Evidence-based guideline recommendations on multiparametric magnetic resonance imaging in the diagnosis of clinically significant prostate cancer: A Cancer Care Ontario updated clinical practice guideline

Masoom A. Haider, MD; Judy Brown, PhD; Jospeh L.K. Chin, MD; Nathan Perlis, MD; Nicola Schieda, MD; Andrew Loblaw, MD

1Sinai Health System and University of Toronto, Joint Department of Medical Imaging, Toronto, ON, Canada; 2Program in Evidence-based Care, Ontario Health (Cancer Care Ontario), McMaster University, Hamilton ON, Canada; 3London Health Sciences Centre, Victoria Hospital, London, ON, Canada; 4Cancer Clinical Research Unit, Princess Margaret Cancer Centre, Toronto, ON, Canada; 5Department of Radiology, University of Ottawa, Ottawa, ON, Canada; 6Sunnybrook Health Sciences Centre, Toronto, ON, Canada

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See related commentary on page 15

Note, this guideline was developed by the CCO and is endorsed by the CUA; however, it did not undergo the standard CUA guideline development and review process.

Abstract

Introduction: This clinical practice guideline is based on a systematic review to assess the use of multiparametric magnetic resonance imaging (mpMRI) in the diagnosis of clinically significant prostate cancer (csPCa) for biopsy-naive men and men with a prior negative transrectal ultrasound-guided systematic biopsy (TRUS-SB) at elevated risk.

Methods: The methods of the clinical practice guideline included searches to September of 2020 of MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. Internal and external reviews were conducted.

Results: The recommendations are:

Recommendation 1: For biopsy-naive patients at elevated risk of csPCa, mpMRI is recommended prior to biopsy in patients who are candidates for curative management with suspected clinically localized prostate cancer.

- If the mpMRI is positive, mpMRI-targeted biopsy (TB) and TRUS-SB should be performed together to maximize detection of csPCa.
- If the mpMRI is negative, consider forgoing any biopsy after discussion of the risks and benefits with the patient as part of shared decision-making and ongoing followup.

Recommendation 2: In patients who had a prior negative TRUS-SB and demonstrate a high risk of having csPCa in whom curative management is being considered:

- mpMRI should be performed.
- If the mpMRI is positive, targeted biopsy should be performed. Concomitant TRUS-SB can be considered depending on the patient’s risk profile and time since prior TRUS-SB biopsy.
- If the mpMRI is negative, consider forgoing a TRUS-SB only after discussion of the risks and benefits with the patient as part of shared decision-making and ongoing followup.

Recommendation 3: mpMRI should be performed and interpreted in compliance with the current Prostate Imaging Reporting & Data System (PI-RADS) guidelines.

Introduction

Prostate cancer is the most common cancer among Canadian men, excluding non-melanoma skin cancers, and is the third leading cause of death in Canadian male cancer patients.1 In most clinical practices, the current standard for diagnosing clinically significant prostate cancer (csPCa) in biopsy-naive men at risk is transrectal ultrasound (TRUS)-guided systematic biopsy (TRUS-SB) of 10–12 cores.2 Transperineal systematic biopsy may also performed but is less commonly applied in Canada. Because TRUS-SB systematically samples areas from the prostate and not a specific imaged target, this approach has been shown to lead to over-detection of clinically insignificant prostate cancer (cisPCa)3 and can miss csPCa.4

Over the past several years, there has been growing use of multiparametric magnetic resonance imaging (mpMRI) as a non-invasive tool to diagnose and localize csPCa. mpMRI followed by targeted biopsy (mpMRI-TB), particularly in men with prior negative biopsy, may be considered in the detection of csPCa, as per the Ontario provincial guidelines previ-
ously published. However, at the time of the writing of that guideline, there was a paucity of high-quality data supporting the use of mpMRI-TB in biopsy-naive men. In addition, there have been no Canadian guidelines published that address the minimum acceptable standards in the acquisition, interpretation, and reporting of mpMRI or the minimal acceptable standards for performance of mpMRI-TB. The guidelines sought to address this latter issue primarily through expert opinion.

