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Original Article

Radiotherapy Management of Muscle Invasive Bladder Cancer: Evaluation of a National Cohort

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Abstract

Aims: With the failure to improve outcomes of patients with bladder cancer over the last 30 years, this study was developed to benchmark contemporary UK radiotherapy practice for the management of muscle invasive bladder cancer (MIBC) against published national guidance.
Materials and methods: All UK radiotherapy centres were invited to complete a questionnaire for each patient with MIBC starting bladder radiotherapy over a 16-week period from December 2016.
Results: Sixty-nine per cent (41/59) of UK radiotherapy centres completed a detailed questionnaire for 508 patients. The median age was 78 years and 64% ($n = 323$ patients) had stage II or III disease. Treatment intent was radical in 54% ($n = 275$). From transurethral resection of the bladder tumour, patients waited 57 days before starting neoadjuvant chemotherapy (NAC) (interquartile range 46–72 days). Patients who had radical radiotherapy as their first definitive treatment waited a median of 82 days (interquartile range 62–105 days). NAC was considered in 66% ($n = 182$) of all radical cases and given in 43% ($n = 119$). Concurrent radiosensitisation (CRT) was considered for 53% ($n = 146$) and delivered in 40% ($n = 109$) of patients. The most common fractionation was 55 Gy/20 fractions/4 weeks in 49% ($n = 134$) for radical patients and 36 Gy/6 fractions/6 weeks in 25% ($n = 57$) for palliative patients.
Conclusion: This is the largest multicentre prospective study to define contemporary management of MIBC in patients receiving radiotherapy within the UK. The population studied is the oldest described to date. Timelines to starting definitive treatment confirm an urgent need to streamline the pathway. An increasing use of NAC is described, although the penetrance of CRT is disappointingly low. Areas for improvement with regards to the delivery and quality of radiotherapy have been identified. The detail within this study can be used to inform practice and future trial design, ultimately with the aim of improving outcomes for patients with MIBC.

Keywords: Concurrent radio sensitisation; MIBC; muscle invasive bladder cancer; national cohort; neo-adjuvant chemotherapy; radiotherapy

Introduction

Bladder cancer is the seventh most common cause of cancer death in the UK, accounting for 3% of all cancer deaths in 2016. One-third of patients will have muscle invasive bladder cancer (MIBC) at diagnosis. Although there have been significant improvements in outcome in other cancers, bladder cancer survival has remained static over 30 years, with a 5-year survival rate in adults of 53% [1,2].

There is a lack of robust evidence showing the superiority of either radical cystectomy with lymphadenectomy over radiotherapy with concurrent radiosensitisation (CRT). Historically, cystectomy has been considered the treatment of choice, reserving radiotherapy for patients deemed unfit for surgery or those who decline surgery. The uncertainty is reflected in the discordance of international treatment guidelines, with some strongly recommending cystectomy over CRT [3–5] and others concluding that both are acceptable [6,7].

An improvement in outcomes is achievable, having been shown within MIBC clinical trials over the last 15 years. The use of neoadjuvant chemotherapy (NAC) confers a 5%

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overall survival benefit prior to cystectomy or radiotherapy [8] and two large UK-led trials have shown a locoregional disease-free survival benefit (BC2001) [9] as well as an overall survival benefit (BCON) [10] with CRT. The penetrance of these interventions within a UK non-trial cohort, however, has not been described.

National standards for patient treatment are designed to optimise outcomes. This study was designed to assess the patient demographics, diagnostic and treatment pathway, uptake of evidenced-based practice, as well as the quality of radiotherapy treatment planning and delivery to evaluate current UK management, ultimately with the aim of improving the quality of treatment.

Materials and Methods

An invitation to participate in this study was sent to all radiotherapy departments with an approved lead for audit registered with the Royal College of Radiologists (RCR) in the UK. Centres were asked to complete one anonymised questionnaire for each patient starting either palliative (23 questions) or radical radiotherapy (75 questions) to the bladder for MIBC over a 16-week period between Monday 5 December 2016 and Monday 27 March 2017 (113 days). The questions were designed to understand patient demographics, the diagnostic and patient pathway, tumour characteristics, treatment intent, use of NAC and CRT, as well as radiotherapy quality and clinical trial recruitment. The responses were submitted electronically and then collated by the RCR.

