

# Current topics in radiotherapy for genitourinary cancers: Consensus statements of the Genitourinary Radiation Oncologists of Canada

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## Abstract

**Introduction:** The biennial meeting of the Genitourinary Radiation Oncologists of Canada (GUROC) took place November 22–23, 2019. A consensus-building session was held during the meeting addressing topics of emerging interest or controversy in the management of genitourinary malignancies.

**Methods:** Draft statements were debated among all meeting attendees in an open forum with anonymous live voting. Statements for which there was at least 75% agreement among attendees were adopted as GUROC consensus.

**Results:** Four evidence-based consensus statements were developed. First, the use of prostate radiotherapy is recommended in the setting of de novo low-volume metastatic hormone-sensitive prostate cancer to improve overall survival. Second, the support of ongoing randomized trials evaluating metastasis-directed ablative local therapy in oligometastatic prostate cancer is recommended; where such trials are available, off-trial use of oligometastasis-directed ablative radiotherapy at this time is strongly discouraged. Third, routine use of prostate-rectal hydrogel spacer devices in patients with localized prostate cancer planned to receive external beam radiotherapy is not recommended; instead, selective use in patients at highest risk of rectal toxicity may be considered. Finally, multidisciplinary consultation is recommended for all patients with newly diagnosed localized muscle-invasive bladder cancer.

**Conclusions:** The GUROC consensus statements provide practical guidance to clinicians in areas of current controversy in the management of prostate and bladder cancer, and it is hoped that their implementation will contribute to improved outcomes in real-world practice and greater support of clinical trials.

## Introduction

Genitourinary Radiation Oncologists of Canada (GUROC) was founded in November 2000 and serves as a national forum for academic exchange and advocacy in genitourinary radiation oncology. The organization convenes a biennial meeting, the latest of which was held November 22–23, 2019 in King City, Ontario. The conference was attended by 76 Canadian radiation oncologists and clinical fellows, representing nine provinces, with expertise in the treatment of genitourinary malignancy. The attendees took part in a range of presentations, discussions, and workshops. Sessions were held on recent developments in the management of prostate, bladder, and kidney cancer, with a focus on emerging and established indications for the use of radiotherapy; technical innovations in radiation oncology practice; use of novel molecular imaging modalities; and use of certain systemic therapies. A plenary lecture was given by the Chair of the Genitourinary Cancer Committee of NRG Oncology.

The conference concluded with a consensus-building session in which statements were developed for endorsement by the GUROC meeting attendees on topics of emerging interest or controversy. In this session, four draft statements were debated in an open forum and anonymous live voting was conducted by hand-held devices. Two statements concerned the use of local therapy in metastatic prostate cancer, a third statement concerned the use of spacer devices in localized prostate cancer to be treated with radiotherapy, and a fourth statement concerned multidisciplinary care in muscle-invasive bladder cancer. Voting on each statement was binary: agreement or disagreement. Statements for which there was at least 75% agreement among meeting attendees were adopted as GUROC consensus. Where there was less than 75% agreement, the statement was revised

and additional rounds of voting were held until consensus was achieved. This paper presents the consensus statements developed at the meeting, along with a discussion of the relevant evidence underpinning the statements.

## Metastatic prostate cancer

### Question 1: Should patients with newly diagnosed low-volume metastatic hormone-sensitive prostate cancer be offered primary tumor-directed local therapy?

- Patients with de novo metastatic prostate cancer and low-volume disease should be referred to a radiation oncologist for consideration of prostate radiotherapy. Low-volume disease is specified according to the conventional CHAARTED trial definition as those not possessing high-volume disease, where the latter is defined as the presence of four or more bone metastases — at least one of which is outside of the axial skeleton — or the presence visceral metastases (100% agreement).
- The role for radical prostatectomy in this setting is unclear and its equivalence to prostate radiotherapy has not been established. The results of randomized trials evaluating radical prostatectomy in metastatic hormone-sensitive prostate cancer are awaited (100% agreement).

