Addressing controversial areas in the management of advanced prostate cancer in Canada

Areas of consensus and controversy from the third Canadian consensus forum

Fred Saad*[1], Sebastien J. Hotte*[2], Krista Noonan[3], Shawn Malone[4], Christopher Morash[5], Tamim Niazi[5], Ricardo A. Rendon[6], Bobby Shayegan[7], Naveen S. Basappa[8], Ilias Cagiannos[4], Brita Danielson[8], Guila Delouya[1], Ricardo Fernandes[9], Cristiano Ferrario[5], Antonio Finelli[10], Geoffrey T. Gotto[11], Robert J. Hamilton[10], Jason P. Izard[12], Anil Kapoor[7], Aly-Khan Lalani[2], Luke T. Lavallée[4], Michael Ong[4], Frédéric Pouliot[13], Alan I So[14], Steven Yip[15], Kim N. Chi[16]

[1]Centre Hospitalier de l'Université de Montréal, University of Montreal, Montreal, QC, Canada; [2]Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; [3]BC Cancer Agency, University of British Columbia, Surrey, BC, Canada; [4]The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada; [5]Jewish General Hospital, McGill University, Montreal, QC, Canada; [6]Queen Elizabeth II Health Sciences Centre, Dalhousie University, Halifax, NS, Canada; [7]St. Joseph's Healthcare, McMaster University, Hamilton, ON, Canada; [8]Cross Cancer Institute, University of Alberta, Edmonton, AB, Canada; [9]London Health Science Centre, Western University, London, ON, Canada; [10]Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; [11]Southern Alberta Institute of Urology, University of Calgary, Calgary, AB, Canada; [12]Kingston Health Sciences Centre, Queen's University, Kingston, ON; [13]Quebec City University Hospital Center & Centre de Recherche of Quebec City University Hospital Center, University of Laval, QC, Canada; [14]Prostate Centre at Vancouver General Hospital, University of British Columbia, Vancouver, BC, Canada; [15]Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada; [16]BC Cancer Agency, University of British Columbia, Vancouver, BC, Canada

Co-first authors

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ABSTRACT

INTRODUCTION: The management of prostate cancer (PCa) is rapidly evolving. Treatment and diagnostic options grow annually, however, high-level evidence for the use of new therapeutics and diagnostics is lacking. In November 2022, the Genitourinary Research Consortium held its 3rd Canadian Consensus Forum (CCF3) to provide guidance on key controversial areas for management of PCa.

METHODS: A steering committee of eight multidisciplinary physicians identified topics for discussion and adapted questions from the Advanced Prostate Cancer Consensus Conference 2022 for CCF3. Questions focused on management of metastatic castration-sensitive prostate cancer (mCSPC); use of novel imaging, germline testing, and genomic profiling; and areas of non-consensus from CCF2. Fifty-eight questions were voted on during a live forum, with threshold for "consensus agreement" set at 75%.

RESULTS: The voting panel consisted of 26 physicians: 13 urologists/uro-oncologists, nine medical oncologists, and four radiation oncologists. Consensus was reached for 32 of 58 questions (one ad-hoc). Consensus was seen in the use of local treatment, to not use metastasis-directed therapy for low-volume mCSPC, and to use triplet therapy for synchronous high-volume mCSPC (low prostate-specific antigen). Consensus was also reached on sufficiency of conventional imaging to manage disease, use of germline testing and genomic profiling for metastatic disease, and poly (ADP-ribose) polymerase (PARP) inhibitors for *BRCA*-positive prostate cancer.

CONCLUSIONS: CCF3 identified consensus agreement and provides guidance on >30 practice scenarios related to management of PCa and nine areas of controversy, which represent opportunities for research and education to improve patient care. Consensus initiatives provide valuable guidance on areas of controversy as clinicians await high-level evidence.

INTRODUCTION

In Canada, prostate cancer (PCa) is the most commonly diagnosed cancer in men. It is estimated that around 24 700 men in Canada will be diagnosed with prostate cancer in 2023, and of those, approximately 4700 of them will die from the disease, accounting for nearly 3% of all deaths in men in Canada.[1]

The management of PCa has rapidly evolved in recent years.[2] The development of next-generation imaging modalities provides accurate details on the extent of disease spread, facilitating early detection of metastatic disease.[3] In addition to diagnostic improvements, the introduction of abiraterone acetate, enzalutamide, apalutamide, and darolutamide has changed the prognosis of prostate cancer patients.[4,5] Other new treatment options include poly (ADP-ribose) polymerase (PARP) inhibitors and lutetium-177 (177Lu)-

KEY MESSAGES

- This consensus forum (CCF3) provided recommendations for various scenarios in the management of advanced prostate cancer, including the management of mCSPC, novel imaging, and genetic testing.
- Of 58 questions posed to the multidisciplinary panel of experts during a virtual forum, 31 reached consensus and 21 reached near-consensus.
- Consensus initiatives play a vital role in providing valuable guidance to clinicians on different topics of controversy as they await high-level evidence.
- There were nine areas of controversy that arose from CCF3 that generated significant discussion among prostate cancer specialists.

