

Bladder cancer RCR consensus statements



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# RCR bladder cancer consensus statements

These statements should be read in conjunction with the accompanying explanatory notes.

# Topic 1. Pathway and follow-up

#### **Diagnosing and staging**

- 1.1 Offer a CT (computed tomography) urogram prior to TURBT (transurethral resection of the bladder tumour) for patients suspected to have muscle-invasive bladder cancer (MIBC).
- 1.2 Offer a CT thorax to patients with suspected or confirmed MIBC.
- 1.3 Consider an FDG-PET (fluorodeoxyglucose positron emission tomography) scan if the multidisciplinary team (MDT) feels it might influence treatment decisions.
- 1.4 Consider magnetic resonance imaging (MRI) pelvis to patients pre-TURBT where muscle-invasive disease is suspected.
- 1.5 Repeat staging scans if there is an interval of more than eight weeks between imaging and start of definitive treatment.
- 1.6 Use a minimum data set to present relevant information at MDT meetings. This should include:
  - Clinical and radiological staging
  - TURBT report including size and number of tumours, extent of resection, presence of carcinoma *in situ* (CIS), location of tumour
  - Renal function, weight and height
  - Performance status and co-morbidities
  - Basic functional assessment including frailty assessment where appropriate.
- 1.7 Each centre should have a clinical nurse specialist (CNS)/advanced specialist practitioner (ASP) with special interest in bladder cancer.

# Radical therapy: preparing patients for treatment and supporting shared decisionmaking

- 1.8 Offer all patients with a new diagnosis of non-metastatic muscle-invasive urothelial bladder cancer clinical consultations with an oncologist, urologist and designated CNS, all of whom have expertise in managing bladder cancer. Patients should have a detailed discussion of radical treatment options including neoadjuvant chemotherapy (NAC), cystectomy and radiotherapy.
- 1.9 Offer multiple opportunities for discussion of treatment options to support shared decision-making.
- 1.10 Consider pre-habilitation for patients in whom radical treatment is planned.

#### Follow-up protocol for patients treated with radical intent

1.11 Offer CT of chest, abdomen and pelvis (CT CAP) at six, 12 and 24 months as a minimum. Then consider annually up to five years (to include upper tract imaging) following radical intent treatment (surgery or radiotherapy).

- 1.12 Offer patients who have completed bladder-preserving radical treatment cystoscopy every three months for first two years, then every six months for next two years and then annually up to five years from the end of treatment.
- 1.13 Offer evaluation and management of patients for late treatment effects and survivorship issues.

# Topic 2. Systemic anti-cancer treatment (SACT)

# Neo-adjuvant chemotherapy (NAC) for localised muscle-invasive urothelial bladder cancer (T2–T4a N0)

- 2.1 Offer three to four cycles of cisplatin and gemcitabine, or MVAC, as standard of care for NAC in MIBC. Do not offer regimens containing carboplatin.
- 2.2 Consider split-dose cisplatin and gemcitabine for patients ineligible for standard chemotherapy due to poor renal function (i.e., glomerular filtration rate [GFR] 40–60 ml/min).
- 2.3 Offer appropriate cross-sectional imaging to include chest, abdomen and pelvis during NAC prior to definitive treatment in a time frame that allows for prompt decision-making.
- 2.4 Do not offer repeat cystoscopy after NAC prior to chemoradiation (CRT) or cystectomy.
- 2.5 Consider correction of unilateral hydronephrosis prior to treatment if GFR <60 ml/ min.

# Radiosensitisers

- 2.6 Offer a radiosensitiser as standard of care for patients suitable for daily radical radiotherapy for urothelial carcinoma of the bladder.
- 2.7 Offer BC2001 (5 FU/mitomycin) chemotherapy regimens or BCON (carbogen/ nicotinamide) as concurrent radiosensitisation (CRS) options. Alternatives include CRS with weekly gemcitabine or cisplatin chemotherapy.

# Topic 3. Technical aspects of radiotherapy – radical, high-dose palliative and palliative

#### Radical and high-dose palliative

- 3.1 Radical bladder radiotherapy: Offer patients with localised MIBC (T2–T4aN0M0) daily hypofractionated radiotherapy 55 Gy in 20 fractions as standard given demonstrated non-inferiority to conventional regime 64 Gy in 32 fractions.
- 3.2 Alternative option in frail patients (high-dose palliative): Consider 36 Gy to the whole bladder in six weekly fractions in those unsuitable for daily radiotherapy because of poor performance status or co-morbidity.\*

\*alternate radiotherapy regime – please see explanatory notes

3.3 Use intensity-modulated radiation therapy (IMRT) techniques given their potential to reduce normal tissue irradiation and toxicity.

- 3.4 Consider normal tissue/organ at risk (OAR) dose constraint guidance as summarised in Table 1 on page 22. Avoid dose compromise to the planning target volume (PTV) to achieve OAR constraints.
- 3.5 Offer all patients receiving daily treatment or ultra-hypofractionated bladder radiotherapy (36 Gy in six fractions) pre-treatment 3D volumetric soft-tissue imaging prior to each fraction using either CBCT (kV or MV) or MRI. The online image should be matched to the reference image, making appropriate soft-tissue adjustment where necessary.
- 3.6 Consider adaptive radiotherapy approaches to accommodate bladder/CTV changes given their demonstrated potential to improve target coverage and reduce normal tissue irradiation.
- 3.7 Avoid treatment interruptions during daily bladder radiotherapy as they can have detrimental effect on outcome. Bladder cancer should be treated as a category 1 tumour.

### Palliative

3.8 Consider palliative bladder radiotherapy for symptom control in patients not suitable for curative treatment.

Fractionation is determined by clinical circumstances, frailty and performance status. Options include:

- 30 Gy-36 Gy in five to six fractions (weekly)
- 21 Gy in three fractions (alternate days)
- 6 Gy or 8 Gy in one fraction
- 20 Gy in five daily fractions.

