 31.8% vs. 50% PI-RADS 5).

Prostate cancer was detected in only the targeted biopsy cores in 38 of the 150 cases that detected cancer, 12 of which were clinically significant as defined in our study. When clinically

significant cancer is defined as Gleason score of 3+4 and above, 31 of the 38 cases had clinically significant prostate cancer. This data demonstrates the importance of utilizing MRI-TRUS fusion biopsies, especially in the case of patients with no detectable cancer on systematic biopsy who have increasing PSA levels. Conversely, 9 of the 150 cases that detected prostate cancer detected cancer in only the systematic biopsy cores, 3 of which had clinically significant cancer detected as defined in our study and 6 that had Gleason scores of 3+4 or higher. This data illustrates the importance of continuing to collect systematic biopsy cores along with targeted ones.

These conclusions align with the study performed by Salami *et al.* in 2014, who found that MRI-TRUS fusion biopsies in men with elevated or rising PSA levels and previously negative prostate biopsies may improve the detection of clinically significant prostate cancer. They also noted that to avoid missing the detection of some clinically significant cancer that was not detected by the MRI-TRUS fusion biopsies, 12-core systematic biopsies may be needed[47]. Thus, it would be in the patient's best interest to continue to collect the systematic biopsy cores along with the targeted ones.

There are some limitations that may have affected the outcome of some of the data in this study. Firstly, there were 4 cases with multiple PI-RADS lesions identified on MRI, but who only had one targeted MRI specimen. It is unknown whether the specimen contained a core from each PI-RADS lesion, or which lesion the highest Gleason score was derived from. Secondly, three of the cases did not state which specific specimen the cribriform pattern was found, only that there was cribriform pattern found in the case. Due to the methods of the study, this information could not be included in these cases and there could potentially be small differences in the clinically significant cancer detection rates reported and the actual rates. Thirdly, it is possible the keywords during the data search may not have capture all the cases that underwent MRI-TRUS fusion

biopsies. There were a small minority of cases where “fusion”, “MRI” and “directed” were not mentioned within the pathology report that included targeted biopsies. Finally, there are few studies on the bkFusion biopsy system, meaning the data analysed in the study had to be compared with other fusion biopsy systems. While they all have fairly similar results, it would have been best to compare our results with studies that also used the bkFusion system.

The biggest strength of this study is that all the data collected was derived from a single provincial database. The vast majority of patients undergo their entire cancer and treatment journey within this database allowing for easy collection of additional data or follow-up information. The use of a single database enables further expansion of the current study, pushing the study in new directions.

In conclusion, this study has established that MRI-TRUS fusion biopsies are effective in detecting additional clinically significant prostate adenocarcinomas in Manitoba. Although this is a stand alone finding, it is recommended that the relevant data be collected on an ongoing basis to provide a continual quality metric to assure that MRI-TRUS fusion biopsies retain utility moving forward into the future. This process might be assisted by the introduction of Artificial Intelligence to manage larger data sets. An additional future direction suggested by this study would be the assessment of individual physician’s performance metrics. Specifically, radiologists could be assessed in terms of their clinically significant cancer detection rate in relation to the various PI-RADS categories. An additional expansion of this study from the pathologist’s perspective would be the inclusion of pattern 4 quantitation on needle core biopsies, in terms of absolute percentage, which would provide additional information on top of the presence or absence of cribriform/intraductal morphology.

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Table 1: Summary of the Gleason Grading System for prostate tumors based on the 2014 International Society of Urological Pathology Consensus Conference[16,28]

Grade Group	Gleason Score	Definition
1	≤ 6	Only individual discrete well-formed glands
2	3 + 4 = 7	Predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands
3	4 + 3 = 7	Predominantly poorly former/fused/cribriform glands with lesser component (*) of well-formed glands
4	4 + 4 = 8	Only poorly formed/fused/cribriform glands
	3 + 5 = 8	Predominantly well-formed glands and lesser component (**) lacking glands (or with necrosis)
	5 + 3 = 8	Predominantly lacking glands (or with necrosis) and lesser component (**) of well-formed glands
5	9 - 10	Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands (*)

*For cases with greater than 95% poorly formed/fused/cribriform glands on a core or at radical prostatectomy, the component of less than 5% well-formed glands is not factored into the grade; should therefore be graded as grade group 4.

