

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

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Abstract

This clinical guideline focuses on: 1) the use of multiparametric magnetic resonance imaging (mpMRI) in diagnosing clinically significant prostate cancer (CSPC) in patients with an elevated risk of CSPC and who are biopsy-naïve; and 2) the use of mpMRI in diagnosing CSPC in patients with a persistently elevated risk of having CSPC and who have a negative transrectal ultrasound (TRUS)-guided systematic biopsy.

The methods of the Practice Guideline Development Cycle were used. MEDLINE, EMBASE, the Cochrane Library (1997–April 2014), main guideline websites, and relevant annual meeting abstracts (2011–2014) were searched. Internal and external reviews were conducted.

The two main recommendations are:

- Recommendation 1:** In patients with an elevated risk of CSPC (according to prostate-specific antigen [PSA] levels and/or nomograms) who are biopsy-naïve:
 - mpMRI followed by targeted biopsy (biopsy directed at cancer-suspicious foci detected with mpMRI) should not be considered the standard of care.
 - Data from future research studies are essential and should receive high-impact trial funding to determine the value of mpMRI in this clinical context.
- Recommendation 2:** In patients who had a prior negative TRUS-guided systematic biopsy and demonstrate an increasing risk of having CSPC since prior biopsy (e.g., continued rise in PSA and/or change in findings from digital rectal examination):
 - mpMRI followed by targeted biopsy may be considered to help in detecting more CSPC patients compared with repeated TRUS-guided systematic biopsy.

Introduction

Prostate cancer is the third leading cause of death in Canadian male cancer patients.¹ The current standard method to diagnose clinically significant prostate cancer (CSPC) is transrectal ultrasound (TRUS)-guided systematic biopsy (10–12 cores),² which may over-diagnose non-CSPC or miss CSPC in patients in the first or repeated biopsy settings.^{3,4} The template transperineal mapping biopsy or saturation biopsy technique should be more sensitive, but are more invasive than TRUS-guided systematic biopsy.⁵

Recently, there have been several publications investigating whether multiparametric magnetic resonance imaging (mpMRI) techniques improve the diagnostic accuracy of CSPC.^{6–8} To determine the location of prostate cancer, the mpMRI examination combines imaging features from at least three of the following data sets: T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI), dynamic contrast-enhanced T1-weighted imaging (DCE-MRI), and proton spectroscopy (MRSI).

The Working Group (guideline authors, including one radiologist, one radiation oncologist, one urological surgeon, and one methodologist) of the MRI in Prostate Cancer Guideline Development Group (GDG), in association with the Program in Evidence-Based Care (PEBC) of Cancer Care Ontario (CCO), developed a clinical guideline based on a systematic review.

The clinical guideline focuses on: 1) the use of mpMRI in the diagnosis of CSPC in patients with an elevated risk of CSPC (according to prostate-specific antigen [PSA] levels and/or nomograms) who are biopsy-naïve; and 2) the use of mpMRI in the diagnosis of CSPC in patients with a persistently elevated risk of having CSPC (e.g., continued rise in PSA and/or change in findings from digital rectal examination such that risk is higher than the baseline risk that led to the initial biopsy) who had a negative TRUS-guided systematic biopsy.

Methods

This guideline was developed using the methods of the Practice Guideline Development Cycle.⁹

Literature search

The systematic review was published separately.¹⁰ Briefly, MEDLINE and EMBASE (from January 1997–April 2014), the Cochrane Library, main guideline websites (from January 2010–October 2013), and main relevant annual meeting abstract websites (from 2011–2014) were searched for relevant existing systematic review-based guidelines, systematic reviews, original studies, and conference abstracts.

Internal review

The report was reviewed and approved by the PEBC Report Approval Panel (RAP), which consists of three members: two oncologists with expertise in clinical and methodological issues, and a methodologist.

External review

The PEBC external review process includes a targeted peer-review that is intended to obtain direct feedback on the draft report from a small number of specified content experts, and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Results

Literature search results

No relevant clinical practice guidelines based on a systematic review were found. A total of 12 systematic reviews^{11–22} were relevant and met the preplanned inclusion criteria; however, none of them covered both of the guideline objectives or used the same study selection criteria as ours. A total of 8663 original studies in English were identified and 15 were analyzed.^{2–4,6–8,23–31} The overall quality varied from low to moderate. Fourteen conference abstracts will require followup in future updated versions.^{32–45}

Internal review

The summary of main comments from the RAP and the Working Group's modifications/actions taken in response are showed in Table 1.

