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Dose-escalated Adaptive Radiotherapy for Bladder Cancer: Results of the Phase 2 RAIDER Randomised Controlled Trial

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Abstract

Background and objective: Delivering radiotherapy to the bladder is challenging as it is a mobile, deformable structure. Dose-escalated adaptive image-guided radiotherapy could improve outcomes. RAIDER aimed to demonstrate the safety of such a schedule.

Methods: RAIDER is an international phase 2 noncomparative randomised controlled trial (ISRCTN26779187). Patients with unifocal T2-T4a urothelial bladder cancer were randomised (1:1:2) to standard whole bladder radiotherapy (WBRT), standard-dose adaptive radiotherapy (SART), or dose-escalated adaptive radiotherapy (DART). Two fractionation (f) schedules recruited independently. WBRT and SART dose was 55 Gy/20f or 64 Gy/32f, and DART dose was 60 Gy/20f or 70 Gy/32f. For SART and DART, a radiotherapy plan (small, medium, or large) was chosen daily. The primary endpoint was the proportion of patients with radiotherapy-related late Common Terminology Criteria for Adverse Events grade $\geq$3 toxicity; the trial was designed to rule out >20% toxicity with DART.

Key findings and limitations: A total of 345 patients were randomised between October 2015 and April 2020: 41/46 WBRT, 41/46 SART, and 81/90 DART patients in the 20f/32f

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cohorts, respectively. The median age was 72/73 yr; 78%/85% had T2 tumours, 46%/52% had neoadjuvant chemotherapy, and 70%/71% had radiosensitising therapy. The median follow-up was 42.1/38.2 mo. Sixty-six of 77 (86%) 20f and 74 of 82 (90%) 32f participants planned for DART met the mandatory medium plan dose constraints. Radiotherapy-related grade ≥3 toxicity was reported in one of 58 patients (90% confidence interval [CI] 0.1, 7.9) with 20f DART and zero of 56 patients with 32f DART. Two-year overall survival was 77% (95% CI 69, 82) for WBRT + SART and 80% (95% CI 73, 85) for DART (hazard ratio = 0.84, 95% CI 0.59, 1.21, p = 0.4). Thirteen of 345 (3.8%) participants had salvage cystectomy.

Conclusions and clinical implications: Grade ≥3 late toxicity was low. DART was safe and feasible to deliver, meeting preset toxicity thresholds. Disease-related outcomes are promising for dose-escalated treatments, with a low salvage cystectomy rate and overall survival similar to that seen in cystectomy cohorts.

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What does this study add?

Complex adaptive radiotherapy can be delivered across multiple centres and countries with appropriate training and quality assurance measures. Most patients require more than one plan to optimise treatment delivery. Adaptive tumour boost radiotherapy allows dose escalation with low rates of significant toxicity in patients receiving 32- or 20-fraction schedules. There was no evidence of a detrimental effect of dose escalation on patient-reported outcomes or health-related quality of life.

Clinical Relevance

Because the bladder is highly mobile and deformable, bladder-sparing (chemo)radiotherapy can be technically challenging as large planning margins around the target are necessary to achieve good tumor coverage, but will necessarily lead to more normal tissue exposure to radiation. Adaptive therapy can address this by adjusting the radiotherapy plan based on the "anatomy of the day", allowing smaller margins and thus less normal tissue dose; further, this might allow dose-escalation to the gross tumor. The two-stage randomised phase II RAIDER trial evaluated standard whole bladder radiotherapy (WBRT), standard-dose adaptive radiotherapy (SART), and dose-escalated adaptive radiotherapy (DART), and was designed to rule out >20% radiotherapy-related late CTCAE grade ≥3 toxicity with DART. 345 patients were randomised. Stage 1 showed the clear feasibility of DART. With a median follow-up of 38.2–42.1 months, the incidence of radiotherapy-related grade ≥3 toxicity with DART was only 1/114. No salvage cystectomies were done for adverse events, and the overall rate of salvage cystectomy was 3.8%. Overall, these results are quite promising with lower rates of grade ≥3 toxicity and salvage cystectomy than in any prior large bladder cancer trial. Limitations are the phase 2, noncomparative design, and the overall small sample size prohibiting comparison of efficacy (though recruiting to a bladder-sparing trial is difficult and in that regards, this is a large trial). Associate Editor: Amar Kishan

Patient Summary

RAIDER looked at whether it is possible to safely deliver complex adaptive radiotherapy for patients with muscle-invasive bladder cancer. Serious side effects were low across all treatment groups, and it was safe and feasible to deliver a higher radiotherapy dose to the tumour alongside a lower dose to the rest of the bladder.

1. Introduction

Improvement in muscle-invasive bladder cancer (MIBC) radiotherapy outcomes, with chemosensitisation and hypofractionation, means that it is a realistic alternative to radical cystectomy with similar cause-specific survival and potential for better quality of life [1,2].

Bladder radiotherapy is technically challenging due to changes in shape and position during a radiotherapy course, requiring large margins around the tumour target that contribute to greater than necessary toxicity whilst not reliably preventing geographical misses [3]. Improving targeting could help limit toxicity.

Image-guided radiotherapy (IGRT) allows soft tissue visualisation, improving accuracy [4]. IGRT led to adaptive radiotherapy strategies that aim to minimise treatment volume whilst maintaining target coverage [4]. This has been shown to achieve target coverage in >95% of fractions whilst reducing target volume by 25–40% [5].

