RADIATION ONCOLOGY—GUIDELINES

FROGG patterns of practice survey and consensus recommendations on radiation therapy for muscle invasive bladder cancer

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Introduction

Muscle invasive bladder cancer (MIBC) is a life-threatening malignancy with a five-year overall survival of approximately 50 to 60%.[1,2] Bladder cancer was the 14th leading cause of cancer death in the world in 2018, with approximately 200,000 deaths related to bladder cancer that year.[3]

Traditionally, the cornerstone of curative treatment of MIBC is a radical cystectomy (RC), which involves the removal of the bladder, a pelvic lymph node dissection and reconstruction of the urinary tract. However, RC is associated with a significant perioperative mortality risk with high readmission rates,[4] substantial morbidity[5] and changes in patient's quality of life (QOL).[6]

Bladder conserving therapy (BCT) involves maximal cystoscopic resection of tumour followed by a combination of chemotherapy and radiation therapy. BCT achieves overall survival rates equal to that obtained with a RC, while preserving a patient's bladder and with low rates of radiotherapy related toxicity.[7,8] No randomised controlled trials have directly compared RC and BCT for MIBC. The SPARE randomised controlled trial attempted to make a direct comparison but due to poor recruitment was abandoned.[9] Propensity-matched analyses suggest equivalent rates of cure and survival[10,11] and international guidelines recommend BCT as a treatment option for selected patients.[12]

The Faculty of Radiation Oncology Genito-Urinary Group (FROGG) is a special interest group of the Royal Australian and New Zealand College of Radiologists (RANZCR). The FROGG executive committee identified a need to provide an update on the previous FROGG consensus guidelines that were published in 2012,[13] to reflect advancements in imaging, treatment technique and data. These guidelines intend to provide direction regarding organ preservation therapy and the technical aspects of how to deliver modern radiation therapy for MIBC. FROGG conducted a consensus meeting, addressing controversies encountered in the management of MIBC, and prior to this meeting, radiation oncologists in Australia and New Zealand were invited to complete a patterns of practice survey. The aim of the survey was to capture a snapshot of current practice in the management of MIBC.

Methods

Radiation oncologists in Australia and New Zealand were invited to complete an electronic survey of their current practice in the management of MIBC. Responses were collected using a commercially available survey engine (Survey Monkey® San Mateo, CA, USA). To obtain a wide range of responses, the survey was sent to all radiation oncologists who were members of FROGG, requesting a response from each institution. All 111 delegates from the FROGG conference were sent the survey with the request that each institution send a single response to reflect the practice at that institution. A limitation of this approach is that variability within one institution may not have been captured. Amongst other things, the survey assessed the annualised number of patients a radiation oncologist treated using BCT, whether patients were discussed in a multidisciplinary team (MDT) meeting, how often radiation oncologists were referred operable patients, the utilisation of MRI and PET imaging, radiotherapy techniques, radiotherapy dose prescriptions and the use of concurrent chemotherapy.

In preparation for a bladder cancer consensus meeting conducted by FROGG in August 2019, the FROGG executive committee performed a literature review and drafted a set of clinical practice guideline statements for the management of MIBC. The consensus conference convened on 8th to the 10th of August 2019 in Cairns, Queensland, Australia. The workshop was attended by 111 delegates, the majority of whom were radiation oncologists, but also included representatives from medical oncology, urology, radiation therapy and radiology. At the bladder consensus meeting, the results of the electronic survey, along with a literature review, were presented. Sessions were scheduled discussing the various aspects of bladder cancer management, with chairs facilitating discussion between delegates and FROGG members about each drafted guideline statement.

A face-to-face approach at the FROGG meeting was used. There are limitations to the method used when developing these guidelines. Factors such as hierarchical group dynamics, fatigue, personality factors may have impacted the guidelines generated at the meeting, but these guidelines were later refined by the FROGG working party group. As a result, consensus clinical practice guidelines were generated, and these were subsequently refined by a smaller FROGG working party following the conference. These verified guideline statements were then used to formulate clinical practice guidelines. All guidelines were thoroughly reviewed by the FROGG working party to ensure agreement amongst this FROGG group to obtain consensus. Future directions in radiation therapy for bladder cancer, such as adaptive radiotherapy, were also explored.

Results

Survey results

Survey responses were received from 32 institutions across Australia and New Zealand, with 41 individual radiation oncologists responding. The survey showed there were several areas of consistency, but also areas of substantial heterogeneity, between institutions in the management of MIBC. In terms of the number of cases of MIBC treated with BCT a year, 32%of respondents treated more than 10 cases, 44%treated between 5 and

10 cases and 24%per cent treated less than 5 cases a year. While 37%of respondents reported that patients with newly diagnosed MIBC are always discussed in an MDT, the remainder of respondents stated that in their practice, some or most patients are not discussed.

