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Platinum Priority – Bladder Cancer
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Chemoradiotherapy in Muscle-invasive Bladder Cancer: 10-yr Follow-up of the Phase 3 Randomised Controlled BC2001 Trial

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Abstract

Background: BC2001, the largest randomised trial of bladder-sparing treatment for muscle-invasive bladder cancer (MIBC), demonstrated improvement in locoregional control by adding fluorouracil and mitomycin C to radiotherapy (James ND, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med 2012;366:1477–88). There are limited data on long-term recurrence risk.
Objective: To determine whether benefit of adding chemotherapy to radiotherapy for MIBC is maintained in the long term.
Design, setting, and participants: A phase 3 randomised controlled 2 × 2 factorial trial was conducted. Between 2001 and 2008, 458 patients with T2-T4a N0M0 MIBC were enrolled; 360 were randomised to radiotherapy (178) or chemoradiotherapy (182), and 218 were randomised to standard whole-bladder radiotherapy (108) or reduced high-dose-volume radiotherapy (111). The median follow-up time was 9.9 yr. The trial is registered (ISRCTN68324339).
Intervention: Radiotherapy: 55 Gy in 20 fractions over 4 wk or 64 Gy in 32 fractions over 6.5 wk; concurrent chemotherapy: 5-fluorouracil and mitomycin C.
Outcome measurements and statistical analysis: Locoregional control (primary endpoint), invasive locoregional control, toxicity, rate of salvage cystectomy, disease-free survival (DFS), metastasis-free survival (MFS), bladder cancer–specific survival (BCSS), and overall survival. Cox regression was used. The analysis of efficacy outcomes was by intention to treat.

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Results and limitations: Chemoradiotherapy improved locoregional control (hazard ratio [HR] 0.61 [95% confidence interval {CI} 0.43–0.86], $p = 0.004$) and invasive locoregional control (HR 0.55 [95% CI 0.36–0.84], $p = 0.006$). This benefit translated, albeit non-significantly, for disease-related outcomes: DFS (HR 0.78 [95% CI 0.60–1.02], $p = 0.069$), MFS (HR 0.78, [95% CI 0.58–1.05], $p = 0.089$), overall survival (HR = 0.88 [95% CI 0.69–1.13], $p = 0.3$), and BCSS (HR 0.79 [95% CI 0.59–1.06], $p = 0.11$). The 5-yr cystectomy rate was 14% (95% CI 9–21%) with chemoradiotherapy versus 22% (95% CI 16–31%) with radiotherapy alone (HR 0.54, [95% CI 0.31–0.95], $p = 0.034$). No differences were seen between standard and reduced high-dose-volume radiotherapy.

Conclusions: Long-term findings confirm the benefit of adding concomitant 5-fluorouracil and mitomycin C to radiotherapy for MIBC.

Patient summary: We looked at long-term outcomes of a phase 3 clinical trial testing radiotherapy with or without chemotherapy for patients with invasive bladder cancer. We concluded that the benefit of adding chemotherapy to radiotherapy was maintained over 10 yr.

1. Introduction

Bladder cancer is the sixth most common cancer in men worldwide and the 17th most common in women. Around 550 000 cases are diagnosed annually, and 5-yr survival for muscle-invasive disease (around 20% of the incidence) is <50% [1]. Treatment for muscle-invasive bladder cancer can be either surgery or radiotherapy (RT) [2]. There are no well-powered trials comparing surgery with bladder preservation, and case mix tends to differ substantially between retrospective series, making comparisons problematic.

Bladder Cancer 2001 (BC2001) is the largest organ-preservation trial in muscle-invasive bladder cancer. It was designed to assess whether radiosensitisation using chemoradiotherapy with 5-fluorouracil (5FU) and mitomycin C (MMC) improved outcomes compared with RT alone, and also to compare standard and reduced high-dose-volume RT (RHDVRT).