**Poorly formed/fused/cribriform glands can be a more minor component.

Table 2: Summary of tumor (T) clinical classification of prostate tumors based on the American Joint Committee on Cancer[30]

T-Primary Tumor (clinical)			
T0	There is no evidence of primary tumor		
T1	Tumor can't be felt during a DRE or seen with an imaging test. It may be found by chance during a biopsy or during surgery for another health issue related to the prostate or bladder	T1a	Cancer is found in 5% or less of the removed tissue
		T1b	Cancer is found in more than 5% of the removed tissue
		T1c	The tumor is found by needle biopsy in one or both sides of the prostate
T2	Tumor can be felt during a DRE and can be seen on an imaging test. Cancer is only in the prostate	T2a	The tumor is in one half or less of one side of the prostate
		T2b	The tumor is in more than one half of one side of the prostate
		T2c	The tumor is in both sides of the prostate
T3	The tumor has broken through the outside layer of the prostate gland	T3a	The tumor has grown outside the prostate but not into the seminal vesicles
		T3b	The tumor has grown outside the prostate and into the seminal vesicles
T4	The tumor has grown outside the prostate and into nearby structures such as the bladder, rectum, pelvic muscles, and pelvic wall		

Table 3: Summary of tumor (T) pathological classification of prostate tumors based on the College of American Pathologists Cancer Protocol Templates[29]

T-Primary Tumor (pathological)			
T2	Organ confined		
T3	Extraprostatic Extension	T3a	Extraprostatic extension or microscopic invasion of bladder neck
		T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall		

*There is no pathologic T1 classification

Table 4: Summary of lymph node (N) pathological classification of prostate tumors based on the College of American Pathologists Cancer Protocol Templates[29]

N-Regional Lymph Nodes (pathological)	
N not assigned	No nodes submitted OR cannot be determined based on available pathological information
N0	No positive regional nodes
N1	Metastasis in regional nodes

Table 5: Summary of distant metastasis (M) pathological classification of prostate tumors based on the College of American Pathologists Cancer Protocol Templates[29]

M-Distant Metastasis (pathological)			
Not applicable	Cannot be determined from the submitted specimen(s)		
M1	Distant metastasis	M1a	Nonregional lymph node(s)
		M1b	Bone(s)
		M1c	Other site(s) with or without bone disease

*When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced.

Table 6: Summary of prognostic stage groups for prostate tumors based on the American Joint Committee[30]

WHEN T IS…	AND N IS…	AND M IS…	AND PSA IS…	AND GRADE GROUP IS…	THEN THE STAGE GROUP IS…
cT1a-c, cT2a	N0	M0	<10 ng/ml	1	I
pT2	N0	M0	<10 ng/ml	1	I
cT1a-c, cT2a	N0	M0	≥10, <20 ng/ml	1	IIA
pT2	N0	M0	≥10, <20 ng/ml	1	IIA
cT2b-c	N0	M0	<20 ng/ml	1	IIA
T1-2	N0	M0	<20 ng/ml	2	IIB
T1-2	N0	M0	<20 ng/ml	3	IIC
T1-2	N0	M0	<20 ng/ml	4	IIC
T1-2	N0	M0	≥20 ng/ml	1-4	IIIA
T3-4	N0	M0	Any	1-4	IIIB
Any T	N0	M0	Any	5	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	Any	M1	Any	Any	IVB

*Note when either PSA or grade group is not available, grouping should be determined by T category and/or either PSA or grade group, as available.