Results

In total, 41 of 59 (69%) radiotherapy centres submitted 508 questionnaires. A median of 11 questionnaires were returned (interquartile range = 4–16 questionnaires) with a completion rate of 499/508 (98.2%).

The completeness of data collection was assessed by comparing the number of patients within this study to national datasets. At the time of this study, the only national data collected was through the Radiotherapy Data Set (RTDS), which mandates National Health Service (NHS) Acute Trust providers of radiotherapy services in England to collect and submit standardised data monthly. The proportion of our study patients recorded by English centres (433 patients) was compared with the total RTDS patients. Our study covered a 113 day period: the RTDS collects information over whole calendar months (equivalent of 121 days, during which time information on 775 patients was collected). Presuming the same rate of treatment per day (6.4 patients per day), we estimated that the RTDS collected information for 724 patients over 113 days. We estimate that our study collected data on 433 patients whose information was also captured by the RTDS, equating to 60% (433/724) of the English population.

The patient demographic characteristics are defined in Table 1.

Table 1
Patient demographics

	Population
n	508
Median age	78 (IQR 46–98)
>70 years	79% (399)
>75 years	63% (299)
Gender (% male)	73% (373)
World Health Organization performance status	
0	17% (87)
1	34% (172)
2	26% (133)
≥3	10% (52)
Pathology	
TCC	87% (443)
Grade (3)	88% (445)
Confirmed T2 at least	81% (409)
Radiological stage	
T2	38% (194)
T3	24% (122)
T4	10% (53)
N0	68% (344)
N1	10% (50)
N2	6% (30)
N3	5% (25)
M1	11% (54)
Stage II or III (T2–4 N0 M0)	64% (323/508)
Stage IV (any T, N1–3 and/or M1)*	25% (125/508)
Stage IV nodal disease (any T, N1–3 M0)	13% (67/508)
Stage IV (any T, any N, M1)	(11%) 54/508
Radiotherapy treatment intent	
Radical	54% (275)
Palliative	45% (228)

IQR, interquartile range; TCC, transitional cell carcinoma.
* TNM7 was used for this study, as this was the version available to use at the time that this study was open.

The standards of the audit and overall performance are listed in Table 2. The standards were derived from unequivocal recommendations from a National Institute for Health and Care Excellence (NICE) guideline (NG2) [6] and also RCR guidance [11,12]. The wording in the NG2 document denotes the certainty with which they are made; the word ‘offer’ anticipates that such interventions are routinely undertaken, whereas ‘consider’ suggests less certain benefit [13]. Although a limited number of standards could therefore be applied, the level of uptake of an intervention within the population could, however, be quantified. Unless otherwise stated, percentages are calculated from the total number of relevant cases, including missing data.

Timelines from transurethral resection of bladder tumour (TURBT) to the first cycle of NAC or radiotherapy are shown in Figure 1.

Neoadjuvant Chemotherapy

NAC was considered in 66% ($n = 182$) of patients treated with radical intent and given in 43% ($n = 119$) of all radical patients. Reasons identified for NAC not being administered

Table 2
Audit standard and penetrance of interventions

	Expected compliance	Study results
Diagnostic work-up		$n = 275$
CT/MRI pelvis	99%	96% (263)
CT urography/other planned CT imaging to detect upper tract involvement		73% (200)
CT thorax		91% (250)
PET CT (of those with high-risk disease (T3b/indeterminate findings)		13% (36)
Patient pathway		275
% of patients discussed at network specialist multidisciplinary meeting	95%	60% (166)
% of patients who saw a clinical oncologist who specialises in bladder radiotherapy	95%	98% (269)
% of patients who saw a urologist who specialises in cystectomy	95%	74% (203)
Neoadjuvant chemotherapy (NAC)		$n = 275$
% of cohort considered for NAC		66% (182)
% of cohort receiving NAC		43% (119)
% of patients receiving cisplatin combination NAC	95%	72% (86)
Definitive radical treatment		$n = 275$
Offer choice of radical cystectomy or radiotherapy with a radiosensitiser to people with MIBC	95%	68% (187)
Radiosensitisation		$n = 275$
Use of a radiosensitiser	95%	40% (109)
Radical radiotherapy delivery		$n = 275$
Dose fractionation (60–64 Gy/30–32 fractions or 52.5–55 Gy/20 fractions) radical-intent radiotherapy*	95%	93% (256)
Palliative radiotherapy delivery		$n = 228$
Dose fractionation (6–8Gy/1 fraction or 30–36 Gy/5–6 fractions) palliative-intent radiotherapy	95%	45% (102)
Treatment verification		275
Radical radiotherapy	100%	97% (268)