### Evidence summary and discussion

Until recently, it was considered nearly an axiom in oncology that treatment of the primary tumor in the face of distant metastatic disease was futile. In prostate cancer, the publication of two randomized trials in 2018 has altered this view. The larger of the two trials, Arm H of the STAMPEDE trial conducted in the U.K., investigated the addition of prostate radiotherapy to standard-of-care systemic therapy (androgen deprivation therapy [ADT] with or without docetaxel) in patients with newly diagnosed metastatic prostate cancer.<sup>1</sup> Radiotherapy was delivered to the prostate at near-radical doses: 55 Gy in 20 daily fractions over four weeks or 36 Gy in six fractions given weekly. For the study population as a whole (n=2061), the addition of prostate radiotherapy to systemic therapy did not improve overall survival (OS) compared to systemic therapy alone (hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.80–1.06, p=0.266). However, in a pre-planned analysis of the subgroup with low metastatic burden, specified using the conventional CHAARTED trial definition,<sup>2</sup> prostate radiotherapy yielded a significant OS benefit (HR 0.68, 95% CI 0.52–0.90, p=0.007). Survival at three years was 73% without radiotherapy and 81% with radiotherapy. The similarly designed but much smaller HORRAD randomized trial (n=432), conducted in the Netherlands, remarkably found a nearly identical benefit for prostate radiotherapy (delivered to 70 Gy in 35 fractions

over seven weeks or 57.76 Gy in 19 fractions three times weekly) in a subgroup of patients with fewer than five bone metastases, but which lacked statistical significance owing to limited power (HR for OS 0.68, 95% CI 0.42–1.10).<sup>3</sup> Given the congruence of the results across these two randomized trials, the magnitude of the benefit observed, and the biological rationale for a greater benefit for radiotherapy in those with lesser-volume disease, there was consensus among GUROC attendees that prostate radiotherapy should be offered as a new standard of care in patients with low metastatic burden. It is of note that an international, multi-disciplinary panel of experts in advanced prostate cancer has also strongly endorsed prostate radiotherapy in this setting.<sup>4</sup>

The precise mechanisms by which radiotherapy improves survival in low-volume metastatic prostate cancer remain unclear. There is a complex interplay between primary tumor and sites of distant metastatic disease. In preclinical models, primary tumors are not merely a source of seeding but also elaborate factors that enter the circulation and prime the so-called “pre-metastatic niche” at distant sites, rendering them more receptive to metastasis; radiotherapy might abrogate this signaling.<sup>5</sup> Beyond this, the survival benefit might be explained by radiotherapy-mediated modulation of the immune response. It is uncertain whether the benefits seen with radiotherapy would extend to radical prostatectomy and, therefore, use of the latter remains investigational. Southwest Oncology Group 1802 (NCT03678025) is another large-scale, randomized trial investigating in the role of definitive local therapy, including radical prostatectomy, in metastatic hormone-sensitive prostate cancer of any disease volume. This trial is currently accruing.

Finally, it should be noted that the systemic therapy landscape for the initial treatment of de novo metastatic prostate cancer has changed since Arm H of the STAMPEDE trial completed its accrual. Specifically, potent androgen receptor (AR) pathway inhibitors, including abiraterone acetate, enzalutamide, and apalutamide, have been shown to improve OS in the initial management metastatic hormone-sensitive prostate cancer.<sup>6–9</sup> It is unclear whether the combination of prostate radiotherapy and a potent AR pathway inhibitor, when added to ADT, will improve survival compared to the addition of either therapy alone. Fortunately, PEACE1 (NCT0195743), a 2x2 factorial randomized trial, is separately addressing the addition of 1) prostate radiotherapy and 2) abiraterone and prednisone to ADT and docetaxel in this setting. It has completed accrual and will ultimately provide important data in this regard.

### Question 2: Should patients with oligometastatic prostate cancer be offered metastasis-directed ablative local therapy?

- Patients with oligometastatic prostate cancer should be referred to a radiation oncologist and, whenever

possible, should be offered participation in randomized trials evaluating ablative local therapy (98% agreement).

- Where clinical trials are available, treatment with oligometastasis-directed ablative radiotherapy outside of these trials is strongly discouraged. Where clinical trials are unavailable or for patients ineligible for trials, oligometastasis-directed radiotherapy should only be offered after case discussion in a multidisciplinary conference (93% agreement).

## Evidence summary and discussion

The oligometastatic hypothesis proposes the existence of an intermediate disease state between localized disease and widely metastatic disease.<sup>10</sup> An implication of such a state is that comprehensive treatment of all sites of metastatic disease with ablative local therapy might prolong disease control, improve survival, and possibly even achieve cure in some cases. Exactly what constitutes the oligometastatic state is a matter of some debate; a recently published European consensus document has developed a standard nomenclature for characterizing and classifying oligometastatic presentations.<sup>11</sup>

There has been intensive study of oligometastasis-directed local therapy across a range of solid malignancies in recent years. The Canadian-led, phase 2 SABR-COMET trial randomized patients 1:2 to standard palliative therapy alone or standard palliative therapy plus comprehensive stereotactic ablative radiotherapy (SABR) to all metastatic sites in patients with 1–5 metastases from a range of histologies.<sup>12</sup> Prostate cancer patients accounted for 16 of the 99 patients enrolled, but of note, 14 of the 16 were randomized to the SABR arm. Improvements in progression-free survival (HR 0.47, 95% CI 0.30–0.76,  $p=0.0012$ ) and OS (HR 0.57, 95% CI 0.30–1.10,  $p=0.090$ ) were observed in the SABR arm that met the prespecified threshold for positivity given the phase 2 screening design. The authors concluded, however, that large-scale phase 3 trials are needed to definitively demonstrate an OS benefit for SABR.