PSMA-617, which have been shown to significantly prolong progression-free survival and overall survival of advanced PCa patients.

High-level evidence to support new diagnostic and therapeutic strategies are limited, and do not provide adequate guidance for incorporating new treatment and management methods into clinical practice.[6] The Genitourinary Research Consortium (GURC) held the first and second Canadian Consensus Forums in 2018 (CCF1) and 2020 (CCF2), respectively, to consolidate expert opinion on areas of controversy in the management of advanced PCa and identify areas in which additional research is required. The third CCF (CCF3), conducted in 2022, builds upon the success of CCF1 and CCF2, addressing areas such as imaging, PARP inhibitors, and genomic profiling. By assessing the extent of agreement on these topics, CCF3 provides guidance and consensus recommendations for Canadian healthcare providers. Although consensus was reached for over 30 questions, there were nine areas that reached only near-consensus (>50% but <75%) or no consensus (≤50%) that generated significant discussion.

METHODS

A consensus forum was held to determine the level of agreement on various areas related to PCa management among a panel of PCa experts from the Canadian GURC. A steering committee of eight multidisciplinary physicians identified areas for discussion from the Advanced Prostate Cancer Consensus Conference 2022 and adapted questions that were finalized following input from a group of 26 PCa specialists. Questions focused on management of metastatic castration-sensitive prostate cancer (mCSPC), including the use of novel imaging, germline testing and genomic profiling, and re-evaluating areas of non-consensus from CCF2.

Questions were administered in two formats: 1) an electronic questionnaire with 76 questions; and 2) a live forum held in November 2022 with 58 questions. The predetermined thresholds for agreement were set at ≥75% for "consensus agreement," >50% for "near-consensus," and ≤50% for "no consensus," and were applied for both electronic and live forum questions. All voting was analyzed descriptively as counts and percentages of total panel votes. No hypothesis-testing was performed.

RESULTS

The panel consisted of 26 physicians, including urologists/uro-oncologists (n=13, 52%), medical oncologists (n=9, 32%), and radiation oncologists (n=4, 16%). Most of the experts (72%) had ≥10 years of independent practice, with representation from Ontario (52%), Western Canada (28%), Quebec (16%), and Atlantic Canada (4%).

Voting was captured under the following topics:

1. mCSPC
2. Use of prostate-specific membrane antigen-positron emission tomography/computed tomography (PSMA-PET/CT) imaging
3. Germline testing
4. Tumor tissue genomic profiling
5. CCF areas of non-consensus

During the live forum, consensus was reached for 31 questions (53%) (Table 1) and near-consensus was reached for 21 questions (36%) (Supplementary Table 1; available at *cuaj.ca*). During the online voting, consensus was reached for 27 questions (36%) (Table 2). Areas of consensus from the live forum and online voting are described, along with topics, including areas of non-consensus, that generated significant discussion (Table 3). Further results from the live voting forums are presented in the online Appendix (*cuaj.ca*). The results described are not specific recommendations and best-practice statements endorsed by the Canadian Urological Association, but elaborations of the consensus of PCa experts as of the time of the consensus meeting.

mCSPC

Stratification between low-volume and high-volume mCSPC to guide initial therapy

Consensus (100%) was reached on the importance of distinguishing low-volume disease from high-volume disease, based on conventional imaging, for local treatment of the primary tumor and for systemic treatment with docetaxel or an androgen receptor axis-targeting therapy (ARAT). If next-generation imaging was done, most physicians (85%) also recommended distinguishing based on those results. When conventional imaging shows low-volume disease, and next-generation imaging shows high-volume, physicians (88%) recommended treating as per low-volume. All physicians (100%) agreed that the use of docetaxel as systemic treatment for mCSPC should be restricted mainly to patients with high-volume disease and 96% agreed that ARATs should be used, but not limited to, low-volume patients.

Treatment strategy for patients with synchronous low-volume (conventional imaging) mCSPC

For patients with synchronous low-volume (conventional imaging) mCSPC with no symptoms from the primary tumor, physicians (96%) recommended using radical local treatment of the primary tumor with additional systemic therapy (with/without metastases-directed therapy), in addition to androgen deprivation therapy (ADT). All physicians (100%) recommended radiation therapy as local treatment for the primary tumor, while 92% did not recommend any metastases-directed therapy for treating metastatic lesions. Upon further discussion, physicians (92%) agreed that additional systemic treatment should be ARATs, and all (100%) recommended ARAT + ADT for patients who were not recommended for radical local treatment of the primary tumor.

Treatment strategy for patients with metachronous low-volume (conventional imaging) mCSPC

Panelists (92%) agreed that systemic therapy alone (ADT ± ARAT), is the preferred treatment for metachronous low-volume (conventional imaging) mCSPC.

