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RADIATION ONCOLOGY—REVIEW ARTICLE

Australian & New Zealand Faculty of Radiation Oncology Genito-Urinary Group: 2011 consensus guidelines for curative radiotherapy for urothelial carcinoma of the bladder

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Summary

Curative radiotherapy, with or without concurrent chemotherapy, is recognized as a standard treatment option for muscle-invasive bladder cancer. It is commonly used for two distinct groups of patients: either for those medically unfit for surgery, or as part of a 'bladder preserving' management plan incorporating the possibility of salvage cystectomy. However, in both situations, the approach to radiotherapy varies widely around the world. The Australian and New Zealand Faculty of Radiation Oncology Genito-Urinary Group recognised a need to develop consistent, evidence-based guidelines for patient selection and radiotherapy technique in the delivery of curative radiotherapy. Following a workshop convened in May 2009, a working party collated opinions and conducted a wide literature appraisal linking each recommendation with the best available evidence. This process was subject to ongoing re-presentation to the Faculty of Radiation Oncology Genito-Urinary Group members prior to final endorsement. These Guidelines include patient selection, radiation target delineation, dose and fractionation schedules, normal tissue constraints and investigational techniques. Particular emphasis is given to the rationale for the target volumes described. These Guidelines provide a consensus-based framework for the delivery of curative radiotherapy for muscle-invasive bladder cancer. Widespread input from radiation oncologists treating bladder cancer ensures that these techniques are feasible in practice. We recommend these Guidelines be adopted widely in order to encourage a uniformly high standard of radiotherapy in this setting, and to allow for better comparison of outcomes.

Key words: chemoradiotherapy; consensus guideline; contouring guideline; muscle invasive bladder cancer; radiotherapy.

Introduction

The curative management of muscle-invasive bladder cancer (MIBC) involves either radical cystectomy or 'radical' radiotherapy (RT), i.e. treatment given with curative intent, with or without synchronous chemotherapy. Traditionally, in many countries, including Australia and New Zealand, radical cystectomy has been the most common treatment for localised carcinoma of the bladder and provides excellent local control.[1–3] Often

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patients referred for RT are elderly and/or medically unfit for surgical management. This selection bias coupled with historically poor RT technique led to the widely held view that RT was inferior to cystectomy.[4–12] More recently, however, there has been increasing evidence that RT gives comparable survival rates with those reported in surgical series.[13]

Increasingly, chemo-radiotherapy (CRT) is being utilised in the bladder-preserving approach to treatment of localised MIBC. In the only published randomised trial comparing RT alone with CRT, investigators showed that the addition of synchronous cisplatin improved local control.[14] An abstract report from another study, the BC2001 trial, comparing RT alone with CRT using mitomycin C and 5FU chemotherapy showed that CRT significantly improved loco-regional disease-free survival.[15] Several prospective, single-arm Phase 2 studies have also shown excellent complete response (CR) rates, local control and overall survival with CRT.[16–26] Cisplatin-based concurrent regimens are most commonly used, are well tolerated and provide overall survival figures comparable with surgical series.[20,21] The major advantage of this approach is that it allows 40–60% of patients to retain a functional bladder at 5 years. Patients undergoing bladder conservation report better overall quality of life, improved urinary tract function and significantly less sexual morbidity compared with patients having initial cystectomy.[27,28] It is important that vigilant, multidisciplinary follow-up is conducted to ensure that local recurrences are detected and treated early in order that survival is not compromised.

While CRT is slowly becoming more accepted as an alternative curative treatment option for MIBC, the published protocols for this general approach vary widely. For this reason, it seemed desirable to establish Australia and New Zealand guidelines to promote consistency in the selection and management of these patients. The aims of this report are: (i) to highlight factors pertaining to patient selection and suitability for this approach; and (ii) to make recommendations concerning optimal RT technique for localised MIBC. These recommendations are evidence based where possible. In addition, some peer-reviewed literature reports relating to previous and current research endeavours in bladder irradiation techniques are included for completeness and to suggest the direction that technical advances may take. These guidelines have been developed through a consensus process conducted by the Faculty of Radiation Oncology Genito-Urinary Group (FROGG).

Guideline development

FROGG is a sub-specialist interest group within the Faculty of Radiation Oncology of the Royal Australia and New Zealand College of Radiologists (RANZCR). The group has previously published Australia and New Zealand guidelines for the delivery of conformal RT for prostate cancer, both in the definitive and post-prostatectomy settings.[29–31]

A workshop conducted by FROGG in May 2009 identified the need to develop evidence-based consensus guidelines for the management of MIBC with RT. At this meeting, participants discussed the Australia and New Zealand practice of, and national study findings relating to, the radiotherapeutic treatment of localised MIBC. The FROGG executive charged a small working party with collating opinions, seeking and critiquing further input from FROGG members and distilling these into a guidelines document. This task involved a wide literature appraisal, linking each recommendation with the best available evidence, where this existed. The subsequent process involved re-presentation of the guidelines to the FROGG membership for ongoing refinement, prior to final endorsement by the working group and FROGG executive.

The literature review addressed the following topics: factors influencing patient selection, radiation target volume delineation, radiation dose and fractionation scheduling and normal tissue constraints as well as other technical and planning-related issues and initiatives. Studies identified through this process were categorised according to their level of evidence as defined by the National Health and Medical Research Council (NHMRC) guidelines.[32] The working party constructed draft guidelines initially using the 2009 workshop presentation material and documented discussion. These were then developed and reviewed during a series of meetings as well as via RANZCR website publication inviting final comment, throughout 2009 and 2010. Where a guideline was agreed upon in the absence of published evidence, the level of evidence was classified as 'consensus'.

The resultant guideline summaries and recommendations are presented in table format within this paper. The corresponding narrative (below) expands on the discussion around each guideline, in the order of presentation in the related table. The numbering of text sections correlates with those in the table for easy cross-referencing. The first part of the Guidelines discussion deals with patient assessment and selection (Table 1), while the second relates to the technical aspects of RT planning and delivery (Table 2).

Guideline discussion

Patient assessment (refer to Table 1)

There are two separate groups of patients in whom 'curative' RT for localised MIBC may be recommended. It is important to distinguish these different patient cohorts.

Patients who choose to undergo bladder-preserving treatment, rather than immediate cystectomy, are by

Table 1. Factors to consider for curative (chemo)radiotherapy for muscle-invasive bladder cancer

Text section	Considerations and recommendations†	Reference	Level of evidence
1	Patient factors		
	'Reasonable' life expectancy;		Consensus
	Performance status ECOG 0–2		Consensus
	Adequate pretreatment bladder function		Consensus
2	Tumour factors		
2.1	Tumour stage T2-T4a, N0 M0		Consensus
2.2	Multiple invasive tumours-may have worse outcome	11,12,33	IV
2.3	Hydronephrosis associated with poorer local control	11,18,34	IV
2.4	CIS outside area of invasion	35–38	IV
3	Treatment factors		
3.1	Maximal resection tumour prior to radiotherapy optimal		Consensus
	Complete TURBT is ideal but not mandatory	17,19,22,23	III-3
3.2	Hb level >100–120 g/L (for radiotherapy)	39,40	IV
3.3	Renal function adequate (for concurrent chemotherapy)		Consensus

†See associated text for further elaboration. CIS, carcinoma *in situ*; ECOG, Eastern Cooperative Oncology Group; TURBT, transurethral resection of bladder tumour.

definition medically fit enough to be potential candidates for surgery. In this group, there are several selection criteria that need to be considered to ensure suitability for the organ-conserving approach. These factors are included in Table 1. Within this group, those with a high risk of local recurrence (see section 2 below) and therefore likely to require salvage cystectomy may be advised to undergo radical cystectomy as definitive treatment.