The Working Group (WG) guideline authors (with expertise in diagnostic imaging, radiation oncology, urology, and health research methodology), in association with the Program in Evidence-based Care (PEBC) of Ontario Health (Cancer Care Ontario) and the mpMRI in Prostate Cancer Guideline Development Group (GDG) conducted an update of a systematic review to develop a clinical practice guideline to assess the use of mpMRI in the diagnosis of csPCa for biopsy-naive men and men with a prior negative TRUS-SB at elevated risk (according to prostate-specific antigen [PSA] levels and/or nomograms).

**Methods**

The systematic review will be published separately. Briefly, MEDLINE (May 2013 through September 1, 2020), EMBASE (May 2013 through September 1, 2020), the Cochrane Central Register of Controlled Trials (OVID CCTR: September 2020), and the Database of Abstracts of Reviews of Effects (OVID DARE: third quarter 2020) were searched for systematic reviews, review-based guidelines, original studies, and conference abstracts.

The report was assessed and approved by the PEBC Report Approval Panel (RAP), which consisted of two oncologists with expertise in clinical and methodological issues. Nine members of the mpMRI in the Diagnosis of Clinically Significant Prostate Cancer Expert Panel (EP) (a larger group of radiologists, urologists, and surgical oncologists of which the WG were selected) also reviewed and approved this report.

Following approval by the RAP and EP, a targeted peer review was conducted to obtain direct feedback on the draft report from a small number of specified content experts, and a professional consultation took place, intended to facilitate dissemination of the final guidance report to Ontario practitioners.

**Results**

**Literature search results**

Of the 3754 studies identified in the literature search, 36 studies from 39 publications met the inclusion criteria. The overall risk of bias of the studies ranged from low to high. Internal and external review

The summary of main RAP and EP comments and the WG’s responses/modifications are shown in Table 1.

Responses were received by two targeted reviewers. Results of the feedback survey are summarized in Table 2. The main comments from targeted peer-reviewers and responses from the WG are summarized in Table 3.

The response rate for professional consultation was 6% (12 respondents). The results of the survey from the 12 participants are summarized in Table 4. The main comments from the professional consultation and the WG’s responses are summarized in Table 5.

**Practice guidelines**

The finalized version of the report reflects feedback from the internal and external review processes, with final approval granted by the mpMRI in Prostate Cancer GDG. These guidelines apply to patients without contraindications to mpMRI (i.e., patients with MRI-incompatible medical devices).

**Recommendation 1**

For biopsy-naive patients at elevated risk of csPCa, mpMRI is recommended prior to biopsy in patients who are candidates for curative management with suspected clinically localized prostate cancer.

- If the mpMRI is positive, mpMRI-TB and TRUS-SB should be performed together to maximize detection of csPCa.
- If the mpMRI is negative, consider forgoing any biopsy after discussion of the risks and benefits with the patient as part of shared decision-making and ongoing followup.

**Key evidence for recommendation 1**

Twenty-three trials (all full-text publications) compared mpMRI with a reference standard (n=5, all cohort studies) or with TRUS-SB (n=18: 2 randomized controlled trials [RCTs] and 16 cohort studies) for biopsy-naive men. The certainty of the aggregate study evidence for each comparison showed 14 of the 21 cohort studies to be at either low, moderate or high risk of bias based on a GRADE approach. Of these five studies, PROMIS was assessed to be at low risk of bias and the other was assessed at being at unclear risk.

- In the five studies where template transperineal mapping biopsy (TTMB) was the reference standard, mpMRI ranges were sensitivity 87–96%, specificity 29–45%, positive predictive values (PPVs) 46–65%, and negative predictive values (NPVs) 76–92%. Of these five studies, PROMIS was a prospective, multicenter trial (MCT). In this study,
Haider et al

it was estimated that unnecessary biopsies could be reduced by up to 27%. mpMRI was more sensitive (88% vs. 48%, 95% confidence interval [CI] 43–54, \(p<0.0001\)) but less specific (45% vs. 99%, 95% CI 97–100, \(p<0.0001\)) than TRUS-SB in this study.