Treatment strategy for patients with high-volume mCSPC

For patients with low baseline prostate-specific antigen (PSA) (≤5 ng/ml) and no neuroendocrine component on biopsy, physicians (92%) recommended triplet therapy (ADT, docetaxel, with an ARAT). Physicians

Table 1. Areas of consensus (≥75%) at live forum

I. Metastatic (M1) castration-sensitive prostate cancer (mCSPC)	
1. It is important to distinguish low-volume from high-volume mCSPC on conventional imaging for local treatment of the primary tumour	100.0%
2. It is important to distinguish low-volume from high-volume mCSPC on next-generation imaging for local treatment of the primary tumour	84.6%
3. Data from the phase III trials (TITAN, ARCHES, and ENZAMET) of apalutamide/enzalutamide can be extrapolated to abiraterone acetate plus prednisone in metachronous mCSPC	79.2%
4. Data from the phase III trials (TITAN, ARCHES, and ENZAMET) of apalutamide/enzalutamide can be extrapolated to abiraterone plus prednisone in low-risk/low-volume mCSPC	92.0%
5. The preferred treatment option in patients without symptoms from the primary tumour with synchronous low-volume (conventional imaging) mCSPC is radical local treatment of the primary tumour plus additional systemic therapy (with/without metastases directed therapy), in addition to ADT	95.7%
6. Metastases directed therapy is not recommended in patients with synchronous low-volume (conventional imaging) mCSPC	91.7%
7. Radiation therapy is the preferred treatment for primary tumour in patients with synchronous low-volume (conventional imaging) mCSPC	100.0%
8. In patients with synchronous low-volume (conventional imaging) mCSPC who will be recommended radical local treatment of the primary tumour (with/without metastases directed therapy), AR pathway inhibitor as the sole additional therapy will be the preferred systemic treatment choice in addition to ADT	92.3%
9. Systemic therapy alone (including ADT with or without ARAT) will be the preferred treatment in patients with metachronous low-volume (conventional imaging) mCSPC	92.0%
10. In patients with metachronous low-volume mCSPC (next-gen imaging) but non-metastatic on conventional imaging, if systemic treatment (ADT with or without additional systemic therapy) without metastases directed therapy is prescribed, preferred systemic therapy duration is intermittent therapy (temporary systemic therapy)	75.0%
11. In patients with mCSPC that have low-volume disease on conventional imaging but high-volume on next-generation imaging, the treatment should be as per low-volume disease	88.0%
12. If triplet therapy (ADT plus docetaxel plus an AR pathway inhibitor) is recommended in patients with mCSPC, it is preferable to administer the drugs concurrently (as for ARASENS, PEACE-1)	95.7%
13. In patients with high-volume (conventional) mCSPC and a low baseline PSA level (e.g., ≤5) before initiation of ADT, and no neuroendocrine component on biopsy, the preferred systemic treatment in addition to ADT is docetaxel plus an AR pathway inhibitor	92.0%
II. Use of PSMA PET/CT imaging	
14. PSMA PET/CT imaging is not recommended for staging of localized prostate cancer	79.2%
15. In a patient with high-risk localized prostate cancer, for whom radical prostatectomy is planned, and who has no evidence of metastatic disease (N0 M0) on PSMA PET/CT, it recommended to perform extended pelvic lymphadenectomy (ePLND)	78.9%
16. In a patient with high-risk localized prostate cancer, for whom radiation therapy of the prostate is planned, and who has no evidence of metastatic disease (N0 M0) on PSMA PET/CT, it is recommended to give radiation therapy to the pelvis	88.2%
17. In patients with mCRPC whose disease is evident on PSMA PET/CT, an additional conventional imaging with CT and bone scintigraphy is recommended before starting a new treatment	88.5%
18. For chemotherapy-fit patients with PSMA imaging-positive mCRPC who meet any relevant criteria for lutetium-PSMA therapy, who have received at least one line of AR pathway inhibitor and one line of taxane-based chemotherapy, lutetium-PSMA therapy is preferred	92.0%
19. For chemotherapy-fit patients with PSMA imaging-positive mCRPC who meet any relevant criteria for lutetium-PSMA therapy, who have received at least one line of AR pathway inhibitor but no chemotherapy, docetaxel is preferred	100.0%