The second group of patients with 'localised' MIBC are those who are either medically unfit and/or surgically inoperable. For these patients, the factors listed in Table 1 that are associated with a relatively higher risk of recurrence may be a lesser consideration, as a radical cystectomy is by definition not an option.

When assessing patients for a bladder-preserving approach as an alternative to surgery, it is essential to select the most suitable patients in order to minimise inappropriate or futile therapy and to optimise the outcomes and quality of life for patients. Analogous to other cancers treated with definitive RT, a histological diagnosis of deep muscle-invasive transitional cell carcinoma of the bladder must be obtained prior to embarking on treatment. Patients should have disease localised to the bladder (and/or the immediate extra-vesical fat and/or adjacent urethra), with no clinical evidence of lymph node involvement or metastases.

The factors discussed below should be considered in those with MIBC who undergo bladder-preserving therapy. The evidence for the impact of these on local recurrence comes from prospective phase 2 studies or retrospective analyses of non-surgical (often RT-only) series. At times, the literature evidence is limited. For this reason, these factors may only represent relative contraindications to an attempt at organ preservation. Clearly, the patient's full understanding, preferences and individual circumstances are central to decision-making.

1. Patient comorbidities

Patients undergoing a curative course of RT should have a life expectancy such that the MIBC is a likely cause of future morbidity or mortality. They should not have any comorbidity that prevents them from completing a course of RT. Patients with an Eastern Cooperative Oncology Group performance status of 3 or 4 are best counselled about a palliative approach to management.

Patients with poor baseline bladder capacity and significant irritative symptoms are not ideal for curative RT. Although there is no fixed threshold, patients with a capacity of around 200 mL or less,[33] and/or those with significant ongoing incontinence, frequency and dysuria, may be more appropriately managed by cystectomy and urinary diversion. In these patients with pre-existing bladder dysfunction, the post-RT bladder function and quality of life may be impaired

2. Tumour factors

2.1 Stage

The disease should be fully staged with cystoscopy and deep biopsies, a CT scan of the thorax, abdomen and pelvis, and a whole body bone scan. Following a transurethral resection of bladder tumour (TURBT), patients must have histological evidence of muscle-invasive disease (T2a–T4), without nodal or distant metastases.

Table 2. Guidelines for planning and treatment of muscle-invasive bladder cancer with curative (chemo)radiotherapy

Text section	Guideline recommendation†	Reference	Level of evidence
1	General		
	CT-guided simulation and 3D conformal RT are standard		Consensus
	Single phase or two phase (where suitable – see under 2.2.6 below) techniques may be used		
	Plan and treat phase 1 (and entire treatment single phase) with empty bladder: if 2-phases used, plan and treat phase 2 with full bladder		Consensus
2	Treatment volumes		
2.1	Gross tumour volume (GTV)		
	GTV = residual tumour (post-TURB) plus gross extra-vesical spread (previous site of tumour if complete TURB)		Consensus
2.2	Clinical target volume (CTV)		
2.2.1	CTV definition		Consensus
	CTV = whole bladder (including GTV) + 0.5 cm margin on gross extra-vesical extension. Regional lymph nodes are not intentionally included.		
2.2.2	CTV contouring guidelines		Consensus
	Contour muscle wall of bladder as solid organ.		
	Include anatomical variants, e.g. cystoceles, diverticulae.		
	Use CTV above for entire treatment (one phase) unless detail of tumour location available (see below)		
2.2.3	Extravesical extension (EVE)	[41]	IV
	Changes suspicious for EVE on planning CT, consistent with tumour location and pathology are included in the CTV, adding a 0.5-cm margin		
2.2.4	Male urethra/prostate	[42–44]	IV
	Inclusion of prostatic urethra (usually whole prostate) recommended if carcinoma *in situ*, multifocal tumour or bladder neck involvement present. If macroscopic involvement, then the prostate is included in the CTV for entire treatment.		
2.2.5	Female urethra	[45–47]	IV
	Consider inclusion of female urethra in phase 1 CTV, as for prostatic urethra criteria (above).	[47,48]	IV
	For macroscopic vaginal involvement, include proximal urethra		
2.2.6	Phase 2 (boost) CTV for 2 phase technique:		Consensus
	This is only suitable when the site of the (solitary) primary is clearly identified or documented at cystoscopy.		
2.2.7	CTV2 definition (i.e. CTV for phase 2)		IV
	CTV2 = GTV or the site of known tumour, adding a 0.5-cm margin on EVE, if present.	[23,48,49]	
2.3	Planning target volume (PTV)		
	PTV = CTV with anisotropic margin expansion using the guideline below. Consider adjacent structures, their relative mobility and anatomical boundaries and location of tumour in bladder when determining precise margins:	[48,50–53]	IV, Consensus
	Anteriorly, posteriorly and laterally 1.5–2.0 cm		
	Cranially 2.0–2.5 cm		
	Inferiorly 1–1.5 cm		
	These may be used to determine PTV1 and 2, ensuring that precise tumour position is known for two phases		
3	Dose/fractionation schedule and normal tissue constraints		
3.1	For single phase: recommended prescription is 64 Gy in 32 daily fractions, treating 10 days a fortnight	[23]	III-3
	For 2 phase technique:		
	phase 1–50 Gy in 25 fractions		
	phase 2 –14 Gy in seven fractions		
3.2	Treatment delays should be avoided	[54,55]	IV
3.3	Normal tissue dose constraints	[31,56,57]	Consensus
	Rectum V50 < 50%, V60 < 35%		
	Femoral head V50 < 30%		

†See text for further discussion. 3D, three-dimensional; RT, radiotherapy.

2.2 Multiple bladder tumours

Multifocal MIBC at presentation is common and is not an absolute contraindication to organ-conserving therapy although multiplicity of tumours may lessen the likelihood of successful bladder preservation. In three published retrospective analyses of radical RT alone, tumour multiplicity was associated with higher bladder failure rates than for solitary lesions.[11,12,58]

2.3 Hydronephrosis

In surgical[34,59] and RT series,[11,12,58] malignant hydronephrosis is an independent adverse prognostic factor in MIBC. However, it is also a marker for poor local response,[11,18] making it less likely that these patients will avoid a cystectomy following RT or CRT. In one prospective analysis of radical RT (including some patients who received chemotherapy), the authors found that hydronephrosis at diagnosis significantly predicted for a lower CR rate compared with patients with no hydronephrosis, 37% and 68%, respectively.[35] Based on this, the current Radiation Therapy Oncology Group (RTOG) and Massachusetts General Hospital protocols exclude patients with malignant hydronephrosis from undergoing bladder conservation.[35] Therefore, patients presenting with hydronephrosis should be considered for a primary radical cystectomy, if they are suitable for cystectomy, as they are less likely to obtain a complete local response to RT or CRT.