We hypothesised that better targeting could allow full-dose radiotherapy to be focused on the gross tumour volume, which could limit toxicity, in combination with using

smaller margins and treating on a fuller bladder to maximise bladder sparing. Mitigation of toxicity could allow routine dose escalation, potentially improving tumour control. A phase 1/2 study showed that dose escalation to 70 Gray (Gy) in 32 fractions (f) was feasible in a single centre [6]. RAIDER was designed to assess the feasibility of delivering this treatment on a multicentre basis, exclude excessive toxicity from dose escalation, and provide preliminary efficacy data.

2. Patients and methods

2.1. Study design

RAIDER is an international multicentre, multiarm, two-stage, phase 2 parallel cohort randomised trial of adaptive, dose-escalated tumour-focused radiotherapy for MIBC (NCT02447549/ISRCTN26779187). Protocol details have been published [7]. It was conducted at 46 hospitals in the UK, Australia, and New Zealand (Supplementary Table 1).

RAIDER was approved by ethics (UK: 15/LO/0539, Australia: HREC/15/HNE/264–15/07/15/3·04; 2016-041, and New Zealand: 15/STH/226), and participants gave informed consent.

Patients with T2-T4aN0M0 unifocal MIBC were randomised (1:1:2) by the Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU) between standard/control whole bladder single plan radiotherapy (WBRT), standard-dose adaptive tumour-focused radiotherapy (SART), or dose-escalated adaptive tumour-focused radiotherapy (DART) using minimisation with a random element. Neoadjuvant chemotherapy prior to randomisation was permitted. Balancing factors were treating hospital, neoadjuvant chemotherapy (yes/no), and concomitant radiosensitisation (yes/no). Treatment allocation for parallel 20f and 32f cohorts was independent and was not masked.

2.2. Procedures

The RAIDER radiotherapy planning and delivery protocol describes treatment details, and a comprehensive radiotherapy quality assurance programme was implemented [7,8]. WBRT and SART dose was 55 Gy/20f or 64 Gy/32f; DART dose was 60 Gy/20f or 70 Gy/32f [7,9]. If medium plan normal tissue dose constraints were not met (Supplementary Table 2) for DART patients, cases were reviewed by the chief investigator or delegate who recommended either proceeding with DART or lowering to SART dose. Before each SART and DART fraction, cone beam computed tomography (CBCT) was performed and the smallest plan that enabled coverage of the planning target volume (PTV) was selected by an accredited individual, verified by a second trained individual. Standard concomitant radiosensitisation was encouraged [10].

At baseline, participants had chest, abdomen, and pelvis computed tomography (CT); histological transitional cell carcinoma confirmation; full blood count; and urea and electrolytes. Acute toxicity was assessed weekly during treatment, at 6 and 10 wk from radiotherapy start, and at 3 mo after radiotherapy with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Follow-up was according to national guidelines [11]. Rigid cystoscopy with biopsy of the tumour bed was performed at 3 mo. Flexible cystoscopy, chest x-ray, late toxicity (CTCAE v4.0), and survival status were assessed at 6, 9, 12, 18, 24, 36, 48, and 60 mo, with abdomen/pelvis CT at 6, 12, and 24 mo.

Optional quality of life paper questionnaires were completed at baseline, last radiotherapy fraction, and 3, 6, 12, 18, and 24 mo after radiotherapy. Patient-reported outcome (PRO) instruments were the following: Kings Health Questionnaire (KHQ) [12], EQ5D-5L [13], Inflammatory Bowel Disease Questionnaire (IBDQ; to protocol v2.0 14/02/2018) [14], and PRO-CTCAE and ALERT-B (from protocol v2.0) [15,16].

2.3. Outcomes

For stage I, the primary outcome was the proportion of DART participants meeting the medium plan mandatory radiotherapy dose constraints (Supplementary material) [7]. Recruitment to stage II continued whilst stage I was evaluated.

For stage II, the primary outcome was the proportion of evaluable participants with treatment-emergent radiotherapy-related grade $\geq$3 CTCAE v4.0 toxicity 6–18 mo after completing radiotherapy. Treatment-emergent toxicity was any adverse event (AE) not present before radiotherapy or any AE already present that worsened following radiotherapy. Radiotherapy relatedness was established by local and central clinical reviews; any grade $\geq$3 event categorised as "possibly", "probably", or "definitely" related by either reviewer was a primary endpoint event.

The secondary outcomes included clinician-reported acute and late toxicity (CTCAE v4.0 and Radiation Therapy Oncology Group [RTOG]), PROs (EQ5D-5L: Visual Analogue Scale [VAS], a measure of overall health status; KHQ: bladder incontinence impact; and PRO-CTCAE: stool frequency), locoregional (invasive) disease control, bladder intact event-free survival, and overall survival.

2.4. Statistical analysis

The noncomparative design of stage II ruled out an upper limit of any late treatment-emergent radiotherapy-related grade $\geq$3 CTCAE toxicity in each cohort's DART group. With 57 participants per DART group, a >20% toxicity rate could be excluded (WBRT: expected 8%; power 80%; one-sided 5% significance; 5% nonevaluable allowance). Evaluable participants had at least one fraction of allocated treatment and at least one toxicity assessment between 6 and 18 mo after radiotherapy and at least 1 mo before death/local/distant recurrence. Toxicity censoring before recurrence/death avoided confounding disease symptoms and radiotherapy-related toxicity. With a 1:1:2 allocation ratio, 120 participants per fractionation cohort were required.

The Independent Data Monitoring Committee (IDMC) reviewed accumulating data against prespecified stopping guidelines (Supplementary material). It recommended inflating nonevaluable participant allowance (20f: 20%; 32f: 33%), to achieve 57 evaluable DART participants per cohort.

The proportion of evaluable participants with radiotherapy-related grade ≥3 CTCAE toxicity between 6 and 18 mo after radiotherapy is presented with 90% two-sided exact confidence intervals (CIs; equivalent to one-sided exact binomial 95% CI).