Only 10%of radiation oncologists reported being referred medically fit, operable patients with muscle invasive bladder cancer to discuss the option of bladder conservation 'most of the time'. No respondents indicated that they always saw these operable patients. One respondent elected to skip this question; therefore, only 40 responses could be used.

Regarding assessment by imaging, 36%of radiation oncologists utilised MRI to define target volumes when using BCT and 46%of radiation oncologists are using PET to stage and/or define target volumes when using BCT. Regarding treatment technique, 85%of radiation oncologists are employing intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) techniques and 49%are employing adaptive radiation therapy (ART).

Regarding radiotherapy dose, 82%of respondents used conventional fractionation while the others used hypofractionation, as per current standard of care. It was demonstrated that 20%of radiation oncologists dose escalate above 55Gy in 20 fractions or 64Gy in 32 fractions to macroscopic disease when treating bladder cancer. Figure 1 highlights important survey findings.

Most respondents (92%) did not perform elective nodal irradiation (ENI) in clinically node negative MIBC patients even though they would be working in centres where the urologists would perform elective nodal dissections for these patients. With regard to radiotherapy technique, 53%of radiation oncologists utilised one planning target volume, that is treat the whole bladder to full dose, while the rest of the cohort used at least two planning target volumes with either a simultaneous integrated boost (SIB) or a two-phase technique. In terms of image verification, 82%of radiation oncologists performed a daily soft tissue match with cone beam computed tomography (CBCT).

With regard to systemic therapy, 90%of radiation oncologists reported use of either fluorouracil with mitomycin C or cisplatin chemotherapy. In patients who are suitable for salvage cystectomy, 76%of radiation oncologist would advocate 3-month surveillance cystoscopies after radiotherapy in the first year.

Consensus guideline summary

From the consensus conference meeting, a series of guidelines were generated. Table 1 provides a summary

