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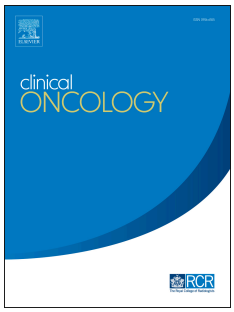

Acute Toxicity of Hypofractionated and Conventionally Fractionated (Chemo)Radiotherapy Regimens for Bladder Cancer: an Exploratory Analysis from the RAIDER Trial

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Title: Acute toxicity of hypo-fractionated and conventionally fractionated (chemo)radiotherapy regimens for bladder cancer: an exploratory analysis from the RAIDER trial.

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Declaration of interest

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Dr. Foroud has nothing to disclose.

Ms. Gribble has nothing to disclose.

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Dr. Hilman has nothing to disclose.

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Dr. Rimmer has nothing to disclose.
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Acute toxicity of hypo-fractionated and conventionally fractionated (chemo)radiotherapy regimens for bladder cancer: an exploratory analysis from the XXXXX trial.

Abstract: 298

Background

Adding concurrent (chemo-)therapy to radiotherapy improves outcomes for muscle invasive bladder cancer patients. Recent meta-analysis demonstrates superior invasive locoregional disease control for a hypofractionated 55 gray (Gy) in 20 fractions (f) schedule compared to 64Gy in 32f. In the XXXXX clinical trial, patients undergoing 20f or 32f radical radiotherapy were randomised (1:1:2) to standard radiotherapy or to standard-dose or escalated-dose adaptive radiotherapy. Neoadjuvant chemotherapy (NAC) and concomitant therapy were permitted. We report exploratory analyses of acute toxicity by concomitant therapy-fractionation schedule combination.

Methods

Participants had unifocal bladder TCC staged T2-T4a N0 M0. Acute toxicity was assessed (CTCAE) weekly during radiotherapy and at 10 weeks after start of treatment. Within each fractionation cohort, non-randomised comparisons of the proportion of patients reporting treatment emergent grade 2 or worse (G2+) genitourinary (GU), gastrointestinal (GI) or other adverse events at any point in the acute period was performed using Fisher's exact tests.

Results

Between September 2015 and April 2020, 345 (163 20f; 182 32f) patients were recruited from 46 centres. Median age was 73 years; 49% received NAC; 71% received concomitant therapy with 5FU/MMC most commonly used: 44/114 (39%) 20f; 94/130 (72%) 32f. Acute G2+ GI toxicity rate was higher in those receiving concomitant therapy compared to RT alone in the 20f cohort (54/111 (49%) vs 7/49 (14%), $p<0.001$) but not in the 32f cohort ($p=0.355$). G2+ GI toxicity was highest for gemcitabine with evidence of significant differences across therapies in the 32f cohort ($p=0.006$), with a similar pattern but no significant differences in the 20f cohort ($p=0.099$). There was no evidence of differences in G2+ GU toxicity between concomitant therapies in either 20f or 32f.

Conclusion

G2+ acute adverse events are common. The toxicity profile varied by type of concomitant therapy, GI toxicity rate appear higher in patients receiving gemcitabine.

Key words:

Radiotherapy

Chemotherapy

Bladder

Acute Toxicity

Original Article

Acute Toxicity of Hypofractionated and Conventionally Fractionated (Chemo)Radiotherapy Regimens for Bladder Cancer: an Exploratory Analysis from the RAIDER Trial

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Abstract

Aims: Adding concurrent (chemo)therapy to radiotherapy improves outcomes for muscle-invasive bladder cancer patients. A recent meta-analysis showed superior invasive locoregional disease control for a hypofractionated 55 Gy in 20 fractions schedule compared with 64 Gy in 32 fractions. In the [AQ1]RAIDER clinical trial, patients undergoing 20 or 32 fractions of radical radiotherapy were randomised (1:1:2) to standard radiotherapy or to standard-dose or escalated-dose adaptive radiotherapy. Neoadjuvant chemotherapy and concomitant therapy were permitted. We report exploratory analyses of acute toxicity by concomitant therapy-fractionation schedule combination.
Materials and methods: Participants had unifocal bladder [AQ2]TCC staged T2-T4a N0 M0. Acute toxicity was assessed (Common Terminology Criteria for Adverse Events) weekly during radiotherapy and at 10 weeks after the start of treatment. Within each fractionation cohort, non-randomised comparisons of the proportion of patients reporting treatment emergent grade 2 or worse genitourinary, gastrointestinal or other adverse events at any point in the acute period were carried out using Fisher's exact tests.
Results: Between September 2015 and April 2020, 345 (163 receiving 20 fractions; 182 receiving 32 fractions) patients were recruited from 46 centres. The median age was 73 years; 49% received neoadjuvant chemotherapy; 71% received concomitant therapy, with 5-fluorouracil/mitomycin C most commonly used: 44/114 (39%) receiving 20 fractions; 94/130 (72%) receiving 32 fractions. The acute grade 2+ gastrointestinal toxicity rate was higher in those receiving concomitant therapy compared with radiotherapy alone in the 20-fraction cohort [54/111 (49%) versus 7/49 (14%), $P < 0.001$] but not in the 32-fraction cohort ($P = 0.355$). Grade 2+ gastrointestinal toxicity was highest for gemcitabine, with evidence of significant differences across therapies in the 32-fraction cohort ($P = 0.006$), with a similar pattern but no significant differences in the 20-fraction cohort ($P = 0.099$). There was no evidence of differences in grade 2+ genitourinary toxicity between concomitant therapies in either the 20- or 32-fraction cohorts.
Conclusion: Grade 2+ acute adverse events are common. The toxicity profile varied by type of concomitant therapy; the gastrointestinal toxicity rate seemed to be higher in patients receiving gemcitabine.