The primary analysis, with a median follow-up of 69.9 mo, reported a hazard ratio (HR) for locoregional control in favour of chemoradiotherapy: 0.68 (95% confidence interval [CI] 0.48–0.96, $p = 0.03$) [3]. A reduction in the volume of the bladder exposed to the highest doses of RT did not significantly reduce late side effects [4]. Recently published patient-reported outcomes showed that health-related quality of life improved for the majority of patients after treatment compared with baseline, with no evidence of an adverse effect from the addition of chemotherapy [5]. Here, we report long-term outcomes with a median follow-up of 10 yr.

2. Patients and methods

2.1. Study design and participants

The BC2001 trial was an open-label phase 3 trial with a partial 2 × 2 factorial design conducted at 45 UK NHS hospitals. Participants were centrally randomised in a 1:1 ratio to (1) RT alone or RT with synchronous 5FU/MMC chemotherapy (cRT; chemotherapy randomisation), and (2) standard whole-bladder RT (sRT) or RHDVRT utilising a tumour boost (RT randomisation). Treatment allocation used computer-generated random permuted blocks. Entry into both categories of randomisation was encouraged but optional, according to patient eligibility and preference.

Full details of trial design, eligibility criteria, randomisation procedures, and treatment schedules have been reported previously [3,5]. In brief, patients were at least 18 yr old with histologically confirmed stage T2-T4a N0 M0 bladder cancer (adenocarcinoma, or transitional or squamous-cell carcinoma). Platinum-based neoadjuvant chemotherapy was permitted but not mandatory, and was a stratification factor. Patients with multiple tumours at diagnosis were ineligible for the RT randomisation but could enter the chemotherapy randomisation; patients unsuitable for chemotherapy could enter the RT randomisation. Patients were assessed for trial outcomes at the end of treatment; at 6, 9, and 12 mo after randomisation; and annually thereafter.

The study was approved by the North West Multi-centre Research Ethics Committee (00/8/075) and the Medicines and Healthcare products Regulatory Agency (EudraCT 2004-000164-26). The trial is registered (ISRCTN68324339 and NCT00024349). Written informed consent was obtained from all participants.

2.2. Outcomes

For this long-term follow-up analysis, the key endpoint of interest as well as the primary endpoint for the chemotherapy comparison was locoregional disease control (LRC), defined as the rate free of recurrence in pelvic nodes or the bladder (including new non–muscle-invasive disease), with data censored at metastasis (if this occurred ≥30 d before locoregional failure), second primary tumour, or death. The primary endpoints for the RT comparison were late RT related therapy–related side effects (at 1 and 2 yr and throughout 5 yr of follow-up) and LRC. Late toxicity was assessed by worst toxicity grade using the Radiation Therapy Oncology Group (RTOG) [6] and Late Effects of Normal Tissue (Subjective, Objective, and Management elements; LENT/SOM) criteria [7,8].

Secondary endpoints included disease-free survival (with data censored at second primary tumour or non–bladder cancer death), metastasis-free survival, rate of salvage cystectomy (time to cystectomy, censored at death), and overall survival. We also analysed exploratory endpoints of invasive locoregional control and bladder cancer–specific survival (BCSS). All time to event endpoints were measured from the date of randomisation. Patient-reported outcomes have been reported in detail separately [5].

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2.3. Statistical analysis

The chemotherapy comparison was planned to demonstrate superiority of cRT in LRC at 2 yr. The RT comparison was planned to show improved toxicity profile in the RHDVRT group, with noninferior 2-y LRC. Primary results for these comparisons have been reported previously [3,5], and here, we report updated estimates with longer follow-up.

Analyses for all time to event endpoints were on an intention-to-treat basis; for the RT noninferiority comparison, LRC is also reported for the per-protocol population. Toxicity endpoints are reported according to the treatment received. A p value of 0.05 was considered to indicate statistical significance, and 95% CIs are used unless otherwise specified. All analyses were adjusted for the alternate randomisation in the partial 2 × 2 design, that is, for the chemotherapy comparison, adjusted by RT group (RHDVRT, sRT, not randomised), and for the RT comparison, adjusted by chemotherapy group (cRT, RT, not randomised).