External review

Following the approval of the document at internal review, the authors circulated the draft document with modifications, as noted above, to external review participants on April 20, 2015.

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

Main comments	Responses
For the second recommendation, I understand the rationale for wanting to say it may be of benefit, but I do not think that the evidence really supports even a "maybe."	We have added more discussion about why we made the second recommendation under <i>Justifications and considerations</i> .
When I look at the summative evidence and the tables, it seems that the ranges of sensitivity, specificity, positive predictive values, and negative predictive values for biopsy-naïve vs negative TRUS-guided systematic biopsy are similar. Is there a reason why it is yes for one (negative TRUS-guided systematic biopsy) and not yes for the other (biopsy-naïve), like MRI availability?	We have added and revised some sentences in <i>Justifications and considerations</i> under <i>Recommendation 2</i> .
Only two options for diagnosing prostate cancer are discussed in Introduction: TRUS-guided biopsy and the MRI technique. Not clear if there are any others.	We have added the discussion of template transperineal mapping biopsy or saturation biopsy in the first paragraph under <i>Introduction</i> .
Given the notable heterogeneity in results, it is likely that large differences are due to the MRI (equipment and protocol) and radiologist. I think we need to stress that diagnostic performance varies widely and should be assessed at each hospital before the test is used.	We have added a sentence to address this issue in <i>Justifications and considerations</i> under <i>Recommendation 2</i> .
Rooij et al did a systematic review on the cost-effectiveness of prostate MRI and their results suggested comparable healthcare costs in MRI-guided biopsy and TRUS-guided biopsy, but an improved quality of life in the imaging.	Since the cost-effectiveness issue is beyond the PEBC guideline scope and we are not sure whether the methods that Rooij et al used in their review were appropriate and fitted the Ontario context, we will not include this review in our document.

MRI: magnetic resonance imaging; PEBC: Program in Evidence-Based Care; TRUS: transrectal ultrasound.

Targeted peer-review

Responses were received from three reviewers by May 11, 2015. Results of the feedback survey are summarized in Table 2. The main comments from targeted peer-reviewers and the Working Group's responses are summarized in Table 3.

Professional consultation

The consultation period ended on June 1, 2015, with a response rate of 30% (22 participants). Six respondents stated that they did not have interest in this area or were unavailable to review this guideline. The results of the feedback survey from 16 clinical practitioners are summarized in Table 4. The main comments from the consultation and the Working Group's responses are summarized in Table 5.

Practice guideline

The final report reflects an integration of the feedback obtained through the external review process, with final approval given by the MRI in Prostate Cancer GDG.

Recommendation 1

In patients with an elevated risk of CSPC (according to PSA levels and/or nomograms) who are biopsy-naïve:

- mpMRI followed by targeted biopsy (biopsy directed at cancer-suspicious foci detected with mpMRI) should not be considered the standard of care.
- Data from future research studies are essential and should receive high-impact trial funding to determine the value of mpMRI in this clinical context.

Key evidence

- Eight eligible studies^{2,3,6,7,23-26} addressed the first objective. The quality of evidence ranged from poor to moderate. Meta-analyses were not feasible because of the high clinical heterogeneity among studies.
- In two studies^{23,25} with a prevalence of CSPC of 21–30%, the ranges of sensitivity, specificity, positive predictive value, and negative predictive value of mpMRI to detect CSPC were 68–94%, 21–72%, 24–50%, and 83–94%, respectively.
- Two percent to 13% of patients were diagnosed as having CSPC by mpMRI followed by targeted biopsy alone, while 0–7% were diagnosed as CSPC by TRUS-guided systematic biopsy alone.^{2,3,6,24,26}
- A randomized, controlled trial (RCT)⁷ found that mpMRI followed by targeted biopsy plus TRUS-guided systematic biopsy (Group 1) identified more CSPC patients than TRUS-guided systematic biopsy alone in 85 patients (25% vs. 5%; $p=0.01$).
- Pokorny et al²⁶ reported that four patients (5%) were upgraded to CSPC category and 11 (15%) were downgraded to non-CSPC category by mpMRI followed by targeted biopsy; four patients (5%) were upgraded to CSPC and 18 (24%) were downgraded to non-CSPC by TRUS-guided systematic biopsy.
- Pokorny et al²⁶ reported that 0.9% of patients developed urosepsis, and 0.4% required admission for hematuria after TRUS-guided systematic biopsy. Furthermore, 0.7% of patients experienced a vasovagal episode after mpMRI followed by targeted biopsy.