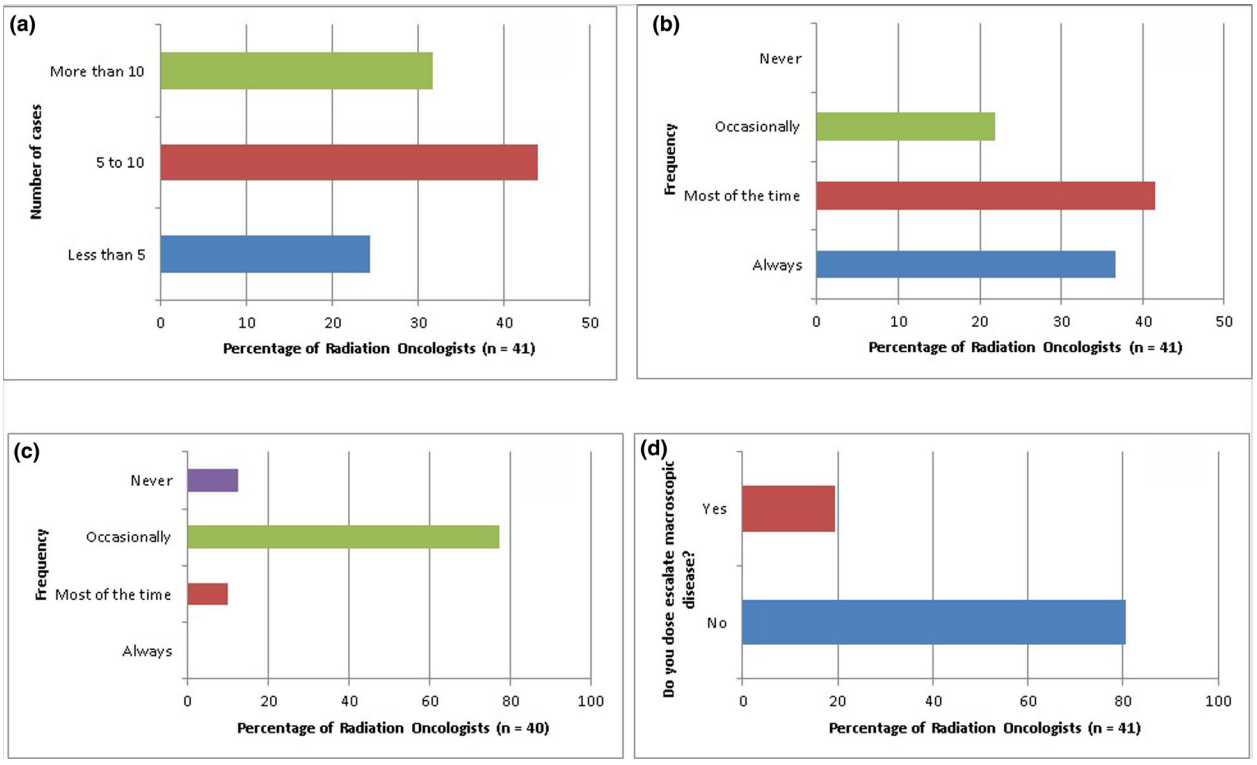

Fig. 1. Survey results: (a) Number of cases of MIBC treated using BCT by radiation oncologists in a year, (b) Frequency that patients with newly diagnosed MIBC are discussed at MDT, (c) Frequency that medically fit, operable patients with MIBC being referred to radiation oncology for bladder conservation and (d) Dose escalation above 55Gy in 20 fractions or 64Gy in 32 fractions to macroscopic disease. [Colour figure can be viewed at wileyonlinelibrary.com]

of recommendations for the multidisciplinary management of MIBC, while Table 2 is summary of recommendations for patient assessment and prognostic factors. Table 3 is a summary of recommendations for treatment modality selection, while Table 4 is a summary of recommendations for radiotherapy simulation and planning. Table 5 is a summary of recommendations for target volume delineation, and Table 6 is a summary of recommendations for radiotherapy dose. Table 7 summarises dose constraints, and Table 8 is a summary of recommendations for radiotherapy delivery. Table 9 is a summary of recommendations for systemic agents to use concurrently with radiation therapy. Table 10 is a summary of recommendations for the management of pelvic nodes. Table 11 is a summary of recommendations for surveillance following BCT.

Discussion

The FROGG survey provides a snapshot of the current clinical practice of Australian and New Zealand radiation oncologists in the management of MIBC. There were responses from 32 institutions (26 public and 6 private institutions) from a total of 69 institutions in Australia and New Zealand; hence, we had survey responses from 46%of all institutions in both nations. These responses represented diverse practices from across Australia and New Zealand, from large tertiary referral urban centres, to smaller regional centres, in both the public and private health sectors.

The survey identified several pertinent findings. Firstly, patients are not consistently referred to a radiation oncologist for consideration of BCT prior to a RC. Furthermore, while there are areas of consistency in practice patterns of radiation oncologists, there exists significant heterogeneity such as variable rates of MDT discussion and dose fractionation. Despite data suggesting equivalent outcomes between moderate hypofractionation and conventional fractionation in MIBC, most respondents advocate conventional fractionation.[14,15] However, a recent presentation of data from a meta-analysis which demonstrated equivalency, also showed that in the absence of systemic therapy, patients who received a hypofractionated 55Gy schedule had a 29% lower risk of invasive locoregional recurrence compared to a 64Gy conventionally fractionated schedule.[16] The publication of these results is awaited, and while these data do not represent a head to head comparison, it may contribute to a change in practice in the future.

The majority of radiation oncologists stated they do not perform elective nodal irradiation for bladder cancer, which is in line with randomised evidence, showing no benefit to nodal radiation therapy for clinically node-

Table 1. Summary of recommendations for the multidisciplinary management of MIBC

Guideline 1: Multidisciplinary management
1.1. All patients with MIBC should be discussed at a multidisciplinary meeting.
1.2. Patients with MIBC should consult with a urologist, a radiation oncologist and a medical oncologist to discuss possible treatment options including BCT and cystectomy with or without neoadjuvant chemotherapy.
1.3. Collaborative efforts to improve multidisciplinary care and informed decision-making should be undertaken.

Table 2. Summary of recommendations for patient assessment and prognostic factors

Guideline 2: Patient assessment and prognostic factors
2.1. Examination under anaesthesia and safe maximal TURBT is recommended.
2.1.1. Where there is biopsy proven MIBC, consider proceeding directly to BCT without further tumour resection if macroscopic clearance is not anticipated, or relook TURBT will add significant delay in commencement of treatment.
2.2. A CT chest, abdomen and pelvis with a whole-body bone scan are recommended for staging.
2.3. An MRI with T2- and diffusion-weighted imaging can be considered to improve assessment of the extent of local disease.
2.4. FDG PET can be considered to improve the assessment of the extent of regional and distant disease.

Table 3. Summary of recommendations for treatment modality selection

Guideline 3: Treatment modality selection
For patients who are eligible for either a RC or BCT, factors to be considered when selecting between treatment modalities include:
3.1. RC preferred for patients with:
• Widespread CIS, multifocal tumours or gross macroscopic disease following TURBT.
• Poor baseline bladder function.
• Relative contraindications to radiotherapy.
• Relative contraindications to chemotherapy.
3.2. Favourable prognostic factors for BCT:
• Either no or limited CIS.
• Unifocal tumour.
• Minimal macroscopic tumour following TURBT.
3.3. BCT preferred for patients:
• Increased perioperative mortality and morbidity risk.
• Patient preference to conserve their bladder.