2.4 Carcinoma in situ *(CIS) in association with MIBC*

Traditionally, extensive CIS in association with MIBC was considered a contraindication to bladder RT. It was thought that widespread CIS beyond the invasive disease was a poor prognostic factor. In large surgical series, there is a link between CIS and higher risk of local recurrence following TURBT for non-muscle invasive (T1) bladder urothelial carcinoma.[36,37] In one multi-institutional series of 728 patients with MIBC treated with surgery, presence of CIS was significantly associated with an increase in overall recurrence on multivariate analysis ($P = 0.046$).[38]

In contrast, only one series has reported the effect of CIS on bladder recurrence following RT. Fung *et al*. reported prognostic factors from 40 patients who underwent neoadjuvant chemotherapy and CRT to 40 Gy.[60] Those with a biopsy proven CR completed 'high dose' CRT, while all others underwent a cystectomy. The absence of CIS was significantly predictive for a CR to the initial therapy but was not significantly associated with response to the whole CRT regimen. The authors reported that CIS correlated with higher local or overall recurrence rates, but the *P*-values reported were all >0.05. This study was limited by small numbers and by the wide variety of treatments received by patients. Therefore, despite the possibility of poorer outcomes, there is no robust evidence for *or* against the use of RT or CRT when CIS is present in the bladder. It cannot, then, be considered an absolute contraindication to curative RT for MIBC per se.

3. Treatment factors

3.1 Maximal (safe) TURBT

Maximal or 'complete' TURBT is regularly advocated and is a prerequisite in many trial protocols. This conclusion is based on limited, retrospective data that associated a 'complete' TURBT with improved CR, local control and freedom from distant metastases.[24,39] However, three more modern studies addressing selective bladder conservation[17,19,22] as well as the TROG phase 2 trial[23] did not show any significant detriment for patients having had less than a complete or maximal TURBT. The inability to achieve a complete TURBT may be a reflection of the extent of the initial tumour and surgical safety, rather than a true treatment effect. Debulking a tumour as much as is feasible, however, is radio-biologically appealing, and maximal TURBT is considered optimal. If a limited biopsy or incomplete TURBT has been done, the patient should be considered for referral back to the urologist for further resection of tumour. A macroscopically complete TURBT is not mandatory, however, especially if this might significantly delayed the commencement of RT.

3.2 Haemoglobin level

Haemoglobin concentration less than 100 g/L may also be associated with a reduced RT response, but the data supporting this are from older retrospective studies.[40,50] These reports give weak evidence for this link, and poorer outcomes may well be related to other confounding factors. However, it seems logical that ensuring haemoglobin concentrations are greater than 100 g/L, preferably >120 g/L, may improve local response and improve the bladder preservation rate as well as aiding tolerance to treatment and reducing anaemia-related symptoms.

3.3 Renal function

For patients undergoing CRT, renal function must be satisfactory for chemotherapy. This decision would usually be made following assessment by a medical oncologist because opinions vary on what constitutes an adequate glomerular filtration rate for the regimen to be employed.

Technique for curative RT (refer to Table 2)

1. General

CT simulation and three-dimensional (3D) conformal RT are mandatory for the delivery of high-quality RT for

MIBC. Intensity Modulated Radiotherapy and Volumetric Modulated Arc Therapy are not considered a standard technique in this situation at the time of writing these guidelines. Particular attention would need to be paid to margin considerations (see below) if these technologies are used for treating MIBC.

A single- or two-phase technique is usual for treatment of the bladder. The conditions that need to be considered in determining which approach might be used are described in more detail in the sections dealing with target volumes. When treating the whole bladder and planning the phase(s) of RT that include the whole bladder, the bladder is ideally empty. This is achieved by asking the patient to void prior to planning, and daily, immediately before each treatment. If a two-phase technique is used, the second phase may be planned with the bladder full. This may help reduce the dose to the small bowel and remove some of the bladder wall (distant from the primary tumour) from the phase 2 volume.

2. Treatment volumes

2.1 What is the definition of the gross tumour volume (GTV)?

The GTV is defined as any gross residual disease seen at cystoscopy, or by means of imaging (such as CT or MRI scan), post-TURBT. This includes disease seen (or palpated), which extends outside the wall of the bladder. It is intended that this include all the primary disease. Following a complete macroscopic TURBT, for a tumour that does not extend outside the bladder wall, there is no definable GTV.

2.2 Clinical target volume (CTV) considerations

2.2.1 What is the definition of the CTV? The CTV incorporates the GTV and any microscopic disease and regions-at-risk or harbouring tumour. This volume is usually considered to be the entire bladder and any extra-vesicular extension. This approach was used in both TROG studies.[23] The CTV is the volume that will receive the prescribed dose. A common practice is to treat the whole bladder to 50 Gy and then reduce the CTV, in order to reduce toxicity (see below).

The 'bladder-only' approach for RT is not universally accepted with several large bladder conservation trial series from North America including the pelvic lymph nodes.[61] This is one of the long-standing controversies in RT for MIBC. Curative surgery for MIBC includes a bilateral pelvic lymphadenectomy. Approximately 25% of patients who undergo curative cystectomy and lymph node dissection will have pathological nodal involvement.[62,63] In several surgical series, the extent of the lymph node dissection predicts improved loco-regional control and survival,[64,65] even in those with pN0 disease.[66,67] In addition, occasional patients having adjuvant chemotherapy for node-positive disease following cystectomy have durable recurrence-free survivals, some even considered as 'cured'.

On the other hand, MIBC involving lymph nodes is usually incurable, and the rationale for treating regional lymphatics as part of a curative bladder-preservation approach is less clear. Although several trials in bladder conservation included the pelvic lymphatics, there is no evidence to show it improves outcomes. Inclusion of the pelvic nodal regions increases the amount of normal tissue, especially small bowel, in the irradiated volume and may lead to an increase in early toxicity as well as late complications.[6]

2.2.2 Contouring the CTV. The CTV, for phase 1 at least, is the entire bladder delineated by the outer surface of the bladder wall, incorporating a 0.5-cm margin on any regions deemed on clinical or radiological grounds to constitute extra-vesicular extension (see below). The bladder is contoured as a solid organ.

The basis for inclusion of the whole bladder is twofold. Firstly, MIBC commonly presents and/or recurs in a multifocal manner.[68] Secondly, following a TURBT, delineating the microscopic extent of the lesion on a planning CT is difficult. In addition, the bladder can sometimes demonstrate anatomical variations, e.g. diverticulae and cystoceles. In these circumstances, appropriate adjustments to the CTV may be necessary to ensure the CTV includes all the urothelium, at least for phase 1.

2.2.3 Extra-vesical disease spread. Extra-vesical disease spread or extension (EVE) is sometimes seen on planning CT images but can be overestimated.[69] Changes on CT such as 'stranding' and 'misting' may suggest EVE, but care is required not to confuse this with postoperative change. Larger tumours (>3.5 cm), lymph-vascular invasion and squamoid differentiation are associated with a greater extent of extra-vesicular extension but not a higher frequency.[69] Any changes suspicious for EVE that are consistent with the lesion's position and pathological features should be included in the CTV (with a 0.5-cm margin applied as described above).

2.2.4 Should the prostate be included in the CTV? Prostatic urothelial carcinoma is seen in 20–43% of cystoprostatectomy specimens.[41,42,70–72] The method of spread to the prostate is thought to be either transmural invasion or *in situ* spread in an intra-epithelial fashion.[41,73] This is a topic of increasing interest in the surgical literature, as prostate-sparing techniques are being studied,[42] but it is difficult to predict extension to the prostatic urethra prior to RT. Several authors have attempted to identify risk factors for urethral involvement, and the three most consistent predictors for this are bladder CIS, multifocal disease and tumour involvement of the trigone/bladder neck.