Table 1 (cont'd). Areas of consensus (≥75%) at live forum

III. Germline testing	
20. Germline counselling and/or testing is recommended in patients with metastatic prostate cancer	91.7%
21. Additional germline testing is recommended in patients with a strong positive family history but with no evidence of DNA damage repair alterations and/or MMR alterations in somatic (tumour) testing	95.8%
IV. Tumor tissue genomic profiling	
22. In patients with metastatic prostate cancer, tumour genomic profiling (tissue or ctDNA) should be recommended at the diagnosis of any mCSPC	84.6%
23. If tumour genomic testing is recommended in patients with prostate cancer, the preferred source of tissue is the most recent archival tumour tissue available	76.0%
24. In a patient with a pathogenic BRCA1/2 aberration (germline/somatic or somatic alone), a PARP inhibitor therapy should be introduced after one line of AR pathway inhibitor	84.0%
25. The use of a PARP inhibitor is recommended in majority of patients with a pathogenic, monoallelic somatic (NOT germline alteration identified) BRCA1/2 alteration	81.8%
26. Treatment with platinum-based therapy is recommended in patients with a confirmed pathogenic aberration BRCA1/2 (germline/somatic or somatic alone) without access to a PARP inhibitor	100.0%
III. CCF 2.0 Areas of non-consensus reaching consensus in CCF 3.0	
27. Systemic (ADT) hormonal treatment in combination with salvage radiation therapy is recommended in majority of patients with PSA recurrence after radical prostatectomy	76.2%
28. Patients with suspected metastatic prostate cancer should have histological confirmation	100.0%
29. AR pathway inhibitor along with ADT is the recommended treatment approach in patients with oligorecurrent (metachronous) oligometastatic prostate cancer	92.3%
30. For patients with nmCRPC (M0 CRPC), with an untreated primary, showing PSA progression only during treatment with AR pathway inhibitor, radiation to the primary is recommended as an approach to stretch the time to next subsequent treatment	75.0%
31. Majority of patients should be routinely screened for osteoporosis risk factors (e.g., current/history of smoking, corticosteroids, family history of hip fracture, personal history of fractures, rheumatoid arthritis, >3 alcohol units/day, BMI) or request bone mineral density test before starting on long-term ADT	88.5%

ADT, androgen deprivation therapy; AR pathway, androgen receptor pathway; BMI, body mass index; CT, computed tomography; mCSPC, metastatic castration-sensitive prostate cancer; mCRPC, metastatic castration-resistant prostate cancer; nmCRPC, non-metastatic castration-resistant prostate cancer; PARP inhibitor, poly ADP-ribose polymerase inhibitor; PSA, prostate-specific antigen; PSMA PET-CT, prostate-specific membrane antigen (PSMA) positron emission tomography (PET)-computed tomography (CT).

(96%) indicated that each component of triplet therapy should be given concurrently.

Extrapolating phase 3 data

Consensus was reached that it is appropriate to extrapolate data from phase 3 trials of apalutamide/enzalutamide (TITAN, ARCHES, ENZAMET) to abiraterone acetate plus prednisone in metachronous mCSPC (79%) or low-risk/low-volume mCSPC (92%).

Use of PSMA-PET/CT imaging

Imaging modality for staging and to guide treatment

For the staging of localized PCa, 79% of the physicians agreed that they would not recommend PSMA-PET/CT imaging. Panelists (89%) agreed that additional conventional imaging with CT and bone scintigraphy is necessary before initiating new treatments in patients with metastatic castration-resistant prostate cancer (mCRPC), even if disease is evident on PSMA-PET/CT. Physicians (79%) agreed that management should not be changed for mCRPC patients with a PSMA-PET standardized uptake value (SUV) mean of <10.

PSMA – High-risk localized PCa

In patients with high-risk localized prostate cancer without evidence of metastatic disease (N0 M0) on PSMA-PET/CT where radical prostatectomy is planned, physicians (79%) recommend performing extended pelvic lymphadenectomy. If radiation therapy of the prostate is planned, physicians (88%) recommend treating the pelvis.

In patients with high-risk localized disease with N0, M0 on conventional imaging, but with 1–3 PSMA-PET/CT-positive lesion(s) in the bone (M1) who were suggested radical local treatment, physicians (94%) recommended definitive radiation therapy of the primary with/without pelvic radiation.

Treatment for PSMA imaging-positive mCRPC

For chemotherapy-fit patients with PSMA imaging-positive mCRPC, who have received at least one line of ARAT and one line of taxane-based chemotherapy, physicians (92%) recommended lutetium-PSMA if they meet criteria. For patients who have not received chemotherapy, physicians (100%) agreed that docetaxel should be used. Lutetium-PSMA is recommended by physicians (86%) for patients who received one line of taxane-based chemotherapy and have an impaired renal function (glomerular filtration rate 30–49 mL/min). For mCRPC patients, consensus was reached (88%) that it is safe to recommend treatment with radium-223 after prior treatment with lutetium-PSMA, or vice-versa.,

Germline testing

Germline counselling and/or testing was recommended by panelists (92%) in patients with metastatic PCa; 65% of panelists order genetic testing directly through mainstreaming. The need for genetic testing generated significant discussion (Table 3).

In patients with a strong positive family history, but without evidence of DNA damage repair alterations and/or MMR alterations in somatic (tumor) testing, 96% of physicians recommended additional germline testing on top of *BRCA1/2*. For patients without significant family history, physicians (79%) preferred testing an extended panel.

Tumor tissue genomic profiling

Tumor tissue genomic profiling

Physicians (85%) agreed that tumor genomic profiling should be performed at mCSPC diagnosis, with 75% recommending it be done at time of germline testing as part of a paired tumor/germline analysis. Consensus (76%) was reached that archival tumor tissue be used for the testing.

PARP inhibitors for patients with *BRCA1/2*-mutated cancers

For treatment selection of PARP inhibitor therapy, physicians (82%) suggested using tissue-based testing to evaluate DNA repair gene alterations when no germline variant is identified. The use of a PARP inhibitor in the majority patients with pathogenic, monoallelic somatic (not germline alteration identified) *BRCA1/2* alterations was recommended by physicians (82%), and 84% of physicians agreed that it should be introduced after one line of ARAT. For patients who progress on/after PARP inhibitor therapy, physicians (75%) recommended docetaxel as the next option.