Table 2. Results from the targeted peer-reviewer questionnaire

Questionnaire item	Reviewer ratings (n=3)				
	Lowest quality (1)	(2)	(3)	(4)	Highest quality (5)
Rate the guideline development methods	0	0	0	1	2
Rate the guideline presentation	0	0	0	1	2
Rate the guideline recommendations	0	0	0	1	2
Rate the completeness of reporting	0	0	0	1	2
Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	0	2	1
Rate the overall quality of the guideline report	0	0	0	2	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	2	1
I would recommend this guideline for use in practice	0	0	0	0	3

Table 3. Responses regarding main comments from targeted peer-reviewers

Main comments	Responses
There is no comparison of rates for diagnosis of low-risk or clinically insignificant prostate cancer (an accepted harm with current diagnostic pathways) between mpMRI and standard TRUS biopsies.	This guideline focuses on the use of mpMRI in the diagnosis of CSPC in patients with an elevated risk of prostate cancer who are either biopsy-naïve or who have a previous negative TRUS-guided biopsy. Thus, we have added “clinically significant” into the guideline objectives to clarify this point.
There is a new study: “Siddiqui MM, Rais-Bahrami S, Turkbey B, George AK, Rothwax J, Shakir N, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. <i>JAMA</i> 2015;313:390-7.” I know there are mixed patient populations in this study, but it is the best assessment to date regarding the role of mpMRI in prostate cancer diagnosis and 807 (of 1003) patients had a previous standard biopsy (therefore addressing the second objective); this is a larger patient number than the other studies cited in the guideline combined. As such, I think this study should be discussed in the guideline as it adds support to <i>Recommendation 2</i> .	We need to consistently follow the study selection criteria for all the literature evidence in this guideline. The Siddiqui et al study mixed patient populations for objectives 1 and 2 together, thus it will not be included for analysis even in future updates of this guideline.
I think two limitations on this topic could have been more clearly outlined. The first issue is the problem with the standardization of MR image acquisition and interpretation. Collected data from different studies have been obtained with different techniques (1.5 vs. 3T scanners, endorectal coil vs. no coil, different b values on DWI, different temporal resolution of DCE-MRI, etc.). MRI has also been interpreted by different radiologists completely based on subjective evaluation. These factors significantly limit the quality and reproducibility of the data. The second issue is the problem with targeting accuracy and standardization. The performance of MR-targeted biopsies depends on targeting accuracy as much as the diagnostic performance of MRI.	We have added a sentence to address this issue in <i>Justifications and considerations</i> under <i>Recommendation 2</i> .
Is <i>Recommendation 2</i> evidenced-based, or expert opinions based on the evidence that exists?	<i>Recommendation 2</i> is mainly based on evidence: “all the eligible studies supported the notion that mpMRI followed by targeted biopsy detected a higher number of CSPC when compared with repeated TRUS-guided systematic biopsy. However, most studies did not reach a statistical difference.” Nonetheless, any recommendation will involve guideline authors’ considerations in the Ontario context.

CSPC: clinically significant prostate cancer; DCE-MRI: dynamic contrast-enhanced T1-weighted imaging; DWI: diffusion-weighted imaging; mpMRI: multiparametric magnetic resonance imaging; TRUS: transrectal ultrasound.

Justifications and considerations

The Working Group does not recommend mpMRI followed by targeted biopsy as a standard care in Ontario for the target population for the following reasons:

- The quality of evidence varied from poor to moderate.
- Specificity and positive predictive value of mpMRI were not high.
- The detection rates from mpMRI followed by targeted biopsy were not consistently higher than TRUS-guided systematic biopsy in the eligible studies.
- Although cost-effectiveness and resource allocation issues are beyond the scope of this PEBC guideline, the Working Group was sensitive to the fact that there are limited MRI resources in Ontario and that these recommendations are aimed at a large target population.

Although an RCT⁷ reported that mpMRI followed by targeted biopsy plus TRUS-guided systematic biopsy detected

a statistically significant higher rate of CSPC than TRUS-guided systematic biopsy alone, the study quality was low. The Working Group was, therefore, concerned regarding reproducibility of these data until another properly designed and powered RCT was to be completed. The patients should be informed of the possibility of false-negative results from TRUS-guided systematic biopsy and the potential complications from biopsy.

Recommendation 2

In patients who had a prior negative TRUS-guided systematic biopsy and demonstrate an increasing risk of having CSPC since prior biopsy (e.g., continued rise in PSA and/or change in findings from digital rectal examination):

- mpMRI followed by targeted biopsy may be considered to help in detecting more CSPC patients compared with repeated TRUS-guided systematic biopsy.