Two RCTs compared CSPCa detection rates of mpMRI-TB vs. TRUS-SB.\(^{20,30}\) Estimates for csPCa when combining the two RCTs showed increased detection favoring mpMRI by 18% (95% CI 5–32, \(p=0.009\)). Estimates for the two RCTs combined for

### Table 1. Responses regarding main comments from the Report Approval Panel and Expert Panel

| Main comments                                                                 | Responses                                                                 |
|-------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| The PRECISE data likely would not influence the recommendations, but they should be incorporated into the evidence discussion. This was a major trans-Canadian initiative, co-funded by the Ontario Institute for Cancer Research, whose goal was to influence funding for prostate MRI in Canada. | PRECISE trial results have been added in the discussion of the systematic review. |
| I have some serious concerns about the wording of Recommendation 2. In particular, the statement, “In patients who had a prior negative TRUS-SB and demonstrate a high or an increasing risk of having csPCa in whom curative management is being considered: mpMRI should be performed.” The problem with this strategy is the risk of overdiagnosis. | The principal role for MRI in biopsy-naive patients is complete biopsy avoidance to reduce the risk of overdiagnosis. This is the primary advantage of the strategy and produces the largest reduction in overdiagnosis. Once a decision to perform a biopsy is made because of a positive MRI, it is assumed there is also an intent to pursue curative intent therapy. mpMRI-TB combined with TRUS-SB in MRI-positive patients still allows for overall reduction in TRUS-SB in those patients who are mpMRI-negative, with only a slight increase in cisPCa detection (8%) while increasing CSPCa detection by 6%. |

Treatment alternatives in Recommendation 1 should be expanded beyond surgery and radiation, (i.e., to include partial gland ablation and energy-based technologies). The statement implying that radiation and surgery are the only curative options is outdated. Suggest including partial gland ablation as a treatment option. (This is not to endorse partial gland ablation, but only to acknowledge they are approved options that are often offered to patients).

Obviously, the issue of the role of systematic biopsies in men having targeted biopsy is not black and white. If the objective is to maximize diagnosis, they are clearly required. But another objective is to minimize morbidity and reduce number of cores. In the lower-risk patient, the NPV in the regions of the gland where the MRI is negative is sufficiently high (90%) that systematic biopsies may be omitted. Therefore, I believe the concept of risk stratification as the basis for decision-making should be addressed in the document more than it is.

We have not further delved into risk stratification, as this is an extensive and complex topic and beyond the scope of this document. A change has been made to the target population definition as follows:

“Patients with an elevated risk of csPCa (defined as International Society of Urologic Pathology [ISUP] grade group [GG] ≥2), as estimated by available clinical information and tools, such as risk calculators and nomograms...”

\(\text{cis}:\) clinically insignificant; csPCa: clinically significant prostate cancer; mpMRI: multiparametric magnetic resonance imaging; NPV: negative predictive value; TB: target biopsy; TRUS-SB: transrectal ultrasound-guided systematic biopsy.

### Table 2. Results from the targeted peer-reviewed questionnaire

| Questions                                           | Lowest quality (1) | (2) | (3) | (4) | Highest quality (5) |
|------------------------------------------------------|--------------------|-----|-----|-----|---------------------|
| Rate the guideline development methods.              | 0                  | 0   | 0   | 0   | 2                   |
| Rate the guideline presentation.                     | 0                  | 0   | 0   | 0   | 2                   |
| Rate the guideline recommendations.                  | 0                  | 0   | 0   | 0   | 2                   |
| Rate the completeness of reporting.                  | 0                  | 0   | 0   | 0   | 2                   |
| Does this document provide sufficient information to inform your decisions? If not, what areas are missing? | 0                  | 0   | 0   | 0   | 2                   |
| Rate the overall quality of the guideline report.    | 0                  | 0   | 0   | 1   | 1                   |

| Strongly disagree (1) | (2) | Neutral (3) | (4) | Strongly agree (5) |
|-----------------------|-----|-------------|-----|-------------------|
| I would make use of this guideline in my professional decisions. | 0   | 0           | 0   | 1                 |
| I would recommend this guideline for use in practice.       | 0   | 0           | 0   | 2                 |
cisPCa showed decreased detection favoring mpMRI by 9% (95% CI 17–1, p=0.03).