Key words: Acute toxicity; bladder; chemotherapy; radiotherapy

Introduction (A head)

Radiotherapy is a bladder-preserving alternative to radical cystectomy for patients with locally advanced muscle-invasive (T2-4) urothelial cancer. Three randomised trials have shown improved results from adding cisplatin, 5-fluorouracil/mitomycin C (5-FU/MMC) or carbogen and nicotinamide (CON) to radiotherapy [1–3]. Radiosensitised radiotherapy is now the standard of care for these patients [4]. Additionally, gemcitabine has been tested in prospective phase II trials, with results comparable with those achieved by 5-FU/MMC and has been adopted by a number of centres worldwide [5,6]. There are, however, no concurrently and prospectively collected data to describe the relative toxicities of these various concomitant therapies.

Major geometric inter-fraction changes can occur during bladder radiotherapy. This has led to the exploration of soft-tissue image guidance and adaptive radiotherapy approaches, aiming to minimise geographical misses, limit normal tissue toxicity and potentially dose escalate to improve local control. These concepts led us to design the

[AQ1]RAIDER trial, which randomised patients to standard radiotherapy or to one of two adaptive tumour boost arms. Two fractionation schedules were permitted, with concomitant therapy recommended.

Here we report an exploratory analysis of acute toxicity data from the [AQ1]RAIDER trial according to fractionation schedule and selected concomitant therapy strategy. These data add to the knowledge base to better understand the toxicity profile of commonly used concomitant therapies and, in particular, gemcitabine, for which data collected within a randomised setting have been lacking.

Materials and Methods (A head)

Trial Design and Participants (B head)

[AQ1]RAIDER is an international multicentre, multi-arm, two-stage non-blinded phase II randomised trial of adaptive tumour-focused radiotherapy for bladder cancer. Participants were randomised to whole bladder radiotherapy with standard planning (WBRT; control), standard dose adaptive tumour-focused radiotherapy (SART) or dose-escalated adaptive tumour boost radiotherapy (DART). The trial is registered: ISCRTN 26779187 and has completed.

Two fractionation schedules were permitted; 32 fractions (tumour dose 64 Gy in WBRT and SART, 70 Gy in DART) or 20 fractions (tumour dose 55 Gy in WBRT and SART, 60 Gy in DART) with each centre specifying its intended fractionation schedule prior to activation.

The full protocol has been published [7]. Briefly, eligible participants had histologically or cytologically confirmed urothelial bladder carcinoma, unifocal disease staged T2-T4a N0 M0, were ≥16 years old, with World Health Organization performance status 0–2 and were fit to receive a radical course of radiotherapy.

Participants were permitted to have received neoadjuvant chemotherapy and were recommended to receive concomitant radiosensitising therapy. Treatment centres nominated a preferred schedule prior to study activation but could use a prespecified ‘back up’ schedule if the primary schedule was contraindicated for specific individuals. Permitted schedules were required to have supportive published data. Schedules approved for use were 5-FU/MMC [1], CON [2], weekly low-dose gemcitabine [5] and single-agent cisplatin [3].

Acute toxicity was assessed using Common Terminology Criteria for Adverse Events (CTCAE) v.4 by local clinicians weekly during treatment (4 weeks for the 20-fraction cohort and 6.5 weeks for the 32-fraction cohort), at 6 and 10 weeks from the start of radiotherapy and 3 months from the last fraction.

Patient-reported outcomes (PRO) were collected from participants who consented to the optional PRO sub-study. PRO instruments were the Kings Health Questionnaire (KHQ) [8], the PRO-CTCAE questionnaire (from protocol amendment v2.0 15/02/2018) [9], ALERT-B [10] and EQ5D-5L [11] questionnaires. PRO questionnaires were administered on paper by the centres within 2 weeks before radiotherapy, at the last fraction of radiotherapy and 3 months from the completion of radiotherapy.

The trial was approved by the London-Surrey Borders Research Ethics Committee (reference 15/LO/0539) in the UK and the relevant institutional review boards in Australia

and New Zealand. [AQ1]RAIDER was conducted in accordance with the principles of Good Clinical Practice. All participants provided voluntary written informed consent.

Statistical Considerations (B head)

Randomisation (C head)

Participants were randomly assigned (1:1:2) to standard radiotherapy (WBRT), SART or DART, within each fractionation cohort. Randomisation was by telephone call to [AQ3]XXXXXXXXX. Treatment allocation was by minimisation with a random element. Balancing factors were treating centre, neoadjuvant chemotherapy use (yes/no) and concomitant therapy use (yes/no). Treatment allocation was not masked.

Sample size (C head)

[AQ1]RAIDER is a non-comparative phase II trial aiming to rule out excessive late CTCAE grade 3 or higher toxicity in each DART fractionation cohort. For the exploratory analyses presented here, the sample size was defined by the number of participants with acute toxicity data and the numbers in each concomitant therapy subgroup were determined by the treatment strategy in use at participating centres.

Endpoints (C head)

A statistical analysis plan was written prospectively for this exploratory analysis. Of primary interest were grade 2 or higher clinician-assessed acute toxicities. The maximum grade of CTCAE toxicity occurring during treatment and up to 3 months after treatment was calculated for any genitourinary (frequency/urgency, cystitis, incontinence, bladder spasm, urinary retention, urinary tract obstruction, nocturia and haematuria), any gastrointestinal (anorexia, nausea, vomiting, constipation, diarrhoea, abdominal pain, dehydration, proctitis, gastrointestinal fistula, obstruction, weight loss, anus/rectum haemorrhage and mucositis) and any prespecified toxicity (any genitourinary, any gastrointestinal, fatigue, febrile neutropenia, chest pain and palmar-plantar syndrome). PROs were important secondary endpoints, with the focus on general quality of life assessed using the ED5D-5L questionnaire, bladder symptoms reported on the KHQ and bowel symptoms reported using PRO-CTCAE.

