APPENDIX

The panelists are from the Genitourinary research consortium (GURC) which is a network of regional prostate cancer centres across Canada that collaborate on research, education, best practices focusing on integrated care models to improve patient care and outcomes. This network consists of a national representation of leading clinicians from academic and community settings who are invited to participate and rotate on a yearly basis.

Other areas of consensus

Use of LHRH agonist: When the use of an LHRH agonist in combination with a novel ARAT is planned for mCSPC patients, physicians (91%) recommended that there is no need to delay starting an LHRH agonist while waiting for the initiation of ARAT (i.e., delay due to funding approval or reimbursement). Bicalutamide can be used for flare protection where necessary.

CCF3 areas of near-consensus

Stratification between synchronous and metachronous mCSPC for treatment decisions: There was near-consensus (74%) that it is important to distinguish synchronous (de-novo) mCSPC from metachronous (relapsing) disease for determining treatment, irrespective of the type of imaging used, in low-volume disease, but only 44% thought this distinction was important for high-volume disease.

Treatment strategy for patients with metachronous low-volume (next-generation imaging) and non-metastatic (conventional imaging) mCSPC: For patients with metachronous low-volume (next-generation imaging) and non-metastatic (conventional imaging) mCSPC, who were prescribed treatment with systemic therapy plus metastases directed therapy, physicians (73%) recommended ADT alone. When prescribing systemic therapy (ADT +/- additional systemic therapy) without metastases directed therapy to these same patients, 75% of panelists suggested intermittent therapy.

Use of PSMA PET/CT Imaging: If PSMA PET/CT is recommended to patients, near-consensus was reached (58%) that it is not necessary to obtain multiparametric MRI (mpMRI) for staging. Near-consensus was reached on recommendations for patients with high-risk localized prostate cancer with N0, M0 on conventional imaging, but with 1-3 PSMA PET/CT positive lymph node(s) only in the pelvis (cN1, M0). In these patients, if radical prostatectomy is planned, 59% of physicians recommend continuing with radical prostatectomy plus extended lymphadenectomy. If definitive radiotherapy of the prostate along with ADT is planned, 57% of physicians recommended radiotherapy of the prostate and pelvis along with long-term ADT in addition to systemic therapy with an ARAT or docetaxel. Following a subsequent question, physicians (72%) recommended abiraterone acetate as systemic therapy used in combination with long-term ADT (2-3 years).

Use of PARP inhibitors: Treatment with a PARP inhibitor is recommended in patients with a pathogenic genomic ATM aberration by 71% of physicians, in patients with a pathogenic genomic CHEK2 aberration by 63% of physicians, and in patients with any other pathogenic DNA damage repair gene alteration by 58% of physicians.

Stopping systemic treatment for patients with deep and prolonged responses: Physicians (61%) voted that they do not discuss the possibility of stopping systemic therapy in mCSPC patients with durable and deep responses.

CCF2 areas of non-consensus

Questions from CCF2[7], in which consensus was not reached, were presented again in CCF3. Several of these areas achieved consensus, as summarized below.

Patients with very high-risk prostate cancer receiving radiation therapy

For patients with very high-risk prostate cancer (+/- cN1, cM0 prostate cancer) who are receiving radiation therapy as radical loco-regional treatment, 84% of physicians preferred long-term treatment with ADT (24–36 months).

Biochemical recurrence after local therapy

At a confirmed PSA level of ≥2 ng/mL above nadir (Phoenix criteria), 83% of the physicians recommend imaging for asymptomatic patients with rising PSA after radical (definitive) radiation therapy.

Management of the primary tumor in the metastatic setting

Three-quarters of the physicians (75%) felt that it is not appropriate to extrapolate data from STAMPEDE (radiation therapy of the prostate) to radical surgery of the prostate in patients with newly diagnosed metastatic (M1) castration-sensitive/naïve prostate cancer (CSPC/CNPC).
In patients with newly diagnosed low-volume/burden mCSPC who also have clinical pelvic N1, 76% of the physicians recommend that the radiation treatment volume encompass the pelvic lymph nodes with radiation therapy of the primary tumor.

Testosterone levels before initiating ADT

Near-consensus (72%) was reached that total testosterone level must be measured in majority of patients before starting first-line treatment with ADT.

Management of non-metastatic CRPC (nmCRPC)

Most physicians (75%) recommend against adding a first-generation non-steroidal AR antagonist (NSAA) to ADT for patients with nmCRPC (M0 CRPC).
For patients with nmCRPC (M0 CRPC), with an untreated primary, showing PSA progression only during treatment with ARAT, 75% of the physicians recommend radiation to the primary as an approach to stretch the time to next subsequent treatment.