Nixon *et al*. analysed 192 consecutive cystoprostatectomy specimens and detected urethral involvement in 30 patients.[74] Thirty-one percent (25/80) of patients

with CIS had urethral involvement, compared with only 4.5% (5/112) of those with no evidence of CIS in the bladder. In patients with multifocal tumours, the risk was 34.7% (25/72), compared with only 4.2% (5/120) in those with only a single tumour. Kefer *et al*.[43] analysed 70 surgical specimens and found CIS, bladder neck involvement and multifocal disease were all statistically significantly predictive of urethral involvement. Richards *et al*. reviewed the clinico-pathological findings in 96 cystoprostatectomy specimens.[42] In their report, multifocality was not associated with increased risk of urethral disease though CIS and bladder neck involvement were.

Given that over 50% of urothelial cancers at the bladder neck invade the prostate stromal tissue in surgical series,[42,71] when one or more of these high-risk factors are present (CIS, trigone position and/or multifocal lesions), consideration should be given to including the whole prostate gland in the CTV for RT or phase 1 of a two-phase course. If there is macroscopic involvement of the prostate and/or urethra, then the prostate should be included in the CTV for the entire treatment.

2.2.5 Should the female urethra be included in the CTV? MIBC is less common in females. However, assessment of the risk of urethral involvement is just as important. In a recent literature review, the overall rate of urethral involvement is 7–46% in female cystectomy series.[44] The authors estimated the average risk to be 12.4%. However, this was calculated as a weighted average of all series reporting this feature. Many of these reports are not recent and did not provide information regarding tumour stage, grade or location. This likely explains the wide range reported.

Coloby *et al*. analysed 47 female cystectomy specimens and found only three patients had urethral involvement;[75] all three primary lesions were located at the bladder neck. Stein *et al*. found bladder neck involvement in 17/67 cystectomy specimens from females. Fifty-three per cent of these had associated urethral involvement. None of the 50 women without bladder neck involvement had urethral involvement. Several other series also show this association of urethral carcinoma with bladder neck involvement.[44–46]

Another consideration in female patients is the potential for microscopic invasion of the anterior vaginal wall[44,46,47] more commonly seen in cystectomy specimens in which urethral involvement is present. It is difficult, however, to determine microscopic vaginal involvement prior to treatment, and it is not recommended that the vagina be routinely included in the CTV (see below).

Unlike reports dealing with male patients with MIBC, no other factors such as multiplicity or CIS have been found to be independently associated with increased risk of urethral involvement in women.[42] This may be due, in part, to the smaller numbers of women in these series. In the absence of good data, it would seem prudent to apply the same considerations to both male and female patients in assessing higher risk of urethral involvement. Anterior vaginal wall invasion seen on imaging or clinical examination should be included in the CTV. Where the vagina is (partially) included for macroscopic disease, it is recommended that the proximal urethra should also be included in the CTV for phase 1.

2.2.6 When might a two-phase technique be considered? If the site of the tumour is not absolutely clear (because of poor documentation, no prior imaging, or complete TURBT or the tumour is multifocal), then the whole bladder should be treated to the total dose. Similarly, if the 'full' bladder is relatively small in relation to the GTV and/or the likely extent of residual microscopic disease, then a single-phase treatment will likely be preferable. If, however, the above situations do not apply, the CTV margin may be reduced after 50 Gy in an attempt to reduce toxicity and maximise long-term bladder function. This two-phase approach may be particularly suitable in cases where the tumour is clearly demonstrated to be well lateralised or situated over the trigone, and there is also good evidence of absence of CIS away from the index lesion. Because of variable bladder filling and the potential geographical miss, lesions on the dome would usually be treated in a single-phase technique,

2.2.7 What is the definition for the phase 2 (boost) CTV? The second phase is reduced to treat either a smaller margin on the bladder (on non-tumour-bearing bladder walls only) or to treat only a portion of the bladder at the site that the primary tumour arose.[23,48,49] This 'boost' phase should only be used if the site of the lesion is clearly identified on imaging and/or through clear documentation of cystoscopy findings that are available at the time of planning. The phase 2 CTV, if used, includes the GTV (see above) and/or the original site of the tumour, either as visualised or as determined from pretreatment imaging and/or cystoscopy reports, including a 1 cm of adjacent normal bladder wall.

2.3 PTV (planning target volume) considerations

2.3.1 What is the definition of the PTV? A PTV incorporates the CTV variation because of organ motion and other set-up uncertainties to ensure that the prescribed dose is delivered to the CTV. It allows for changes during each fraction (intra-fraction), changes between fractions (inter-fraction) and alterations in bladder shape, size and position over the full treatment course as well as the other daily set-up variations. In determining the optimal PTV definitions and delineation in the treatment of MIBC, and in particular the CTV to PTV margin, the following issues require consideration:

2.3.2 Intra-fraction motion. The bladder continues to fill during the time it takes to set up and deliver RT.[76] It is important to consider this to ensure that the CTV is covered throughout each fraction. Manger *et al*.

assessed nine patients by cine-MRI before starting a course of RT to the bladder and during week four of treatment.[77] They monitored changes over a 20-minute time frame and found that the bladder volume increased by a mean of 1.6 cm^3/min, representing a mean volumetric increase of 30–40%. This filling effect altered the wall position in a linear fashion: 0.06 cm/cm^3 superiorly, 0.01 cm/cm^3 inferiorly and 0.013 cm/cm^3 anteriorly. The authors found the linear relationship was maintained for volumes up to 150 cm^3. The period of 20 minutes would approximate the set-up and treatment delivery time for a standard bladder treatment fraction. They concluded that a generalised 1.5-cm margin from CTV to PTV was appropriate for more than 95% of treatments in this setting.

2.3.3 Inter-fraction motion. Changes in bladder volume, shape and position over a course of RT are complex.[51] From the literature, it appears that the majority of patients have a consistent or decreasing bladder volume over time, but a proportion may have an increase in the bladder volume from the start to the finish of the treatment course.[48,51,52,76–79] The bladder shape varies with no apparent pattern. Analysis of treatment imaging suggests the week-to-week variation in size and shape is in the order of $\pm$20–30% overall.[48,53]

Changes in bladder volume and movements of various regions of the bladder are not isotropic. The largest movement and variability is in the superior (cranial) and anterior portions of the bladder.[61,62,78,79] Thus, a tumour on the dome of the bladder will have more variation in location than a lesion on the trigone, for instance. Several studies show that between 15% and 65% of all fractions delivered for MIBC have one or more bladder wall (effectively the CTV) outside the set PTV margins.[48,79,80] Although these studies demonstrate large maximal ranges, it is the overall deviation from the planned treatment that will determine tumour control.

2.3.4 What is a suitable CTV to PTV margin? Calculations of an appropriate CTV to PTV expansion are drawn from limited institutional experiences of bladder motion in patients planned and treated with an empty bladder.[53] Empirically, in the past, a 1.5- to 2-cm margin has been added to the outer bladder wall to generate a PTV to account for this bladder motion and for day-to-day set-up variation.