Clinician- and patient-reported side effects were analysed descriptively by treatment received and fractionation cohort. Times to first grade ≥2 CTCAE and grade ≥3 RTOG genitourinary and gastrointestinal toxicities were analysed using the Kaplan-Meier method. Stacked bar charts indicate the distribution of data (severity) at each time point. PRO items of key interest are EQ5D-5L VAS, KHQ incontinence impact (how much do you think bladder problems affect your life?), and KHQ Symptom Severity Scale.

For disease-related outcomes, fractionation cohorts were combined and an intention-to-treat population was used. Locoregional (invasive) disease control was censored at metastases, second primary tumour, or death. Patients alive and event free were censored at the date of last follow-up, with censoring at the date of last cystoscopy for bladder intact event-free survival. The Kaplan-Meier method and log-rank test stratified by fractionation cohort were used for a prespecified exploratory comparison of WBRT and SART combined versus DART.

Estimates of treatment effect (with 95% CIs) were made with unadjusted and adjusted (by the use of neoadjuvant chemotherapy and radiosensitising therapy, respectively) Cox regression models (stratified by cohort). A hazard ratio (HR) of <1 favoured DART. Proportional hazards assumption was tested by examining Schoenfeld residuals and held for all disease outcomes.

Analyses used a snapshot of data taken on May 17, 2022 and were conducted using Stata version 17.0.

3. Results

Between October 21, 2015 and March 18, 2020, 345 participants were randomised (20f: 163 from 25 centres: 41 WBRT, 41 SART, and 81 DART; 32f: 182 from 24 centres: 46 WBRT, 46 SART, and 90 DART). The final four 32f cohort participants switched to 20f to reduce treatment time during the COVID-19 pandemic and were included in 20f cohort analyses (Fig. 1). Participants' characteristics were balanced between treatment groups (Table 1 and Supplementary Table 3). One participant was ineligible due to bilateral hip replacements but received allocated radiotherapy.

3.1. Treatment details

Seventy-three of 82 (89%) 20f DART participants and 74 of 89 (83%) 32f DART participants received allocated treatment (Fig. 1). In DART cohorts, 66/77 (86%) 20f and 74/82 (90%) 32f participants planned for DART met the mandatory medium plan dose constraints (Supplementary material). Eleven of 77 (14%) 20f and eight of 82 (10%) 32f participants did not meet dose constraints, and of them, four of 11 20f and all 32f participants received SART. The remaining seven 20f patients planned for DART but not meeting this dose constraint received DART on investigator decision (Supplementary material). Of 6222 fractions delivered to SART and DART participants, 2297 (37%) used small plans and 1291 (21%) used large (Supplementary Table 4). For participants receiving WBRT, 35/43 20f and 41/48 32f had daily CBCT. Of the patients, 70% used, at least once, all the three plans; 1.6% used the same plan throughout.

Concomitant therapy was given to 116/167 (70%) 20f and 127/178 (71%) 32f participants. More 32f cohort participants received mitomycin C/5-fluorouracil (Supplementary Table 3).

3.2. Late toxicity

3.2.1. Primary endpoint

In the 20f cohort (median follow-up 42.1 mo [interquartile range {IQR} 35.6, 50.1]), grade ≥3 treatment-emergent radiotherapy-related toxicity was reported (urosepsis) in one of 58 (1.7%, 90% CI 0.1–7.9) patients in the DART group; one WBRT and one SART participant had grade ≥3 radiotherapy-related late CTCAE toxicity (Table 2). In the 32f cohort (median follow-up 38.2 mo [IQR 26.2, 50.2]), no late CTCAE grade ≥3 radiotherapy-related toxicities were reported. In both cohorts, >20% grade ≥3 radiotherapy-related late toxicity with DART was excluded.

Any late treatment-emergent grade ≥3 DART toxicity rates were 5/58 (8.6%, 90% CI 3.4–17) for 20f and 3/56 (5.4%, 1.5–13) for 32f (Table 2). Any late treatment-emergent grade ≥2 was similar across DART groups, with 18/57 (31%) for 20f and 20/56 (36%) for 32f (Table 2). Late CTCAE toxicity grades are reported in Supplementary Table 5; the severity and cumulative incidence of gastrointestinal and genitourinary toxicity are depicted in Figure 2 and Supplementary Figure 1, respectively. The 2-yr cumulative incidence of RTOG grade ≥3 toxicity was 2.4% (95% CI 0.8%, 7.4%) for 20f and 1.0% (0.1%, 6.7%) for 32f (Supplementary Fig. 2). See Supplementary Figure 3 for acute toxicity [10].

3.3. Participant-reported outcomes

The EQ5D-5L VAS was maintained at or above baseline apart from a small drop at the end of treatment in the 20f cohort (Supplementary Fig. 4). KHQ symptom severity score and bladder incontinence impact were worst at the end of radiotherapy, but had improved by 12 mo from pretreatment scores (Supplementary Figs. 5 and 6). Stool frequency was also worse at the end of treatment (Supplementary Fig. 7) for both fractionation cohorts.