We used a stratified log-rank test to analyse time to event endpoints. We plotted Kaplan-Meier survival estimates and used the Cox model to calculate HRs (HR <1 favouring the experimental group). The proportional hazard assumption of the Cox model, which was tested with the use of Schoenfeld residuals, held for all endpoints in the RT comparison and for most endpoints in the chemotherapy comparison. There were slight departures in the assumptions for overall survival, so we performed exploratory analyses with time-varying effects in both comparisons to further understand the effect of the intervention with time.

HRs adjusted for the use of neoadjuvant chemotherapy, age, RT dose, tumour stage, performance status, and tumour grade were calculated (with Wald p values) in a preplanned analysis to assess the robustness of results. A frailty model adjusting for centre was fitted, but showed no significant centre effect on any outcome. Further exploration of the different types of death was conducted via ad hoc competing risk analysis and by plotting annualised hazard rates.

For the RT randomisation, the noninferiority hypothesis was tested by computing the absolute difference in 2-yr point survival estimates, calculated using the HR of the main model together with the Kaplan-Meier survival estimates for the sRT control group.

Toxicity was analysed by comparing the proportion of grade 3 or 4 adverse events in each randomised treatment group using a stratified Mantel-Haenszel test. To avoid interpreting disease symptoms as side effects, late toxicity data were censored 3 mo before recurrence, second primary tumour, or death from bladder cancer. Furthermore, data on the LENT/SOM bladder scale and RTOG genitourinary items were treated as missing if they were reported after a cystectomy.

Analyses were performed using STATA version 13 or later (StataCorp, College Station, TX, USA).

3. Results

Between August 2001 and April 2008, 458 patients were recruited from 45 UK centres. Of these patients, 360 (178 RT and 182 cRT) entered the chemotherapy randomisation; 219 patients (108 sRT and 111 RHDVRT) entered the RT randomisation, including 121 who entered both types of randomisation. Patient and tumour characteristics, and treatment details are given in Supplementary Table 1 by randomised comparison. The median follow-up, estimated by reverse censoring, was 9.9 yr (interquartile range, 8.4–11.4).

Disease outcomes were improved with chemoradiotherapy. Locoregional disease control was significantly better in the cRT group than in the RT group, with 5-yr recurrence-free rates of 63% (95% CI 54–71%) in the cRT group versus 49% (95% CI 41–57%) in the RT-only group (stratified log-rank p = 0.004), with an HR of 0.61 (95% CI 0.43–0.86; Fig. 1A). After adjusting for relevant prognostic factors, HR was 0.59 (95% CI 0.42–0.84, p = 0.004). Such differences also existed for invasive locoregional control, with an unadjusted HR of 0.55 (95% CI 0.36–0.84, p = 0.006; Fig. 1B) and an adjusted HR of 0.52 (95% CI 0.33–0.81, p = 0.004). Both disease-free survival (HR 0.78 [95% CI 0.60–1.02], p = 0.069) and metastasis-free survival (HR 0.78 [95% CI 0.58–1.05], p = 0.089) exhibit a nonsignificant benefit of chemoradiotherapy, further highlighted in the adjusted models (Supplementary Table 2). Outcome rates at 2, 5, and 10 yr for all endpoints by treatment group are also reported in Supplementary Table 2.

Chemoradiotherapy was associated with a reduction in cystectomy, with a 5-yr cystectomy rate of 14% (95% CI 9–21%) in the cRT group versus 22% (95% CI 16–31%) in the RT group (HR 0.54 [95% CI 0.31–0.95], p = 0.034). The majority of the cystectomies (43/53, 81%) were performed for disease recurrence, with five (9.4%) for late effects of RT and five (9.4%) for other/unknown reasons. By 2 yr after randomisation, 18/182 (9.8%) patients in the cRT group had experienced an invasive locoregional recurrence without evidence of distant recurrence. Of these 18 patients, six (33%) had a subsequent cystectomy, with two of these six (33%) later developing metastasis. Of 12 of the 18 patients with invasive recurrence but no cystectomy, five (42%) developed metastases. In the RT group, by 2 yr after randomisation, 33/178 (19%) had invasive recurrence without the presence of distant disease; of these 33 patients, 15 (46%) had cystectomy, six of whom (40%) developed subsequent distant recurrence. Of the 18 of 33 patients in the RT group with invasive recurrence but no cystectomy, seven (39%) developed metastases.