Statistical methods (C head)

Analyses were conducted in the safety population defined as all randomised patients who received at least one fraction of study treatment. Results are reported for each randomised fractionation cohort separately and according to concomitant therapy given.

The frequency and percentages of worst acute toxicity grade were tabulated by concomitant therapy (radiotherapy alone, 5-FU/MMC, gemcitabine, CON) and are visualised with stacked bar charts. For post-radiotherapy assessments, tabulations present treatment emergent adverse events, i.e. those adverse events graded higher than at baseline (where grade 0 represents an adverse event at a grade the same or lower than baseline). Where pre-radiotherapy signs and symptoms were missing, week 1 adverse events graded 0 or 1 were used as ‘pre-radiotherapy’ to define treatment emergent toxicities. All data reported

were included with the exception of the 3-month assessment, for which a 16-week cut-off was used.

Acute toxicity was compared (i) for any concomitant therapy versus radiotherapy alone and (ii) across concomitant therapy regimens using chi-squared tests or Fisher's exact test (where cell frequencies were <5). Within each fractionation cohort, to account for multiple testing (any genitourinary, any gastrointestinal and any prespecified toxicity) *P*-values < 0.0167 were considered statistically significant. If statistically significant differences were seen in the primary summary measure of interest, the concomitant therapy groups were compared with respect to individual adverse events that contribute to the domain; these secondary analyses used a significance level of 0.01. A post-hoc comparison of fractionation cohorts was made, adjusting for concomitant therapy.

The analysis of PROs was descriptive to support the interpretation of clinician-reported toxicity. PRO data were analysed in accordance with the relevant scoring manuals. The KHQ standardised scoring system ranges from 0 (best) to 100 (worst). This is used for all KHQ domains other than the symptom severity scale, which is the total of 10 items and ranges from 0 (best) to 30 (worst). For the EQ5D-5L general health score, 0 indicates the worst and 100 the best health. Domain scores were summarised by the median and interquartile range (IQR) at each time point.

Due to the small number of participants receiving cisplatin (three in each fractionation cohort), these data were not included in any of the analyses (except Table 1).

Analyses were based on a data snapshot taken on 5 July 2021 and were conducted using Stata version 17.0.

Results (A head)

From September 2015 to April 2020, 345 participants were enrolled from 46 sites in the UK, Australia and New Zealand (20 fractions: *n* = 163; 32 fractions: *n* = 182). Concomitant therapies were planned for 103/163 (63%) and 132/182 (73%) participants in the 20- and 32-fraction cohorts, respectively. Baseline characteristics are given in Table 1. Of those who received concomitant therapy, 5-FU/MMC was the most commonly used in 44/114 (39%) 20-fraction and 94/130 (72%) 32-fraction participants. Gemcitabine was the next most commonly used regimen in 40/114 (35%) 20-fraction and 22/130 (17%) 32-fraction participants. Delivered doses of concomitant therapy are given in Supplementary Table S1. 5-FU/MMC doses were similar in both cohorts, with median doses consistent with those seen in the BC2001 trial [12]. For gemcitabine, in the 20-fraction cohort, all participants were planned to receive 100 mg/m^2 weekly, resulting in a median total dose of 400 mg/m^2 (IQR 300–400) with 8% (3/40) of participants having one or more doses of gemcitabine omitted. In the 32-fraction cohort, most participants (12/22; 55%) were planned to receive 100 mg/m^2 weekly and 10/22 (45%) received 75 mg/m^2 weekly as the centre's standard dose, resulting in a median total dose of 450 mg/m^2 (IQR 400–500).

Table 1 here

Acute Toxicity – Fractionation Cohort (B head)

The worst grade of any acute toxicity at each time point by fractionation cohort is shown in Figure 1. Symptoms peaked at the end of the radiotherapy but recovered to pre-

radiotherapy levels in both fractionation cohorts by 3 months post-radiotherapy. Over the 3 months from the start of radiotherapy, 74/111 (67%) of the 20-fraction and 67/127 (53%) of the 32-fraction cohort had at least one episode of grade 2+ toxicity reported. After adjusting for concomitant therapy use, an exploratory analysis showed there was no evidence of any difference in acute toxicity between fractionation cohorts (odds ratio 1.21; 95% confidence interval 0.77–1.92; *P* = 0.409). Grade 3/4 toxicity affected a modest proportion of patients, with grade 3 toxicity reported in 14/111 (13%) of the 20-fraction cohort and 8/127 (6%) of 32-fraction cohort. One grade 4 toxicity (urinary tract obstruction at 10 weeks post-radiotherapy) was reported in the 20-fraction cohort.

Figure 1 here

Acute Toxicity – Concomitant Therapy and Radiotherapy Alone (B head)

Acute toxicity by concomitant therapy and fractionation cohort is summarised in Figure 2 and Table 2.

Figure 2 here
Table 2 here

In the 20-fraction cohort, patients receiving concomitant therapy experienced significantly more (*P* < 0.001) grade 2+ toxicity compared with those receiving radiotherapy alone [74/111 (67%) versus 17/49 (35%) grade 2+]. This was largely due to higher rates of gastrointestinal toxicity [grade 2+ 54/111 (49%) with concomitant therapy; 7/49 (14%) with radiotherapy alone, *P* < 0.001]. There was no evidence of a difference in grade 2+ genitourinary toxicity between concomitant therapy versus radiotherapy alone (*P* = 0.099).