3.4. Efficacy outcomes

The 2-yr locoregional disease control rates were 66% (95% CI 57, 73) for WBRT + SART and 74.0% (66, 80) for DART (Fig. 3A). There was no statistical evidence of a difference between groups (unadjusted HR = 0.80 [95% CI 0.5, 1.17] and adjusted HR = 0.81 [0.55, 1.19]; p = 0.2). For invasive locoregional disease, the 2-yr control rates were 80% (95% CI 73, 86) for WBRT + SART and 83% (95% CI 76, 89) for DART (p = 0.4; Fig. 3B, Supplementary Table 6 and Supplementary Table 7). A post hoc analysis of invasive locoregional disease control by fractionation cohort is provided in Supplementary Figure 8 and that by protocol treatment received is pro-

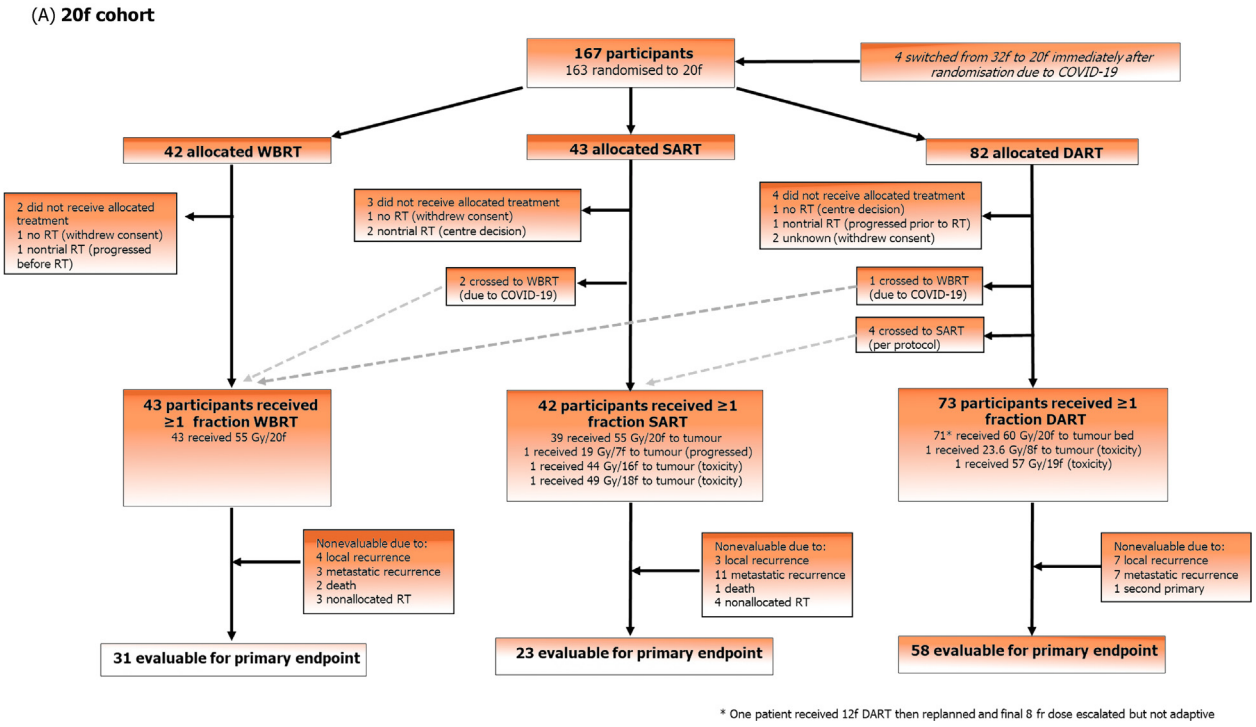

Fig. 1 – RAIDER CONSORT flowchart: (A) 20f cohort and (B) 32f cohort. COVID-19 = coronavirus disease 2019; DART = dose-escalated adaptive radiotherapy; f/fr = fractions; RT = radiotherapy; SART = standard-dose adaptive radiotherapy; WBRT = whole bladder radiotherapy.