Table 4. Results from the professional consultation survey

Survey item	Number (%)				
	Lowest quality (1)	(2)	(3)	(4)	Highest quality (5)
Rate the overall quality of the guideline report	0	0	0	38	62
I would make use of this guideline in my professional decisions	0	0	6	13	81
I would recommend this guideline for use in practice	0	0	6	31	63

Key evidence

- Seven eligible studies^{4,8,27-31} addressed the second objective. The quality of evidence ranged from poor to moderate. It was not feasible to conduct meta-analyses because of high clinical heterogeneity.
- In three studies (n=570)^{8,27,31} with a prevalence of CSPC of 18–34%, the ranges of sensitivity, specificity, positive predictive value, and negative predictive value of mpMRI to detect CSPC were 68–100%, 41–91%, 29–87%, and 79–100%, respectively.
- mpMRI followed by targeted biopsy detected more CSPC patients than repeated TRUS-guided systematic biopsy in all four studies with a total of 516 patients,^{4,28-30} but only one study reached a statistically significant difference (24% vs. 5%; p=0.02).³⁰ Two percent to 21% of patients were diagnosed as CSPC by mpMRI followed by targeted biopsy alone, and 0–5% were diagnosed as CSPC by repeated TRUS-guided systematic biopsy alone.
- The Hoeks et al 2012 study²⁷ stated 0.4% of patients had sepsis and 1.5% experienced a vasovagal reaction after MRI-guided targeted biopsy. In the Pepe et al 2013 study,⁸ no patients had significant complications that needed hospital admission from saturation biopsy.

Justifications and considerations

The quality of evidence ranged from poor to moderate, and there was a low specificity and positive predictive value of mpMRI for patients with prior negative TRUS-guided systematic biopsy and persistently elevated risk of CSPC. However, all the eligible studies supported that mpMRI followed by targeted biopsy detected a higher number of CSPC when compared with repeated TRUS-guided systematic biopsy.

Table 5. Responses regarding main comments from professional consultants

Main comments	Responses
Data still limited for some issues, so this will need to be revisited in a few years.	All PEBC documents are maintained and updated through an annual assessment and subsequent review process. Please see the <i>Updating</i> section.
The next guideline should address the mpMRI for the staging and surgical planning in prostate cancer.	The CCO PEBC has another ongoing guideline to address this concern (Magnetic resonance imaging in staging for prostate cancer).
Was a subgroup analysis for patients with PSA <10 ng/mL studied in <i>Recommendation 1</i> ?	Eight studies focused on patients who were biopsy-naïve. There are no obvious differences in results between the studies only including patients with PSA <10 ng/mL and the studies including patients with various PSA levels. Thus, we did not conduct a subgroup analysis for patients with PSA <10 ng/mL studied in <i>Recommendation 1</i> .
I would consider rewording <i>Recommendation 2</i> : mpMRI followed by targeted biopsy may be considered to help in detecting more clinically significant prostate cancer patients compared with repeated TRUS-guided systematic biopsy. I would suggest replacing "may be considered" with "should be considered."	To date, there is insufficient evidence to support making such a strong recommendation. Thus, we kept the original wording for <i>Recommendation 2</i> .

CCO: Cancer Care Ontario; mpMRI: multiparametric magnetic resonance imaging; PEBC: Program in Evidence-Based Care; PSA: prostate-specific antigen; TRUS: transrectal ultrasound.

Furthermore, variability in mpMRI techniques, the radiologists' clinical experience, and the definitions of mpMRI positive results and CSPC, added more uncertainty to using MRI in the diagnosis of CSPC. Thus, the Working Group members recommend that mpMRI followed by targeted biopsy may be considered to aid in detecting more CSPC patients, but should not be a reflexive next step in this population.

Patients should be informed of the possibility of false-negative and false-positive results from both biopsies, and the potential complications of prostate biopsy. Cost-effectiveness is beyond the scope of the PEBC guideline; the Working Group leaves resource considerations to other decision-makers. Before adopting mpMRI in clinical practice, diagnostic performance in each centre should be assessed, and physicians should be familiar with current international prostate MRI performing and reporting standards.⁴⁶

Updating

All PEBC documents are maintained and updated through an annual assessment and subsequent review process. <https://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=122178>.

Competing interests: Dr. Haider is a member of an advisory board and on the speaker bureau for Bayer. Both Dr. Haider and Dr. Loblaw are principal investigators in several clinical trials related to MRI application in prostate research. The remaining authors report no competing personal or financial interests.

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This paper has been peer-reviewed.

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