In the 32-fraction cohort, there was no evidence of a difference in any grade 2+ toxicity between patients receiving concomitant therapy 67/127 (53%) compared with radiotherapy alone 24/52 (47%) (*P* = 0.510). Similarly, there was no evidence of increased genitourinary or gastrointestinal toxicity between those receiving concomitant therapy and those receiving radiotherapy alone (*P* = 0.355 for gastrointestinal and *P* = 0.605 for genitourinary grade 2+ toxicities).

Acute Toxicity – Across Concomitant Therapies (B head)

For grade 2+ gastrointestinal toxicity, there was no evidence of a difference between concomitant therapies for the 20-fraction cohort (*P* = 0.099) but there were significant differences between therapies in the 32-fraction cohort (*P* = 0.006) (Table 2). In the 32-fraction cohort, 12/22 (54%) participants receiving gemcitabine reported a grade 2+ acute gastrointestinal toxicity compared with 20/94 (21%) participants receiving 5-FU/MMC. In the 20-fraction cohort, the gemcitabine group also had the highest proportion of gastrointestinal grade 2+ toxicity (25/40; 63%) of all the therapies, but this was not statistically significantly different from the other concomitant therapies (*P* = 0.099).

Table 3 shows specific grade 2+ gastrointestinal toxicities reported in more than 10% of participants in any concomitant therapy group. Toxicity profiles seemed to differ between different therapies. For gemcitabine, diarrhoea (in both fractionation cohorts) and proctitis (in the 20-fraction cohort) were reported at grade 2+ for more than 20% of participants. For

CON, grade 2+ toxicities were dominated by nausea and vomiting. Grade 2+ toxicity for 5-FU/MMC were more diverse, with no one symptom dominating.

Table 3 here

For grade 2+ genitourinary toxicity there was no evidence of a difference between concomitant therapies for the 20-fraction cohort (P = 0.779) or the 32-fraction cohort (P = 0.771).

An unadjusted exploratory comparison of fractionation cohorts indicated there was no evidence of a difference for genitourinary toxicities (P = 0.758) but there was for grade 2+ gastrointestinal toxicities (P = 0.019). However, when adjusted for concomitant therapy there was no evidence of statistically significant differences in grade 2+ gastrointestinal toxicity between the fractionation cohorts.

Patient-reported Outcomes (B head)

EQ5D overall health scores are summarised in Figure 3 and Supplementary Table S2. In the 20-fraction cohort, all groups showed a decrease in overall health score from pre-radiotherapy to the end of treatment, with the 5-FU/MMC group showing the largest decrease, with the median score falling from 80 (IQR 75, 90) to 75 (IQR 63, 82). By 3 months after radiotherapy, median scores had returned to or exceeded pre-radiotherapy values. In the 32-fraction cohort, compared with the 20-fraction cohort, there appeared to be less of a decrease in overall health scores from before radiotherapy to the end of radiotherapy across all concomitant therapy groups. In the 32-fraction 5-FU/MMC group, the pre-radiotherapy median score was 80 (IQR 70, 90); at the end of radiotherapy it was 80 (IQR 65, 90). Three months after completing radiotherapy, the median score had returned to pre-radiotherapy levels in the gemcitabine and radiotherapy-alone groups, exceeded the pre-radiotherapy score in the 5-FU/MMC group, but was still lower than pre-radiotherapy in the CON group [median 83 (IQR 70, 90) pre-radiotherapy and median 78 (IQR 70, 85) at 3 months].

Figure 3 here

The KHQ bladder problem scores indicated that at the end of radiotherapy there were fewer participants who were symptom free (Figure 4B). At 3 months, the proportion of participants with no bladder problems was similar for 5-FU/MMC and gemcitabine within each fractionation cohort. However, more 32-fraction gemcitabine participants reported severe bladder problems than in the 20-fraction cohort (no statistical comparison made).

Figure 4 here

The KHQ urinary symptom severity scores were highest at the end of radiotherapy for all 20-fraction groups except for 5-FU/MMC, which had scores that remained at pre-radiotherapy levels (Table 4). For both fractionation cohorts, the 5-FU/MMC group had the lowest median severity scores of all groups (no statistical comparisons made) 3 months after completing radiotherapy [20-fraction cohort: median 3.5 (IQR 2–8); 32-fraction cohort: 4 (IQR 2–7)].

Table 4 here

The data available for PRO-CTCAE were limited, as this questionnaire was added after recruitment had started. In general, responses mirrored the clinician-based score and are tabulated in Supplementary Table S3 for information.

Discussion (A head)

Here we describe the acute toxicity seen with contemporary radiosensitising therapy for muscle-invasive bladder cancer in the context of a multicentre, multinational randomised clinical trial. Our primary interest was to investigate the pattern of grade 2+ toxicity, rather than grade 3+ toxicity, as previous studies have shown grade 3+ events to be relatively infrequent and grade 2 events still represent significant changes that may impact on quality of life. Our results have confirmed low levels of grade 3+ toxicity and highlighted some differences in the toxicity profiles of commonly used concomitant therapy fractionation schedules.

Due to differences in scales and the reporting of lower grade toxicities, our data may not be directly comparable with previous series. However, the pattern of toxicity is consistent with previous studies, showing that both toxicity and PRO quality of life measures worsen at the end of radiotherapy before returning to baseline or better levels at the 3-month point [13].