- In total, 16 cohort studies and the two RCTs mentioned above presented detection rate comparisons favoring mpMRI-TB to TRUS-SB. Estimates for cisPCa showed increased detection favoring mpMRI-TB by 3% (95% CI 0–7, p=0.03). For cisPCa, the estimate showed decreased detection favoring TRUS-SB by 8% (95% CI -11–5%, p<0.00001).

- Of the above cohort studies examining mpMRI-TB vs. TRUS-SB, two were prospective MCTs. A paired diagnostic study (MRI-FIRST) enrolled 251 patients. Patients received both TRUS-SB and mpMRI-TB. There were no significant differences in the detection of csPCa in mpMRI-TB vs. TRUS-SB (32% vs. 30%, p=0.225). However, mpMRI-TB detected significantly less cisPCa than TRUS-SB (6% vs. 20%, p<0.0001). Five percent of csPCa was detected by TRUS-SB that was missed by mpMRI-TB and 8% was detected by mpMRI-TB and missed by TRUS-SB. Thus, detection of csPCa was improved by combining TRUS-SB and mpMRI-TB. Another prospective MCT enrolled 646 men to receive MPMRI followed by TRUS-SB and in-bore MRI-TB. This study showed similar csPCa detection rates (25% vs. 23%, p=0.392); however, cisPCa was detected in significantly fewer patients by mpMRI-TB than in TRUS-SB (14% vs. 25%, p<0.0001). mpRI-TB enabled biopsy avoidance in 49% of patients while missing only 35 cases with csPCa. Meanwhile, TRUS-SB would have overdetectected cisPCa in 20% of patients.

Overall estimates for the studies comparing mpMRI-TB plus TRUS-SB to targeted biopsy alone showed 6% increased csPCa detection when combining the systematic and targeted biopsy (95% CI 4–8, p<0.00001) and 8% increased detection of cisPCa (95% CI 6–10, p<0.00001).

**Table 3. Responses regarding main comments from targeted peer-review**

| Main comments | Responses |
|---------------|-----------|
| One thing that I was uncertain of is the nature of a “negative biopsy” i.e., no prostate cancer seen or does a negative biopsy include GG 1 prostate cancer. It might be worthwhile to make a disclaimer that this guideline is not addressing the use of mpMRI for men diagnosed with cisPCa on previous biopsies. I wonder if a quick sentence to clarify that may ensure clinicians are not expecting recommendations on the use of mpMRI in patients on active surveillance. | We added a phrase: “Patients with an elevated risk of cisPCa (defined as ISUP Gg ≥2), as estimated by available clinical information and tools, such as risk calculators and nomograms, of who are A) biopsy-naive or B) have had a prior negative TRUS-SB, defined as no prostate cancer on biopsy of any grade group.” A definition has been added under qualifying statements for Recommendation 2 “Prior negative TRUS-SB is defined as no cancer of any GG on prior biopsy.” |

cisPCa: clinically insignificant prostate cancer; cs: clinically significant; ISUP: International Society of Urologic Pathology [ISUP] grade group; mpMRI: multiparametric magnetic resonance imaging; TRUS-SB: transrectal ultrasound-guided systematic biopsy.

**Table 4. Results from the profession consultation survey**

| Number 12 (5.9%) | Lowest quality (1) | (2) | (3) | (4) | Highest quality (5) |
|------------------|-------------------|-----|-----|-----|-------------------|
| Rate the overall quality of the guideline report. |                      |     |     |     |                   |
| Strongly disagree (1) | 0 | 0 | 0 | 6 | 6 |
| I would make use of this guideline in my professional decisions. |                      |     |     |     |                   |
| Strongly disagree (1) | 0 | 0 | 2 | 3 | 7 |
| I would recommend this guideline for use in practice. |                      |     |     |     |                   |
| Strongly disagree (1) | 0 | 1 | 0 | 5 | 6 |
complications, including urosepsis, urinary retention, hematuria, and rectal bleeding. The patients that gain the most in the biopsy-naive group are the mpMRI-negative patients. The primary goal is safe avoidance of csPCA detection (over-detection) in this cohort. If no biopsy is performed, it is essential that the patient and urologist commit to ongoing followup, given the risk of under-detection of csPCA by mpPMRI.