Salvage radiation therapy

In post-prostatectomy patients with isolated rising PSA only, if salvage radiation therapy is planned, 65% of the physicians recommend referring these patients to radiation oncology at a confirmed PSA level beyond 0.1 ng/mL. Systemic (ADT) hormonal treatment in combination with salvage radiation therapy is recommended by 76% of physicians in majority of patients with PSA recurrence after radical prostatectomy – 55% of physicians suggest that systemic (ADT) hormonal treatment should be given for less than 1 year in these patients.

Histological confirmation for suspected metastatic prostate cancer

There was a full consensus (100%) that the patients with suspected metastatic prostate cancer should have histological confirmation.

Treatment strategy for oligorecurrent (metachronous) oligometastatic prostate cancer

The recommended treatment approach, as per 92% of physicians, in patients with oligorecurrent (metachronous) oligometastatic prostate cancer is ARAT plus ADT.

Treatment approach with drug-holidays, intermittent, or fixed duration

When the physicians were asked if there is any subset of patients with mCSPC for whom they would consider drug-holidays, intermittent, or fixed duration treatment approach, 54% indicated that they would not recommend this approach, noting that more evidence is required.

Treatment approach based on imaging modalities

Sixty-two percent of the physicians said that they will not or very rarely change the decision to treat the primary tumor in a patient originally classified as low-volume on conventional imaging appears to be high-volume on PET.

Screening for osteoporosis risk factors

Before starting long-term ADT, 89% of physicians will routinely screen most of their prostate cancer patients 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.

Heterogeneity of patients with prostate cancer

Physicians (75%) do not recommend a geriatric assessment prior to treatment selection in patients with advanced prostate cancer who are at least 70 years old.

Comparison with second consensus forum (CCF2)

Results of CCF3 are well-aligned with results from CCF2, however there are a number of recommendations that diverge or expand on those from CCF2. In the results of CCF2, 90% of physicians highlighted the importance of stratification between high-/low-volume disease to guide treatment decision for docetaxel, which was further strengthened in CCF3 (100% physicians). During both the consensus forums, physicians agreed that PARP inhibitors should be used in patients with BRCA1/2 mutations.

During CCF2, no consensus was reached on whether any change in management strategy is necessary if PSMA PET showed high-volume disease but had low-volume disease on conventional imaging. In CCF3, consensus was reached, and the experts agreed that patients should be treated as per low-volume disease.

In CCF2, the question of whether metastases-directed therapy should be considered for patients with low-volume disease who experience worrisome side effects from their ARATs or systemic therapies, 79% agreed to consider metastases-directed therapy; however, they acknowledged that there is a lack of clear evidence guiding this decision and further research is warranted in this area. During CCF3, 92% of physicians recommended not using metastases directed therapy to treat metastatic lesions in patients without symptoms from the primary tumor with synchronous low-volume mCSPC.

Supplementary Table 1. Areas of near-consensus (<50–74%) at live forum	
I. Metastatic (M1) Castration-sensitive prostate cancer (mCSPC)	
1. It is important to distinguish synchronous (de-novo) metastatic (M1) castration-sensitive prostate cancer (CSPC) from metachronous (relapsing) metastatic prostate cancer (recurring after radical local therapy given with curative intent in the M0 setting) for making treatment decisions, irrespective of imaging used in low-volume disease	73.9%
2. It is not important to distinguish synchronous (de-novo) metastatic (M1) castration-sensitive prostate cancer (CSPC) from metachronous (relapsing) metastatic prostate cancer (recurring after radical local therapy given with curative intent in the M0 setting) for making treatment decisions, irrespective of imaging used in high-volume disease	56.0%
3. There is no upper limit of bone metastases, based on next-generation imaging, while recommending local treatment of the primary tumor in mCSPC	60.0%
4. In patients with metachronous high-volume (on conventional imaging or unequivocal on NGI) mCSPC, ADT in addition to apalutamide or enzalutamide is the preferred systemic treatment	73.1%
5. Patients with synchronous high-volume mCSPC, presence of liver metastases and/or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis should be considered for chemotherapy	72.0%
6. In patients with metachronous low-volume mCSPC on next-generation imaging and non-metastatic on conventional imaging, if systemic treatment in addition to metastases directed therapy is prescribed, ADT alone should be the preferred option (assume in a patient with high risk [rapid PSA DT, High Gleason score] metachronous low volume PSMA PET positive only)	72.7%
7. In patients with mCSPC with durable deep remission to systemic treatment with PSA undetectable (e.g., ≤0.2 at 2-3 years), physicians do not want to discuss with selected patients the possibility of stopping all systemic therapy (ADT with or without AR pathway inhibitor)	60.9%
II. Use of PSMA PET/CT imaging	
8. If PSMA PET/CT is recommended for staging of localized prostate cancer, it is not necessary to obtain a mpMRI for local tumor staging	58.3%
9. In 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), radical prostatectomy plus extended lymphadenectomy as planned should be recommended	59.1%