Consensus (100%) was reached that patients with confirmed pathogenic aberration *BRCA1/2* (germline/somatic or somatic alone) mutations who can not access PARP inhibitors should be treated with platinum-based therapy.

Areas of controversy from CCF3

There were nine areas that reached near-consensus or no consensus that generated significant discussion (Table 3).

Doublet or triplet therapy for mCSPC

In patients with synchronous high-volume (conventional imaging) or unequivocal (next-generation imaging) mCSPC, 48% of panelists preferred a doublet therapy (ADT and apalutamide or enzalutamide), while 48% preferred triplet therapy (ADT, docetaxel, and darolutamide or abiraterone acetate). In patients with metachronous de novo high-volume mCSPC, physicians (73%) preferred doublet therapy, while 27% preferred triplet therapy.

Table 2. Areas of consensus (≥ 75%) in online component

Metastatic (M1) Castration-sensitive prostate cancer (mCSPC)	
1. It is important to distinguish low-volume mCSPC from high-volume disease on conventional imaging for selecting systemic treatment with docetaxel; docetaxel should be restricted mainly to high-volume patients	100.0%
2. It is important to distinguish low-volume mCSPC from high-volume disease on conventional imaging for selecting systemic treatment with AR pathway inhibitors; AR pathway inhibitors should be restricted mainly to low-volume patients	96.0%
3. In patients with synchronous low-volume (conventional imaging) mCSPC who were not recommended radical local treatment of the primary tumour, AR pathway inhibitors as the sole additional therapy to ADT should be preferred	100.0%
4. In patients with metachronous low-volume (conventional imaging) mCSPC, if systemic treatment alone is recommended, ADT + AR pathway inhibitor is the preferred option	100.0%
5. In patients with metachronous low-volume (conventional imaging) mCSPC, if systemic treatment in addition to metastases directed therapy is recommended, ADT + AR pathway inhibitor is the preferred option	100.0%
6. In patients with metachronous low-volume (conventional imaging) mCSPC on next-generation imaging and non-metastatic on conventional imaging mCSPC, if systemic treatment alone is recommended, ADT plus AR pathway inhibitor is the preferred option	77.0%
7. In patients with mCSPC and liver metastases, the number of liver metastases does not matter in deciding what to recommend in addition to ADT	88.0%
8. In patients with mCSPC with durable deep remission to ADT plus an AR pathway inhibitor with PSA undetectable (e.g., ≤0.2 at 2–3 years), the physicians do not discuss with the patient the possibility of stopping only the AR pathway inhibitor while continuing ADT	84.0%
9. In patients with mCSPC in whom LHRH agonist in combination therapy with an AR antagonist (enzalutamide/apalutamide) is planned, it is not recommended to start the AR antagonist immediately upfront instead of using bicalutamide for flare protection reasons	91.0%
PSMA PET/CT-based imaging	
10. The data generated by 68Ga-PSMA-PET/CT-based imaging can be extrapolated to other PSMA tracers (e.g., 18F-DCFPyL, 18F-PSMA-1007) for staging purposes	95.0%
11. If radical local treatment is recommended in patients with high-risk localized prostate cancer with N0, M0 on conventional imaging, but with 1–3 PSMA-PET/CT positive lesion(s) in the bone (M1), definitive radiation therapy of the primary with or without pelvic radiation is preferred in	94.0%
12. A PSMA-PET SUV mean of <10 in patients with mCRPC does not change management	79.0%
13. For chemotherapy-fit patients with PSMA imaging-positive mCRPC who meet any relevant criteria for lutetium-PSMA therapy and who have received at least one line of AR pathway inhibitor and one line of taxane-based chemotherapy and have an impaired renal function (GFR 30–49 mL/min), lutetium-PSMA therapy is preferred	86.0%
14. It is safe to recommend treatment with radium-223 after prior treatment with lutetium-PSMA in patients with mCRPC	88.0%
15. It is safe to recommend radioligand treatment with lutetium-PSMA after prior treatment with radium-223 in patients with mCRPC	88.0%

Impact of PSMA-PET imaging in high-risk localized PCa

When N0, M0 on conventional imaging, but with 1–3 PSMA-PET/CT-positive lymph node(s) only in the pelvis (cN1, M0), where radical prostatectomy is planned, the vote was split between radical prostatectomy plus extended lymphadenectomy as planned (58%);