Considering that 50% of participants received an escalated dose of radiotherapy to their tumour, the overall rate of acute toxicity is modest. The most directly comparable data are from the BC2001 trial, which permitted the same fractionation schedules and tested the addition of 5-FU/MMC, with toxicity reported using the NCI CTCAE scale [12]. This study reported a 36% grade 3+ acute toxicity rate in those receiving chemoradiotherapy versus 28% in those receiving radiotherapy alone. In contrast, we identified a much lower treatment emergent acute grade 3+ toxicity rate in those receiving 5-FU/MMC with 4/94 (4%) and 5/44 (11%) in the 32- and 20-fraction cohorts, respectively, and 11% and 5%, respectively, in those receiving no concomitant therapy. Likewise in the UK's GemX phase II study of concomitant gemcitabine [14], grade 3+ acute toxicity was reported in 18–20% of patients (all treated with 20-fraction radiotherapy). A smaller US RTOG [6] study reported grade 3+ toxicity in 55% of patients, although much of this was haematological, with 15% experiencing grade 3+ gastrointestinal/genitourinary toxicity. In our comparable 20-fraction cohort, 5/40 (13%) reported grade 3+ toxicity. With CON, 13% of patients experienced 'severe' nausea in the BCON trial, with 5% gastrointestinal and 20% genitourinary 'severe' toxicity [2]; compared with 3/27 (11%) with grade 3+ toxicity in [AQ1]RAIDER.

Comparing toxicity results across trials and decades is fraught with potential biases, but taken as whole, the acute toxicity results here seem more moderate than expected and could suggest a benefit for the more advanced radiotherapy techniques used in this study compared with those used >10 years ago.

Accepting the potential biases involved and noting the non-randomised nature of our comparisons, some clear messages emerge. First, the incidence and pattern of urinary toxicity is little affected by either the sensitisation approach used or the fractionation; a result also seen in BC2001 and BCON trials. However, when we look at gastrointestinal toxicity, the overall trend is that the addition of sensitisation increases the risk of acute

gastrointestinal toxicity. Despite the overall lack of impact of sensitisation on gastrointestinal toxicity in the 32-fraction cohort; there were significantly higher rates of gastrointestinal toxicity in patients receiving gemcitabine (5-FU/MMC 21%, gemcitabine 54%, CON 27%; *P* = 0.006). It is noteworthy that in this fractionation group, 94/123 (76%) received 5-FU/MMC, which had similar grade 2+ toxicity rates to the no concomitant therapy group, thus, perhaps, explaining the lack of evidence of an overall increase in gastrointestinal toxicity in this cohort. In the 20-fraction group, similar rates of gastrointestinal toxicity were seen for the gemcitabine and CON groups, but no statistically significant difference between regimens was seen, perhaps due in part to a higher grade 2+ toxicity in the 20-fraction 5-FU/MMC group. This was also reported in the BC2001 trial, with 9.6% grade 3+ gastrointestinal toxicity with 5-FU/MMC versus 2.7% without (odds ratio 3.84, *P* < 0.007). The net effect of this is that in the 20-fraction [AQ1]RAIDER cohort, chemosensitised patients had a higher overall rate of gastrointestinal toxicity compared with no chemotherapy.

For 5-FU/MMC and especially gemcitabine, our results support the classic small and large bowel radiation toxicity syndromes of diarrhoea and proctitis. Consistently across fractionation cohorts, rates of grade 2+ gastrointestinal toxicity appeared higher with gemcitabine than with 5-FU/MMC. Gemcitabine has been recognised as an excellent radiosensitiser, but may have a narrow therapeutic window [5,6]. A meta-analysis of gemcitabine radiosensitisation protocols in bladder radiotherapy has shown a wide variety of doses and schedules have been studied [15]. The GemX protocol suggested that a combination of gemcitabine 100 mg/m^2 weekly × 4 weeks is safe and effective when given with 52.5 Gy in 20 fractions; and this was chosen for most patients in the [AQ1]RAIDER 20-fraction cohort and around 50% in the 32-fraction cohort (with the remainder receiving lower weekly doses, most often 75 mg/m^2). Eight per cent (5/62) of patients had one or more doses of gemcitabine omitted. Our data suggest that further exploration to optimise the gemcitabine administration schedule is necessary if we are to maximise its chemosensitisation benefits.

The pattern for CON is very different. Although there seems to be a higher rate of grade 2+ gastrointestinal toxicity than for those receiving no sensitisation, the rate of diarrhoea and proctitis is similar to those receiving radiotherapy alone, but these patients experience significant levels of nausea, vomiting and anorexia. This is probably related to the nicotinamide tablets, which are recognised to cause these symptoms.

A recent meta-analysis on the BC2001/BCON trial did not show any evidence of increased toxicity with 20-fraction radiotherapy [16]. The graphical display suggests more frequent acute toxicity with 20 fractions. It should be noted that there were differences in the proportions of patients receiving different sensitisation regimens in the two fractionation cohorts and specifically more patients in the 20-fraction cohort receiving gemcitabine or CON, which as reported above are associated with higher rates of gastrointestinal toxicity. A non-randomised exploratory analysis found that once confounding factors are accounted for, no significant differences between fractionation cohorts could be seen.

Data from PROs mirror those seen in recently reported data in showing a decline in health-related quality of life immediately after radiotherapy, which recover to baseline or above by 3 months [13]. There is no clear or consistent message in relation to fractionation or concomitant therapy, although these data are compromised by limited data on bowel toxicity due to the need to change the bowel PRO instrument part way through the trial.

We acknowledge that there are limitations in the analysis reported here. Both the fractionation and the choice of sensitisation were not randomised and, especially, sensitisation choice was probably influenced by patient factors. Additionally, the analysis of acute toxicity was not the primary endpoint of the trial, the numbers were small in some groups of patients and the trial was not powered to look at comparisons between concomitant therapy groups. Finally, too few patients received cisplatin sensitisation to comment on its toxicity profile.