CT, computed tomography; MIBC, muscle invasive bladder cancer; MRI, magnetic resonance imaging; PET, positron emission tomography.
* Includes five patients treated with radical radiotherapy schedules approved within nationally approved clinical trials.

were: age (26%, $n = 39$), poor World Health Organization performance status (26%, $n = 39$), renal function (21%, $n = 31$), comorbidities (59%, $n = 88$), patient choice (12%, $n = 18$), unfavourable histology (1%, $n = 2$), symptoms (1%, $n = 1$) and no specific reason identified (12%, $n = 18$).

NAC regimens administered are summarised in Figure 2.

NAC was given as intended (dose and intensity) in 71% (85/119). Of the 33 patients who did not have NAC as intended, dose reduction was necessary in 27% ($n = 9$); doses were omitted due to chemotherapy toxicity (need to change from cisplatin to carboplatin; 3%, $n = 1$), delay and/or dose reduction in 33% ($n = 11$) due to myocardial infarct in 3% ($n = 1$) or omission due to other non-specified chemotherapy side-effects (55%, $n = 18$). Most patients (68%, $n = 81$) received either three or four cycles of NAC, with 20% ($n = 24$) discontinuing after one or two cycles and 10% ($n = 12$) of patients proceeding to receive either five or six cycles, including 10 with evidence of pelvic lymphadenopathy.

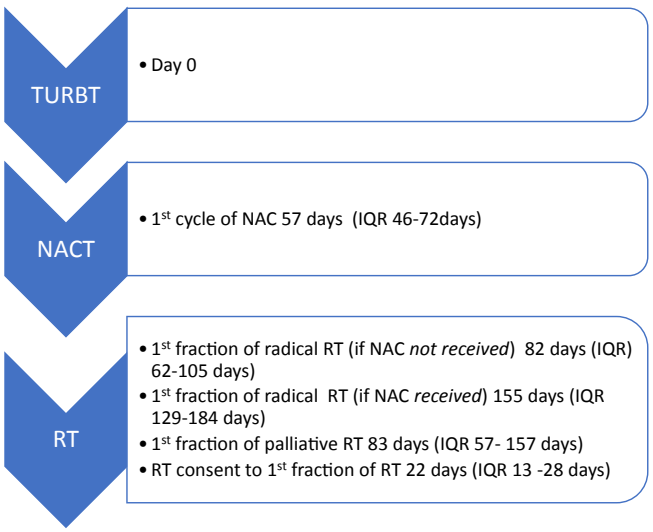

Fig 1. Timelines to definitive treatment.

Radiotherapy Schedules

The radical radiotherapy prescriptions are shown in Figure 3. Nine per cent ($n = 24$) of the radical-intent population were treated with one of eight non-RCR guideline or trial protocol radical radiotherapy prescriptions (21) or an unknown prescription (three). Patients with palliative-intent treatment were prescribed 6 or 8 Gy/1 fraction (14%, 33), 30–36 Gy in 5–6 fractions (30%, 69) or 21 Gy/3 fractions (14%, 31) in 58% ($n = 133$) of cases. The remainder (42%, $n = 95$) received one of 11 non-RCR guideline palliative radiotherapy prescriptions (89) or an unknown prescription (six) [11].

The audit period included Christmas and New Year of 2016, during which period there were three public