Table 2 (cont'd). Areas of consensus (≥ 75%) in online component	
Germline testing and tumor tissue genomic profiling	
16. When germline DNA testing is recommended in patients with prostate cancer without significant family history, they should be tested for a more extended panel including, for example but not limited to ATM, BRCA1, BRCA2, CHEK2, PALB2, MLH1, MSH2, MSH6, PMS2, RAD51C, HOXB13	79.0%
17. Tumor genomic testing should be done at the same time as germline testing, e.g., as part of a paired tumor/germline analysis	75.0%
18. Tissue-based testing is preferred to evaluate DNA repair gene alterations when no germline variant identified while selecting treatment with PARP inhibitors	82.0%
19. For treatment selection of PARP inhibitor therapy, recently obtained biopsy is preferred for tumor tissue-based (somatic) testing; however, archival tissue would also be sufficient	95.0%
20. For patients with a pathogenic BRCA1/2 aberration (germline/somatic or somatic alone) progressing on or after treatment with a PARP inhibitor in the second-line after one line of AR pathway inhibitor, docetaxel is the next preferred treatment option	75.0%
21. PARP inhibitor therapy is the recommended treatment strategy after AR pathway inhibitor therapy in patients with a confirmed pathogenic aberration BRCA1/2 (germline/somatic or somatic alone)	96.0%
CCF2 areas of non-consensus	
22. For patients with very high-risk prostate cancer ± cN1, cM0 prostate cancer who are receiving radiation therapy as radical locoregional treatment, ADT long-term (24–36 months) should be recommended	84.0%
23. At confirmed PSA level ≥2 ng/mL above nadir (Phoenix criteria), imaging for asymptomatic patients with rising PSA after radical (definitive) radiation therapy is recommended	83.0%
24. For patients with newly diagnosed metastatic (M1) castration-sensitive/naive prostate cancer (CSPC/CNPC), data from STAMPEDE (radiation therapy of the prostate) can not be extrapolated to radical surgery of the prostate	75.0%
25. Radiation treatment volume should encompass the pelvic lymph nodes with radiation therapy of the primary tumour in patients with newly diagnosed low-volume/burden metastatic (M1) castration-sensitive/ naïve prostate cancer (CNPC) who also have clinical pelvic N1	76.0%
26. It is not recommended to add first-generation non-steroidal AR antagonist (NSAA) to ADT for patients with nmCRPC (M0 CRPC)	75.0%
27. A geriatric assessment is not recommended prior to treatment selection in patients with advanced prostate cancer who are ≥70 years old	75.0%

ADT: androgen deprivation therapy; ARAT: androgen receptor axis-targeted therapy; AR: androgen receptor; BMI: body mass index; CT: computed tomography; mCSPC: metastatic castration-sensitive prostate cancer; mCRPC: metastatic castration-resistant prostate cancer; nmCRPC: non-metastatic castration-resistant prostate cancer; PARP inhibitor: poly ADP-ribose polymerase inhibitor; PSA: prostate-specific antigen; PSMA PET-CT: prostate-specific membrane antigen positron emission tomography -computed tomography.

changing treatment plan to radiotherapy of prostate plus pelvis along with long-term ADT and additional systemic therapy with ARAT or docetaxel (23%); and changing to radiotherapy of prostate plus pelvis, along with long-term ADT (18%)

Lutetium-PSMA for chemotherapy-unfit patients with PSMA-PET imaging-positive mCRPC

For chemotherapy-unfit patients with mCRPC (PSMA-PET imaging) who meet criteria for lutetium-PSMA therapy progressing after at least one line of ARAT who cannot enroll in a clinical trial and without any molecular alteration with approved therapy, 50% recommended lutetium-PSMA, while 33% recommended lutetium-PSMA, provided criteria for radium-223 treatment is not met.

Referral to radiation oncologists for salvage radiation therapy post-prostatectomy

In patients with isolated rising PSA only, for whom salvage radiation therapy is planned, physicians (65%) refer to radiation oncology at confirmed PSA level >0.1 ng/mL, whereas 35% refer at >0.2 ng/mL.

Histopathologic confirmation in patients with high suspicion of metastatic disease before initiating ADT

In symptomatic patients with suspected metastatic disease based on PSA levels and/or imaging, physicians (84%) would initiate ADT before histopathologic confirmation; 48% would initiate in a minority, whereas 36% would initiate in a majority of symptomatic patients.

Docetaxel and cabazitaxel after prior docetaxel

For the majority of patients who received docetaxel in castration-sensitive, castration-naive settings, for whom treatment with a second chemotherapy course in the mCRPC setting is suggested, 50% of physicians preferred docetaxel rechallenge in those with prior response (>12 months progression-free interval) to docetaxel, and 50% preferred treatment with cabazitaxel.

CCF2 Areas of non-consensus

Questions from CCF2[7] where consensus was not reached were presented again in CCF3 and are described in the online Appendix (*cuaj.ca*).

DISCUSSION

CCF3 collected perspectives and opinions of Canadian PCa specialists on controversial areas in advanced PCa management to aid clinical decision-making. During CCF3, there were significant discussions on select areas of management that did not reach consensus.