Despite these limitations, the acute toxicity rates using modern radiotherapy are encouraging compared with previous randomised trials. Overall, the use of concomitant therapy had a minor impact on overall toxicity rates and no impact on the most common urinary toxicities. However, the increased rates of short-term bowel toxicity with gemcitabine suggest caution in its use and its dosing. Patients receiving CON should be warned as to the risk of nausea and be monitored carefully for this problem. Whether there will be any differences in late toxicity between concomitant therapy regimens remains to be seen; this will be assessed after the primary analysis of the trial in early 2023 [AQ4].

Conclusion (A head)

Acute toxicities in this study of dose-escalated image-guided radiotherapy were moderate in severity, with lower rates of grade 3 toxicity than previously reported. The use and choice of concomitant therapy had no impact on overall or genitourinary toxicity and patient-reported quality of life. Gemcitabine and to a lesser extent CON were associated with higher rates of acute gastrointestinal toxicity.

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The funder reviewed the study design but had no role in data collection, data analysis, data interpretation or writing of the report. All authors had full access to all the data; the corresponding author had final responsibility for the decision to submit for publication.

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Conflicts of interest

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Author contributions

RH and EH are the guarantors of integrity of the entire study. RH, EH, SH, AC, AH, DMcL, FF, HMcN, RL and CG were responsible for study concepts and design (protocol development group). RH carried out the literature research. RH, AC, IS, BH, OP, AN, YR, SHi, RM, RA, MV and AB were responsible for clinical studies. EH, CG, AO, AW, SH, LP, HG, AO and AT carried out the data analysis. EH, CG and AO carried out the statistical analysis. RH, EH, CG, AO, RL and LP prepared the manuscript. All authors edited the manuscript.

Appendix A. Supplementary data

[AQ5]Supplementary data to this article can be found online at

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Fig 1. Worst grade treatment emergent acute toxicity by fractionation cohort.

Fig 2. Worst grade treatment emergent acute toxicity according to fractionation and concomitant therapy: (A) genitourinary, (B) gastrointestinal, (C) overall. 5FU/MMC, 5-fluorouracil/mitomycin C; GEM, gemcitabine; CON, carbogen and nicotinamide; RT, radiotherapy.

Fig 3. Box plots showing the EQ5D-5L overall health score at each acute time point by concomitant therapy: (A) 20-fraction cohort, (B) 32-fraction cohort. 5FU/MMC, 5-fluorouracil/mitomycin C; GEM, gemcitabine; CON, carbogen and nicotinamide; RT, radiotherapy.

Fig 4. Stacked bar charts illustrating the distribution of Kings Health Questionnaire bladder problem scores by concomitant therapy and fractionation cohort: (A) pre-radiotherapy, (B) at the end of radiotherapy and (C) 3 months after radiotherapy. 5FU/MMC, 5-fluorouracil/mitomycin C; GEM, gemcitabine; CON, carbogen and nicotinamide; RT, radiotherapy.

Table 1
Patient demographics and baseline characteristics according to radiosensitising strategy for (A) 32-fraction and (B) 20-fraction cohorts

(A)	5-FU/MMC (*n* = 94) *n* (%)		Gemcitabine (*n* = 22) *n* (%)		Cisplatin (*n* = 3) *n* (%)		CON (*n* = 11) *n* (%)		Radiotherapy alone (*n* = 52) *n* (%)		Total (*n* = 182) *n* (%)	
Age (years)												
Median (interquartile range)	70.9 (63.7, 76.7)		76.0 (72.8, 80.2)		72.5 (62.3, 73.7)		68.9 (63.4, 74.0)		77.1 (71.5, 83.6)		73.1 (67.9, 79.1)	
Gender												
Male	74	79	18	82	2	67	10	91	40	77	144	79
Female	20	21	4	18	1	33	1	9	12	23	38	21
Neoadjuvant chemotherapy												
Yes	55	59	10	45	1	33	6	55	11	21	83	46
No	39	41	12	55	2	67	5	45	41	79	99	54
Grade												
G1	2	2	0	0	0	0	0	0	0	0	2	1
G2	7	7	0	0	0	0	1	9	1	2	9	5
G3	83	88	22	100	3	100	10	91	51	98	169	93
Gx	2	2	0	0	0	0	0	0	0	0	2	1
CIS present												
Yes	19	20	5	23	1	33	3	27	13	25	41	23
No	74	79	16	73	2	67	7	64	35	67	134	74
Unobtainable	1	1	1	5	0	0	1	9	4	8	7	4
Residual disease present												
Yes	32	34	8	36	2	67	4	36	18	35	64	35
No	60	64	13	59	1	33	7	64	31	60	112	62
Unobtainable	2	2	1	5	0	0	0	0	3	6	6	3
WHO performance status												
0	63	67	10	48	3	100	5	45	28	54	109	60
1	29	31	11	52	0	0	6	55	17	33	63	35
2	2	2	0	0	0	0	0	0	7	13	9	5
Clinical stage												
T2	79	84	21	95	3	100	10	91	38	73	151	83
T3a	6	6	0	0	0	0	0	0	8	15	14	8
T3b	8	9	0	0	0	0	1	9	5	10	14	8

T4a	1	1	1	5	0	0	0	0	1	2	3	2
Nodal staging												
N0	94	100	22	100	3	100	11	100	52	100	182	100
Metastatic staging												
M0	94	100	22	100	3	100	11	100	52	100	182	100