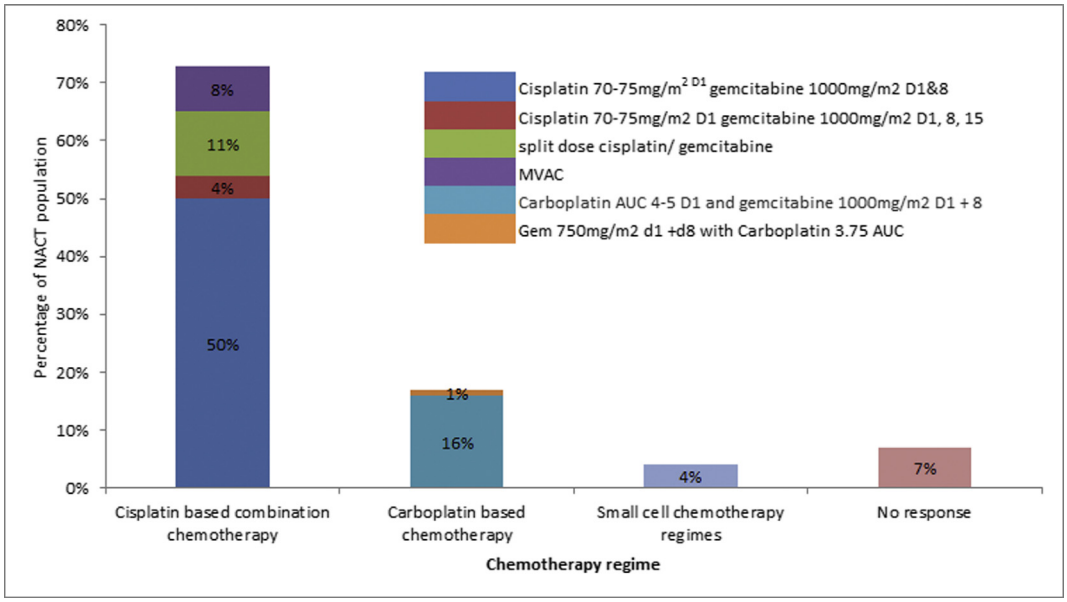

Fig 2. Combination cisplatin-based neoadjuvant chemotherapy (NAC) was most frequently used. The most common combination cisplatin regimen was cisplatin 70–75 mg/m^2 day 1 with gemcitabine 1000 mg/m^2 days 1 and 8 (50%, $n = 59$), then a split-dose combination cisplatin regimen (cisplatin [35 mg/m^2 days 1 and 8] with days 1 and 8 gemcitabine 1000 mg/m^2; 11%, $n = 13$), then methotrexate 30 mg/m^2, vinblastine 3 mg/m^2, doxorubicin 30 mg/m^2, cisplatin 70 mg/m^2 (MVAC; 8%, $n = 9$); the least common was cisplatin 70–75 mg/m^2 day 1, gemcitabine 1000 mg/m^2 days 1, 8, 15 (4%, $n = 5$). Carboplatin AUC 4–5 day 1 and gemcitabine 1000 mg/m^2 days 1 and 8 was used in 19 patients (16%). Gemcitabine 750 mg/m^2 days 1 and 8 with carboplatin 3.75 AUC was used in one patient (1%). Small cell regimens (carboplatin/etoposide or etoposide) alone were used in four (3%) and one patient (1%), respectively.