Overall, there were 250 deaths (69%) in the chemotherapy randomisation. Five-year overall survival rates were 49% (95% CI 41–56%) in the cRT group and 37% (95% CI 30–44%) in the RT-alone group, with 10-yr rates of 30% (95% CI 23–38%) and 26% (95% CI 19–33%), respectively. No significant differences were found in the main model (HR 0.88 [95% CI 0.69–1.13], p = 0.3; Fig. 1C) or after adjusting for significant prognostic variables (HR 0.81 [95% CI 0.62–1.04], p = 0.10). Separation of survival curves between groups started after approximately 2 yr. Sensitivity analyses with time-varying effects in the adjusted models reflected this: before 2 yr, HR 0.94 (95% CI 0.67–1.32, p = 0.71); after 2 yr, HR 0.66 (95% CI 0.45–0.98, p = 0.037), although time by treatment interaction was not significant (p = 0.19).

There were 180 deaths due to bladder cancer, 82 in the cRT group and 98 in the RT-alone group (Fig. 1D). There was a nonsignificant benefit in BCSS in the cRT group (HR 0.79 [95% CI 0.59–1.06], p = 0.11), which was borderline significant when adjusted by known prognostic factors (HR 0.73 [95% CI 0.54–0.99], p = 0.043). After incorporating a time-varying effect in the adjusted model, before 2 yr, HR was 0.86 (95% CI 0.59–1.25, p = 0.7), while after 2 yr, HR was 0.54 (95% CI 0.33–0.90, p = 0.019), although, again, time by treatment interaction was not significant (p = 0.15).

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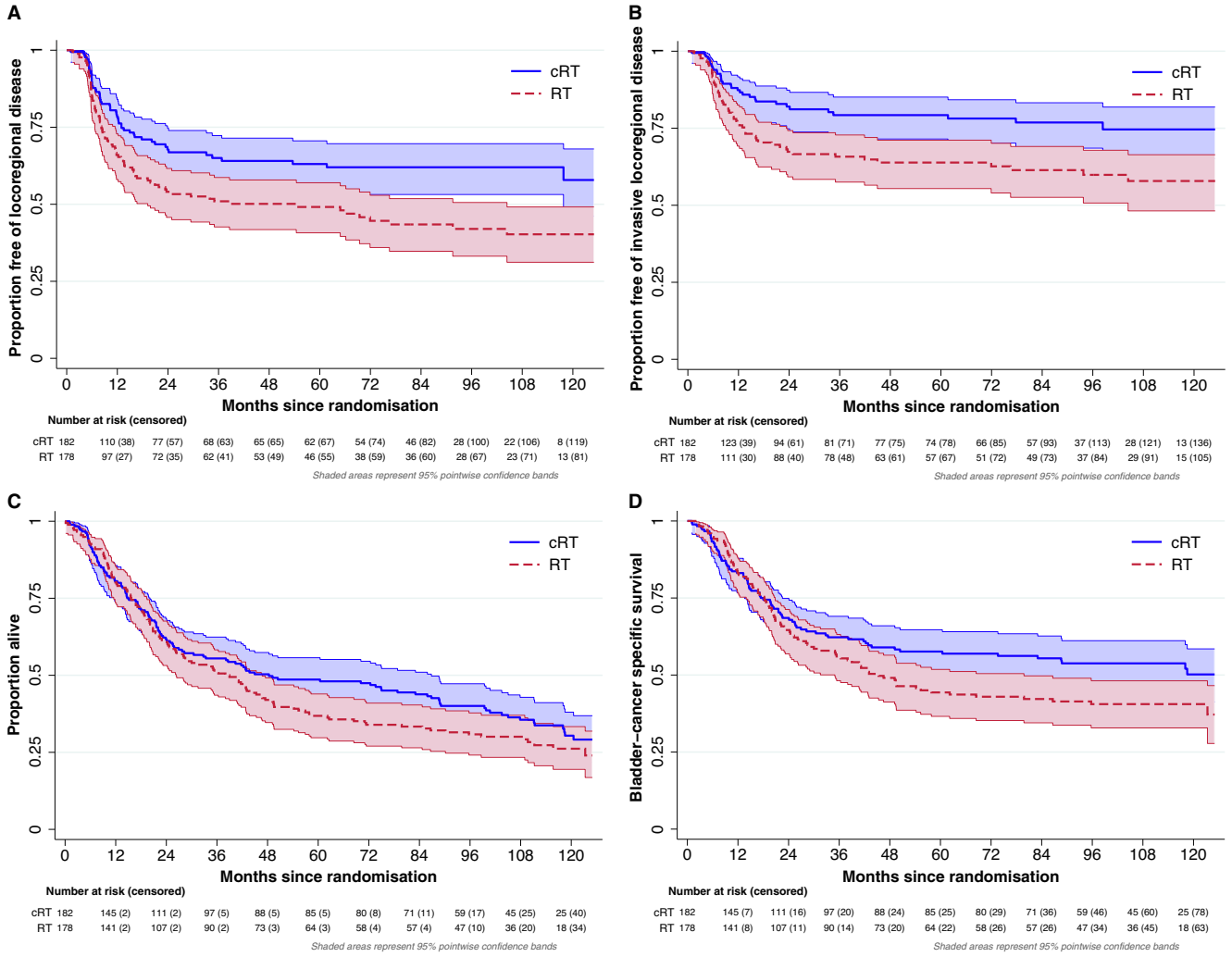