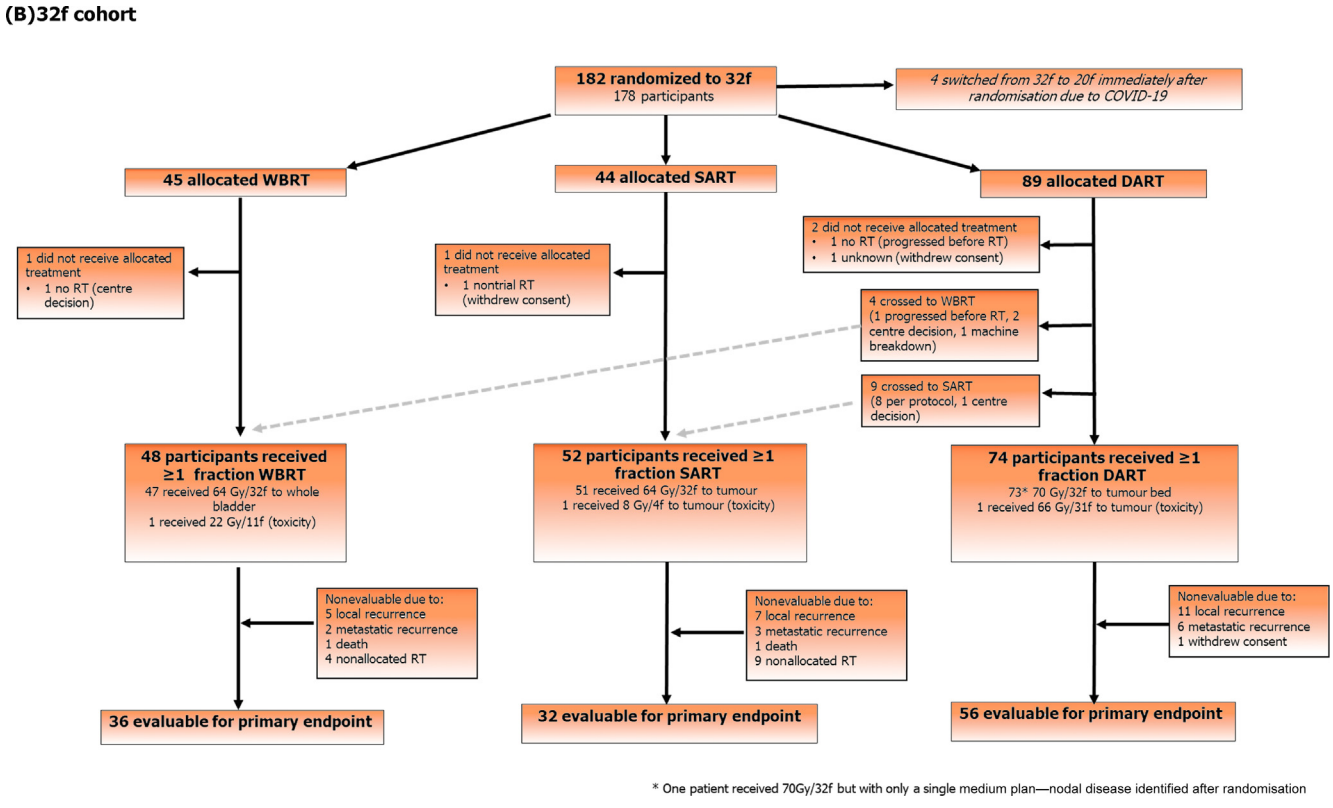

Fig. 1 (*continued*)

Table 1 – Participant and tumour characteristics at trial entry and treatment details by randomised treatment group

	20f				32f			
	WBRT (*N* = 42)	SART (*N* = 43)	DART (*N* = 82)	Total (*N* = 167)	WBRT (*N* = 45)	SART (*N* = 44)	DART (*N* = 89)	Total (*N* = 178)
Age (yr), median (IQR)	74 (69–80)	74 (65–80)	71 (65–77)	72 (67–79)	72 (67–78)	73 (65–79)	73 (68–79)	73 (67–79)
Gender, *N* (%)								
Male	32 (76)	35 (81)	67 (82)	134 (80)	35 (78)	37 (84)	69 (78)	141 (79)
WHO performance status, *N* (%)								
0	24 (57)	20 (47)	42 (52)	86 (52)	28 (64)	24 (55)	56 (63)	108 (61)
1	15 (36)	21 (49)	29 (36)	65 (39)	11 (25)	19 (43)	30 (34)	60 (34)
2	3 (7)	2 (5)	10 (12)	15 (9)	5 (11)	1 (2)	3 (3)	9 (5)
Unobtainable	0	0	1	1	0	0	0	0
Clinical stage, *N* (%)								
T2	35 (83)	33 (77)	61 (75)	129 (78)	39 (87)	32 (73)	77 (87)	148 (83)
T3a	2 (5)	7 (16)	9 (11)	18 (11)	1 (2)	4 (9)	8 (9)	13 (7)
3b	5 (12)	2 (5)	9 (11)	16 (10)	3 (7)	8 (18)	3 (3)	14 (8)
T4a	0	1 (2)	2 (2)	3 (2)	2 (4)	0	1 (1)	3 (2)
Unobtainable	0	0	1	1	0	0	0	0
Neoadjuvant chemotherapy, *N* (%)								
Yes	21 (50)	24 (56)	43 (52)	88 (53)	20 (44)	18 (41)	42 (47)	80 (45)
Concomitant therapy given								
Yes, *N* (%)	31 (76)	31 (76)	54 (69)	116 (73)	32 (73)	31 (72)	64 (74)	127 (73)
Unobtainable, *N*	1	2	4	7	1	1	3	5

CIS = carcinoma in situ; DART = dose-escalated adaptive radiotherapy; f = fractions; IQR = interquartile range; SART = standard-dose adaptive radiotherapy; WBRT = standard whole bladder radiotherapy; WHO = World Health Organization.
Tumour grade, presence of CIS, presence of residual disease, and type of concomitant therapy given are presented in Supplementary Table 3.

Table 2 – Any grade ≥3 treatment-emergent radiotherapy-related, any grade ≥3 treatment-emergent, and any grade ≥2 treatment-emergent CTCAE toxicity (occurring 6–18 mo after completing radiotherapy) in the evaluable patient population

	20 fraction		32 fraction	
	N (%)	90% CI	*N* (%)	90% CI
Radiotherapy-related grade ≥3				
WBRT	1/31 (3.2)	0.2, 14.4	0/36	0, 8.0
SART	1/23 (4.3)	0.2, 19.0	0/32	0, 8.9
DART	**1/58 (1.7)**	**0.1, 7.9**	**0/56**	**0, 5.2**
Any grade ≥3				
WBRT	4/31 (12.9)	4.5, 27.1	2/36 (5.6)	1.0, 16.5
SART	1/23 (4.3)	0.2, 19.0	1/32 (3.1)	0.2, 14.0
DART	5/58 (8.6)	3.4, 17.3	3/56 (5.4)	1.5, 13.3
Any grade ≥2				
WBRT	10/31 (32.3)	18.7, 48.5	18/36 (50.0)	35.3, 64.7
SART	9/23 (39.1)	22.2, 58.3	13/32 (40.6)	26.0, 56.7
DART	18/57 (31.0)	21.1, 42.5	20/56 (35.7)	25.1, 47.5

CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; DART = dose-escalated adaptive radiotherapy; SART = standard-dose adaptive radiotherapy; WBRT = standard whole bladder radiotherapy.
The shaded row indicates the primary endpoint for the trial.