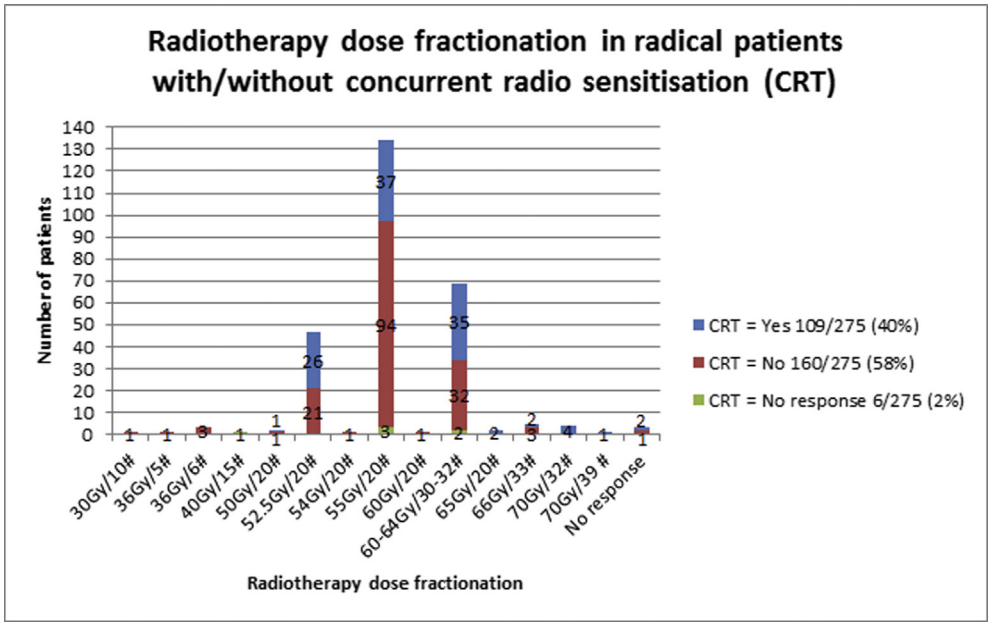

Fig 3. Of the radical-intent doses prescribed, 91% ($n = 251$ patients) had radical doses 52.5–55 Gy/20 fractions or 60–64 Gy/30–32 fractions. Five additional patients received radical fractionation defined by clinical trials (1% [$n = 4$] receiving 70 Gy/32 fractions and 0.4% [$n = 1$] receiving 60 Gy/20 fractions).

holiday days. Treatment time was prolonged in 42 radical patients (15%), with 60% ($n = 25$) having ≤2 day prolongation. Of five patients who had >5 day prolongation, four did not have compensation as they were receiving hypofractionated schedules, in keeping with the RCR document that states that this is not recommended when the dose per fraction exceeds 2.2 Gy [12].

Table 3
Radiotherapy planning technique and delivery

Planning technique		
Radiotherapy target	Bladder	89% ($n = 245$)
	Bladder and pelvic lymph nodes	8% ($n = 22$)
	Partial bladder	1.5% ($n = 4$)
Margins	CTV - > PTV growth	70% ($n = 193$)
	Complex variable margins (RAIDER trial)	16% ($n = 44$)
Radiotherapy delivery		
Technique	Conformal	51% ($n = 140$)
	Intensity-modulated radiotherapy	15% ($n = 42$)
	Volumetric arc radiotherapy	30% ($n = 82$)
Compensation for bladder filling/motion	Image-guided radiotherapy	45% ($n = 125$)
	CTV - > PTV margin alone	29% ($n = 79$)
	Plan of the day	12% ($n = 34$)
Critical structure definition	Rectum	95% ($n = 261$)
	Small bowel	66% ($n = 182$)
	Femoral heads	76% ($n = 208$)
Treatment verification	Cone beam computed tomography	79% ($n = 218$)
	kV imaging	15% ($n = 40$)
	MV imaging	4% ($n = 10$)

CTV, clinical target volume; PTV, planning target volume.

The radiotherapy planning technique and delivery are summarised in Table 3.

Concurrent Radiosensitisation

Radiosensitisation was considered in 53% (146) of radical patients, delivered in 40% ($n = 109$), as intended in 82% ($n = 89$) with the regimens used summarised in Figure 4. Reasons for not administering a radiosensitiser included (centres able to highlight more than one reason): age 18% ($n = 28$), poor performance status 21% ($n = 33$), renal function 15% ($n = 24$), comorbidities 49% ($n = 79$), patient choice 6% ($n = 9$), availability 6% ($n = 10$), concern over potential toxicity 3% ($n = 4$), complications of NAC 4% ($n = 5$) and