Table 7: Summary of the risk stratification schema for localized prostate cancer based on the National Comprehensive Cancer Network[31]

Risk Group	Clinical/Pathologic Features
Very Low	• cT1c AND • Grade group 1 AND • PSA <10 ng/ml AND • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core AND • PSA density <0.15 ng/ml/g
Low	• cT1 to cT2a AND • Grade group 1 AND • PSA <10 ng/ml AND • Does not qualify for very low risk

Favourable Intermediate	• No high or very high-risk features
	• No more than one intermediate risk factor:
	  • cT2b to cT2c
	  • Grade group 2 or 3
	  • PSA 10 to 20 ng/ml
	AND
	• Grade group 1 or 2
	AND
	• Percentage of positive biopsy cores <50%

Unfavourable Intermediate	• No high or very high-risk features
	• Two or three of the intermediate risk factors:
	  • cT2b to cT2c
	  • Grade group 2 or 3
	  • PSA 10 to 20 ng/ml
	AND/OR
	• Grade group 3
	AND/OR
	• ≥50% of positive biopsy cores

High	• No very high-risk features AND • T3a OR • Grade group 4 or 5 OR • PSA >20 ng/ml
Very High	• T3b to T4 OR • Primary Gleason pattern 5 OR • Two or three high-risk features OR • >4 cores with Grade group 4 or 5

Table 8: Summary of the key changes between PI-RADS versions[39]

Key changes from PI-RADS v1 to v2	Key changes from PI-RADS v2 to v2.1
Inclusion of high b-value DWI among other specific technical parameters for prostate MRI performance	Continued revision to technical specifications to improve adherence and to modernize multiparametric MRI performance for newer scanners and available sequences
Concept of "dominant" sequence based on lesion location to aid in overall lesion categorization	Distinction between typical and atypical nodules in the TZ
De-emphasis of DCE-MRI with use of binary scoring as opposed to 5-point scale	Greater emphasis placed on DWI for overall lesion scoring, especially at lower T2W scores
Delineation of PI-RADS 4 vs. PI-RADS 5 lesions based on size cut-off (>1.5cm) and/or presence of extraprostatic extension	Discussion of clinical indications for utilization of biparametric MRI over multiparametric MRI
Explicit criteria for delineating imaging features for PI-RADS 3 lesions with expanded array of lesion descriptors	Modifications of sector map to include medial PZ locations, specifically at the prostate base

Tables 9: Summary of scoring of peripheral zone suspicious areas for PI-RADS v2.1[6]

DWI	T_2W	DCE	PI-RADS
1	Any*	Any	1
2	Any	Any	2
3	Any	–	3
		+	4
4	Any	Any	4
5	Any	Any	5

* "Any" indicates 1-5

Table 10: Summary of scoring of transition zone suspicious areas for PI-RADS v2.1[6]

T_2W	DWI	DCE	PI-RADS
1	Any*	Any	1
2	≤3	Any	2
	≥4	Any	3
3	≤4	Any	3
	5	Any	4
4	Any	Any	4
5	Any	Any	5

* "Any" indicates 1-5

Table 11: Summary of scoring T_2W for suspicious areas in the peripheral zone for PI-RADS v2.1[6]

Score	Peripheral Zone
1	Uniform hyperintense signal intensity (normal)
2	Linear or wedge-shaped hypointensity or diffuse mild hypointensity, usually indistinct margin
3	Heterogenous signal intensity or non-circumscribed, rounded, moderate hypointensity Includes others that do not qualify as 2, 4, or 5
4	Circumscribed, homogenous moderate hypointense focus/mass confined to prostate and <1.5cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behaviour

Table 12: Summary of scoring T_2W for suspicious areas in the transition zone for PI-RADS v2.1[6]

Score	Transition Zone
1	Normal appearing transition zone (rare) or a round, completely encapsulated nodule
2	A mostly encapsulated nodule OR a homogeneous circumscribed nodule without encapsulation. (“atypical nodule”) OR a homogeneous mildly hypointense area between nodules
3	Heterogenous signal intensity with obscured margins Includes others that do not qualify as 2, 4, or 5
4	Lenticular or non-circumscribed, homogenous, moderately hypointense, and <1.5cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behaviour

Table 13: Summary of scoring DWI for suspicious areas in the peripheral and transition zones for PI-RADS v2.1[6]