#### Topic 4. Node-positive disease

- 4.1 Define and document the recommended treatment intent (palliative or radical) following discussion at an MDT meeting.
- 4.2 Offer patients who can be considered for radical intent treatment (based on fitness and disease extent) a choice of either radical cystectomy and nodal dissection or bladder preservation treatment as per recommendations for N0 cancer.
- 4.3 Consider extending upfront chemotherapy to six cycles prior to radical treatment.
- 4.4 Perform restaging cross-sectional imaging after chemotherapy and before radical treatment.
- 4.5 Consider radical radiotherapy with radiosensitiser to the bladder with pelvic nodes.
- 4.6 Offer platinum-based chemotherapy (with cisplatin if suitable) to patients being treated with palliative intent. Offer maintenance immunotherapy if patients do not have progressive disease after palliative chemotherapy.

# Topic 5. Variant pathology

- 5.1 Consider managing tumours of mixed histology with a component of urothelial carcinoma as per standard urothelial carcinoma guidance.
- 5.2 Offer platinum-based combination chemotherapy prior to restaging and consideration of radical treatment for limited stage small cell carcinoma.
- 5.3 Prioritise radical surgery over radiotherapy for pure adenocarcinoma or squamous histology where a patient's fitness allows.

Bladder cancer RCR consensus statements

# Introduction

There has been a failure to improve outcomes in bladder cancer over the past 30 years,<sup>1</sup> despite a clear benefit of evidence-based interventions such as neo-adjuvant chemotherapy (NAC) and concurrent radio sensitisation (CRS) being demonstrated within clinical trials. The reasons for this are multifactorial but include concerns about treatment-related toxicity in a typically older, often more co morbid, cohort of patients leading to underutilisation of available therapies. Furthermore, not all patients receive adequate counselling about available options to make informed choices between radical surgery and bladder-sparing treatment. Bladder cancer patient experience remains poor with reduced long-term quality of life.<sup>2-4</sup>

The Royal College of Radiologists (RCR) audit, published in 2018, sought to benchmark contemporary practice on MIBC across the UK for the first time against published national guidance.<sup>5</sup> Key findings were:

- Older median patient age (78 years)
- Delays to definitive treatment from initial transurethral resection of the bladder tumour (TURBT) (median 57 days for NAC; median 82 days to radical radiotherapy)
- Improved use of NAC (43%), although 17% received non-recommended chemotherapy regimens
- CRS is used in only 40% of the radical radiotherapy population
- 25% of radical intent patients prescribed both NAC and CRS, with 16% of the radical population able to complete as initially prescribed
- Variation in radical and palliative radiotherapy schedules, and underutilisation of contemporary radiotherapy treatment techniques.

Though several of the consensus statements reiterate National Institute for Clinical Excellence (NICE) guidance it was felt important to include these given the variation identified in the RCR study. The other statements work to support a streamlined diagnostic pathway for patients, introducing the concept of co-morbidity assessment, consideration of pre-habilitation and improving standards of radiotherapy delivery akin to other tumour sites. The statements have been developed to support complex and unbiased decision-making for patients. In challenging scenarios where robust evidence to guide practice is limited, such as node-positive and variant pathology, it is hoped that these consensus statements will help support clinical decision-making.

We are very grateful to Sarah Griffin and Emma Burgum for their support in producing this work. We acknowledge the time, effort and commitment of the committee, the various stakeholder associations and the participants of the consensus meeting.

It is intended that these bladder cancer consensus statements will be used in conjunction with NICE guidance. It is hoped that they will serve as a practical stimulus for uro-oncology multidisciplinary teams (MDTs) to reflect on their own pathways and treatments to ensure optimal, streamlined patient-centred care for all, ultimately with a view to standardising care and improving outcomes.

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Bladder cancer RCR consensus statements

# What are consensus statements?

Consensus statements are developed by a group of experts on a topic for which 'consensus is sought using an explicit methodology to identify areas of agreement and disagreement'.<sup>6</sup> The consensus statements reflect the group's collective analysis and evaluation of the best available evidence as well as their expert opinion on a topic.

Clinical consensus statements are separate from clinical practice guidelines. While clinical consensus statements and clinical guidelines both provide recommendations on clinical practice, there are subtle but important differences between them. Clinical guidelines are usually based on a formal systematic review of high-level evidence, while consensus statements are most appropriate on topics where evidence is limited or lacking and therefore where a consensus approach offers the best way to address variability in clinical practice and improve patient outcomes.<sup>7,8</sup>

# RCR consensus methodology

The RCR consensus statements<sup>9-15</sup> are produced to guide and support clinicians in controversial areas of practice that lack strong evidence. They aim to reduce unacceptable variation in UK radiotherapy.

Bladder cancer experts were recruited to a steering group to develop a series of consensus statements around bladder cancer practice for the RCR. This multidisciplinary group included clinical oncologists, urological surgeons, medical oncologists, a radiographer, a medical physicist and a chief executive from the bladder cancer charity Fight Bladder Cancer.

The group was asked to focus on topics where there was current variation in the UK and was asked to avoid duplicating other guidelines unless there were good reasons for reiterating them. The group focused on the areas of variation highlighted by the RCR bladder audit.<sup>5</sup>

Five broad topic areas were selected. Following an appraisal of the available research literature, statements were drafted and refined over a six-month period.

Bladder leads from all of the UK cancer centres that deliver bladder radiotherapy were invited to share the first draft statements with their multidisciplinary bladder teams and to provide feedback.

All feedback received was reviewed in detail by the steering group and the statements and accompanying notes revised for consideration at a consensus meeting.

In advance of the consensus meeting these revised draft statements were circulated to all bladder leads along with pre-recorded presentations by the steering group summarising the evidence for each topic's statements.

On 30 June 2022 bladder leads from each centre were invited to attend a virtual consensus meeting to discuss and vote on the draft statements. Representatives were present from 45 centres, with a bladder cancer patient representative and a representative from bladder cancer charity Fight Bladder Cancer also in attendance.