Two randomized phase 2 trials of ablative therapy have been completed that were limited to patients with oligometastatic hormone-sensitive prostate cancer. Both trials entered only patients with metachronous oligometastatic (or “oligorecurrent”) disease that had developed after initial therapy for localized prostate cancer. In the STOMP trial, conducted in Belgium, 62 patients with asymptomatic, non-castrate, oligometastatic relapses consisting of no more than three metastatic lesions seen on choline positron emission tomography-computed tomography (PET-CT), were randomized 1:1 to comprehensive metastasis-directed therapy (surgery or SABR) or observation.<sup>13</sup> The primary endpoint was survival free of ADT, and metastasis-directed local therapy was shown to significantly prolong this compared to observation (HR 0.60, 80% CI 0.40–0.90,  $p=0.11$ ), again meeting

the threshold established for the phase 2 screening design. Longer-term results have been presented in abstract form; at five years, 34% of those that received metastasis-directed local therapy were free of ADT compared to just 8% of those randomized to observation, suggesting that durable disease control can be achieved with ablative local therapy alone in a proportion of patients.<sup>14</sup> Recently, the results of the phase 2 ORIOLE trial from Johns Hopkins University have been published.<sup>15</sup> Similar in design to STOMP, 54 patients with non-castrate oligometastatic recurrences of up to three lesions on conventional imaging were randomized 2:1 to SABR or observation. The primary endpoint was the proportion free of biochemical, imaging, or symptomatic progression at six months: 19% of those randomized to SABR and 61% of those randomized to observation experienced progression by this time point ( $p=0.005$ ). Progression-free survival was also improved by SABR (HR 0.30, 95% CI 0.11–0.81,  $p=0.002$ ).

While the results of ablative radiotherapy for oligometastatic prostate cancer reported to date in these early-phase trials are promising, they are by no means practice-changing, and the evidentiary base overall remains weak. The completed trials are small, have employed unconventional endpoints, and compare SABR to an observation approach with no active therapy. Definitive, large-scale, randomized trials with standard-of-care comparators are needed to assess whether ablative local therapy truly improves hard oncological outcomes. Fortunately, several such trials are underway in both the hormone-sensitive and castration-resistant settings. The PLATON study (NCT03784755) conducted by the Canadian Cancer Trials Group (CCTG) is one such trial in which patients with hormone-sensitive oligometastatic prostate cancer — either synchronous or metachronous and defined by either molecular or conventional imaging — are randomized to standard systemic therapy (ADT with or without docetaxel or a potent AR pathway inhibitor) or standard systemic therapy plus comprehensive ablative local therapy (either SABR or surgery). Patients with up to five metastatic lesions are eligible. All patients with synchronous, low-volume disease by the CHARTED definition also are required to receive prostate radiotherapy or surgery. The study’s primary endpoint is failure-free survival with an accrual goal of 410 patients. There was a strong consensus among GUROC meeting attendees that enrollment in trials such as PLATON (CCTG PR.20) is the preferred management of men with hormone-sensitive oligometastatic prostate cancer at present.

## Localized prostate cancer

**Question 3: Should prostate-rectal spacer devices be used in patients with localized prostate cancer receiving external beam radiotherapy?**

- Routine use of prostate-rectal spacer devices such as SpaceOAR® is not recommended (80% agreement).
- Judicious use of prostate-rectal spacer devices such as SpaceOAR® should be considered in certain clinical scenarios (78% agreement):
  - o In patients at elevated risk of toxicity from radiotherapy (e.g., those on anticoagulants) or at risk of severe toxicity from radiotherapy (e.g., patients with inflammatory bowel disease) where no alternative to radiotherapy exists.
  - o Where rectal dose-volume constraints cannot be met in the absence of a spacer device, regardless of the dose-fractionation regimen being used.