Fig. 1 – Disease outcomes for the chemotherapy comparison: (A) locoregional control; (B) invasive locoregional control; (C) overall survival; and (D) bladder cancer–specific survival. cRT = chemoradiotherapy; RT = radiotherapy.

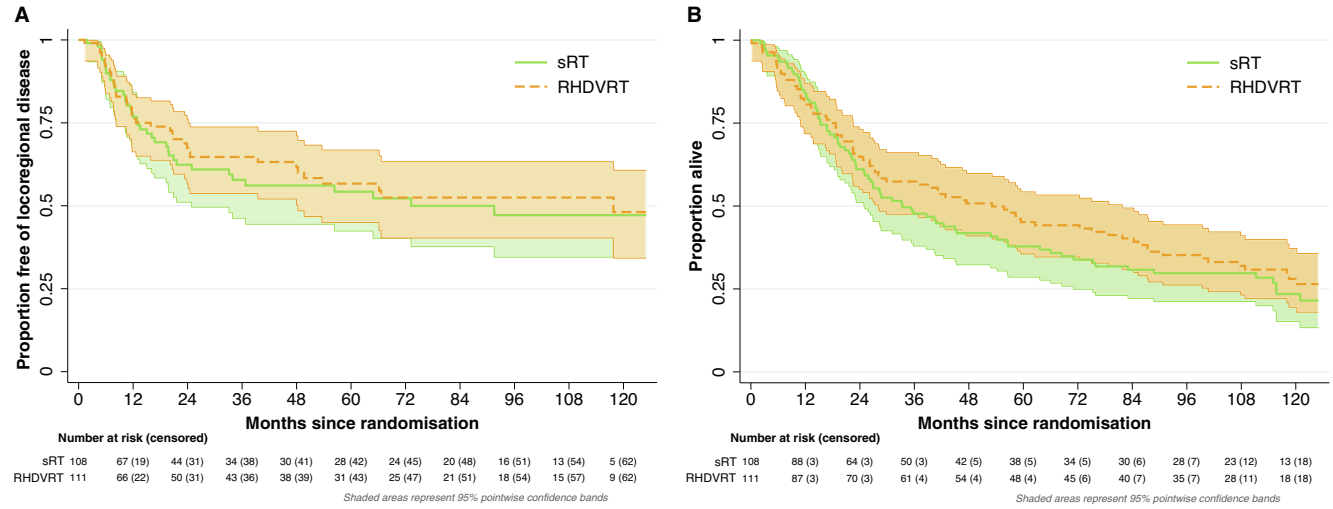

Fig. 2 – Disease outcomes for the radiotherapy comparison: (A) locoregional control and (B) overall survival. RHDVRT = reduced high-dose-volume RT; RT = radiotherapy; sRT = standard whole-bladder RT.