(B)	5-FU/MMC (*n* = 44) *n* (%)		Gemcitabine (*n* = 40) *n* (%)		Cisplatin (*n* = 3) *n* (%)		CON (*n* = 27) *n* (%)		Radiotherapy alone (*n* = 49) *n* (%)		Total (*n* = 163) *n* (%)	
Age (years)												
Median (interquartile range)	71.4 (66.4, 78.0)		68.2 (63.8, 72.2)		77.8 (61.6, 79.5)		76.7 (65.9, 81.0)		75.3 (71.1, 81.9)		72.7 (67.1, 79.4)	
Gender												
Male	34	77	37	93	3	100	19	70	38	78	131	80
Female	10	23	3	8	0	0	8	30	11	22	32	20
Neoadjuvant chemotherapy												
Yes	23	52	36	90	0	0	13	48	13	27	85	52
No	21	48	4	10	3	100	14	52	36	73	78	48
Grade												
G1	0	0	0	0	0	0	0	0	0	0	0	0
G2	2	5	1	3	1	33	0	0	3	6	7	4
G3	42	95	39	98	2	67	27	100	44	90	154	95
Unobtainable	0	0	0	0	0	0	0	0	2	4	2	1
CIS present												
Yes	5	11	12	30	0	0	5	19	11	22	33	20
No	39	89	28	70	3	100	22	81	36	74	128	79
Unobtainable	0	0	0	0	0	0	0	0	2	4	2	1
Residual disease present												
Yes	10	23	8	20	2	67	9	33	13	27	42	26
No	30	68	28	70	1	33	17	63	34	69	110	67
Unobtainable	4	9	4	10	0	0	1	4	2	4	11	7
WHO performance status												
0	25	56	30	75	2	67	12	44	16	33	85	52
1	17	39	10	25	1	33	11	41	23	48	62	38
2	2	5	0	0	0	0	4	15	9	19	15	9
Missing	0	0	0	0	0	0	0	0	1	1	1	1
Clinical stage												
T2	37	84	27	68	2	67	20	74	40	83	126	78
T3a	4	9	8	20	0	0	2	7	3	6	17	10
T3b	2	5	5	13	0	0	4	15	5	10	16	10
T4a	1	2	0	0	1	33	1	4	0	0	3	2
Nodal staging												
N0	44	100	40	100	3	100	27	100	48	100	162	100
Metastatic staging												
M0	44	100	40	100	3	100	27	100	48	100	162	100

5-FU/MMC, 5-fluorouracil/mitomycin C;
CIS
CON, carbogen and nicotinamide; WHO, World Health Organization.

Table 2

Summary of treatment emergent acute toxicities

32-fraction cohort	5-FU/MMC (*n* = 94)		Gemcitabine (*n* = 22)		CON (*n* = 11)		Grade 2+ *P*-value (between regimens)	Radiotherapy alone (*n* = 52)		Grade 2+ *P*-value (concomitant therapy versus radiotherapy alone)
CTCAE grade 2+ toxicity	*n*	%	*n*	%	*n*	%		*n*	%	
Gastrointestinal	20	21	12	54	4	27	0.006	11	21	0.355
Genitourinary	33	35	9	41	3	27	0.779	16	31	0.605
Any pre-specified toxicity*	47	50	15	69	5	45	0.281	24	47	0.510
20-fraction cohort	5-FU/MMC (*n* = 44)		Gemcitabine (*n* = 40)		CON (*n* = 27)		Grade 2+ *P*-value (between regimens)	Radiotherapy alone (*n* = 49)		Grade 2+ *P*-value (concomitant therapy versus radiotherapy alone)
CTCAE grade 2+ toxicity	*n*	%	*n*	%	*n*	%		*n*	%	
Gastrointestinal	18	41	25	63	11	40	0.099	7	14	<0.001
Genitourinary	17	39	13	33	11	41	0.771	11	22	0.099
Any pre-specified toxicity*	27	61	30	76	17	63	0.484	17	35	<0.001

*Includes gastrointestinal toxicities (anorexia, nausea, vomiting, constipation, diarrhoea, abdominal pain, dehydration, proctitis, gastrointestinal fistula, obstruction, weight loss, haemorrhage and mucositis); genitourinary toxicities (frequency/urgency, cystitis, incontinence, bladder spasm, urinary retention, urinary tract obstruction, nocturia and haematuria); other pre-specific recorded on the Case Report Forms were fatigue, febrile neutropenia, chest pain and palmar-plantar syndrome.

5-FU/MMC, 5-fluorouracil/mitomycin C; CON, carbogen and nicotinamide; CTCAE, Common Terminology Criteria for Adverse Events.

Table 3

Treatment emergent individual gastrointestinal toxicities with >10% grade 2+

20 fractions		5-FU/MMC (*n* = 44)		Gemcitabine (*n* = 40)		CON (*n* = 27)		Grade 2+ *P*-value	Radiotherapy alone (*n* = 49)	
	Grade	*n*	%	*n*	%	*n*	%		*n*	%
Anorexia	0/1	40	81	35	87	23	85		42	86
	2+	4	9	5	13	4	15	0.755	0	0
	Missing	0	0	0	0	0	0		7	14
Nausea	0/1	41	93	38	95	20	74		40	82
	2+	3	7	2	5	7	26	0.022	2	4
	Missing	0	0	0	0	0	0		7	14
Vomiting	0/1	44	100	40	100	24	89		42	76
	2+	0	0	0	0	3	11	0.013	0	0
	Missing	0	0	0	0	0	0		7	14
Constipation	0/1	40	91	36	89	27	100		41	84
	2+	4	9	4	11	0	0	0.267	1	2
	Missing	0	0	0	0	0	0		7	14
Diarrhoea	0/1	39	89	24	60	24	89		38	78
	2+	5	11	16	40	3	11	0.003	4	8
	Missing	0	0	0	0	0	0		7	14
Abdominal pain	0/1	39	89	37	92	27	100		41	84
	2+	5	11	3	8	0	0	0.212	1	2
	Missing	0	0	0	0	0	0		7	14
Proctitis	0/1	39	88	29	72	26	96		41	84
	2+	5	11	11	28	1	4	0.027	1	2
	Missing	0	0	0	0	0	0		7	14