Initial discussions were had in small breakout rooms followed by a whole-group discussion facilitated by the steering group. Several statements were refined based on the meeting discussions. Representatives were then asked to vote on each statement on behalf of their centre, with one vote per centre. Some statements were redrafted and voted on again so that wording could be clarified.

The following voting categories were agreed to Indicate strength of voting. Consensus in the responses was defined as agreement among at least 70% of participants.

Unanimous support	100%
Very strongly supported	90–99%
Strongly supported	70–89%
Majority support	60–69%
Equipoise	50–59%
Rejected	< 50%

Members of the steering group took notes of the discussion.

The final statements were then approved by the RCR's Clinical Oncology Professional Support and Standards Board for publication.

#### Wording the consensus statements

The RCR statements have been worded to make them concise, unambiguous and easy to translate into practice.

The wording of the RCR statements is based on the NICE technical manual.<sup>16</sup>

Each statement starts with a verb describing what the reader should do. The verb chosen reflects the strength of the recommendation.

- Statements that should (or should not) be offered use directive language such as 'offer' (or 'do not offer'), 'delineate', 'omit', 'treat' and so on.
- If there is a closer balance between benefits and harms the statement starts with 'consider'. These are recommendations for activities or interventions that *could* be used but where discussion with clinical teams and the patient, carefully considering the alternatives, is advised.

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# 1 Pathway and follow-up

Topic 1 statements

Statem	ent	Voting outcome
Diagno	osing and staging	
1.1	Offer a CT (computed tomography) urogram prior to TURBT (transurethral resection of the bladder tumour) for patients suspected to have muscle-invasive bladder cancer (MIBC).	Unanimous support
1.2	Offer a CT thorax to patients with suspected or confirmed MIBC.	Unanimous support
1.3	Consider an FDG-PET (fluorodeoxyglucose positron emission tomography) scan if the multidisciplinary team (MDT) feels it might influence treatment decisions.	Very strongly supported
1.4	Consider a magnetic resonance imaging (MRI) pelvis to patients pre-TURBT where muscle- invasive disease is suspected.	Strongly supported
1.5	Repeat staging scans if there is an interval of more than eight weeks between imaging and start of definitive treatment.	Strongly supported
1.6	<ul> <li>Use a minimum data set to present relevant information at MDT meetings. This should include:</li> <li>Clinical and radiological staging</li> <li>TURBT report including size and number of tumours, extent of resection, presence of carcinoma <i>in situ</i> (CIS), location of tumour</li> <li>Renal function, weight and height</li> <li>Performance status and co-morbidities</li> <li>Basic functional assessment including frailty assessment where appropriate.</li> </ul>	Very strongly supported

**1.7** Each centre should have a clinical nurse Unanimous support specialist (CNS)/advanced specialist practitioner (ASP) with special interest in bladder cancer.

# Radical therapy: preparing patients for treatment and supporting shared decision-making

1.8	Offer all patients with a new diagnosis of non-metastatic muscle-invasive urothelial bladder cancer clinical consultations with an oncologist, urologist and designated CNS, all of whom have expertise in managing bladder cancer. Patients should have a detailed discussion of radical treatment options including neoadjuvant chemotherapy (NAC), cystectomy and radiotherapy.	Unanimous support
1.9	Offer multiple opportunities for discussion of treatment options to support shared decision-making.	Very strongly supported
1.10	Consider pre-habilitation for patients in whom Strongly supported radical treatment is planned.	
Follow-up	protocol for patients treated with radical intent	
1.11	Offer CT of chest, abdomen and pelvis (CT CAP) at six, 12 and 24 months as a minimum. Then consider annually up to five years (to include upper tract imaging) following radical intent treatment (surgery or radiotherapy).	Very strongly supported
1.12	Offer patients who have completed bladder- preserving radical treatment cystoscopy every three months for first two years, then every six months for next two years and then annually up to five years from the end of treatment.	Very strongly supported
1.13	Offer evaluation and management of patients for late treatment effects and survivorship issues.	Unanimous support

#### Topic 1 explanatory notes

#### **Diagnosing and staging**

#### Statements 1.1 and 1.2

In patients with muscle-invasive disease, distant staging should be carried out with contrast-enhanced CT of chest, abdomen and pelvis (CT CAP) with urographic phase, preferably done prior to TURBT. This scan can be used to assess extravesical invasion (T3b or above disease) but is often unable to reliably differentiate between T stages. CT is useful to detect enlarged lymph nodes but has low sensitivity (48–87%) and specificity for the detection of lymph node metastasis.<sup>1</sup> Staging for distant metastases can best be done with CT.<sup>2</sup>

#### Statement 1.3

The role of FDG-PET (fluorodeoxyglucose positron emission tomography) imaging is not defined in the staging of bladder cancer and is not routinely indicated for initial staging evaluation. In patients with proven MIBC and fit for radical treatment, it can be considered if there are indeterminate findings on conventional staging investigations (such as T3b disease).<sup>3,4</sup>

At the consensus meeting it was felt that FDG-PET should be considered on an individual basis, following MDT review of imaging, and if the FDG-PET result was likely to influence treatment recommendations. It was appreciated that FDG-PET may upstage patients and preclude patients from radical treatments. It was also acknowledged that there are known limitations of FDG-PET (for example, in the interpretation of enlarged nodes that may be inflammatory, rather than malignant, in nature).

#### Statements 1.4 and 1.5

MRI has better soft-tissue contrast resolution compared with CT and therefore could potentially be a better tool for assessing muscle-invasive disease. A meta-analysis of 17 studies showed a 91% sensitivity and 96% specificity for 3.0-T device MRI combined with diffusion-weighted imaging (DWI) to differentiate between non-muscle-invasive bladder cancer (NMIBC) and MIBC.<sup>5</sup> The VI-RADS scoring has been proposed, which is a structured reporting scheme for multiparametric bladder MRI in the evaluation of suspected bladder cancer.<sup>6</sup> MRI is currently not offered routinely, although preliminary results of the BladderPath study suggest that substitution of TURBT with MRI and biopsy shortened the duration to commencement of treatment.<sup>7</sup>

At the consensus meeting there were differing views on how strong the recommendation on performing pelvis MRI should be. It was acknowledged that MRI is used to stage other pelvic cancers.