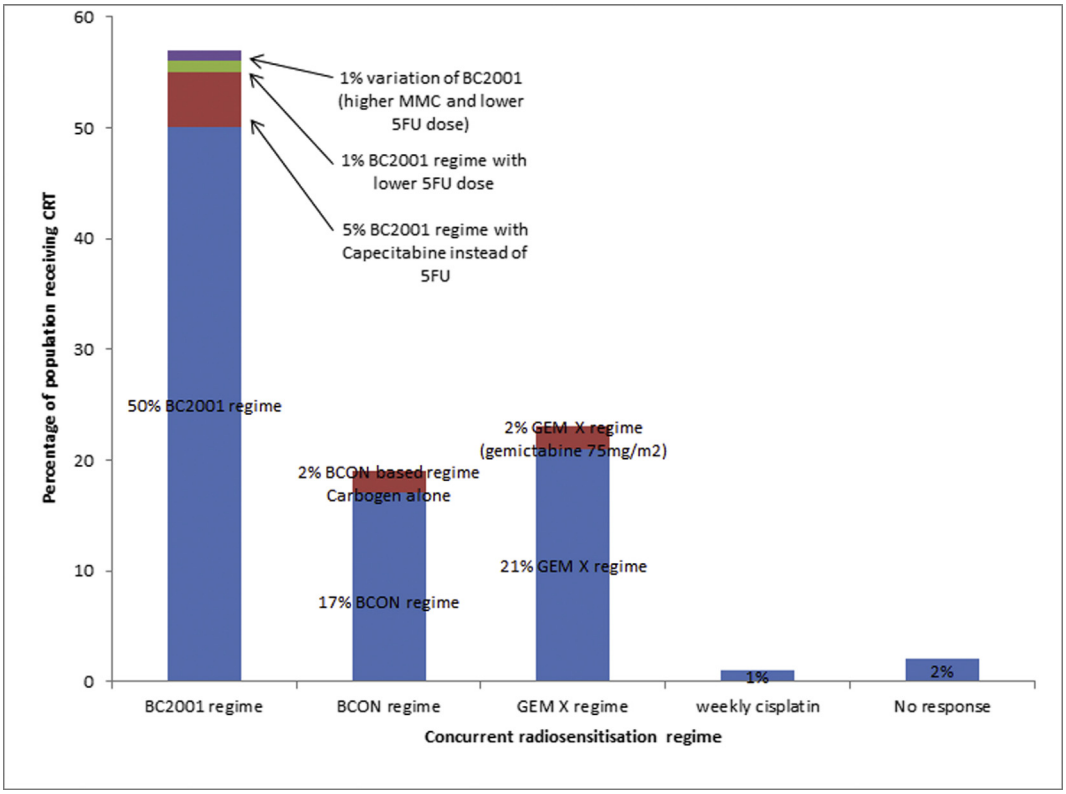

Fig 4. Concurrent radiosensitisation (CRT).

reason unknown in 18% ($n = 29$). Where CRT was not received as intended, this was due to radiotherapy toxicity in 53% ($n = 9$) and chemotherapy toxicity in 24% ($n = 4$).

Sixty-nine (25%) radical-intent radiotherapy patients had NAC then CRT with radical radiotherapy and 45 (16%) patients were able to receive this as prescribed for both NAC and CRT systemic regimens. One hundred and nine patients (40%) had neither NAC nor CRT. The presence of comorbidities was identified as a contributory factor in 66% (72) of these patients regarding NAC and in 58% (63) in the case of CRT.

Patient Follow-up

Eighty-nine per cent ($n = 244$) of radical patients were planned for review by oncology after completion of radiotherapy, mainly at 6 weeks (61%, $n = 148$) but also at 4 weeks (16%, $n = 39$) and 8 weeks (9%, $n = 21$). A combination of urology and oncology follow-up was planned in 60% ($n = 164$) or urology alone in 29% ($n = 80$).

Discussion

This is the first prospective study aimed at evaluating contemporary UK practice for patients undergoing radiotherapy for MIBC. We conclude that the current study is the most accurate representation of contemporary UK practice that has been described to date.

The demographics of this study are similar to reported case series from the UK [14,15], although the median age (78 years) of this population is much older than that previously described. The management of bladder cancer in an ever-aging population presents increasing challenges, as the prevalence of registered comorbidity in newly diagnosed cancer patients can be up to 80% in those over 80 years [16]. The percentage of elderly people is dramatically increasing [17], with the expected life expectancy of EU citizens quoted as 15.9 and 9.2 years at ages 70 and 80 years, respectively, in 2015 [17]. Cancer-specific survival after chemoradiotherapy did not show a worsening of outcome with increasing age, with a 5-year cancer-specific survival of 70 and 71% for patients aged $\leq$75 years and older, respectively [18]. Analysis of a UK population-based cancer registry indicates that the percentage of patients who receive curative treatment drops from 52% to 12% for patients aged $<$60 years versus $>$80 years [19]. The finding of an increasingly elderly population in this study warrants evaluation of geriatric assessment tools in optimising MIBC management in the elderly, similar to work that has started in older prostate cancer patients [20].

Data on treatment intent revealed that 54% ($n = 275$) were intended to have radical radiotherapy, despite 64% (323/508) having stage II or III disease, indicating that other factors (e.g. age and associated comorbidities) had an influence. There is evidence that a palliative treatment intent was more likely to be assigned with increasing age of the patient (median age for palliative and radical = 80 years and 75 years, respectively, U = 20,378.5, $P < 0.00001$).