Table 4. Summary of recommendations for radiotherapy simulation and planning

Guideline 4: Radiotherapy simulation and planning
4.1. The use of IMRT and VMAT is encouraged with improved toxicity and better oncological outcomes than historical controls.
4.2. Consider decreased fluid intake prior to simulation and treatment and avoiding chemotherapy with fluid loading or diuretic therapy immediately prior to planning and treatment to maximise bladder volume reproducibility.

Table 5. Summary of recommendations for target volume delineation

Guideline 5: Target volume delineation
5.1. The GTV is the gross tumour (post-TURBT) as defined on CT +/- MRI and includes any extra-vesical spread.
5.2. The CTV is the whole bladder (including GTV) + 0.5cm margin on gross extra-vesical extension.
5.3. In the setting of planned dose escalation or differential dose levels, a high-risk CTV can be created. It is defined as a GTV + 0.5cm, edited to anatomical boundaries or, if no visible disease, a high-risk CTV would be the tumour bed following complete TURBT.
5.3.1 MRI with T1-weighted, T2-weighted and diffusion-weighted imaging (DWI) aids in the delineation of the GTV and high-risk CTV if used.
5.4. Fiducials can be used to assist with target volume delineation and image guidance.
5.5. The PTV is the CTV with an institution and image-guided radiation therapy (IGRT)-specific anisotropic margin expansion.

Table 6. Summary of recommendations for radiotherapy dose

Guideline 6: Radiotherapy dose
6.1. Standard radiotherapy doses include either 55Gy in 20 fractions or 64Gy in 32 fractions with concurrent chemotherapy.
6.2. For patients suitable for curative intent treatment but not suitable for chemotherapy, hypofractionated radiotherapy alone using 55Gy in 20 fractions can be offered with or without carbogen and nicotinamide.
6.3. Consider scheduling approaches to minimise overall duration of treatment course.

Table 7. Summary of recommendations for dose constraints

Guideline 7: Dose constraints for radiotherapy
7.1 For 55Gy in 20 fractions:
7.1.1 The rectum and large bowel, a V44 < 50%.
7.1.2 The femoral heads, a V44 < 10%.
7.2 For 64Gy in 32 fractions:
7.2.1 The rectum and large bowel, a V50 < 50%.
7.2.2 The femoral heads, a V50 < 10%.
7.3 For small bowel, the degree of overlap must be considered.

negative patients.[17] The survey also demonstrated a wide variation of dose escalation approaches.

Since the 2012 FROGG consensus bladder guidelines were published,[13] there have been many advances in imaging, radiation delivery techniques and image verification. These updated clinical practice guidelines cover the role of multidisciplinary management of patients with MIBC, patient assessment and prognostic factors, as well as specifics regarding radiotherapy treatment techniques, systemic therapy and an approach to node-positive disease.

Table 8. Summary of recommendations for radiotherapy delivery

Guideline 8: Radiotherapy delivery
8.1. Patients should have daily CBCTs with soft tissue matching prior to radiation treatment.
8.2. Online or offline adaptive radiation therapy (ART) can used to account for the variation of the bladder volume by using a 'plan of the day'.
8.3. Encourage the use of VMAT to minimise treatment time and intrafraction bladder filling.

Table 9. Summary of recommendations for systemic agents to use in BCT concurrently with radiation therapy

Guideline 9: Systemic agents to use in BCT concurrently with radiation therapy
9.1. Patients referred for BCT should all be seen by a medical oncologist for consideration of concurrent chemotherapy. The most common agents include fluorouracil in combination with mitomycin C or cisplatin alone.
9.2. Hypoxia modifying agents such as carbogen and nicotinamide should be considered for patients with contraindications to conventional chemotherapy.
9.3 In situations where radiation is likely to be delayed and in patients with locally advanced disease, consideration should be given to neoadjuvant chemotherapy.

Table 10. Summary of recommendations for the management of pelvic nodes

Guideline 10: Management of pelvic nodes
10.1. Node positivity is a poor prognostic factor with a 5-year survival of approximately 29%.
10.2. In fit patients with node-positive disease confined to the pelvis, BCT may be offered as a treatment option.
10.3. Involved nodes should be treated to the prescribed dose given to the GTV respecting surrounding normal tissue tolerances.
10.4. For clinically node negative patients, elective nodal irradiation (ENI) increases toxicity and there is no evidence that ENI improves outcomes.

Table 11. Summary of recommendations for surveillance following BCT

Guideline 11: Surveillance following BCT
11.1. A CT chest, abdomen and pelvis should be performed at 3, 6, 12 and 24 months.
11.2. For patients fit for a salvage cystectomy, cystoscopic evaluation should be conducted every three months for the first two years, every six months for the following two years and then annually.
11.3. For patients not fit for a salvage cystectomy, follow-up can be customised.