Guidance on streamlining of the diagnostic pathway is expected in the upcoming NHS England publication.

The consensus group also raised concerns about prolonged waiting times between TURBT and commencing definitive first treatment. The publication and ongoing widespread implementation of the National Cancer Waiting Times Monitoring Dataset in September 2020<sup>8</sup> is fully supported by the consensus group.

#### Statement 1.6

To facilitate meaningful MDT discussions and inform complex decision-making, a minimum data set was very strongly supported by the group. This proposed data set is not intended to delay the patient pathway to treatment.

#### Preparing patients for treatment and supporting shared decision-making

#### Statement 1.7

To address poor patient experience, there was unanimous support for having a named CNS with a special interest in bladder cancer at each centre. Both the British Association of Urological Nurses (BAUN) and the Fight Bladder Cancer charity advocated supported consultations with both oncology and a urologist with expertise in managing MIBC to enable patients to navigate complex decision-making.

#### Statements 1.8-1.10

The consensus group felt that a coordinated multidisciplinary approach is needed to optimally manage patients with MIBC who are being considered for radical treatment. This involves comprehensive MDT meeting discussions and clear local pathways to facilitate directed consultations with both an oncologist and a urologist with a special interest in bladder cancer.<sup>9</sup> Several centres have a joint clinic model, with others supporting separate appointments with relevant specialists. Our BAUN and Fight Bladder Cancer representatives discussed current limitations in patient access to all relevant specialists and information burden.

Pre-habilitation means optimising a patient's health to improve outcomes and tolerability of treatment, for example with an exercise regimen, dietary advice or smoking cessation. The practicalities of the implementation of a frailty assessment will be outlined in the forthcoming JCCO/RCR guidelines on frailty assessment due to be published in 2023.

#### Follow-up

#### Statements 1.11–1.13

At the consensus meeting it was agreed that the statement should align with NICE follow-up guidance.<sup>10</sup> The recommendation to consider CT CAP for up to five years aligns with clinical trial protocols. There is no published data showing that early detection of relapse improves survival. The benefits of follow-up beyond five years are unclear, and it is reasonable to discharge patients.<sup>11</sup> Discussion with the British Association of Urological Surgeons (BAUS) representatives supported the consideration of discontinuation of cystoscopic follow-up after five years, understanding that this will be influenced by clinical judgement as to whether radical salvage therapies remain appropriate.

Data from retrospective series influence current surveillance protocols. The aims of surveillance are:

- 1. To detect relapse; distant metastases after radical surgery and local as well and systemic relapses after bladder preservation<sup>12</sup>
- 2. To detect upper tract cancers (these occur in 4–10% of cases after radical cystectomy)<sup>13</sup>
- 3. To highlight urinary diversion concerns such as hydronephrosis
- 4. To detect long-term toxicity after treatment and associated quality of life impact.

Detection of long-term toxicity and quality-of-life issues may be achieved via clinical consultations and/or patient-reported outcome measures such as the ALERT-B tool<sup>14</sup> or FACT–BI (www.facit.org).<sup>15-17</sup>

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# 2 Systemic anti-cancer treatment (SACT)

# Topic 2 statements

Statem	nent	Voting outcome
	djuvant chemotherapy (NAC) for localised muscle- er cancer (T2–T4a N0)	invasive urothelial
2.1	Offer three to four cycles of cisplatin and gemcitabine, or MVAC, as standard of care for NAC in MIBC. Do not offer regimens containing carboplatin.	Very strongly supported
2.2	Consider split-dose cisplatin and gemcitabine for patients ineligible for platinum due to poor renal function (i.e., glomerular filtration rate [GFR] 40–60 ml/min).	Very strongly supported
2.3	Offer appropriate cross-sectional imaging to include chest, abdomen and pelvis during NAC prior to definitive treatment in a time frame that allows for prompt decision-making.	Unanimous support
2.4	Do not repeat cystoscopy after NAC prior to chemoradiation (CRT) or cystectomy.	Very strongly supported
2.5	Consider correction of unilateral hydronephrosis prior to treatment if GFR <60 ml/min.	Very strongly supported
Radios	ensitisers	
2.6	Offer a radiosensitiser as standard of care for patients suitable for daily radical radiotherapy for urothelial carcinoma of the bladder.	Very strongly supported
2.7	Offer BC2001 (5FU/mitomycin) chemotherapy regimens or BCON (carbogen/nicotinamide) as concurrent radiosensitisation (CRS) options. Alternatives include CRS with weekly gemcitabine or cisplatin chemotherapy.	Very strongly supported

#### Topic 2 explanatory notes

# NAC (neoadjuvant chemotherapy) for localised muscle invasive urothelial bladder cancer (T2–T4aN0)

#### Statement 2.1

Randomised trials have consistently shown that neoadjuvant cisplatin-based chemotherapy improves survival prior to radical treatment for bladder cancer.<sup>1–2</sup> This has subsequently been confirmed by a number of meta-analyses, with overall survival improvements of around 5–10%, and NAC should be considered the standard of care. There is still variable use of NAC, particularly in patients who are older or with co-morbidities, but the majority of patients fit for radical treatment would be fit for NAC.

In the UK, the most commonly used cisplatin combination is with gemcitabine. An acceptable alternative is MVAC. There is no evidence for benefit with carboplatin in place of cisplatin if patients have poor renal function (see 2.2 below).

The choice of three or four cycles is not clear. Some guidelines (such as National Comprehensive Cancer Network [NCCN]) suggest four cycles, but in practice often three cycles are used. Retrospective analyses have shown similar outcomes.<sup>3-6</sup>

This statement aligns with NICE guidance.7

#### Statement 2.2

For patients with moderate renal impairment with glomerular filtration rate (GFR) of 40– 60 ml/min it is recommended that split-dose cisplatin and gemcitabine is considered rather than carboplatin based on the phase II study.<sup>8</sup>

#### Statement 2.3

Offer appropriate cross-sectional imaging to include CT CAP during NAC prior to definitive treatment in a time frame that allows for prompt decision-making.