It appears that empirical margins of CTV to PTV of 1.5–2.0 cm are not unreasonable. Several authors have retrospectively analysed this margin dimension. These studies are all limited in their design yet the results are similar; that is that a 1.5 to 2.0 cm margin from CTV to PTV will encompass the CTV > 93% of the time.[48,52,53,80]

A more sophisticated CTV to PTV margin calculation may be derived from one of the many published 'margin recipes'. The application of these formulae is more challenging in bladder cancer, as the changes to CTV are not symmetrical. Meijer *et al*. published a detailed paper addressing the required expansion from CTV to PTV, accounting for daily variation, set-up uncertainty and inter-observer variation.[51] The authors used two-dimensional scalar maps and applied the van Herk margin method[81] to derive appropriate PTV expansion anisotropically. In this analysis, organ motion was the major geometric uncertainty. They found that the expansion required was anisotropic: 10 mm anteriorly and laterally, 12 mm caudally, 14 mm posteriorly and 20 mm cranially. The values from this paper may not be generalisable to all situations but they are remarkably similar to commonly used 'empiric' values.

Based on all the available evidence, we recommend the minimum CTV to PTV margin is 1–1.5 cm in all directions and 2.0–2.5 cm in the cranial (superior) direction when using conventional, non-adaptive RT delivery. The inferior expansion may be reduced to 1 cm if the prostate or urethra has been included. Consideration should also be made of what wall(s) are involved by the cancer (i.e. its precise position in the bladder) and the relative mobility (and therefore uncertainty) of this particular portion of the bladder. Further reductions in PTV margin from the recommendation given above should be used with caution outside an investigative protocol.

3. Dose/fractionation schedule and normal tissue constraints

3.1 Total dose

MIBC is a radiosensitive malignancy and appears to demonstrate a dose-response relationship. Based on retrospective series, both local control and overall survival appear to be improved with higher doses.[12,40,82] The gains from this must be balanced with the additional toxicity of dose escalation. Based on the feasibility report for TROG 99.06,[23] the current recommended dose to the tumour is 64 Gy in 32 fractions, delivered once daily, treating 10 fractions a fortnight. For a two-phase treatment, 50 Gy is delivered in 25 fractions for phase 1. For phase 2, 14 Gy in seven fractions is delivered to the reduced volume.

3.2 Overall treatment time

Urothelial carcinoma has been shown to have a high proliferative activity and short potential doubling time.[83] The clinical evidence for MIBC is conflicting.[6,54,55,82–85] Two retrospective studies found that prolonged treatment time because of split course techniques impacted on local control.[54,55] However, in a randomised trial, accelerated RT failed to show any benefit over conventional fractionation.[86] There are no strong data to show overall treatment time has an impact on MIBC outcomes but neither is there good evidence to the contrary. In general, delays should be avoided.

3.3 Dose constraints for normal structures

RT, with or without chemotherapy, is generally well tolerated. It is important to ensure that patients who undergo curative RT or concurrent CRT are closely followed-up and late toxicity documented. This ensures that late toxicity is identified and allows comparison of a particular treatment centre's toxicity data to published results. It is recommended that a validated toxicity scale such as the CTCAE v4.0[87] is used.

Recommended dose constraints for organs at risk are described in Table 2. The organs at risk are the rectum and femoral heads. Our guidelines process found that some radiation oncologists attempt to contour the small bowel, or at least note the portion included in the high-dose region. During the consensus process, there remained controversy as to how much emphasis should be placed on small bowel doses. The constraints for rectum and femoral head/neck are based on the published guidelines and contouring methods reported for prostate cancer.[31,56,57,88]

Past and future investigation of RT technique

Altered fractionation schedules

Hyper-fractionation

Many variations of a twice-daily fractionation schedule have been assessed in an attempt to improve the biological response in MIBC of the bladder.[35] Investigators at the University of Paris published a phase I/II trials of concurrent CRT given as a twice-daily hyper-fractionated regimen, in 54 patients. At cystoscopy, 74% of the patients had a CR and went on to complete a second phase of combined treatment.[22] Several RTOG studies[19,20,89] have suggested that twice-daily RT combined with concurrent chemotherapy is feasible, well tolerated and achieves response rates comparable with conventional fractionation. Although a meta-analysis of hyper-fractionated schedules for all sites concluded that hyper-fractionated treatment conferred a significantly superior survival in MIBC,[90] this conclusion is flawed. It included only two randomised trials assessing hyper-fractionation in MIBC and both trials incorporated a 2-week break in the treatment regimen. A more recent randomised trial compared a twice-daily accelerated RT schedule with more conventional once-daily fractionation.[86] No chemotherapy was given in the trial. This study failed to show a benefit for the accelerated arm, but there was a significant increase in gastrointestinal toxicity. On this evidence, there is no clear benefit to accelerated RT in bladder conservation. Given that accelerated and hyper-fractionated protocols may increase toxicity and are logistically more difficult, this approach is not considered standard.

Hypo-fractionation

No randomised trials have compared hypo-fractionation with conventional fractionation for MIBC. However, several large uncontrolled series show that 50–57.5 Gy in 16–20 fractions is comparable with conventional fractionation series when RT is given without chemotherapy.[6–8,10] There are no data regarding hypo-fractionation with concurrent chemotherapy. Large fraction size has been associated with increased acute and late toxicity.[49] Based on the lack of data in this setting, altered fractionation with concurrent chemotherapy should only be considered as part of a prospective trial.

Partial bladder irradiation

Partial bladder irradiation reduces the volume and potentially toxicity of treatment in the curative setting. Cowen *et al*. addressed the concept of partial bladder irradiation in a three-arm randomised trial that also assessed different hypo-fractionation schedules.[91] One hundred forty-nine patients were randomised to whole bladder or one of two partial bladder RT arms. The overall survival and local control at 5 years were 58% and 50%, respectively and not statistically different between the groups. In the patients who received partial bladder irradiation, only 7% had an out-of-field bladder recurrence, of which only one was muscle invasive. Although this trial appears to support the concept of partial bladder irradiation, this approach does not reflect Australian and New Zealand practice. Treating a partial bladder volume would require strict bladder instruction, excellent surgical documentation, high patient compliance and, ideally, daily image guidance. A partial bladder technique for the full treatment course is only recommended in the context of a clinical trial.

Adaptive radiotherapy (ART)

ART is a relatively new approach in bladder RT. One method is to use imaging information from the initial treatment fractions to reoptimise the treatment plan.[83] This can reduce the PTV volume and potentially reduce normal tissue toxicity. One adaptive strategy is to use daily selection of a PTV based on pretreatment volumetric imaging. This has been shown to be feasible in a pilot study,[83] and the Trans-Tasman Radiation Oncology Group has an open multicentre phase 2 trial to further assess the generalisability of this approach. In the TROG trial, patients being treated with curative intent for T2-T3 N0 M0 MIBC are eligible. The most conformal of three bladder plans (small, medium or large) is chosen before each fraction, by appropriately trained radiation therapists.

ART may reduce dose to surrounding normal structures, potentially reducing toxicity and possibly allowing dose escalation. Hopefully this will lead, in turn, to improved bladder preservation rates in this disease.

Conclusion

Modern CRT with the aim of bladder preservation and cancer cure is an established treatment option for localised MIBC of the bladder. This document is intended to provide guidelines for selection and treatment based on the available evidence. Each patient must, however, be considered on an individual basis.

The urinary bladder presents unique challenges because of large uncertainties and variability in position, and there are potentially significant further gains to be made with strategies aimed at improving technique. Image-guided RT and ART are approaches that are being assessed in ongoing trials; clinicians treating MIBC should participate, wherever possible, in such investigations.