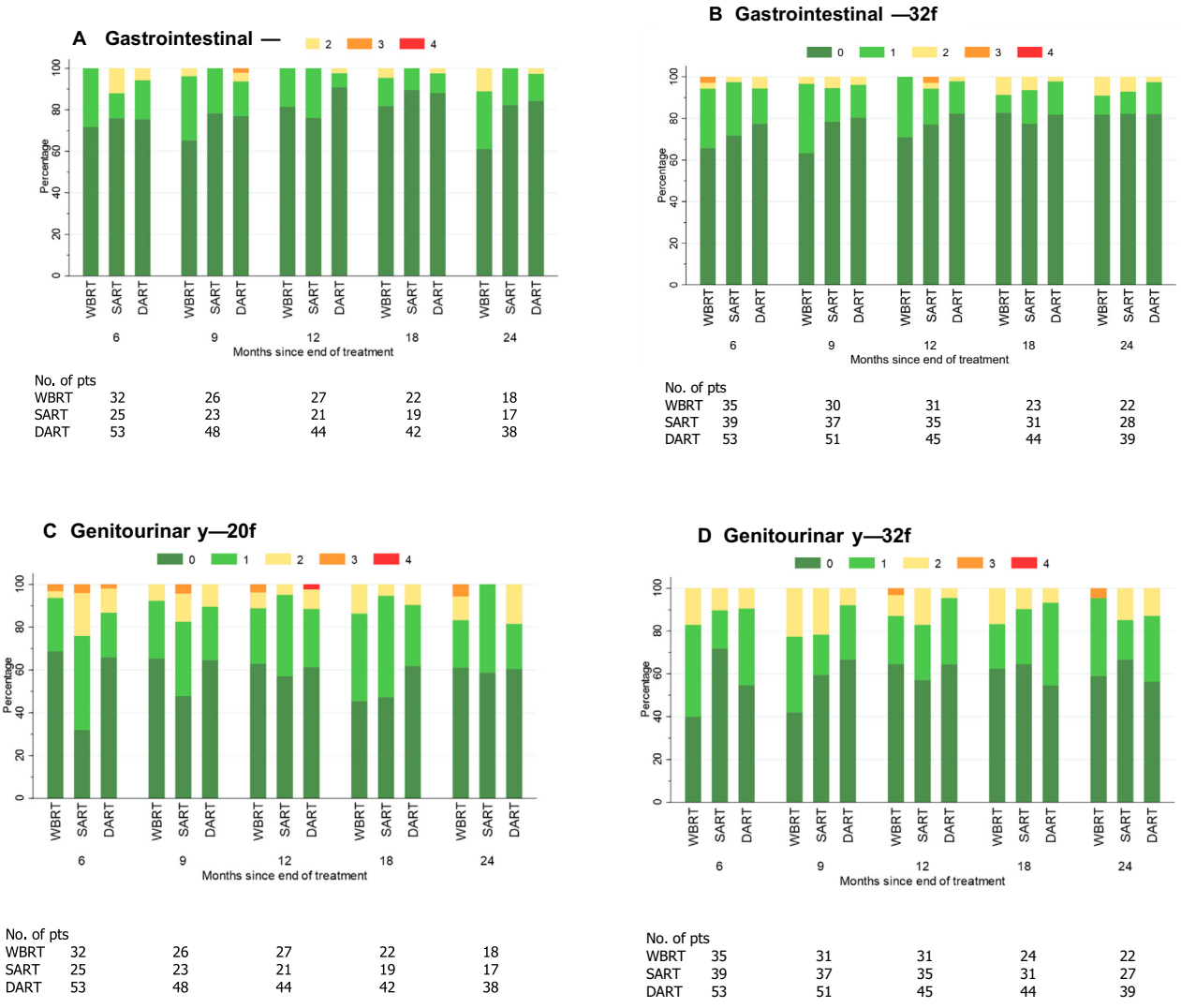

Fig. 2 – Stacked bar charts illustrating treatment-emergent CTCAE (A and B) gastrointestinal and (C and D) genitourinary worst toxicity at each late time point assessed by treatment received and fractionation cohort. Treatment emergent is defined as any adverse event that was not present prior to radiotherapy or any adverse event already present that worsened following exposure to trial treatment, that is, grade 0 includes those with CTCAE grade 0 at the time point assessed and participants with no change in CTCAE score since baseline. CTCAE = Common Terminology Criteria for Adverse Events; DART = dose-escalated adaptive radiotherapy; f = fractions; pts = patients; SART = standard-dose adaptive radiotherapy; WBRT = whole bladder radiotherapy.

vided in Supplementary Figure 9 and Supplementary Table 8.

The 2-yr bladder intact event-free survival estimates were 67% (95% CI 59, 74) for WBRT + SART and 72% (64, 79) for DART (Fig. 3C), with no evidence of a difference between groups (p = 0.3; Supplementary Tables 6 and 7). Thirteen of 345 (3.8%) participants had cystectomies, 11 due to disease recurrence, one for radical bladder cancer treatment instead of allocated radiotherapy, and one for unknown reason. No cystectomies were reported due to AEs.

There were 120 deaths—64/174 for WBRT + SART and 56/171 for DART. The 2-yr overall survival rates were 77% (95% CI 70, 82) for WBRT + SART and 80% (73, 85) for DART (Fig. 3D). No significant differences were evident in unadjusted (HR = 0.84; 95% CI 0.59, 1.21; p = 0.4) or adjusted (HR = 0.88; 95% CI 0.61, 1.26) models (Supplementary Table 6). There were 73 bladder cancer deaths; 39 were from other causes, and eight causes were unknown.

4. Discussion

We have confirmed that tumour radiotherapy dose escalation can be delivered successfully whilst reducing the dose to the uninvolved bladder, by multiple international sites, without causing excessive late toxicity.