Guideline 1: Multidisciplinary management

RC is the most common treatment for MIBC with large RC series reporting five year overall survival rates ranging from 40%to 58%.[18–20] There is, however, significant morbidity associated with RC with approximately one quarter of patients having long-term urinary or bowel morbidity.[21] Despite previous efforts such as the SPARE study,[9] there are no randomised controlled trials directly comparing RC and BCT for MIBC, but evidence exists showing comparative efficacy. A meta-analysis has shown that patients who have BCT have a complete response rate of 78%and a five year survival of 56%.[22] While a pooled analysis of six Radiation Therapy Oncology Group (RTOG), studies showed a ten year disease specific survival of 65%for patients who have BCT.[23] It is well established that comparative data report equivalent survival outcomes with RC and BCT.[24] Efstathiou et al. showed that bladder conservation rates when using BCT for MIBC are 70%with an overall survival of 50%at 5 years and that BCT is well tolerated.[25] With BCT, acute genitourinary and gastrointestinal toxicity of RTOG Grade 3 or 4 occurs in 30–40%of patients, but the vast majority of patients have complete resolution within weeks to short months resulting in RTOG late toxicity of Grade 3 or 4 at 1 year of 3.3%for genitourinary and 1.3%for gastrointestinal symptoms.[26]

There have been important developments in the management of bladder cancer where radiation is often under-utilised and can be suboptimally delivered. It has been established that a deficit in radiation therapy use has a significant adverse impact on patient outcomes.[27]

Despite the evidence existing for BCT as an alternative treatment modality for patients with MIBC, a multidisciplinary approach to treatment decision-making is often overlooked. A population-based study from Canada showed that only 10%of patients treated with a RC had a pre-operative radiation oncology consultation[28] and this is similar to the low perceived rates of referral prior to a RC that our survey identified. Having patients with MIBC discussed at a multidisciplinary meeting should be standard practice and patients deemed suitable for either RC or BCT, should have consultations with a urologist, a radiation oncologist and a medical oncologist to discuss available treatment options. This approach is supported by the recent EAU-ESMO consensus statement[29] and the UK NICE guidelines.[30]

Guideline 2: Patient assessment and prognostic factors

Pre-treatment evaluation is important to optimise outcomes for BCT. The standard approach is an examination under anaesthesia and a safe maximal transurethral resection of bladder tumour (TURBT). While maximal TURBT is recommended, there are no randomised data to support its need and clinicians should consider proceeding directly to BCT if further resection will add undue delay.

A CT chest, abdomen and pelvis with a whole-body bone scan are recommended for staging, and McInnes et al. have even shown that pre-operative chest and bone imaging are associated with improved outcomes.[31] This imaging should be done at baseline prior to surgery, so metastatic disease is not missed, and cystectomy unnecessarily performed.

An MRI with T2- and diffusion-weighted imaging of the bladder before TURBT can be used to assess the tumour size, depth of invasion and nodal involvement.[32,33] T2- and diffusion-weighted MRI is useful for distinguishing normal bladder tissue from bladder tumour and this can be used in patient assessment and in radiotherapy planning to outline the boost radiotherapy volume.[34,35]

An FDG PET may be used to assess the patient for nodal or distant metastatic disease and has been shown to be more sensitive than CT in upstaging MIBC.[36] In the pre-operative setting, FDG PET been shown to improve the diagnostic accuracy lymph node staging.[37]

Guideline 3: Treatment modality selection

When selecting patients for organ conservation therapy, several factors need to be considered. To optimise long-term local control and morbidity for patients undergoing BCT, patients should have good bladder function, low tumour volume, limited or no carcinoma in situ (CIS) and be suitable for concurrent radiosensitisation. The presence of extensive CIS outside the area of invasion is associated with poorer local control and would be considered a relative contraindication to BCT.[38] However, these relative contraindications carry less weight with advancing age and comorbidity, both of which, increase the morbidity and mortality risks of RC.[39] Therefore, BCT is the preferred treatment option in older patients and those who wish to try to preserve their bladder, or those patients with comorbidities and increased perioperative risk. Ideally, patients do not have contraindications to chemotherapy; however, definitive radiotherapy alone with or without dose escalation and with or without carbogen and nicotinamide can be offered as an alternative curative option to chemoradiation.

When both radical cystectomy and radiotherapy are suitable options, consideration of patient preferences and shared decision-making that recognises the patient's individual priorities is recommended. Relevant factors may include the perceived importance of bladder preservation, the potential morbidity and quality-of-life impacts of the different treatments, impact on sexual function, changes in body image, options for urinary diversion, efficacy of salvage therapy and requirements for post-treatment surveillance.