The role of triplet therapy and added value of docetaxel in combination with standard of care (ADT and ARAT) for mCSPC was of particular interest. Data from ARASENS, ENZAMET, and PEACE-1 trials support the addition of an ARAT in patients with high-volume and high-risk mCSPC who are already being

Table 3. Areas of controversy in the management of advanced prostate cancer that generated significant discussion

Practice scenario questions	Responses	
In the majority of patients with metachronous high-volume (on conventional imaging or unequivocal on NGI) mCSPC, what is your preferred systemic treatment?	73%	ADT + Apalutamide OR Enzalutamide
	27%	Triplet therapy combinations (ADT+ Docetaxel + Darolutamide or ADT+ Docetaxel + Abiraterone acetate)
For the majority of post-prostatectomy patients with isolated rising PSA only, if salvage radiation therapy is planned, at what confirmed PSA level do you recommend referring to a radiation oncology to start salvage radiation therapy?	65%	PSA up to 0.1 ng/ml
	35%	PSA up to 0.2ng/ml
Do you order genetic testing?	65%	Yes – directly (mainstreaming)
	26%	Yes – through the genetic counsellor/hereditary cancer program
	9%	No
In patients with mCSPC with durable deep remission to systemic treatment with PSA undetectable (e.g., ≤0.2 at 2–3 years), do you occasionally discuss with the patient the possibility of stopping all systemic therapy (ADT with or without AR pathway inhibitor)?	61%	No
	22%	Yes, stop everything
	17%	Yes, but only stop AR pathway inhibitor (continue ADT)
In the majority of patients with high-risk localized prostate cancer for whom radical prostatectomy is planned with N0, M0 on conventional imaging, but with 1–3 PSMA-PET/CT positive lymph node(s) only in the pelvis (cN1, M0), what is your treatment recommendation?	59%	Radical prostatectomy plus extended lymphadenectomy as planned
	23%	Change to radiotherapy (prostate plus pelvis) plus long-term ADT plus additional systemic therapy (AR pathway inhibitor or docetaxel)
	18%	Change to radiotherapy (prostate plus pelvis) plus long-term ADT
For chemotherapy unfit patients with PSMA imaging-positive mCRPC who meet any relevant criteria for lutetium-PSMA therapy progressing after at least one line of AR pathway inhibitor who cannot enroll in a clinical trial and if there is no molecular alteration with approved therapy, do you recommend lutetium-PSMA therapy?	50%	Yes
	33%	Yes, but only if the patient does not meet the criteria for treatment with radium-223
	17%	No
In patients who received docetaxel in castration-sensitive, castration-naïve setting, what is your treatment approach for the majority of patients for whom you like to treat with a second chemotherapy course in the mCRPC setting?	50%	Docetaxel rechallenge in those with prior response to docetaxel
	50%	Cabazitaxel
In symptomatic patients with high suspicion of metastatic prostate cancer (PSA, imaging), do you initiate ADT before histopathologic confirmation of prostate cancer?	48%	Yes, in a minority of patients
	36%	Yes, in the majority of symptomatic patients
	16%	No
In the majority of patients with synchronous high-volume (on conventional imaging or unequivocal on NGI) mCSPC, what is your preferred systemic treatment?	48%	ADT + Apalutamide OR Enzalutamide
	48%	Triplet therapy combinations (ADT + Docetaxel + Darolutamide or ADT + Docetaxel +Abiraterone acetate)
	4%	ADT + Abiraterone acetate +prednisone

ADT: androgen deprivation therapy; AR: androgen receptor pathway; BMI: body mass index; CT: computed tomography; mCSPC: metastatic castration-sensitive prostate cancer; mCRPC: metastatic castration-resistant prostate cancer; NGI: next-generation imaging; nmCRPC: non-metastatic castration-resistant prostate cancer; PARP inhibitor: poly ADP-ribose polymerase inhibitor; PSA: prostate-specific antigen; PSMA-PET/CT: prostate-specific membrane antigen-positron emission tomography/computed tomography.

considered for an ADT-docetaxel based therapy;[8-10] however, these trials have not shown the benefit of triplet therapy over the current standard of care (ADT plus ARAT). The need for, or the tolerability and impact of chemotherapy, is a complex decision between patient and physician, particularly for elderly patients due to chemotherapy-related toxicities, including neutropenia, anemia, and thrombocytopenia.[11]

Several clinical factors should be considered, including burden of disease, visceral metastases (especially liver), performance status, and synchronous vs. metachronous at presentation.[12-14] A majority of PCa patients in Canada die having never received docetaxel, despite its survival benefits, reflecting challenges of applying trial data to real-world patients who are older with more comorbidities. A Canadian, retrospective, population-based study showed that only 11% of de novo mCSPC patients received ADT-docetaxel when it was the only available ADT-intensification option, and only 44% completed ≥6 cycles of docetaxel.[15] Patients already considered for chemotherapy, such as de novo high-risk or high-volume patients with visceral metastases and/or ≥4 bone lesions with ≥1 beyond the vertebral bodies, should also be considered for triplet therapy.[8,9,14]

Further, whether PSMA-PET/CT results should change therapy plans for high-risk localized patients raised concerns. Some physicians agreed that radical prostatectomy should proceed as planned based on conventional imaging, even though PSMA-PET results may suggest other options. Others argued that radiation therapy with systemic therapy should be considered over surgery, given the advances in radiation therapy.[16] Results from the PATRON trial will provide insight on the role of PSMA-PET/CT in guiding the intensification of therapy in patients at risk of advanced PCa by directly comparing outcomes where treatments were guided by conventional imaging compared to PSMA-PET/CT imaging.[17]