This is the first study to attempt to define the patient pathway prior to either NAC or radical radiotherapy. It is recognised that the optimal management of patients with MIBC demands cohesive multidisciplinary team (MDT) working [6,21]. This study has identified that there remain a significant number of patients not discussed at a specialist MDT, or who do not have the opportunity to see relevant specialists, revealing a variation with NICE guidance.

Time from TURBT to starting NAC or radiotherapy has not previously been described for MIBC patients intended for radiotherapy, and this study defines unacceptable delays. This reflects the complex pathway of MIBC patients. Within the NHS in the UK, cancer targets are driven by time to treatment, with time to TURBT being the principal target for bladder cancer regardless of whether a patient has superficial (non-muscle invasive) or muscle invasive disease. It is notable that in no other cancer site are cancer targets met once a biopsy is obtained and the lack of a measurable target relating to definitive treatment (NAC, CRT or cystectomy) could be contributing to the lack of improvement in survival seen over the last 30 years.

There is level 1 evidence to support the use of cisplatin-based NAC, with an overall survival benefit of 5% prior to either radical cystectomy or radiotherapy published in a meta-analysis in 2003, which was updated in 2005 [8]. The role of NAC prior to radiotherapy with CRT is less clear, as CRT was not established practice at the time [21,22]. However, it seems that the benefits of NAC are mostly on distant recurrence and therefore complementary to CRT, as the benefit that CRT conferred on locoregional control within BC2001 was consistent whether NAC was used or not. It is reported that up to 50% of patients with MIBC may have occult micro-metastases [23]. Therefore, there remains a strong rationale for consideration of cisplatin-based NAC in suitable patients [13,21].

Previous estimates for the use of NAC in the non-trial setting range from 4 to 40% predominantly in cystectomy series [24–30]. Evidence of stringent MDT collaboration leading to increased utilisation of NAC exists, with NAC uptake of up to 55% [26]. Within this study, NAC was considered in two-thirds of patients, with 43% (119) of radical patients receiving it, indicative of increasing use within the UK. The predominant chemotherapy regimens were cisplatin/gemcitabine regimens, typically for three or four cycles prior to radiotherapy. Seventeen per cent (20) received carboplatin combination regimens despite a lack of published evidence for its use.

The use of CRT in an unselected multicentre UK population has not previously been described. National [6] and international guidelines [3–5,7] state using CRT with radical radiotherapy. Within the UK, the largest phase III randomised controlled trials of CRT have influenced practice [9,10]. Comparable levels of toxicity are reported with no significant increase in late urinary or gastrointestinal morbidity noted. Low dose gemcitabine has also been shown to be an active and potent radiosensitiser in phase II studies (Gem X protocol) [31].

Despite the reported acceptable tolerability and toxicity reported in the CRT trials, CRT in this non-trial population

was only prescribed in just 40% of this UK cohort. A recent publication by Ghate *et al.* [32], detailing the penetrance of CRT between 1999 and 2013, using the Ontario Cancer Registry, describes increasing use with time, to a level of 48% of patients receiving CRT 2009–2013. This low-level uptake within the UK, despite unequivocal recommendations, reflects hesitancy in the treating clinicians and a reluctance to embrace evidence-based medicine. The fact that the minority of patients were able to have both NAC and CRT (25%, $n = 69$), and even fewer having this as initially prescribed (16%, $n = 45$), indicates that we have not addressed optimal systemic management with CRT in most patients.

Although some variation in radical radiotherapy prescription was evident, most patients had treatment prescribed as per the RCR guidance document, with the hypofractionated regimens being favoured. More variation was seen in the palliative setting, with 11 palliative regimens prescribed in addition to that advised by the RCR. Confusion over treatment intent is evident, as patients with palliative intent were prescribed RCR-advised radical doses and similar was seen for radical intent patients, resulting in sub-optimal radiotherapy dosing for radical patients and potentially protracted courses of radiotherapy for palliative patients.