Guideline 4: Radiotherapy technique for BCT

Our survey demonstrated that 85%of responding radiation oncologists in Australia and New Zealand are using a highly conformal radiation techniques such as IMRT and VMAT. This allows for a high dose of radiation to be delivered to the tumour, while sparing organs at risk (OARs) such as the rectum, femoral heads and the small bowel.

Toxicity and outcome data for the use of IMRT and VMAT using different fractionation schedules and simultaneous integrated boosts are emerging.[40–42] The use of IMRT and VMAT is now encouraged with improved toxicity and better oncological outcomes than historical controls.[41] Recent evidence suggests that acute radiation enteritis is significantly reduced when using IMRT for MIBC.[43] When IMRT is employed, a single-phase technique with either a uniform dose or a simultaneous integrated boost is recommended. A second phase with a full bladder may occasionally be required to respect OAR constraints and a partially/comfortably full bladder from the start if using integrated boost technique can be utilised. Ultimately, the aim is to have little interfraction bladder volume variability to allow tighter margins. Whether treating with bladder empty or comfortably full, the bladder filling needs to be reproducible daily and to maximise that reproducibility, consideration needs to be given to restrict oral and intravenous fluids and diuretic therapy in the 2–4 hours prior to planning and treatment delivery.

Guideline 5: Target volume delineation

The gross tumour volume (GTV), clinical target volume (CTV) and planning target volume (PTV) need to be standardised. It is accepted that the GTV is the residual tumour (post TURBT) plus any gross extra-vesical spread seen on CT and MRI. The CTV is defined as the whole bladder (including GTV) + 0.5cm margin on gross extra-vesical extension seen on CT. Clinicians with experience in MRI may also use MRI to help delineate the CTV. Depending on the extent and location of the tumour, other structures such as the prostatic or proximal urethra and distal ureters may need to be included in the CTV.[44] Where there is involvement of the bladder neck/trigone, CIS or multifocal disease, the proximal 1–2 cm of the proximal urethra is included within CTV, and if proximal prostatic urethral biopsies are positive, then the whole prostatic urethra is included. If there is direct prostate invasion (T4 disease), the entire prostate is included in the CTV. If there is involvement of the ureteric orifice, the distal 1.0cm of the distal ureter is included in the CTV. A high-risk CTV can also be created. It is defined as a GTV + 0.5cm, edited to anatomical boundaries or the resected cavity following maximal TURBT as defined by pre TURBT imaging, that is CT/MRI/PET. Cystoscopic insertion of fiducial markers such as gold seeds or lipiodol may also be used to assist with target volume delineation.

The PTV should be generated by applying a variable anisotropic margin expansion to the CTV and should be institution specific taking account the image-guided radiation therapy (IGRT) utilised and any adaptive planning techniques to account for any inter- and intrafraction bladder volume change. One example is 1.5cm superiorly and anteriorly and 1.0 cm in other directions, which has been shown to be a safe PTV approach when daily CBCT imaging is used.[45] With the availability of adaptive planning, and a'plan of the day' approach, PTV margins can be potentially reduced further to account for only intrafraction bladder volume change and departmental set-up error. This reduction in PTV margin may translate to reduced dose to surrounding OAR, that is small bowel.

Guideline 6: Radiotherapy dose

Standard radiotherapy doses for BCT include either 64Gy in 32 fractions or 55Gy in 20 fractions with or without concurrent chemotherapy or carbogen and nicotinamide. When chemotherapy is contraindicated, hypofractionated radiotherapy alone using 55Gy in 20 fractions with or without carbogen and nicotinamide can be offered as a curative alternative to RC.[26] We also recommend that scheduling be managed to minimise overall treatment time – for example, the use of a hypofractionated regimen of twenty fractions starting on a Monday and finishing on a Friday. There is retrospective evidence that suggests prolonged treatment time because of split course techniques has a negative impact on local control.[46]

In the absence of widespread field change or multifocal tumours, an investigational approach is to dose escalate the high-risk PTV. There is recent evidence to suggest that higher radiotherapy doses are associated with better overall survival and hence the rationale to dose escalate.[47] The ICR UK/TROG RAIDER trial is currently evaluating adaptive image-guided standard or dose-escalated radiotherapy in the treatment of MIBC.[48] Dose escalation remains investigational, and this should be performed in the setting of prospective data collection or a clinical study. Consideration must be given an individual patient's anatomy and organs at risk adjacent to the high-risk CTV. Options include utilising 20 fractions with boost doses of 60Gy to gross disease, 55Gy to a high-risk PTV and 50Gy to the whole bladder. When utilising 32 fractions can use boost doses of 70Gy to gross disease, 64Gy to a high-risk PTV and 60Gy to the whole bladder. Example doses used in dose escalation are shown in Table 12.