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Table 1 – Late toxicity: RTOG and LENT/SOM grades at 1, 2, and 5 yr and over the entire follow-up period[a,b]

	Worst grade ≥3	Chemotherapy comparison					Radiotherapy comparison				
		cRT (*N* = 178)		RT (*N* = 182)		*p* value	sRT (*N* = 120)		RHDVRT (*N* = 95)		*p* value
RTOG	At 1 yr	3/94	3.2%	2/80	2.5%	0.7	3/56	5.4%	2/53	3.8%	0.5
	At 2 yr	3/69	4.3%	3/60	5.0%	0.9	1/43	2.3%	3/37	8.1%	0.3
	At 5 yr	2/53	3.8%	1/38	2.6%	0.9	0/24	0	1/17	5.9%	0.2
	After 5 yr	2/44	4.6%	1/34	2.9%	0.8	1/25	4%	1/15	6.7%	0.8
	Over all follow-up[c]	11/120	9.2%	19/110	17%	0.06	12/86	14%	13/67	19%	0.5
RTOG GU	At 1 yr	3/94	3.2%	1/80	1.3%	0.3	2/56	3.6%	1/53	1.9%	0.5
	At 2 yr	3/69	4.3%	3/60	5.0%	0.9	1/43	2.3%	2/37	5.4%	0.5
	At 5 yr	2/52	3.9%	1/37	2.7%	0.9	0/24	0	1/17	5.9%	0.2
	After 5 yr	2/44	4.6%	1/33	3.0%	0.8	1/25	4%	1/15	6.7%	0.8
	Over all follow-up[c]	10/120	8.3%	14/110	13%	0.3	9/86	11%	11/67	16%	0.4
LENT/SOM	At 1 yr	29/79	37%	24/77	31%	0.5	17/53	32%	18/42	43%	0.3
	At 2 yr	21/64	33%	21/55	38%	0.5	11/36	31%	14/33	42%	0.2
	At 5 yr	13/47	28%	7/33	21%	0.5	5/23	22%	4/16	25%	1
	Over 5 yr	65/117	56%	55/101	55%	0.9	39/78	50%	38/61	62%	0.18

cRT = chemotherapy; LENT/SOM = Late Effects of Normal Tissue (Subjective, Objective, and Management elements); RHDVRT = reduced high-dose-volume RT; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; sRT = standard whole-bladder RT.

[a] Analysis performed by treatment received (safety population) rather than by treatment allocated.

[b] The *p* values were calculated by means of the stratified Mantel-Haenszel chi-square test.

[c] For LENT/SOM, follow-up includes all visits from 6 mo to 5 yr after randomisation, and for RTOG, it includes long-term follow-up (>5 yr).

Bladder cancer–specific death rates were also estimated by a competing risks analysis, which yielded similar results (Supplementary Figs. 1 and 2, and Supplementary Table 3).

No differences between sRT and RHDVRT were found for any time to event endpoint (see Supplementary Table 4, which includes 2-, 5-, and 10-yr rates, and unadjusted and adjusted HR estimates). The 2-yr LRC rates were 67% (95% CI 57–76) for RHDVRT and 62% (95% CI 51–72) for sRT (Fig. 2A). In the intention-to-treat population, the absolute difference in LRC rate at 2 yr is an RHDVRT improvement of 2.6% (95% CI –11.2 to 13), but in the per-protocol population, it is an RHDVRT worsening of –1.9% (95% CI –17 to 11). Both CIs contain the noninferiority margin of –10%; therefore, noninferiority cannot be concluded. The HR for treatment comparison for overall survival was 0.91 (95% CI 0.67–1.24, $p = 0.4$; (Fig. 2B), while BCSS HR was 0.80 (95% CI 0.54–1.17, $p = 0.18$). A competing risk analysis for this comparison is presented in Supplementary Figs. 3 and 4, and Supplementary Table 5.