With 82% of patients allocated DART having dose-escalated treatment, stage I demonstrated achievable dose escalation for most participants within cautious constraints. Stage II successfully excluded >20% grade ≥3 late radiotherapy-related toxicity with DART. In both adaptive groups, upper 90% CI for any late grade ≥3 treatment-emergent toxicity was <20%. Adaptive IGRT permits dose escalation to 60 Gy in 20f or 70 Gy in 32f (~9–10% dose increment). This confirms the single-centre dose escalation study identifying that 70 Gy/32f could be achieved safely [6] and a prior prospective study achieving dose escalation to 68 Gy/32f [17,18].

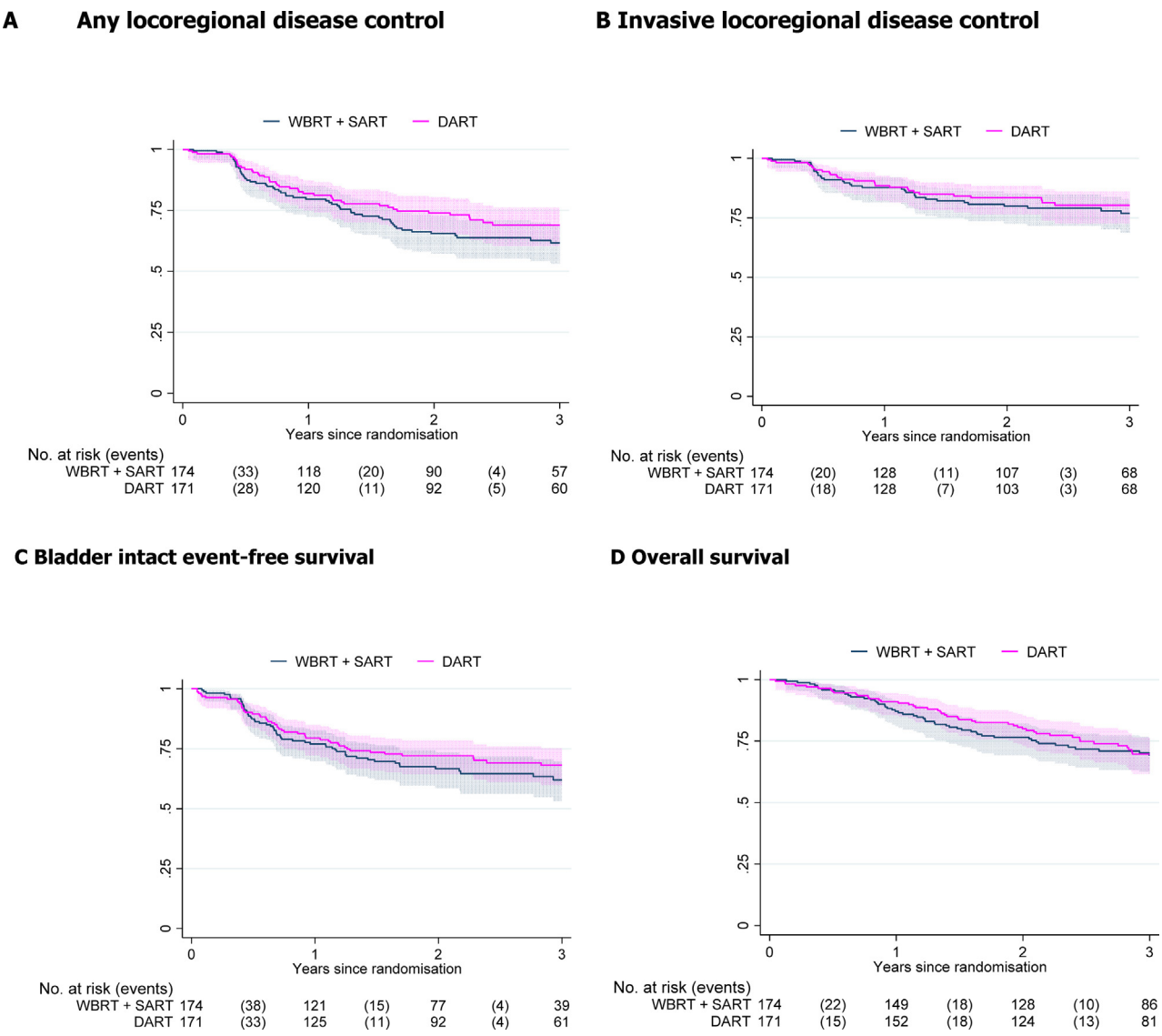

Fig. 3 – Kaplan-Meier curves comparing standard dose (WBRT + SART) with dose escalation (DART) for (A) any locoregional disease control, (B) invasive locoregional disease control, (C) bladder intact event-free survival, and (D) overall survival. Locoregional disease control: events are bladder cancer recurrence (muscle and non–muscle invasive) and pelvic node recurrence; censoring events are metastases (if occurred ≥30 d before locoregional failure), second primary tumour, and death. Locoregional invasive disease control: locoregional disease control but excluding noninvasive bladder cancer recurrences (neither censoring nor counting as events); for these endpoints and overall survival, patients who are alive and event free are censored at the date of last follow-up. Bladder intact event-free survival: events are muscle-invasive bladder cancer, pelvic node recurrence, distant metastases, cystectomy (for any reason), and bladder cancer–related death; patients who are event free are censored at the date of last cystoscopy. DART = dose-escalated adaptive radiotherapy; SART = standard-dose adaptive radiotherapy; WBRT = whole bladder radiotherapy.