The FROGG consensus process has led to publication of guidelines for definitive RT for prostate cancer and for post-prostatectomy RT. These have in turn been adopted broadly in Australia and New Zealand and have been incorporated into protocols of new trials. It is intended that these MIBC curative RT guidelines will be used in future trials in this area. Principally, however, they are designed to be a practical guide for radiation oncologists who treat this disease. Through an inclusive process of collaboration, review of the literature, widespread consultation and discussion, we have endeavoured to blend evidence with what likely represents feasible practice in Australia and New Zealand. We recommend these guidelines be adopted by all radiation oncologists treating this disease to enhance the quality of RT delivery in this setting, to allow for better comparison of outcomes and to act as a platform from which to answer new research questions. Over the next few years, it is likely that new technologies and techniques will become common practice. It is important that these guidelines be regularly updated to remain current for radiation oncologists practicing in this area.

References

1. Madersbacher S, Hochreiter W, Burkhard F *et al*. Radical cystectomy for bladder cancer today – a homogeneous series without neoadjuvant therapy. *J Clin Oncol* 2003; **21**: 690–6.
2. Hautmann RE, Gschwend JE, de Petriconi RC, Kron M, Volkmer BG. Cystectomy for transitional cell carcinoma of the bladder: results of a surgery only series in the neobladder era. *J Urol* 2006; **176**: 486–92; discussion 491–482.
3. Stein JP, Lieskovsky G, Cote R *et al*. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol* 2001; **19**: 666–75.
4. Fossa SD, Waehre H, Aass N, Jacobsen AB, Olsen DR, Ous S. Bladder cancer definitive radiation therapy of muscle-invasive bladder cancer. A retrospective analysis of 317 patients. *Cancer* 1993; **72**: 3036–43.
5. Smaaland R, Akslen LA, Tonder B, Mehus A, Lote K, Albrektsen G. Radical radiation treatment of invasive and locally advanced bladder carcinoma in elderly patients. *Br J Urol* 1991; **67**: 61–9.
6. Davidson SE, Symonds RP, Snee MP, Upadhyay S, Habeshaw T, Robertson AG. Assessment of factors influencing the outcome of radiotherapy for bladder cancer. *Br J Urol* 1990; **66**: 288–93.
7. Jenkins BJ, Caulfield MJ, Fowler CG *et al*. Reappraisal of the role of radical radiotherapy and salvage cystectomy in the treatment of invasive (T2/T3) bladder cancer. *Br J Urol* 1988; **62**: 343–6.
8. Duncan W, Quilty PM. The results of a series of 963 patients with transitional cell carcinoma of the urinary bladder primarily treated by radical megavoltage X-ray therapy. *Radiother Oncol* 1986; **7**: 299–310.
9. Jahnson S, Pedersen J, Westman G. Bladder carcinoma – a 20-year review of radical irradiation therapy. *Radiother Oncol* 1991; **22**: 111–7.
10. Gospodarowicz MK, Rider WD, Keen CW *et al*. Bladder cancer: long-term follow-up results of patients treated with radical radiation. *Clin Oncol (R Coll Radiol)* 1991; **3**: 155–61.
11. Pollack A, Zagars GK, Swanson DA. Muscle-invasive bladder cancer treated with external beam radiotherapy: prognostic factors. *Int J Radiat Oncol Biol Phys* 1994; **30**: 267–77.
12. Moonen L, vd Voet H, de Nijs R, Hart AA, Horenblas S, Bartelink H. Muscle-invasive bladder cancer treated with external beam radiotherapy: pretreatment prognostic factors and the predictive value of cystoscopic re-evaluation during treatment. *Radiother Oncol* 1998; **49**: 149–55.
13. Kotwal S, Choudhury A, Johnston C, Paul AB, Whelan P, Kiltie AE. Similar treatment outcomes for radical cystectomy and radical radiotherapy in invasive bladder cancer treated at a United Kingdom specialist treatment center. *Int J Radiat Oncol Biol Phys* 2008; **70**: 456–63.
14. Coppin CM, Gospodarowicz MK, James K *et al*. Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1996; **14**: 2901–7.
15. James ND, Hussain SA, Hall E *et al*. Results of a phase III randomized trial of synchronous chemoradiotherapy (CRT) compared to radiotherapy (RT) alone in muscle-invasive bladder cancer (MIBC) (BC2001 CRUK/01/004)(Abstract). *J Clin Oncol* 2010; **28**: 4517.
16. Rodel C, Grabenbauer GG, Kuhn R *et al*. Combined-modality treatment and selective organ preservation in invasive bladder cancer: long-term results. *J Clin Oncol* 2002; **20**: 3061–71.
17. Shipley WU, Winter KA, Kaufman DS *et al*. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder

preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89-03. *J Clin Oncol* 1998; **16**: 3576–83.
18. Shipley WU, Kaufman DS, Zehr E *et al*. Selective bladder preservation by combined modality protocol treatment: long-term outcomes of 190 patients with invasive bladder cancer. *Urology* 2002; **60**: 62–7; discussion 67–68.
19. Hagan MP, Winter KA, Kaufman DS *et al*. RTOG 97-06: initial report of a phase I-II trial of selective bladder conservation using TURBT, twice-daily accelerated irradiation sensitized with cisplatin, and adjuvant MCV combination chemotherapy. *Int J Radiat Oncol Biol Phys* 2003; **57**: 665–72.
20. Kaufman DS, Winter KA, Shipley WU *et al*. Phase I-II RTOG study (99-06) of patients with muscle-invasive bladder cancer undergoing transurethral surgery, paclitaxel, cisplatin, and twice-daily radiotherapy followed by selective bladder preservation or radical cystectomy and adjuvant chemotherapy. *Urology* 2009; **73**: 833–7.
21. Arias F, Dominguez MA, Martinez E *et al*. Chemoradiotherapy for muscle invading bladder carcinoma. Final report of a single institutional organ-sparing program. *Int J Radiat Oncol Biol Phys* 2000; **47**: 373–8.
22. Housset M, Maulard C, Chretien Y *et al*. Combined radiation and chemotherapy for invasive transitional-cell carcinoma of the bladder: a prospective study. *J Clin Oncol* 1993; **11**: 2150–7.
23. Gogna NK, Matthews JH, Turner SL *et al*. Efficacy and tolerability of concurrent weekly low dose cisplatin during radiation treatment of localised muscle invasive bladder transitional cell carcinoma: a report of two sequential Phase II studies from the Trans Tasman Radiation Oncology Group. *Radiother Oncol* 2006; **81**: 9–17.
24. Sauer R, Dunst J, Altendorf-Hofmann A, Fischer H, Bornhof C, Schrott KM. Radiotherapy with and without cisplatin in bladder cancer. *Int J Radiat Oncol Biol Phys* 1990; **19**: 687–91.
25. Dunst J, Sauer R, Schrott KM, Kuhn R, Wittekind C, Altendorf-Hofmann A. Organ-sparing treatment of advanced bladder cancer: a 10-year experience. *Int J Radiat Oncol Biol Phys* 1994; **30**: 261–6.
26. Sauer R, Birkenhake S, Kuhn R, Wittekind C, Schrott KM, Martus P. Efficacy of radiochemotherapy with platin derivatives compared to radiotherapy alone in organ-sparing treatment of bladder cancer. *Int J Radiat Oncol Biol Phys* 1998; **40**: 121–7.
27. Caffo O, Fellin G, Graffer U, Luciani L. Assessment of quality of life after cystectomy or conservative therapy for patients with infiltrating bladder carcinoma. A survey by a self-administered questionnaire. *Cancer* 1996; **78**: 1089–97.
28. Henningsohn L, Wijkstrom H, Dickman PW, Bergmark K, Steineck G. Distressful symptoms after radical radiotherapy for urinary bladder cancer. *Radiother Oncol* 2002; **62**: 215–25.
29. Skala M, Berry M, Duchesne G *et al*. Australian and New Zealand three-dimensional conformal radiation therapy consensus guidelines for prostate cancer. *Australas Radiol* 2004; **48**: 493–501.
30. Sidhom MA, Kneebone AB, Lehman M *et al*. Post-prostatectomy radiation therapy: consensus guidelines of the Australian and New Zealand Radiation Oncology Genito-Urinary Group. *Radiother Oncol* 2008; **88**: 10–9.
31. Hayden AJ, Martin JM, Kneebone AB *et al*. Australian & New Zealand Faculty of Radiation Oncology Genito-Urinary Group: 2010 consensus guidelines for definitive external beam radiotherapy for prostate carcinoma. *J Med Imaging Radiat Oncol* 2010; **54**: 513–25.
32. Anonymous. *National Health and Medical Research Council (NHMRC) Publication: Guidelines for the Development and Implementation of Clinical Practice Guidelines*. NHMRC, Canberra, 1999.
33. Skolyszewski J, Reinfuss M, Weiss M. Radical external beam radiotherapy of urinary bladder carcinoma. An analysis of results in 500 patients. *Acta Oncol* 1994; **33**: 561–5.
34. Resorlu B, Baltaci S, Resorlu M *et al*. Prognostic significance of hydronephrosis in bladder cancer treated by radical cystectomy. *Urol Int* 2009; **83**: 285–8.
35. Mak RH, Zietman AL, Heney NM, Kaufman DS, Shipley WU. Bladder preservation: optimizing radiotherapy and integrated treatment strategies. *BJU Int* 2008; **102**: 1345–53.
36. Denzinger S, Otto W, Fritsche HM *et al*. Bladder sparing approach for initial T1G3 bladder cancer: do multifocality, size of tumor or concomitant carcinoma in situ matter? A long-term analysis of 132 patients. *Int J Urol* 2007; **14**: 995–9.
37. Hong SJ, Cho KS, Han M *et al*. Nomograms for prediction of disease recurrence in patients with primary Ta, T1 transitional cell carcinoma of the bladder. *J Korean Med Sci* 2008; **23**: 428–33.
38. Karakiewicz PI, Shariat SF, Palapattu GS *et al*. Nomogram for predicting disease recurrence after radical cystectomy for transitional cell carcinoma of the bladder. *J Urol* 2006; **176**: 1354–61; discussion 1361–1352.
39. Shipley WU, Prout GR Jr, Kaufman SD, Perrone TL. Invasive bladder carcinoma. The importance of initial transurethral surgery and other significant prognostic factors for improved survival with full-dose irradiation. *Cancer* 1987; **60**: 514–20.
40. Greven KM, Solin LJ, Hanks GE. Prognostic factors in patients with bladder carcinoma treated with definitive irradiation. *Cancer* 1990; **65**: 908–12.
41. Ayyathurai R, Gomez P, Luongo T, Soloway MS, Manoharan M. Prostatic involvement by urothelial carcinoma of the bladder: clinicopathological features

and outcome after radical cystectomy. *BJU Int* 2007; **100**: 1021–5.
42. Richards KA, Parks GE, Badlani GH, Kader AK, Hemal AK, Pettus JA. Developing selection criteria for prostate-sparing cystectomy: a review of cystoprostatectomy specimens. *Urology* 2010; **75**: 1116–20.
43. Kefer JC, Voelzke BB, Flanigan RC, Wojcik EM, Waters WB, Campbell SC. Risk assessment for occult malignancy in the prostate before radical cystectomy. *Urology* 2005; **66**: 1251–5.
44. Stein JP, Penson DF, Wu SD, Skinner DG. Pathological guidelines for orthotopic urinary diversion in women with bladder cancer: a review of the literature. *J Urol* 2007; **178**: 756–60.
45. Chen ME, Pisters LL, Malpica A, Pettaway CA, Dinney CP. Risk of urethral, vaginal and cervical involvement in patients undergoing radical cystectomy for bladder cancer: results of a contemporary cystectomy series from M. D. Anderson Cancer Center. *J Urol* 1997; **157**: 2120–3.
46. Stein JP, Cote RJ, Freeman JA *et al*. Indications for lower urinary tract reconstruction in women after cystectomy for bladder cancer: a pathological review of female cystectomy specimens. *J Urol* 1995; **154**: 1329–33.
47. Maralani S, Wood DP Jr, Grignon D, Banerjee M, Sakr W, Pontes JE. Incidence of urethral involvement in female bladder cancer: an anatomic pathologic study. *Urology* 1997; **50**: 537–41.
48. Pos FJ, Koedooder K, Hulshof MC, van Tienhoven G, Gonzalez Gonzalez D. Influence of bladder and rectal volume on spatial variability of a bladder tumor during radical radiotherapy. *Int J Radiat Oncol Biol Phys* 2003; **55**: 835–41.
49. Sengelov L, von der Maase H. Radiotherapy in bladder cancer. *Radiother Oncol* 1999; **52**: 1–14.
50. Gospodarowicz MK, Hawkins NV, Rawlings GA *et al*. Radical radiotherapy for muscle invasive transitional cell carcinoma of the bladder: failure analysis. *J Urol* 1989; **142**: 1448–53; discussion 1453–1444.
51. Meijer GJ, Rasch C, Remeijer P, Lebesque JV. Three-dimensional analysis of delineation errors, setup errors, and organ motion during radiotherapy of bladder cancer. *Int J Radiat Oncol Biol Phys* 2003; **55**: 1277–87.
52. Henry AM, Stratford J, McCarthy C *et al*. X-ray volume imaging in bladder radiotherapy verification. *Int J Radiat Oncol Biol Phys* 2006; **64**: 1174–8.
53. Mangar SA, Miller NR, Khoo VS *et al*. Evaluating inter-fractional changes in volume and position during bladder radiotherapy and the effect of volume limitation as a method of reducing the internal margin of the planning target volume. *Clin Oncol (R Coll Radiol)* 2008; **20**: 698–704.
54. Maciejewski B, Majewski S. Dose fractionation and tumour repopulation in radiotherapy for bladder cancer. *Radiother Oncol* 1991; **21**: 163–70.
55. De Neve W, Lybeert ML, Goor C, Crommelin MA, Ribot JG. Radiotherapy for T2 and T3 carcinoma of the bladder: the influence of overall treatment time. *Radiother Oncol* 1995; **36**: 183–8.
56. Boersma LJ, van den Brink M, Bruce AM *et al*. Estimation of the incidence of late bladder and rectum complications after high-dose (70–78 GY) conformal radiotherapy for prostate cancer, using dose-volume histograms. *Int J Radiat Oncol Biol Phys* 1998; **41**: 83–92.
57. Fiorino C, Valdagni R, Rancati T, Sanguineti G. Dose-volume effects for normal tissues in external radiotherapy: pelvis. *Radiother Oncol* 2009; **93**: 153–67.
58. Mameghan H, Fisher R, Mameghan J, Brook S. Analysis of failure following definitive radiotherapy for invasive transitional cell carcinoma of the bladder. *Int J Radiat Oncol Biol Phys* 1995; **31**: 247–54.
59. Chapman DM, Pohar KS, Gong MC, Bahnson RR. Preoperative hydronephrosis as an indicator of survival after radical cystectomy. *Urol Oncol* 2009; **27**: 491–5.
60. Fung CY, Shipley WU, Young RH *et al*. Prognostic factors in invasive bladder carcinoma in a prospective trial of preoperative adjuvant chemotherapy and radiotherapy. *J Clin Oncol* 1991; **9**: 1533–42.
61. Coen JJ, Zietman AL, Kaufman DS, Shipley WU. Benchmarks achieved in the delivery of radiation therapy for muscle-invasive bladder cancer. *Urol Oncol* 2007; **25**: 76–84.
62. Buscarini M, Josephson DY, Stein JP. Lymphadenectomy in bladder cancer: a review. *Urol Int* 2007; **79**: 191–9.
63. Abdel-Latif M, Abol-Enein H, El-Baz M, Ghoneim MA. Nodal involvement in bladder cancer cases treated with radical cystectomy: incidence and prognosis. *J Urol* 2004; **172**: 85–9.
64. Dhar NB, Klein EA, Reuther AM, Thalmann GN, Madersbacher S, Studer UE. Outcome after radical cystectomy with limited or extended pelvic lymph node dissection. *J Urol* 2008; **179**: 873–8; discussion 878.
65. Koppie TM, Vickers AJ, Vora K, Dalbagni G, Bochner BH. Standardization of pelvic lymphadenectomy performed at radical cystectomy: can we establish a minimum number of lymph nodes that should be removed? *Cancer* 2006; **107**: 2368–74.
66. Canter D, Guzzo TJ, Resnick MJ *et al*. A thorough pelvic lymph node dissection in presence of positive margins associated with better clinical outcomes in radical cystectomy patients. *Urology* 2009; **74**: 161–5.
67. Herr HW, Faulkner JR, Grossman HB *et al*. Surgical factors influence bladder cancer outcomes: a cooperative group report. *J Clin Oncol* 2004; **22**: 2781–9.
68. Brausi M, Collette L, Kurth K *et al*. Variability in the recurrence rate at first follow-up cystoscopy after TUR in stage Ta T1 transitional cell carcinoma of the bladder: a combined analysis of seven EORTC studies. *Eur Urol* 2002; **41**: 523–31.