### Evidence summary and discussion

Despite technical innovations in external beam radiotherapy planning and delivery, late rectal adverse effects remain the major dose-limiting toxicity from prostate radiotherapy. These effects range from altered bowel habit with urgency, frequency, or loose stools; radiation proctitis with rectal bleeding; and, rarely, fecal incontinence. Each can negatively affect health-related quality of life.<sup>16</sup> There is an unmet need for interventions to further reduce the risk and severity of radiotherapy-related rectal complications. To this end, several strategies have been investigated to reduce the radiation dose received by the rectum, including the transperineal insertion of biodegradable spacers that increase the distance between the prostate and anterior rectal wall.

To date, only one such hydrogel spacer device, SpaceOAR® (Boston Scientific Corporation, Marlborough, MA), has been evaluated in a randomized clinical trial. A total of 222 patients with low-risk and intermediate-risk prostate cancer planned for conventionally fractionated intensity-modulated radical external beam radiotherapy were randomly assigned 2:1 in a blinded fashion at the time of intraprostatic fiducial marker placement to insertion of the hydrogel rectal spacer or no spacer insertion.<sup>17</sup> The primary efficacy endpoint was dosimetric, namely, the proportion of patients achieving at least a 25% reduction in rectal volume receiving at least 70 Gy (rectal V70), with a threshold proportion of 70% established for positivity. Ultimately, this endpoint was met, with 97.3% of patients randomized to the hydrogel spacer achieving the required reduction in rectal V70. The primary safety endpoint was the proportion of patients experiencing grade  $\geq 1$  rectal or procedural adverse events in the first six months of follow-up. It too was met; the observed proportions for spacer and control patients were 34.2% and 31.5%, respectively ( $p=0.7$ ).

Results at a median followup of three years were subsequently reported, with 63% of both control and spacer patients evaluable.<sup>18</sup> Cumulative incidence of grade  $\geq 2$  rectal toxicity at three years was 5.7% in the control group and 0% in the spacer group ( $p=0.012$ ). Bowel quality of life

(QOL) at three years favored the spacer group, with a 5.8-point drop in the Expanded Prostate Cancer Index (EPIC) bowel QOL summary score compared to the control group ( $p<0.05$ ), exceeding the prespecified threshold for a minimally important difference. While this trial represents the highest-quality evidence available, the relatively small absolute reductions in clinically significant rectal toxicity and modest absolute gains in bowel QOL were such that the GUROC attendees deemed the accumulated evidence to be insufficient to support routine use of SpaceOAR® or other spacer devices for all patients receiving external beam radiotherapy. The absolute benefits of this technology are liable to be greater in scenarios where there is greater baseline risk of developing rectal toxicity from radiotherapy, such as those described above, and judicious use of hydrogel spacers in these settings should be considered in concert with other rectal dose-reduction strategies. Hydrogel spacers may also be considered for use with ultrahypofractionated prostate radiotherapy (SABR), given the paucity of long-term comparative toxicity data from randomized trials for this treatment approach at this time. It is acknowledged, however, that robust data are lacking to quantify the benefit of spacer insertion both in the high-risk subgroups noted above and in patients receiving SABR. Further study is warranted.

### Muscle-invasive bladder cancer

#### Question 4: Which specialists should patients with newly diagnosed muscle-invasive bladder cancer (MIBC) be seen by prior to finalizing a treatment plan?

- Patients diagnosed with muscle-invasive bladder should be seen in consultation by a urologist/uro-oncologist, medical oncologist, and radiation oncologist to discuss all available treatment options, ideally in a multidisciplinary clinic setting, and in centers with expertise in the care of these patients (100% agreement).

### Evidence summary and discussion

MIBC is an aggressive malignancy and is currently the fifth leading cause of cancer death in Canadian men.<sup>19</sup> Radical cystectomy is the traditional and most commonly used definitive local therapy for MIBC and is often combined with neoadjuvant chemotherapy. There is a growing body of literature, however, to support the use of tri-modality therapy comprising maximal transurethral resection followed by bladder radiotherapy and concurrent chemotherapy. No modern randomized data exist comparing cystectomy with this tri-modality treatment approach. However, when used in appropriately selected patients, such an approach offers the quality of life advantages afforded by bladder preservation without appearing to compromise oncological outcomes.<sup>20</sup>

In the absence of level I evidence, a recent propensity score-matched analysis comparing radical cystectomy with tri-modality therapy was undertaken within the multidisciplinary bladder cancer clinic at Princess Margaret Cancer Centre.<sup>21</sup> Propensity scores took account of clinical stage, performance status, comorbidity, age, and other known prognostic factors. A total of 112 patients were included in the analysis, and five-year bladder cancer-specific survival was 73.2% in those managed with cystectomy and 76.6% in those receiving tri-modality therapy ( $p=0.49$ ), suggesting similar oncological outcomes with these two approaches.