Overall toxicity in RAIDER was modest despite dose escalation. Our previous bladder radiotherapy trial BC2001 reported 2-yr 13% cumulative grade 3–4 RTOG toxicity [19], and the BCON trial reported 3-yr 3% genitourinary and 7% gastrointestinal LENT-SOMA toxicity rates [20]. In RAIDER, despite 50% of patients receiving dose escalation, we observed lower 2-yr rates of RTOG grade ≥3 toxicity in both cohorts. A meta-analysis of RTOG bladder radiotherapy studies reported 7% late grade 3 pelvic toxicity (5.7% genitourinary and 1.9% gastrointestinal), whilst our results are similar to the 3% grade 3 late toxicity reported in a meta-analysis of patients receiving gemcitabine chemoradiotherapy [21,22]. Though there could be population or reporting differences, technical developments used in RAIDER including intensity-modulated radiotherapy, and adaptive and tumour focused treatment would be a logical explanation for lower than expected toxicity.

Variability of the bladder during radiotherapy and the impact on target coverage have been well documented [4,23,24]. Our data provide additional support for the need for adaptive planning to optimise target coverage. Most participants received treatment with all three plans. PoD radiotherapy is complex, and requires clear guidelines and ongoing quality assurance at the time of its introduction. We initially found relatively low concordance between the plan selected during treatment and a subsequent review [8,25]. Retraining and revised guidance led to improved compliance in the later parts of the study. This emphasises the

need for training and peer review when implementing new complex interventions.

As in the BC2001 trial, despite favourable trends, we could not prove that reducing high dose volume reduces bladder toxicity. Explanations include that the global bladder dose is a less important determinant of toxicity than previously thought or that bladder sparing remains suboptimal even with these techniques. Newer online magnetic resonance imaging–based or CT-based real-time adaptive techniques with/without functional monitoring may allow more extreme bladder sparing and could further contribute to answering this question.

The standard dose groups had similar 2-yr event-free rates to those seen in BC2001 chemoradiotherapy arms for locoregional (BC2001 63%; RAIDER 65%) and invasive local-regional (BC2001 82%; RAIDER 80%) control [26]. Dose escalation achieved what might be, if confirmed, meaningful clinical benefits (though not statistically significant), with 9% and 4% absolute improvement in 2-yr locoregional and invasive locoregional recurrence rates, respectively. A comparison with cystectomy series is difficult due to inherent selection biases. Recently, Zlotta and colleagues [1] reported survival in a series of cystectomy patients suitable for trimodality therapy. Five-year survival was 66% and it was around 80% at 2 yr, which is similar to the rates observed in RAIDER in an older less fit cohort (median age 71 yr in cystectomy series vs 73 yr in RAIDER). This would support that modern high-quality chemoradiotherapy achieves at least equivalent survival results to surgery.

To date, 13 (4%) participants have had a cystectomy, and though follow-up is short, this is similar to that seen in our pilot dose escalation study [29], comparing favourably with previously published reports (BC2001 14%; MGH retrospective series 29%) [1,27,28].

One concern of adaptive treatment to the bladder alone is whether nodal recurrences would be increased due to reduced "bystander nodal irradiation", but we saw little evidence of this, with 25/345 (7%) having a nodal recurrence; this was the first event in the bladder intact event-free survival analysis for only nine (2.6%) participants. This compares with the 4.9% rate in the BC2001 chemoradiotherapy group.

Limitations mainly relate to the phase 2 design—the study was not designed to compare treatment groups, compounded by lower than expected overall toxicity. The assessment of PRO was compromised by the need to change instrument mid-trial, so patient-reported data on gastrointestinal toxicity are incomplete.

Overall, this trial supports evidence that adaptive chemoradiotherapy is a safe alternative to radical cystectomy, achieving local control for most patients with low rates of salvage cystectomy and modest toxicity. Though these data do not conclusively confirm the superiority of this approach, these data support on-going implementation and further development of adaptive radiotherapy, potentially through approaches of real-time adaption currently under development. Proof of this benefit will require further randomised studies.

5. Conclusions

In this phase 2 study, an image-guided adaptive strategy enabled radiotherapy dose escalation to over 86% of patients' bladder tumours without significant increase in toxicity. Utilisation of multiple adaptive plans suggests an on-going need for adaptive therapy to optimise treatment delivery. Dose-escalated therapy achieves promising tumour control and survival rates similar to that achieved with cystectomy, with low rates of salvage cystectomy, and should be studied in future trials.

Author contributions: Robert Huddart 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.

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Acquisition of data: Huddart, Hafeez, Choudhury, Syndikus, Hindson, Webster, Birtle, Varughese, Parikh, Nikapota, Tang, Henry, McLaren.
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Drafting of the manuscript: Huddart, Griffin, Gribble, Lewis, Cheung, Hall.
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Data sharing statement: Deidentified individual participant data, together with a data dictionary defining each field in the set, will be made available to other researchers on request. Trial documentation including the protocol is available online. The ICR-CTSU supports wider dissemination of information from the research that it conducts and increased cooperation between investigators. Trial data are obtained, managed, stored, shared, and archived according to ICR-CTSU standard operating procedures to ensure the enduring quality, integrity, and utility of the data. Formal requests for data sharing are considered in line with ICR-CTSU procedures, with due regard given to funder and sponsor guidelines. Requests are to be made via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement, which describes the conditions for release and requirements for data transfer, storage, archiving, publication, and intellectual property. Requests are reviewed by the trial management group in terms of scientific merit and ethical considerations, including patients' consent. Data sharing is undertaken if proposed projects have a sound scientific or patients' benefit rationale, as agreed by the trial management group and approved by the independent data monitoring and steering committee, as required. Restrictions relating to patients' confidentiality and consent will be limited by aggregating and anonymising identifiable patients' data. Additionally, all indirect identifiers that could lead to deductive disclosures will be removed in line with ICR-CTSU data sharing guidelines.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2024.09.006.

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