The technical delivery of radiotherapy for bladder cancer has historically received little attention outside the remits of clinical trials. This study sought to detail the technical delivery of radiotherapy for radical-intent patients within the NHS. All UK centres are now intensity-modulated radiotherapy (IMRT)/volumetric arc radiotherapy (VMAT) enabled, but this treatment technique was used in just under half of radical patients prescribed in 29 of all 41 participating centres, the remainder having three-dimensional conformal planned radiotherapy. Although IMRT/VMAT offers the opportunity for increased conformality and potential dosimetric improvements to organs at risk, in comparison with conformal planning, the benefit of IMRT/VMAT is not clear [33]. Radiotherapy departments were asked for further details on the radical bladder radiotherapy process. Variation was shown with regards to organ at risk dose constraints, compensation for bladder movement and treatment verification. Compensation for bladder filling/motion was accounted for predominantly by the use of image guidance (45%, $n = 125$), although 29% of centres stated that compensation was achieved by the clinical target volume to planning target volume margin ($n = 79$), despite evidence that the most commonly used growth of 1.5 cm can result in a geographical miss [34–37] or potential increased toxicity. It is therefore feasible that by using more advanced techniques for compensation of bladder movement or filling (image-guided radiotherapy [IGRT] or plan of the day [38]), outcomes and toxicity of treatment would be improved.

Treatment verification occurred in 97% (268) of patients, mainly using cone beam computed tomography. Fifteen per cent (40) of patients had image verification using kV imaging despite computed tomography-guided set-up being confirmed to be superior to kV portal positioning to reduce treatment-related toxicity [37]. Given the challenges of delivering radiotherapy to the bladder, the UK National Radiotherapy Implementation Group report on the implementation of IGRT advised routine use of cone beam computed tomography to ensure adequate targeting of the bladder. These guidelines also note that adaptive IGRT has the potential to optimise treatment of bladder cancer [39].

All patients were reviewed during treatment, with 76% (210) reviewed at least once a week. Toxicity of treatment was recorded in 89% (245) of cases. The RCR advises categorisation of tumours into one of three categories, reflecting tumour proliferation potential, with guidelines for managing treatment breaks. Some confusion over RCR treatment category persists, with 28% (76) of patients being incorrectly treated as category one patients. Patients with transitional cell carcinoma of the bladder treated radically are listed in category two, which includes tumours where a greater than 5 day prolongation in radiotherapy treatment time has been shown to be detrimental to local control and patient outcomes [12]. Our study period identified that the treatment gaps were manged well, despite this study being conducted over a Christmas/New Year period with only five radical patients having a treatment prolongation of >5 days, and four of these patients were managed according to RCR guidance.

This study has highlighted variation in radiotherapy treatment schedule, delivery and verification. Working towards treating radiotherapy centres having uniform radical bladder protocols would be beneficial to provide a UK-wide standard of care to optimise the opportunities for clinical research and improvements in MIBC outcomes. Unifying radical radiotherapy protocols is achievable across the NHS, as has been shown by the UK anal cancer treating community [40].

A small proportion of patients were enrolled within clinical trials. It is established that despite bladder cancer being the most expensive for the NHS to treat, as well as having the highest rate of recurrence of any cancer, research for this tumour site has been disproportionately low and chronically underfunded [41]. There is also an onus on treating clinicians to develop clinical trials relevant to the typical MIBC population to improve outcomes and not just a select few who are 'trial fit', if the treating uro-oncology community are to improve outcomes, which thus far have remained static.

Conclusion

This is the largest multicentre prospective study to define in detail contemporary management of MIBC in patients receiving radiotherapy within the UK to date. It has shown variation with NICE and RCR guidance.

The identification of the oldest population described to date demands that the uro-oncology community develop age and morbidity appropriate treatments.

Several areas in the patient pathway warrant improvement, including discussing all MIBC patients at specialist MDT, ensuring discussion of all radical treatment options

with patients and working to improve time to definitive treatment.

An increasing use of NAC in a non-trial population is described, but the penetrance of CRT is low, despite national and international guidance being unambiguous in this recommendation. Increasing the use of CRT demands immediate consideration.

The quality of radiotherapy delivery can be significantly improved by adherence to RCR fractionation and dose guidance, as well as utilising contemporary methods of treatment verification and IGRT.

It is hoped that the detail within this study can be used to inform practice, future trial design relevant to most of the MIBC population and ultimately improve outcomes.

Conflict of Interest

The authors declare no conflicts of interest.

Acknowledgements

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