10. In patients with high-risk localized prostate cancer for whom definitive radiotherapy of the prostate plus ADT 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), radiotherapy of the prostate and pelvis along with long-term ADT plus additional systemic therapy (AR pathway inhibitor or docetaxel) should be recommended	56.5%
11. If additional systemic therapy in combination with ADT (2-3 years) is recommended in patients with high-risk localized prostate cancer with N0, M0 on conventional imaging, but with 1-3 PSMA PET/CT positive lymph node(s) only in the pelvis (cN1, M0), abiraterone acetate is preferred	72.2%
II. Germline testing	
12. Genetic testing is ordered directly through mainstreaming	65.2%
III. Tumor tissue genomic profiling	
13. Treatment with a PARP inhibitor is recommended in the course of the disease in patients with a pathogenic genomic ATM aberration (germline/somatic or somatic alone)	71.4%
14. Treatment with a PARP inhibitor is recommended in the course of the disease in patients with a pathogenic genomic CHEK2 aberration (germline/somatic or somatic alone)	62.5%
15. Treatment with a PARP inhibitor is recommended in the course of the disease in patients with any other pathogenic DNA damage repair gene alteration (germline/somatic or somatic alone) (e.g., BARD1, BRIP1, CHEK1, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L)	58.3%
III. CCF 2.0 Areas of non-consensus discussed during CCF 3.0	
16. Post-prostatectomy patients with isolated rising PSA only in whom salvage radiation therapy is planned should be referred to radiation oncology at PSA beyond 0.1 ng/mL	65.0%
17. Systemic (ADT) hormonal treatment should be given for less than 1 year when recommended in combination with salvage radiation therapy	55.0%
18. Total testosterone level should be measured in majority of patients before starting first-line treatment with ADT	72.0%
19. Drug-holidays, intermittent, or fixed duration treatment approach is not recommended in patients with mCSPC until more evidence becomes available	54.2%
20. PET does not change or very rarely changes the decision to treat the primary tumor in a patient originally classified as low-volume on conventional imaging now appears to be high volume on PET	61.5%

ADT: androgen deprivation therapy; ARAT: androgen receptor axis-targeted 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 positron emission tomography-computed tomography

Supplementary Table 2. Areas of no consensus (≤50%) at live forum	
I. Metastatic (M1) castration-sensitive prostate cancer (mCSPC)	
1. For selection of local and or systemic treatment in mCSPC if staging by PSMA PET/CT shows 4-10 bone metastases and a bone scintigraphy has not been done, do you recommend an additional bone scintigraphy?	
Yes, for definition of low- or high-volume mCSPC	*19.2%*
Yes, as a baseline for future monitoring	*15.4%*
Yes, for both purposes	*46.2%*
No, PSMA PET/CT is enough	*19.2%*
2. In the majority of patients with synchronous high-volume (on conventional imaging or unequivocal on NGI) mCSPC, what is your preferred systemic treatment?	
ADT + apalutamide OR enzalutamide	*47.8%*
ADT + abiraterone acetate	*4.3%*
ADT + docetaxel	*0.0%*
Triplet therapy combinations (ADT + Docetaxel + Darolutamide or ADT + Docetaxel + Abiraterone acetate)	*47.8%*
II. Use of PSMA PET/CT imaging	
3. 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?	
Yes	*50.0%*
Yes, but only if the patient does not meet the criteria for treatment with radium-223	*33.3%*
No	*16.7%*
III. CCF 2.0 Areas of non-consensus	
4. Which duration of ADT do you most often recommend with adjuvant radiation therapy in the majority of patients with pN1 disease?	
Less than 1 year	*15.0%*
1 to 2 years	*40.0%*
2 years or longer	*35.0%*
ADT lifelong	*5.0%*
I don't recommend adjuvant radiation therapy	*5.0%*
5. In symptomatic patients with high suspicion of metastatic prostate cancer (PSA, imaging) do you initiate ADT before histopathological confirmation of prostate cancer?	
Yes, in the majority of symptomatic patients	*36.0%*
Yes, in a minority of patients	*48.0%*
No	*16.0%*

6. 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?	
Docetaxel re-challenge in those with prior response to docetaxel	*50.0%*
Cabazitaxel	*50.0%*

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