- mpMRI-TB combined with TRUS-SB in MRI-positive patients still allows for overall reduction in TRUS-SB in those patients who are mpMRI-negative, with only a slight increase in csPCA detection (8%) while increasing csPCA detection by 5%.

### Recommendation 2

In patients who had a prior negative TRUS-SB and demonstrate a high risk of having csPCA in whom curative management is being considered:

- mpMRI should be performed,
- If the mpMRI is positive, targeted biopsy should be performed. Concomitant TRUS-SB can be considered depending on the patients risk profile and time since prior TRUS-SB biopsy.
- If the mpMRI is negative, consider forgoing a TRUS-SB only after discussion of the risks and benefits with the patient as part of shared decision-making and ongoing followup.

### Key evidence for recommendation 2

Twenty-two trials (all full-text publications) compared mpMRI with a reference standard (n=7) or with TRUS-SB (n=15) for previously negative men. The certainty of the aggregate study evidence for each comparison showed 15 of the 22 studies to be at either low,10,15,37, moderate,7,12,16,21,22,25 or unclear7,19,27-29 risk of bias based on a GRADE approach.48

- Seven studies reported on the diagnostic accuracy of mpMRI for previously negative patients with sensitivities of 78–100%, specificities of 30–100%, PPVs of 36–100%, and NPVs of 69–100%.18,19,25,27-29,37
- The overall improvement in csPCA detection rate for the 15 studies comparing mpMRI-TB alone to TRUS-SB was 5% (95% CI 3–7, p<0.0001), with a reduction of csPCA detection of 7% (95% CI 4–9, p<0.0001).
- The overall improvement in csPCA detection for the five cohort studies comparing mpMRI-TB plus TRUS-SB to mpMRI-TB alone was 5% (95% CI 2–8, p=0.0005).
- The overall improvement across studies in csPCA detection for mpMRI-TB plus TRUS-SB compared with TRUS-SB alone was 11% (95% CI 8–14, p<0.0001).

### Justification for recommendation 2

- All the eligible studies show mpMRI-TB detected a higher number of csPCAs when compared with TRUS-SB.

### Recommendation 3

- mpMRI should be performed and interpreted in compliance with the current Prostate Imaging Reporting & Data System (PI-RADS) guidelines (v2.1 as of summer 2020; see https://www.acr.org/Clinical-Resources/Reporting-and-DataSystems/PI-RADS).
- mpMRI-TB is recommended for MRI lesions with a PI-RADS score of 4 or 5.
- mpMRI-TB or followup is recommended for MRI lesions with a PI-RADS score of 3 depending on the patient’s risk profile.
- Biopsy avoidance should be considered when maximum PI-RADS score is 1 or 2 (see Recommendations 1 and 2).
- A structured mpMRI reporting template as recommended by the PI-RADS committee should be
When a targeted biopsy is being performed, a minimum of two cores should be taken per target, with recommendation of four cores for the index lesion. If multiple lesions are described on mpMRI, the biopsy operator may distribute the number of biopsies to keep a reasonable overall core count during the biopsy session.

- mpMRI interpretation and mpMRI-TB should be performed by experienced operators.
- A provincial quality assurance program should be developed. Until this is in place, practitioners should have some form of local quality assurance in place.

**Key evidence for recommendation 3**

- This recommendation is based on expert opinion and review of the PI-RADS committee guidelines, as well as the Standard Operating Procedure of the American Urological Association (AUA) (https://www.auanet.org/guidelines/mri-of-the-prostate-sop).
- Four cores per lesion have been performed in recent MCTs evaluating mpMRI but if one combines systematic biopsy and four cores/lesion in a patient with multiple mpMRI lesions, the core count will be unreasonable. Prior single-center studies have shown small incremental and diminishing increases in target biopsy yield as core count increases\(^{39-51}\). For this reason, the operator is given discretion in the choice of number of cores per target for non-index lesions or when multiple lesions are present. mpMRI diagnostic performance varies by reader experience, as does mpMRI-TB performance.\(^{52}\)

**Implementation considerations**

Before mpMRI is used in clinical practice, radiologists who perform and interpret mpMRI and physicians treating PCa should be familiar with current PI-RADS prostate MRI minimum technical specifications and reporting standards.\(^{19}\) The patient care pathway in Ontario and the incorporation of mpMRI will need ongoing evaluation for its impact on patient care and outcomes.