There were no statistically significant differences in late toxicity with either LENT/SOM or RTOG grading between any of the randomised groups (Table 1 and Supplementary Figs. 5–8). The overall cumulative RTOG G3/4 toxicity rate in patients receiving cRT was 9.2% versus 17% for RT alone ($p = 0.06$); for the RT comparison, 14% patients receiving sRT exhibited G3/4 toxicity, while with RHDVRT, the rate was 19% ($p = 0.5$).

In 121 patients randomly assigned to both comparisons, no significant interactions were found for any outcome.

4. Discussion

An updated analysis with extended follow-up of patients treated within the BC2001 trial confirms the improved locoregional control reported previously [3] for chemoradiotherapy over RT alone. We now additionally report improved BCSS and a reduced salvage cystectomy rate with chemoradiotherapy compared with RT alone. Results also suggest that the improved locoregional control translates into improved overall survival from 2 yr onwards. This "delayed" effect is logical, as early survival is likely to be dominated by existing subclinical metastatic disease that is not significantly impacted by improving local control. It is noteworthy that over 50% of patients with an invasive local recurrence did not have a salvage cystectomy. This may reflect the age and comorbidity of the study participants (hence, the original choice of radiation treatment) and emphasises that the particular importance of maximising local control in patients where salvage options may not be available.

Updated toxicity results are similar to those reported previously, with no evidence of increased clinician-assessed toxicity from the addition of chemotherapy to RT; reassuringly, severe late toxicity was relatively rare. This is in line with our recently published patient-reported outcomes, which show a decline in health-related quality of life corresponding to the treatment period followed by prompt recovery to baseline by 6 mo, with no quality of life penalty associated with the addition of chemotherapy [5]. Our results suggest no detriment to tumour control from using partial bladder RT, but also could not identify a toxicity advantage. Therefore, this more targeted approach cannot currently be recommended as the standard of care. Our results support further assessment of reduced volumes using modern RT techniques as an alternative to treatment of the whole bladder, as in the current RAIDER trial (Randomised phase II trial of Adaptive Image guided standard or Dose Escalated tumour boost Radiotherapy in the treatment of transitional cell carcinoma of the bladder; NCT02447549).

A number of previous studies evaluated the efficacy of synchronous chemoradiation compared with RT alone in tumours arising from a range of primary sites, including oesophagus [9], head and neck [10,11], and anus [12]. These all found substantial improvements in local control using combined therapy. The first randomised study in bladder cancer to examine this approach used three cycles of cisplatin 100 mg/m^2 given 2 weekly in conjunction with a

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split-dose RT schedule [13]. Those who received combined therapy had a significantly lower rate of locoregional recurrence than those receiving RT alone (40% vs 59%, $p = 0.026$). However, cisplatin at this dose and schedule is not broadly deliverable to patients with bladder cancer who tend to be older, with significant comorbidities and renal impairment. We therefore sought to evaluate the 5FU/MMC schedule developed for anal cancer [12], as we anticipated that it would be better tolerated and less restricted by impaired renal function than cisplatin-based regimens. Pilot phase 1/2 work demonstrated the feasibility of RT and concurrent chemotherapy with MMC and 5FU with acceptable toxicity in patients with poor prognosis and impaired renal function [14,15], leading to the BC2001 trial. We initially reported primary outcome data from BC2001 in 2012 [3] and showed an effect of similar magnitude (locoregional control HR 0.68) to the above-described cisplatin trial [13], but in a significantly older population. An alternative approach testing hypoxic sensitisation was tested in a second UK trial (BCON, multicentre randomised trial of radical radiotherapy with carbogen in the radical treatment of locally advanced bladder cancer), which enrolled similar locally advanced bladder cancer patients for RT alone (either 55 Gy in 20 fractions in 4 wk or 64 Gy in 32 fractions in 6.5 wk) or synchronous radiosensitisation (carbogen and nicotinamide) [16]. Hypoxic sensitised RT did not improve cystoscopic control at 6 mo compared with RT alone (81% vs 76%, $p = 0.3$; the primary endpoint of BCON), but improvements were seen for relapse-free (HR 0.86) and overall (HR 0.85) survival, which were statistically significant in adjusted models. Subsequent work has shown that, in contrast to BC2001 patients, this benefit is restricted to patients with evidence of hypoxia at baseline [17–19]. Other chemosensitisation approaches have also shown promise. For instance, a non-randomised UK trial showed that synchronous weekly gemcitabine 100 mg/m^2 with 52.5 Gy in 20 fractions for whole-bladder RT could achieve an 88% complete response rate at post-treatment cystoscopy [20]. However, no comparative studies of this regimen versus RT alone or other radiosensitisation approaches have been undertaken.