The purpose of statement 2.3 is to ensure there is a plan in place to move to radical definitive treatment in a timely manner, ensuring no delays in the treatment pathway.

Patients should be scanned prior to radical radiotherapy (CT CAP or equivalent). This should be performed in a time frame that allows appropriate decision-making, for example to avoid radical surgery if there is interim development of metastatic disease.

The cross-sectional imaging pre-radical therapy should be the same modality as the patient underwent at baseline. The statement does not mandate any particular mode of imaging.

At the consensus meeting it was noted that there is significant variability about the timing of reassessment. Some centres scanned after two cycles, while some centres scanned after three cycles.

The consensus group agreed that it was paramount for scans to be scheduled to allow time for scan reporting and decision-making without a break in the treatment pathway.

#### Statement 2.4

Repeat cystoscopy is not necessary prior to chemoradiation (CRT) or cystectomy if staging has taken place and there is no concern for locally recurrent or progressive disease.

#### Statement 2.5

Routine correction of unilateral hydronephrosis prior to treatment is not always necessary for patients with good renal function (if GFR >60 ml/min).<sup>9,10</sup> This should be discussed with the urology team and agreed at an MDT.

#### Radiosensitisers

#### Statements 2.6 and 2.7

Outcomes for radical radiotherapy to the bladder are improved when a radiosensitiser such as chemotherapy or carbogen and nicotinamide are given concurrently.<sup>11</sup> It should be considered for all daily radical bladder radiotherapy patients.

At the consensus meeting it was noted that this is a strong recommendation in the NICE guidance; however, the RCR audit demonstrated this evidence-based treatment is vastly underutilised. The consensus group felt very strongly that a radiosensitiser for patients should be used as the standard of care for those suitable for daily radical radiotherapy.

The group acknowledged there would be a small minority of patients who would not be suitable to receive any systemic treatment. In those occasional instances the reason(s) for not offering a radiosensitiser should be documented.

The group felt continued education would be beneficial for health professionals treating bladder cancer on the evidence for using radiosensitisers.

Superiority of one radiosensitiser over another is not known. Therefore, if contraindication with one regime is anticipated, an alternative evidence-based radiosensitiser should be considered.<sup>11</sup>

The BC2001 trial showed that concurrent chemotherapy with fluorouracil and mitomycin C combined with radiotherapy significantly improved locoregional control of bladder cancer, as compared with radiotherapy alone, with no significant increase in adverse events.<sup>12</sup> Two-year locoregional disease-free survival rates were improved from 54% to 67%. The chemotherapy was generally well tolerated. Grade 3 or 4 adverse events were slightly more common in the chemoradiotherapy group than in the radiotherapy group during treatment (36.0% versus 27.5%, P=0.07) but not during follow-up.

The BCON trial with carbogen and nicotinamide similarly showed improved cystoscopic control at six months and also improved overall survival and lower relapse rates. Radiotherapy schedules of 55 Gy in 20 fractions and 64 Gy in 32 fractions were used. There was no evidence of significant differences in late urinary or gastrointestinal morbidity between treatment groups or between fractionation schedules.<sup>13</sup>

Exploratory subgroup analysis from BC2001 evaluating NAC followed by radical chemoradiotherapy demonstrates it is feasible and overall well tolerated.<sup>14,15</sup> A non-significant excess of toxicity was observed in the chemoradiotherapy group, but it did not impact on quality of life.

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Technical aspects of radiotherapy – radical, high-dose palliative and palliative

# Topic 3 statements

Statem		Voting outcome
Staten	lent	Voting outcome
Radica	I and high-dose palliative	
3.1	Radical bladder radiotherapy: Offer patients with localised MIBC (T2– T4aN0M0) daily hypofractionated radiotherapy 55 Gy in 20 fractions as standard given demonstrated non-inferiority to conventional regime 64 Gy in 32 fractions.	Unanimous support
3.2	Alternative option in frail patients (high-dose palliative): Consider 36 Gy to the whole bladder in six weekly fractions in those unsuitable for daily radiotherapy because of poor performance status or co-morbidity.* *alternate radiotherapy regime – please see explanatory notes below	Strongly supported
3.3	Use intensity-modulated radiation therapy (IMRT) techniques given their potential to reduce normal tissue irradiation and toxicity.	Unanimous support
3.4	Consider normal tissue/organ at risk (OAR) dose constraint guidance as summarised in Table 1 on page 22. Avoid dose compromise to the planning target volume (PTV) to achieve OAR constraints.	Unanimous support
3.5	Offer all patients receiving daily treatment or ultra-hypofractionated bladder radiotherapy (36 Gy in six fractions) pre-treatment 3D volumetric soft-tissue imaging online prior to each fraction using either CBCT (kV or MV) or MRI. The online image should be matched to the reference image making appropriate soft- tissue adjustment where necessary.	Unanimous support

3.6	Consider adaptive radiotherapy approaches to accommodate bladder / CTV change given demonstrated potential to improve target coverage and reduce normal tissue irradiation.	Very strongly supported
3.7	Avoid treatment interruptions during daily bladder radiotherapy as they can have detrimental effect on outcome. Bladder cancer should be treated as a category 1 tumour.	Unanimous support
Palliative		
3.8	Consider palliative bladder radiotherapy for symptom control in patients not suitable for curative treatment. Fractionation is determined by clinical	Unanimous support
	circumstances, overall frailty and performance status. Fractionation options include:	
	• 30 Gy–36 Gy in five to six fractions (weekly)	
	<ul> <li>21 Gy in three fractions (alternate days)</li> </ul>	
	• 6 Gy or 8 Gy in one fraction	
	<ul> <li>20 Gy in five daily fractions</li> </ul>	