The value of mpMRI cannot be realized without attention to quality assurance. Studies have demonstrated only moderate agreement in PI-RADS scoring among readers\(^{30,41}\) and a wide CI for the PPVs of PI-RADS score \(\geq 3\) (35%, 95% CI 27–43%).\(^{42}\) There is currently no quality assurance program in place for mpMRI in Ontario or nationally. Quality standards or development of a quality assurance program is advisable before widespread adoption of these recommendations occurs outside of centers with established expertise. Since prostate mpMRI and mpMRI-TB involve new technologies, skills, and education, knowledge transfer to practitioners should also be considered as part of implementation. In developing a local or provincial quality assurance program, metrics to consider collecting include: target yield (defined as the number of csPCa detected per lesion biopsied), stratified by PI-RADS score, and the number of false-negative mpMRI (i.e., instances where mpMRI is reported as negative and a csPCa is diagnosed at TRUS-SB or prostatectomy). Changes may be required in biopsy collection and reporting at institutions that begin performing mpMRI-TB, where all targeted biopsy specimens are labeled and placed in a separate vial labeled with target number and location.

Although cost-effectiveness and resource allocation issues are beyond the scope of this PEBC guideline, the WG was sensitive to the fact that there are limited MRI resources in Canada. Further study into the resource implications of the implementation of these guidelines is required, especially in the biopsy-naive population addressed in Recommendation 1. The lack of ready access to computer/software-aided fusion biopsy systems may require the use of cognitive fusion biopsy in many centers, which will require additional operator training, though the former are becoming more widely available. Cost savings from biopsy deferral in selected men choosing to forego TRUS-SB with negative mpMRI through shared decision-making could be considerable. Further cost savings may be realized through judicious use of biparametric MRI (bpMRI). The use of bpMRI in Canada is an attractive option to improve access and lower cost; however, this requires rigorous quality assurance, expertise, radiology/pathology feedback, and informed use from all stakeholders, including patients and physicians treating PCa.

The use of bpMRI, meaning omitting the dynamic contrast-enhanced MRI (DCEMRI), from mpMRI remains a controversial subject. This is being considered as an alternative to mpMRI, principally due to resource issues. By omitting DCEMRI, considerable savings in contrast agent cost and MRI time can be achieved. This is highly relevant in the context of the expected increase in volume of prostate MRI, with major implications on Canadian MRI capacity, once mpMRI becomes the anticipated standard of care in biopsy-naive patients. There are both single-center studies
and meta-analyses showing non-inferiority of bpMRI to mpMRI;[46-49] however, concern remains regarding the retrospective nature of these studies and the potential increase in indeterminate (PR-3) interpretations using only bpMRI. Prospective MCT or trials comparing impact on decision-making and outcomes between bpMRI and mpMRI are lacking. For this reason, mpMRI is still recommended as the standard of care; however, given anticipated resource pressures, bpMRI can be performed at the discretion of the radiologist in centers that have demonstrated local bpMRI performance similar to mpMRI.

It is expected that additional compelling evidence on the tradeoffs in diagnostic performance between mpMRI and bpMRI—its relationship to cost, safety, decision-making, and outcomes—will alter practice in the future. As the cost implications of implementing mpMRI in Ontario for biopsynaive patients may be prohibitive, the WG recognized that bpMRI may ease the financial burdens of performing MRI in this population and is a viable alternative to mpMRI if carefully monitored.

## Updating

All PEBC documents are maintained and updated through an annual assessment review process (https://www.cancercareontario.ca/sites/ccocancercare/files/assets/CCOPEBCDARP.pdf).

### Competing interests:
The authors do not report any competing personal or financial interests related to this work.

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Correspondence: Dr. Judy Brown, Program in Evidence-based care, Ontario Health (Cancer Care Ontario), Hamilton, ON, Canada; brown@cmcmaster.ca