Substantial unexplained geographic variation remains in local and systemic therapy use for MIBC, suggesting factors beyond the evidentiary base may influence treatment decisions. A recent population-based study in Ontario, for example, showed that only one-third of MIBC patients treated with curative intent were seen in consultation by a radiation oncologist during their care and only 10% of those that underwent cystectomy saw a radiation oncologist preoperatively.<sup>22</sup> Rates of radiation oncology consultation prior to any radical therapy varied widely across regions, ranging from 20–57%. Similarly, the rate of referral to medical oncology prior to cystectomy was only 32% in a similar population-based study conducted in Ontario.<sup>23</sup>

While it is evident that MIBC is a disease that requires multidisciplinary assessment for optimal management, there is no direct evidence as to the best model for delivery of this care.<sup>24</sup> A randomized trial conducted in the U.K. comparing radical cystectomy and radical radiotherapy after neoadjuvant chemotherapy used a multidisciplinary care model for patients, but unfortunately closed prematurely due to lack of accrual.<sup>25</sup> In the Princess Margaret analysis cited above, almost 80% of patients required further investigations after initial consultation before a final management recommendation could be made.<sup>21</sup> Of the 20% where a decision could be made about management, it was a minority (15%) where it was felt that an actual change in management occurred as result of the multidisciplinary bladder cancer clinic. Although it might not be necessary to institute this specific care model to facilitate multidisciplinary input, these data do certainly support the value of multidisciplinary care, as the vast majority of patients were referred from the uro-oncology community as opposed to the primary care community. The GUROC meeting attendees unanimously endorsed the concept of multidisciplinary consultation for all patients with localized MIBC that are candidates for definitive treatment, ideally within the context of a dedicated multidisciplinary clinic, such that all patients can be presented with the full range of treatment options available to them.

## Conclusions

The use of radiotherapy in the management of genitourinary cancers is evolving rapidly. First, prostate cancer is the only malignancy for which radiotherapy directed at the primary tumor, with near-radical doses, has now been shown convincingly in randomized trials to improve OS, albeit in a subset of patients with low metastatic burden. These results herald a new treatment paradigm that will undoubtedly spur investigation of this approach across other malignancies. Second, improvements in imaging and computing in recent years have permitted the development of high-precision, high-dose-per-fraction radiotherapy techniques such as SABR. While these ablative approaches have been quite widely studied in the primary treatment of localized prostate cancer<sup>26</sup> — a subject not discussed in detail in these statements — there is great enthusiasm for their application in the treatment of oligometastatic prostate cancer. However, the evidence base at this time remains immature, and support of large-scale, randomized trials is required to definitively assess the value of this treatment strategy. Third, a number of technological improvements, such as prostate-rectal spacer devices, have helped enhance the therapeutic ratio for prostate cancer radiotherapy, and their continued development in subpopulations that stand to benefit most from their use is encouraged. Finally, in the view of GUROC, radiotherapy remains underused in the management of localized MIBC, notably as part of trimodal bladder preservation approaches. A greater emphasis on multidisciplinary care in this population is encouraged.

In this rapidly evolving landscape, it is hoped that these consensus statements will provide guidance to clinicians involved in the care of patients with genitourinary cancers.

**Competing interests:** Dr. Morgan has been an advisory board member for and received honoraria from Astellas, Bayer, and Janssen; and has participated in clinical trials supported by Janssen. Dr. Berlin was a member of the board of directors of Vaccinex Inc. until May 2020; and has received research grants and honoraria for advisory board participation from AbbVie, Astellas, Bayer, Ferring, Janssen, and TerSera. Dr. Cheung has received research funding for clinical trials from AbbVie, Sanofi Aventis, Pfizer, and TerSera. Dr. Chung has received honoraria from Sanofi and has participated in clinical trials supported by AbbVie. Dr. Ménard has received research grants from Philips InVivo, Progenics, Siemens, and Varian; and is co-chair of clinical trial NRG GU005. Dr. Pickles has been an advisory board member and/or consultant for Astellas, Bayer, Ferring, Sanofi, Servier, and TerSera; and has participated in several NCIC-sponsored clinical trials. Dr. Souhami has received honoraria for advisory board participation from AbbVie and Janssen; has received travel support from Varian Medical Systems; and participated in a clinical trial supported by NRG Oncology. Dr. Lukka has been a speakers' bureau member for Astellas; has received honoraria and/or study and travel grants from AbbVie, Actavis, Amgen, Astellas, Bayer, Ferring, Janssen, Sanofi, and TerSera; owns stock in Vertex Pharmaceuticals; and has participated in clinical trials supported by Bayer and Janssen. The remaining authors report no competing personal or financial interests related to this work.

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