#### Table 1. Suggested OAR dose constraints

	Fractionation	n scheme							
Structure	55 Gy in 20 fractions		64 Gy in 32 fractions		36 Gy in 6 fractions				
	Constraint to be achieved	Level 1	Level 2	Constraint to be achieved	Level 1	Level 2	Constraint to be achieved	Level 1	Level 2
Rectum	V25 Gy	50%	80%	V30 Gy	50%	80%	V17 Gy	50%	80%
	V41.7 Gy	20%	60%	V50 Gy	20%	60%	V28 Gy	20%	60%
	V50 Gy	15%	50%	V60 Gy	15%	50%	V33 Gy	15%	50%
	V54.2 Gy	5%	30%	V65 Gy	5%	30%	V36 Gy	5%	30%
Femoral heads	V41.7 Gy	<5	50%	V50 Gy	<5	60%	V28 Gy	<5	0%
Other bowel	V28 Gy	149 cc	178 cc	V30 Gy	149 cc	178 cc	V25 Gy	139 cc	208 cc
	V37.5 Gy	116 cc	139 cc	V45 Gy	116 cc	139 cc	V28 Gy	122 cc	183 cc
	V41.7 Gy	104 cc	127 cc	V50 Gy	104 cc	127 cc	V31 Gy	105 cc	157 cc
	V45.8 Gy	91 cc	115 cc	V55 Gy	91 cc	115 cc	V33 Gy	84 cc	126 cc
	V50 Gy	73 cc	98 cc	V60 Gy	73 cc	98 cc	V36 Gy	26 cc	39 cc
	V54.2 Gy	23 cc	40 cc	V65 Gy	23 cc	40 cc			

The given normal tissue/organ at risk (OAR) dose constraints as summarised in Table 1 above are provided as a guide and therefore are not presented as mandatory and optimal constraints but as level 1 and level 2, where level 1 constraints are to be met if possible and level 2 to be met wherever possible.

# Topic 3 explanatory notes

#### Statement 3.1

The recommended radical bladder fractionation is informed by individual patient metaanalysis of BC2001 and BCON demonstrating non-inferiority of 55 Gy in 20 fractions to conventional regime 64 Gy in 32 fractions.<sup>1</sup> This provides the best evidence to date supporting 55 Gy in 20 fractions as the preferred standard of care for bladder fractionation given improved invasive locoregional control.

It Is acknowledged that subgroup analysis of toxicity indicated a detrimental effect of 55 Gy in 20 fractions in patients receiving a concurrent radiosensitiser. However, this should be interpreted with caution as the authors note that the differences may relate to these patients having increased follow-up to collect toxicity data because of combined benefit from sensitiser and hypofractionation.<sup>1</sup> Importantly no difference was observed in patient-reported health-related quality of life (HRQOL) in the long term after recovery from acute toxicity in the BC2001 trial with both fractionation schedules.<sup>20</sup>

Improved local disease control is evident with concurrent use of a radiosensitiser as discussed in topic  $2.^{1-3}$ 

#### Statement 3.2

At the consensus meeting opinions differed on whether 36 Gy in six fractions should be presented in the 'radical' section. Advocates of this regime felt strongly that the HYBRID

trial, which utilised this regime in an older, frailer patient population with T2–T4aN0M0 bladder cancer, demonstrated good disease control for the duration of patients' remaining life. The proportion of patients free of invasive local recurrence at one year was 85.5% (95% CI, 70.1–93.3%). Median survival was 18.9 months, with 61.5% (95% CI, 48.6–72.1%) alive at one year and 46.2% (95% CI, 33.8–57.7%) alive at two years.<sup>6</sup>

Opponents of the statement that 36 Gy in six fractions over six weeks should be in the radical section argued radiobiological inferiority of this schedule compared with standard daily dose fractionation schedules for bladder cancer. They felt it should be considered only in the palliative section and that the 21 Gy in three fractions would be as beneficial for long-term and symptom control.

Overall agreement was to support the use of 36 Gy in six fractions over six weeks in patients not suitable for daily treatment for whom long-term control was the intent of treatment. There was agreement that 36 Gy in six fractions over six weeks was not biologically equivalent to 55 Gy in 20 fractions in the radical setting. However, 21 Gy in three fractions remains an important palliative radiotherapy option for symptom control. The issue was therefore resolved by badging the 36 Gy in six fractions regime as an alternative radiotherapy schedule to be considered for those with localised muscle-invasive disease but not suitable for daily radiotherapy where long-term disease control was the treatment intent.

Partial bladder radiotherapy as evaluated in two randomised control trials demonstrate no significant difference in local disease or toxicity compared with whole-bladder radiotherapy.<sup>22,23</sup> Contemporary evidence for partial bladder/reduced high-dose bladder volume with image-guided adaptive radiotherapy delivery from RAIDER (NCT02447549) study is awaited.<sup>9,10</sup>

#### Statement 3.3

In comparisons of clinical outcomes of bladder cancer radiotherapy, intensity-modulated radiation therapy (IMRT) has been reported to significantly reduce acute common terminology criteria for adverse events (CTCAE) grade >2 diarrhoea by almost 50% compared with 3D conformal radiotherapy (56% versus 30%; p=0.008).<sup>7</sup> The retrospective design and the relatively low patient numbers in this study do not allow firm conclusions to be made, but it suggests the potential importance of dose sparing to the bowel that can be achieved by IMRT.<sup>7,24,25</sup> IMAT has the additional benefit of faster treatment delivery times. This minimises intrafractional bladder filling and improves resource utilisation, as well as providing additional dosimetric advantage.<sup>8</sup>

At the consensus meeting it was generally thought that IMRT was being offered in most centres. Nevertheless, it was noted that it was important to be aspirational even if it was not available in all centres at this time.

#### Statement 3.4

The suggested radiotherapy OAR dose constraints are as applied in recent early phase and subsequent randomised bladder radiotherapy studies.<sup>5,6,9–13</sup> It should be noted that bowel constraints have been modelled from grade 1 and grade 2 late bowel toxicity events from evaluable subgroups of patients in BC2001.<sup>11</sup> Therefore, if maintained, it is associated with very low risk of >grade 2 bowel toxicity. However, the OAR constraints are a guide and the dose to planning target volume (PTV) should not be routinely compromised to achieve them.