Use of lutetium-PSMA therapy in chemotherapy-unfit mCRPC patients generated discussion, as physicians noted there is no clear definition for chemotherapy-unfit (e.g., which category do patients who refuse chemotherapy belong in?). The VISION trial showed treatment with ^{177}Lu-PSMA-617 plus standard of care prolonged survival in patients with PSMA-positive mCRPC previously treated with at least one ARAT and one or two taxane regimens;[18] however, the majority of Canadian men with mCRPC never receive docetaxel in their lifetime.[19] In contrast, radium trials include a category of post-docetaxel or unfit-for-docetaxel patients.[20] Ongoing clinical trials, such as PSMAFore, SPLASH, and ENZA-P, are adding evidence regarding treatment outcomes of chemotherapy-unfit patients on lutetium-PSMA.[21-23]

With the introduction of PARP inhibitors for the treatment of advanced PCa, identifying suitable patients through germline and somatic testing becomes important.[24-26] Historically, patients were referred to genetics service or hereditary cancer clinics for genetic counselling and testing.[27,28] Mainstreaming is an alternative method for performing germline testing and affords clinicians (oncologists, urologists, oncology surgeons) the advantage of ordering testing after pre-test counselling and taking consent from patients, rather than referring to another provider (e.g., genetic counsellor, clinical geneticist). Physicians acknowledged the desire for mainstream genetic testing; however, in Canada, this approach is limited to Ontario, Quebec, and British Columbia, with the turnaround time for mainstreamed tests ranging 3–6 weeks.[28] Genetic testing by a medical oncologist is required in many provinces, which may delay testing and results until a referral can be made. Regardless of ordering processes, gaps in accessing genetic testing exist and will require addressing to assure equity for all patients with metastatic PCa across Canada.[28]

The need for genetic testing is an important area of discussion due to the effectiveness of PARP inhibitors. Results from the phase 3 PROpel clinical trial demonstrated longer radiographic progression-free survival (rPFS) with olaparib plus abiraterone acetate in mCRPC regardless of homologous recombination repair (HRR)mutational status, though *BRCA*-mutated patients derived greatest rPFS and overall survival benefits.[24,29] The MAGNITUDE trial demonstrated significant rPFS benefit with the addition of niraparib for HRR+ mCRPC.[25] These results build upon findings of the PROfound trial, demonstrating that olaparib improves rPFS in patients with mCRPC with genetic alterations and whose disease had progressed on enzalutamide/abiraterone acetate.[30]

The results of PROpel and MAGNITUDE validate the efficacy of PARP inhibitors plus ARAT for HRR+ mCRPC patients and emphasize the need for genetic testing. In this forum, physicians recommended treatment with PARP inhibitors for *BRCA*-positive prostate cancer, with introduction after one line of ARAT; however, if patients are unable to access PARP inhibitors, platinum-based therapy is recommended. New trial results may expand the role of PARP inhibitors beyond controlling mCRPC.

Panelists discussed whether salvage radiation therapy in post-prostatectomy patients should be recom-

mended to patients with PSA >0.2 ng/ml or earlier. Histology and risk factors are important in determining PSA levels to initiate salvage radiation therapy.[31,32] Results from the RADICALS trial showed no additional benefit with adjuvant radiation therapy after radical prostatectomy compared with early salvage radiation therapy for PSA biochemical progression.[33] Individual consideration is important before suggesting adjuvant or salvage radiotherapy in prostatectomy patients based on factors such as PSA levels, Gleason score, adverse risk factors, nodal status, and the postoperative clinical condition of the patient.[34]

Finally, physicians were divided on using docetaxel again or cabazitaxel for mCRPC patients who received docetaxel in the first-line castration-sensitive/naive setting. Data suggests patients who initially respond to docetaxel and maintain progression-free interval >6 months show good response with docetaxel rechallenge;[35] however, as cabazitaxel is approved in second-line after prior docetaxel, other physicians do not see need for docetaxel rechallenge. Until further evidence demonstrates improved outcomes from cabazitaxel in second-line therapy compared to docetaxel rechallenge, experts agreed that either treatment could be used.

Limitations

Consensus forums have limitations, as physician opinions rely on available evidence, which evolves rapidly. New data may conflict with recommendations over time. Many experts across specialties and regions are involved in this forum, and their opinions are based on individual access to diagnostic techniques and therapies. Nonetheless, a key strength of a live forum setting is the ability for the physicians to discuss queries, obtain clarification, and if needed, re-vote.

CONCLUSIONS

CCF3 provides guidance for addressing controversial topics surrounding PCa management and is aligned with Canadian real-world practice. Initiatives such as CCF3 play an important role in providing valuable guidance to clinicians on areas of controversy in PCa management. Areas of non-consensus represent an opportunity for future research.

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CORRESPONDENCE: Dr. Fred Saad, Centre Hospitalier de l'Université de Montréal, University of Montreal, Montreal, QC, Canada; fredsaad@videotron.ca