BC2001 is the largest trial of bladder preservation, completed at >30 UK sites with patient characteristics that reflect "real-world" patients. The population was not restricted to patients who had a complete transurethral resection of bladder tumour and thus differs from studies reporting on "trimodality therapy". The key limitation of the BC2001 data is that the reduced volume arm closed early due to slow recruitment and because a proportion of randomised patients did not receive their allocated treatment [4]. This meant that any signals of reduced toxicity were less likely to be identified than had the enrolment into this comparison completed as planned. The study was conducted in the 2000s and as such is based on patients largely receiving non–image-guided conformal RT, which would not be considered current best practice and may also have contributed to a lack of signal of reduced toxicity.

Our primary publication concomitant chemotherapy has been recommended as the standard of care in a number of national and international guidelines, though uptake has been inconsistent [21]. The 10-yr survival rate with the BC2001 chemoradiotherapy schedule was 30% (95% CI 23-38, see Supplementary Table 2). Ten-year outcomes from BCON have been reported recently [22], with an identical 30% (95% CI 23–39) 10-yr overall survival rate for RT with carbogen and nicotinamide, and, as with BC2001, results remain consistent with the initial publication [16]. These updated results should provide further impetus to ensure that patients receiving bladder-preserving treatment also receive radiosensitising therapy. Together with a recent meta-analysis of data from BC2001 and BCON that demonstrated superior invasive locoregional control for the 55 Gy in 20 fractions RT schedule over 64 Gy in 32 fractions [23], they extend the evidence base to support informed decision-making for those choosing between a surgical or a bladder-preservation approach to radical treatment. These data also further support the use of RT combined with 5FU and mitomycin as the control arm in future trials testing the addition of novel agents to chemoradiotherapy. For example, two forthcoming randomised trials of synchronous immunoradiotherapy trials Keynote-992 (Efficacy and safety of pembrolizumab in combination with chemoradiotherapy versus chemoradiotherapy alone in MIBC; NCT04241185) and RADIO (A comparison of standard chemoradiotherapy treatment to standard chemoradiotherapy treatment given in combination with durvalumab to see if the addition of durvalumab leads to improved survival; ISRCTN43698103) have adopted this schedule.

5. Conclusions

This updated report from a large randomised trial with 10-yr follow-up provides strong evidence for concurrent chemoradiotherapy using MMC and 5FU as a standard of care for patients opting for organ-preservation therapy for muscle-invasive bladder cancer. These results support organ preservation as a valid alternative to radical cystectomy for this patient group.

Author contributions: Emma Hall had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hall, Hussain, Huddart, James.
Acquisition of data: Hall, Crundwell, Jenkins, Rawlings, Tremlett, Sreenivasan, Wallace, Syndikus, Sheehan, Lydon, Huddart, James.
Analysis and interpretation of data: Hall, Hussain, Porta, Lewis, Crundwell, Jenkins, Rawlings, Tremlett, Huddart, James.
Drafting of the manuscript: Hall, Hussain, Porta, Lewis, Huddart, James.
Critical revision of the manuscript for important intellectual content: Hall, Hussain, Porta, Lewis, Crundwell, Jenkins, Rawlings, Tremlett, Sreenivasan, Wallace, Syndikus, Sheehan, Lydon, Huddart, James.
Statistical analysis: Hall, Porta.
Obtaining funding: Hall, Hussain, Huddart, James.
Administrative, technical, or material support: Lewis.
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Supplementary data

Peer Review Summary and Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.eururo.2022.04.017.

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