#### Statement 3.5

There was general agreement on this statement at the consensus meeting. It was noted that there were resource constraints in some centres. However, the consensus group felt it was an important aspiration.

#### Statement 3.6

Resource implications for implementation were noted.

Some centres wanted to strengthen this statement by changing the starting verb to 'offer'. The group agreed to leave it as 'consider' pending publication of the RAIDER trial and evidence of clinical benefit.

# Statement 3.7

The consensus group agreed that bladder cancer should be category 1 given the adverse impact on prolonging treatment times.

#### Statement 3.8

Discussion generated on the day related to what constituted the definition of the palliative radiotherapy schedule. The statement was redrafted on the consensus day, with issues discussed covered in the notes above for statement 3.2.

The consensus was that palliative radiotherapy of the bladder should be considered in those not suitable for cure, either because of advanced stage or frailty, but who were experiencing local symptoms such as pain or bleeding. Fractionation schedules utilised for this varied but 30 Gy–36 Gy in five to six fractions (weekly), 21 Gy in three fractions and 6–8 Gy in one fraction were offered as potential options. The most appropriate palliative fractionation is dependent on the clinical assessment.

It was felt important to try to minimise doses to OAR by utilising volumetric modulated arc therapy (VMAT) for 21 Gy in three fraction schedules and 36 Gy in six fractions schedules where possible.

In line with findings from the RCR audit, many centres also advocated the use of 20 Gy in five fractions, often to facilitate rapid delivery of treatment for a symptomatic patient using a parallel opposed pair.

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4

# Topic 4 statements

Node-positive disease

Statem	nent	Voting outcome
4.1	Define and document recommended treatment intent (palliative versus radical) through the MDT discussion.	Unanimous support
4.2	Offer patients who can be considered for radical intent treatment (based on fitness and disease extent) a choice of either radical cystectomy and nodal dissection or bladder preservation treatment as per recommendations for N0 cancer.	Unanimous support
4.3	Consider extending upfront chemotherapy to six cycles prior to radical treatment.	Strongly supported
4.4	Perform restaging cross-sectional imaging after chemotherapy and before radical treatment.	Unanimous support
4.5	Consider radical radiotherapy with radiosensitiser to the bladder with pelvic nodes.	Strongly supported
4.6	Offer platinum-based chemotherapy (with cisplatin if suitable) to patients treated with palliative intent. Offer maintenance immunotherapy if patients do not have progressive disease after palliative chemotherapy.	Very strongly supported

# Topic 4 explanatory notes

The statements within this section refer to patients with non-metastatic urothelial cancer who are deemed node-positive on diagnostic imaging.

# Statement 4.1

Defining treatment intent at the MDT is to provide some direction to the treatment plan; it does not preclude treatment intent changing at a later stage. At the consensus meeting it was acknowledged that clear evidence is lacking and it was felt it was a matter for the MDT to decide how treatment intent was defined.

It was felt that the diagnostic statements (including use of PET) voted upon in section 1 were also of relevance within the non-metastatic node-positive patients, so they have not been repeated again within this section.

#### Statement 4.2

Appropriate patients with node-positive disease should have the same choice (of either radical cystectomy and nodal dissection or bladder preservation treatment) as patients with N0 disease.

Given the lack of randomised or prospective data specifically for N1–3M0 patients, patients should be offered a discussion on the relative potential merits of each modality.

#### Statement 4.3

Given the lack of randomised or prospective data specifically for N1–3M0 patients, consideration should be given to an extended course of NAC. This recommendation is on the basis of data from the T2–4aN0M0 setting showing a survival advantage and from the locally advanced/metastatic disease setting where patients without visceral metastases to bone, liver or lung had a median overall survival of 18.4 months and a five-year survival rate of 20.9% (95% CI, 15.3–26.5%) following cisplatin-based chemotherapy for six cycles.<sup>1–3</sup>

#### Statement 4.5

At the consensus meeting most centres felt that positive pelvic nodes should be treated along with the bladder if they were involved at the outset. However, some centres were concerned about the statement being too prescriptive given the lack of randomised data regarding whole-pelvis radiotherapy to bladder.

Some centres felt that clinicians should have the option to treat with or without nodes in discussion with the patient, taking into consideration risks and benefits.

The statement starts with 'consider' to reflect that clinical decision-making, taking into account risk and benefit, is advised. The group also felt that centres should audit their outcomes. An audit of this across the UK would be beneficial.

It is noted that toxicity from radiotherapy to bladder and pelvic lymph nodes with concurrent chemotherapy has been shown to be low in a small phase II study. Similarly, radiotherapy to prostate and pelvic lymph nodes with hypoxia modification (carbogen and nicotinamide) in another small phase Ib/II study has also demonstrated low rates of acute toxicities.<sup>6,7</sup>

#### Statement 4.6

Given the lack of randomised or prospective data specifically for N1–3M0 patients, it was felt that cisplatin-based chemotherapy should be recommended for those suitably fit to receive it on the basis of extrapolation from node-negative and advanced disease settings suggesting superior outcomes.<sup>1–3</sup>

# Topic 4 references

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# 5 Variant pathology

# Topic 5 statements

Stateme	ent	Voting outcome
5.1	Consider managing tumours of mixed histology with a component of urothelial carcinoma as per standard urothelial carcinoma guidance.	Very strongly supported
5.2	Offer platinum-based combination chemotherapy prior to restaging and consideration of radical treatment for limited stage small cell carcinoma.	Very strongly supported
5.3	Prioritise radical surgery over radiotherapy for pure adenocarcinoma or squamous histology where this is possible.	Unanimous support

# Topic 5 explanatory notes

# Statement 5.1

At the consensus meeting there was discussion on whether treatment was dependent on the amount of variant pathology within a TURBT specimen if urothelial carcinoma was also present. It was agreed that careful discussion at an MDT with the histopathologist was warranted, but that current evidence supports utilising treatment procotols for urothelial cancer as there is no clear evidence to suggest otherwise. The group felt the statement should remain worded as it is as the priority is for people with cancer to get access to NAC and a radiosensitiser by treating as for transitional cell carcinoma (TCC).