Guideline 7: Organ at risk tolerances

To prevent unacceptable radiotherapy-related toxicity and minimise acute and late radiation morbidity, constraints for the rectum, femoral heads, large bowel and small bowel are used. Previous FROGG consensus guidelines by

Hindson et al. include femoral heads V50Gy < 30%and rectum V50Gy < 50%and V60Gy < 35%.[13] Due to improvements in radiotherapy delivery, for 55Gy in 20 fractions, for the rectum and large bowel, a V44 < 50%is recommended. When using this hypofractionated approach, for the femoral heads, a V44 < 10%is recommended. For 64Gy in 32 fractions, for the rectum and large bowel, a V50 < 50%. Furthermore, when using 64Gy in 32 fractions, for the femoral heads, a V50 < 10%. However, with modulated treatment techniques, doses to surrounding tissues are further minimised and utilising the ALARA principle, doses should be kept as low as possible. These constraints for the rectum, femoral heads and large bowel (same as rectal constraints) should be used, but the organ at risk, which often causes concern, is the small bowel and the presence of overlap of small bowel with the treatment PTV. Recommended constraints that are dependent on the degree of overlap between the small bowel and the target volumes. In patients where the whole bladder is treated in a single phase, < 1cc of small bowel should receive greater than the prescribed dose. For dose escalation, suggested small bowel constraints for 55Gy in 20 fractions are summarised in Table 13, while Table 14 details suggested small bowel constraints for 64Gy in 34 fractions. These were generated at the FROGG consensus meeting held in 2019, based on expert opinion, and are representative of an approximate 5%risk at 5 years of having grade 3 or greater radiation therapy toxicity. In patients with unfavourable anatomy and high small bowel doses in whom there is an alternative of a RC, this should be considered and rediscussed with the patient.

Guideline 8: Radiotherapy delivery

With the widespread availability of image guidance, it is now possible to have daily CBCTs to verify bladder size and location, minimising geographic miss. Our survey showed 82%of radiation oncologists performed a daily soft tissue match with CBCT. Matching to ensure the bladder is within the PTV or matching to the area of highest risk in the bladder with daily CBCT is both feasible and safe.[41]

More recently, the principle of adaptive radiation therapy (ART) has been used to account for the variation of the bladder volume by using a 'plan of the day' from a library of plans, with daily soft tissue imaging prior to each fraction followed by choosing a plan from a pre-generated library of radiotherapy plans. An offline adaptive treatment strategy has been shown to result in a higher conformity index, better CTV dose coverage compared to conventional planning and to reduce PTV margins and, hence, reduce toxicity.[49]

The TROG 10.01 BOLART feasibility study has shown that from a technical perspective, an online adaptive radiotherapy technique can be instituted in a multicentre setting.[50] We strongly encourage the use of VMAT to minimise treatment time to reduce treatment duration and reduce the amount of intrafraction bladder filling during radiotherapy delivery.

Table 12. Example doses for dose escalation

Fractions	Gross Disease (Gy)	CTV high risk (Gy)	PTV high risk (Gy)	CTV and PTV intermediate risk (Gy), i.e. whole bladder
20	60	57	55	50
32	70	67	64	60

Guideline 9: Systemic agents to use in BCT

The use of chemotherapy not only increases the impact of radiotherapy on local control via radiosensitisation, it also assists in eliminating local and systemic disease.[51,52] According to our survey, 90%of radiation oncologists use either fluorouracil in combination with mitomycin C or cisplatin-based chemotherapy. The effectiveness of treating MIBC using fluorouracil during fractions 1 to 5 and 16 to 20 of radiotherapy with mitomycin C on day 1 with concurrent radiotherapy was shown in a phase 3 multicentre trial.[26] In this trial, at 2 years, the rates of loco-regional disease-free survival in patients who had concurrent chemoradiotherapy were 67%compared with 54%in patients who had radiotherapy alone.

A further trial showed concurrent cisplatin improves local control for bladder cancer with definitive radiation, but this did not translate into an overall survival

Table 13. Small bowel dose constraints for dose prescription 55Gy in 20 fractions

Degree of Overlap	Constraint		Constraint	
	Dose (Gy)	Volume (cc)	Dose (Gy)	Volume (cc)
No overlap with dose escalated area	50	<5	55	<1
PTV high-risk close, e.g. lateral wall GTV	50	<10	55	<5
GTV/CTV high-risk close or PTV high-risk overlap, e.g. dome GTV	50	<40	55	<10

Table 14. Small bowel dose constraints for dose prescription 64Gy in 32 fractions