Score	Peripheral Zone or Transition Zone
1	No abnormality (i.e., normal) on ADC and high b-value DWI
2	Linear/wedge-shaped hypointense on ADC and/or linear/wedge-shaped hyperintense on high b-value DWI
3	Focal (discrete and different from the background) hypointense on ADC and/or focal hyperintense on high b-value DWI; may be markedly hypointense on ADC or markedly hyperintense on high b-value DWI, but not both
4	Focal markedly hypointense 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 behaviour

*Signal intensity in a lesion should be visually compared to the average signal of "normal" prostate tissue in the histologic zone in which it is located

Table 14: Health Sciences Centre prostate MRI protocol

	Flip Angle(deg)	SEQUENCE	SL#	ST (mm)	TR (ms)	Matrix (Base x Phase)	TE (ms)	#Avg.	FOV (mm)	Voxel size (mm)
Localizer multiplaner	20	GRE	7	6	7.8	256 x 204	3.69	1	320	1.6 x 1.3 x 6
T2 SAG	140	TSE	24	3	4290	320 x 288	99	2	200	0.7 x 0.6 x 3
T2 COR	140	TSE	24	3	4290	320 x 288	99	2	200	0.7 x 0.6 x 3
T2 AXIAL	140	TSE	30	3	5360	320 x 240	99	2	200	0.8 x 0.6 x 3
T1 AXIAL	150	TSE	30	3	730	256 x 192	11	1	200	1.0 x 0.8 x 3
Diffusion AXIAL B0, B1000		EPI	30	3.5	7100	102 x 102	83	10	200	2.0 x 2.0 x 3.5
Diffusion AXIAL B1400		EPI	20	3.6	6600	160 x 120	93	8	220	1.8 x 1.4 x 3.6
T1 AX VIBE pre	9	3D FLASH VIBE	36	2	4.55	256 x 192	1.49	2	220	1.1 x 0.9 x 2
T1 AX VIBE DYNAMIC (pre/post)	15	3D FLASH VIBE	20	3.5	5.6	192 x 138	1.97	1	220	1.6 x 1.1 x 3.6
T1 AX VIBE delay 3 min	9	3D FLASH VIBE	36	2	4.55	256 x 192	1.49	1	220	1.1 x 0.9 x 2

Table 15: St. Boniface prostate MRI protocol

	Flip Angle(deg)	SEQUENCE	SL#	ST (mm)	TR (ms)	Matrix (Base x Phase)	TE (ms)	#Avg.	FOV (mm)	(mm)	
Localizer multiplaner	20	2D Flash	15	6	7.6	256 x 192	3.6	1	400	2.1 x 1.6 x 6	
T2 SAG	150	TSE	24	3	3600	320 x 310	101	3	200	0.6 x 0.6 x 3	
T2 COR	150	TSE	24	3	3500	320 x 310	101	3	200	0.6 x 0.6 x 3	
T2 AXIAL	150	TSE	26	3	3740	320 x 310	101	3	200	0.6 x 0.6 x 3	
T1 AXIAL	150	TSE	28	3	700	256 x 192	11	1	200	1.0 x 0.8 x 3	
Diffusion AXIAL B50, B800		EPI	20	3	7000	160 x 114	84	7	270	2.3 x 1.7 x 3	
Diffusion AXIAL B1500		EPI	20	4	10500	192 x 123	93	8	260	1.8 x 1.4 x 4	
T1 AX SPGR	2	3D FLASH	20	4	5.08	192 x 138	1.74	8	260	1.9 x 1.4 x 4	
T1 AX SPGR	15	3D FLASH	20	4	5.08	192 x 138	1.74	6	260	1.9 x 1.4 x 4	
T1 AX SPGR DYNAMIC (pre/post)	12	3D FLASH	20	4	5.08	192 x 138	1.74	1	260	1.9 x 1.4 x 4	20 measurements = TEMP resolution: 9s
T1 AX SPGR Fat Sat Post Gad (LFOV)	9	3D VIBE	64	3.5	4.7	320 x 192	2.1	1	330	1.7 x 1.0 x 3.5	