### Statement 5.2

At the consensus meeting there was agreement on a need to prioritise SACT due to the high risk of distant micrometastatic disease even with localised disease staging. The group took the decision not to mandate etoposide given the lack of evidence in this area. The main priority is to ensure centres are giving platinum-based combination chemotherapy.

### Statement 5.3

At the consensus meeting there was discussion about pure versus predominant variant pathology. There was concern about sampling and setting thresholds as per statement 5.1. The group agreed that careful MDT discussion was required on a case-by-case basis.

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Bladder cancer RCR consensus statements

# Acknowledgements

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- Gregory Smyth, scientific lead physicist, Institute of Physics and Engineering in Medicine (IPEM) Radiotherapy Special Interest Group

#### **RCR consensus project team**

- Emma Burgum, Professional Support & Standards Administrator, RCR
- Sarah Griffin, Clinical Oncology Projects and Development Officer, RCR

# Consensus participants

The following centres were represented at the virtual RCR bladder cancer consensus meeting held on 30 June 2022.

- Aberdeen Royal Infirmary
- Arden Cancer Centre, University Hospitals Coventry & Warwickshire
- Barking, Havering & Redbridge University Hospitals NHS Trust
- Barts Cancer Centre, Barts Health NHS Trust
- Beatson West of Scotland Cancer Centre
- Cambridge University Hospitals
- Dorset Cancer Centre, Poole Hospital
- Edinburgh Cancer Centre
- James Cook Cancer Institute, South Tees NHS Foundation Trust
- Kent Oncology Centre
- Lancashire Teaching Hospitals NHS Foundation Trust
- Leeds Cancer Centre
- Leicester Royal Infirmary
- Mount Vernon Cancer Centre
- Musgrove Park Hospital, Taunton
- Ninewells Hospital & Medical School
- North Middlesex University Hospital
- Northern Centre for Cancer Care
- Northern Ireland Cancer Centre
- Nottingham University Hospitals NHS Trust
- Oxford Cancer Centre
- Peterborough City Hospital

- Portsmouth Oncology Centre, Queen Alexandra Hospital
- Raigmore Hospital, NHS Highland
- Royal Berkshire Hospital
- Royal Cornwall Hospital
- Royal Devon and Exeter Foundation Trust Hospital
- Royal Free Hospital, London
- Royal Marsden NHS Foundation Trust
- Royal Shrewsbury Hospital
- Royal Surrey County Hospital
- Royal United Hospital Bath
- South West Wales Cancer Centre
- Southampton General Hospital
- Southend University Hospital
- The Christie Hospital
- The Clatterbridge Cancer Centre
- Torbay and South Devon NHS Foundation Trust
- University College London Hospitals
- University Hospitals Birmingham
- University Hospital of North Midlands NHS Trust
- University Hospitals Plymouth NHS Trust
- Velindre Cancer Centre
- Weston Park Hospital, Sheffield
- Worcestershire Oncology Centre

We are also very grateful to patient representative Eric Edwards, who attended on the day to provide a patient perspective, along with Lydia Makaroff, chief executive officer of Fight Bladder Cancer.

The first draft of the consensus statements was circulated to all of the UK cancer centres that deliver bladder radiotherapy to discuss with their multidisciplinary bladder teams and to provide feedback. Feedback received was incorporated into the draft voted on at the 30 June 2022 consensus meeting.

Centres that provided written feedback on the statements prior to the 30 June meeting but who were unable to attend on the day:

- Bristol Haematology & Oncology Centre
- Cheltenham General Hospital
- Guy's and St Thomas' NHS Foundation Trust
- Hull University Teaching Hospitals
- Ipswich Hospital
- Northampton General Hospital
- Sussex Cancer Centre Brighton
- United Lincolnshire Hospitals Trust
- University Hospitals Derby and Burton

#### **Stakeholders**

We are very grateful to the following stakeholder organisations for providing a representative on the RCR bladder consensus steering group:

- British Association of Urological Surgeons
- Society and College of Radiographers
- Institute of Physics and Engineering in Medicine
- Association of Cancer Physicians
- Fight Bladder Cancer

Bladder cancer RCR consensus statements

# Abbreviations

ASP	advanced specialist practitioner
BAUN	British Association of Urological Nurses
BAUS	British Association of Urological Surgeons
CIS	carcinoma in situ
CNS	clinical nurse specialist
CRS	concurrent radiosensitisation
CRT	chemoradiation
СТ	computed tomography
CTCAE	common terminology criteria for adverse events
СТ САР	computed tomography chest abdomen and pelvis
СТV	clinical target volume
DWI	diffusion-weighted imaging
FDG-PET	fluorodeoxyglucose (FDG) positron emission tomography (PET)
GFR	glomerular filtration rate
HRQOL	health-related quality of life
IMAT	intensity-modulated arc radiotherapy
IMRT	intensity-modulated radiation therapy
0001	Joint Collegiate Council for Oncology
MDT	multidisciplinary team

MIBC	muscle-invasive bladder cancer
MRI	magnetic resonance imaging
MVAC	name of a chemotherapy combination that includes methotrexate, vinblastine, doxorubicin (Adriamycin) and cisplatin
NAC	neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NMIBC	non-muscle-invasive bladder cancer
OAR	organ at risk
ΡΤν	planning target volume
QoL	quality of life
RC	radical cystectomy
SACT	systemic anti-cancer treatment
тсс	transitional cell carcinoma (otherwise known as urothelial carcinoma)
TURBT	transurethral resection of the bladder tumour
VI-RADS	vesical imaging-reporting and data system
VMAT	volumetric modulated arc therapy



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