69. Jenkins P, Anjarwalla S, Gilbert H, Kinder R. Defining the clinical target volume for bladder cancer radiotherapy treatment planning. *Int J Radiat Oncol Biol Phys* 2009; **75**: 1379–84.
70. Njinou Ngninkeu B, Lorge F, Moulin P, Jamart J, Van Cangh PJ. Transitional cell carcinoma involving the prostate: a clinicopathological retrospective study of 76 cases. *J Urol* 2003; **169**: 149–52.
71. Shen SS, Lerner SP, Muezzinoglu B, Truong LD, Amiel G, Wheeler TM. Prostatic involvement by transitional cell carcinoma in patients with bladder cancer and its prognostic significance. *Hum Pathol* 2006; **37**: 726–34.
72. Wood DP Jr, Montie JE, Pontes JE, VanderBrug Medendorp S, Levin HS. Transitional cell carcinoma of the prostate in cystoprostatectomy specimens removed for bladder cancer. *J Urol* 1989; **141**: 346–9.
73. Lerner SP, Colen J, Shen S. Prostatic biology, histologic patterns and clinical consequences of transitional cell carcinoma. *Curr Opin Urol* 2008; **18**: 508–12.
74. Nixon RG, Chang SS, Lafleur BJ, Smith JJ, Cookson MS. Carcinoma in situ and tumor multifocality predict the risk of prostatic urethral involvement at radical cystectomy in men with transitional cell carcinoma of the bladder. *J Urol* 2002; **167**: 502–5.
75. Coloby PJ, Kakizoe T, Tobisu K, Sakamoto M. Urethral involvement in female bladder cancer patients: mapping of 47 consecutive cysto-urethrectomy specimens. *J Urol* 1994; **152**: 1438–42.
76. McBain CA, Green MM, Stratford J *et al*. Ultrasound imaging to assess inter- and intra-fraction motion during bladder radiotherapy and its potential as a verification tool. *Clin Oncol (R Coll Radiol)* 2009; **21**: 385–93.
77. Mangar SA, Scurr E, Huddart RA *et al*. Assessing intra-fractional bladder motion using cine-MRI as initial methodology for Predictive Organ Localization (POLO) in radiotherapy for bladder cancer. *Radiother Oncol* 2007; **85**: 207–14.
78. Muren LP, Smaaland R, Dahl O. Organ motion, set-up variation and treatment margins in radical radiotherapy of urinary bladder cancer. *Radiother Oncol* 2003; **69**: 291–304.
79. Fokdal L, Honore H, Hoyer M, Meldgaard P, Fode K, von der Maase H. Impact of changes in bladder and rectal filling volume on organ motion and dose distribution of the bladder in radiotherapy for urinary bladder cancer. *Int J Radiat Oncol Biol Phys* 2004; **59**: 436–44.
80. Turner SL, Swindell R, Bowl N *et al*. Bladder movement during radiation therapy for bladder cancer: implications for treatment planning. *Int J Radiat Oncol Biol Phys* 1997; **39**: 355–60.
81. van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys* 2000; **47**: 1121–35.
82. Majewski W, Maciejewski B, Majewski S, Suwinski R, Miszczyk L, Tarnawski R. Clinical radiobiology of stage T2-T3 bladder cancer. *Int J Radiat Oncol Biol Phys* 2004; **60**: 60–70.
83. Pos FJ, Hart G, Schneider C, Sminia P. Radical radiotherapy for invasive bladder cancer: what dose and fractionation schedule to choose? *Int J Radiat Oncol Biol Phys* 2006; **64**: 1168–73.
84. Salminen E. Split-course radiotherapy for urinary bladder cancer. *Radiother Oncol* 1989; **15**: 327–31.
85. Marcial VA, Amato DA, Brady LW *et al*. Split-course radiotherapy of carcinoma of the urinary bladder stages C and D1. A Radiation Therapy Oncology Group Study. *Am J Clin Oncol* 1985; **8**: 185–99.
86. Horwich A, Dearnaley D, Huddart R *et al*. A randomised trial of accelerated radiotherapy for localised invasive bladder cancer. *Radiother Oncol* 2005; **75**: 34–43.
87. Anonymous. Common Terminology Criteria for Adverse Events (CTCAE) National Cancer Institute, Bethesda. 2010.
88. Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. *Int J Radiat Oncol Biol Phys* 2010; **76**: S123–129.
89. Kaufman DS, Winter KA, Shipley WU *et al*. The initial results in muscle-invading bladder cancer of RTOG 95-06: phase I/II trial of transurethral surgery plus radiation therapy with concurrent cisplatin and 5-fluorouracil followed by selective bladder preservation or cystectomy depending on the initial response. *Oncologist* 2000; **5**: 471–6.
90. Stuschke M, Thames HD. Hyperfractionated radiotherapy of human tumors: overview of the randomized clinical trials. *Int J Radiat Oncol Biol Phys* 1997; **37**: 259–67.
91. Cowan RA, McBain CA, Ryder WD *et al*. Radiotherapy for muscle-invasive carcinoma of the bladder: results of a randomized trial comparing conventional whole bladder with dose-escalated partial bladder radiotherapy. *Int J Radiat Oncol Biol Phys* 2004; **59**: 197–207.