Degree of Overlap	Constraint		Constraint	
	Dose (Gy)	Volume (cc)	Dose (Gy)	Volume (cc)
No overlap with dose escalated area	58	<5	64	<1
PTV high-risk close, e.g. lateral wall GTV	58	<10	64	<5
GTV/CTV high-risk close or PTV high-risk overlap, e.g. dome GTV	58	<40	64	<10

benefit.[53] Two TROG phase 2 trials investigated the duration of concurrent cisplatin with radiation therapy and found that six cycles were better tolerated than seven cycles.[54] It is accepted that either fluorouracil with mitomycin C or cisplatin chemotherapy is used concurrently with radiotherapy for MIBC.[55] An alternative chemotherapy agent that can be used is gemcitabine.[55] The use of immunotherapy is currently under investigation, and data on this are still pending.[56] When chemotherapy cannot be given, the use of hypoxia modifying agents such as carbogen and nicotinamide can be considered, if available, due to its proven benefit.[57]

Neoadjuvant chemotherapy can be utilised as a reasonable approach, particularly if there is any delay with commencing BCT. A phase 3 multicentre trial conducted by James et al. allowed participating centres to use cisplatin-based neoadjuvant chemotherapy, and a total of 118 out of 360 patients received neoadjuvant chemotherapy prior to BCT. They found no significant difference in outcome for patients receiving neoadjuvant chemotherapy prior to chemoradiation.[26] Jiang et al. showed that when gemcitabine and cisplatin neoadjuvant chemotherapy were given for 2 to 4 cycles prior to BCT, patients had 2-year overall survival of 74%.[58] Furthermore, Tester et al. used two cycles of neoadjuvant methotrexate, cisplatin and vinblastine (MCV) prior to BCT and also showed that overall survival is similar to that reported with surgical approaches.[59] Thompson et al. also showed patients treated with neoadjuvant chemotherapy followed by BCT with gemcitabine had manageable toxicity and acceptable treatment completion rates.[60]

Guideline 10: Management of pelvic nodes

Node-positive disease is a poor prognostic factor with historical data suggesting a 5-year survival of only 29%.[61] However, surgical series data show that long-term control is achievable in a subset of patients after cystectomy and lymph node dissection[62,63] and BCT has become an increasingly accepted option for these patients. In our survey, 19%of radiation oncologists stated they would offer BCT to all patients with nodes confined to the pelvis who did not have contraindications to BCT.

Even though node positivity is a poor prognostic factor, in a fit patient with nodal disease confined to the pelvis, it is recommended, when anatomically feasible, that involved nodes be treated to the prescribed dose given to the GTV. In the setting of involved nodes, the patient should be considered for neoadjuvant chemotherapy followed by radiotherapy to the bladder, the involved pelvic nodes, and elective uninvolved bilateral pelvic nodes with concurrent radiosensitive therapy. Neoadjuvant chemotherapy has been shown to have encouraging results in these patients.[58] Previous contouring guidelines suggest bilateral uninvolved nodes should receive in the order of 45Gy to 50.40 Gy in 1.80 Gy fractions.[64]

Elective nodal irradiation (ENI) is controversial and remains optional in node negative patients. SWOG 8710 reported improved survival in bladder cancer patients who had radical cystectomies with at least ten lymph nodes removed.[65] Some BCT trials incorporated elective nodal irradiation, such as the RTOG trials, which utilised mini pelvis fields with the superior border at S2–S3 to allow sparing of bowel in case of future urinary diversion. Other trials, such as the BC2001 and BCON trials, did not specifically target pelvic lymph nodes, but did include low pelvis and obturator nodes since the field included the whole bladder plus a 1.5-cm margin.[57,66] The role of ENI was investigated in a single institution, randomised control trial of 230 patients, and ENI did not have any impact on disease free or overall survival nor on bladder preservation rates.[17] Another trial reported that excluding elective pelvic nodal irradiation did not worsen the pelvic control rate and reduced acute radiation toxicity markedly.[67] If elective nodal treatment is performed, it should include presacral nodes and the bilateral distal common iliac, external iliac, internal iliac and obturator nodes as detailed in previous node contouring guidelines for MIBC.[64]

Guideline 11: Surveillance following BCT

An important component of BCT is ongoing surveillance following treatment for patients who would be suitable for cystoscopic management or surgery (including a salvage cystectomy) for an isolated local recurrence, and we endorse the NICE guidelines for follow-up.[30] Hence, patients who proceed with BCT require diligent cystoscopic follow-up. For patients not fit for salvage cystectomy, follow-up should still occur, and cystoscopic management considered if an isolated local recurrence is superficial.

In conclusion, the FROGG survey identified significant variations in clinical practice from participating institutions across Australia and New Zealand in the management of MIBC. These clinical practice guidelines provide a framework to support decisions making, reduce variance in patient management and standardise modern BCT techniques. Patients who are suitable for BCT should consult with a urologist, a radiation oncologist and a medical oncologist to discuss potential treatment options and be adequately informed of their alternatives.

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