32 fractions		5-FU/MMC (*n* = 94)		Gemcitabine (*n* = 22)		CON (*n* = 11)		Grade 2+ *P*-value	Radiotherapy alone (*n* = 52)	
	Grade	*n*	%	*n*	%	*n*	%		*n*	%
Anorexia	0/1	90	96	17	77	9	82		43	67
	2+	3	3	4	18	2	18	0.011	2	4
	Missing	1	1	1	5	0	0		7	13
Nausea	0/1	89	95	19	86	9	82		44	85
	2+	4	4	2	9	2	18	0.086	1	2
	Missing	1	1	1	5	0	0		7	13
Diarrhoea	0/1	85	91	16	72	10	81		37	71
	2+	8	8	5	23	1	9	0.091	8	16
	Missing	1	1	1	5	0	0		7	13

5-FU/MMC, 5-fluorouracil/mitomycin C; CON, carbogen and nicotinamide.

Table 4
Descriptive statistics for the Kings Health Questionnaire (KHQ) Symptom Severity Scale (0–30) by concomitant therapy, fractionation cohort and acute time point assessed

KHQ Symptom Severity Scale	5-FU/MMC	Gemcitabine	CON	Radiotherapy alone
	n Median (interquartile range)	*n* Median (interquartile range)	*n* Median (interquartile range)	*n* Median (interquartile range)
20 fractions				
Pre-radiotherapy	39 6.0 (4.0, 9.0)	36 4.0 (2.5, 6.0)	26 5.5 (3.0, 9.0)	31 6.0 (3.0, 13.0)
End of Treatment	36 6.0 (4.0, 9.0)	36 5.5 (3.5, 10.0)	21 8.0 (6.0, 10.0)	17 7.0 (6.0, 8.0)
3 months post-radiotherapy	30 3.5 (2.0, 8.0)	32 4.0 (1.0, 7.0)	12 5.0 (4.0, 8.0)	24 6.0 (2.0, 8.5)
32 fractions				
Pre-radiotherapy	73 4.0 (2.0, 9.0)	17 6.0 (3.0, 9.0)	10 6.0 (4.0, 14.0)	37 5.0 (3.0, 9.0)
End of Treatment	65 6.0 (4.0, 10.0)	10 8.0 (6.0, 10.0)	8 7.5 (3.0, 10.0)	28 7.0 (3.5, 10.0)
3 months post-radiotherapy	66 4.0 (2.0, 7.0)	13 6.0 (4.0, 9.0)	8 11.0 (3.0, 16.5)	30 5.0 (3.0, 10.0)

Author queries

References [12] and [14] were the same. Therefore, [14] has been removed from the reference list, all citations changed to [12] and the subsequent references renumbered

AQ1 XXX has been changed to RAIDER. Please confirm that this is correct
AQ2 Please clarify TCC
AQ3 XXX – Please provide the missing information
AQ4 Any update?
AQ5 Please update web address once known

Table 1: please clarify CIS

Table 1: Patient demographics and baseline characteristics according to radio-sensitising strategy for (A) 32f and (B) 20f cohorts

(A) 32f cohort

	5FU/MMC (N=94) N (%)		GEM (N=22) N (%)		Cisplatin (N=3) N (%)		CON (N=11) N (%)		RT alone (N=52) N (%)		Total (N=182) N (%)	
Age (years)												
Median (IQR)	70.9 (63.7, 76.7)		76.0 (72.8, 80.2)		72.5 (62.3, 73.7)		68.9 (63.4, 74.0)		77.1 (71.5, 83.6)		73.1 (67.9, 79.1)	
Gender												
Male	74	79	18	82	2	67	10	91	40	77	144	79
Female	20	21	4	18	1	33	1	9	12	23	38	21
Neoadjuvant chemotherapy												
Yes	55	59	10	45	1	33	6	55	11	21	83	46
No	39	41	12	55	2	67	5	45	41	79	99	54
Grade												
G1	2	2	0	0	0	0	0	0	0	0	2	1
G2	7	7	0	0	0	0	1	9	1	2	9	5
G3	83	88	22	100	3	100	10	91	51	98	169	93
Gx	2	2	0	0	0	0	0	0	0	0	2	1
CIS present												
Yes	19	20	5	23	1	33	3	27	13	25	41	23
No	74	79	16	73	2	67	7	64	35	67	134	74
Unobtainable	1	1	1	5	0	0	1	9	4	8	7	4
Residual disease present												
Yes	32	34	8	36	2	67	4	36	18	35	64	35
No	60	64	13	59	1	33	7	64	31	60	112	62
Unobtainable	2	2	1	5	0	0	0	0	3	6	6	3
WHO performance status												
0	63	67	10	48	3	100	5	45	28	54	109	60
1	29	31	11	52	0	0	6	55	17	33	63	35
2	2	2	0	0	0	0	0	0	7	13	9	5
Clinical stage												
T2	79	84	21	95	3	100	10	91	38	73	151	83
T3a	6	6	0	0	0	0	0	0	8	15	14	8
T3b	8	9	0	0	0	0	1	9	5	10	14	8
T4a	1	1	1	5	0	0	0	0	1	2	3	2
Nodal staging												
N0	94	100	22	100	3	100	11	100	52	100	182	100
Metastatic staging												
M0	94	100	22	100	3	100	11	100	52	100	182	100

(B) 20f cohort

	5FU/MMC (N=44) N (%)		GEM (N=40) N (%)		Cisplatin (N=3) N (%)		CON (N=27) N (%)		RT alone (N=49) N (%)		Total (N=163) N (%)	
Age (years)												
Median (IQR)	71.4 (66.4, 78.0)		68.2 (63.8, 72.2)		77.8 (61.6, 79.5)		76.7 (65.9, 81.0)		75.3 (71.1, 81.9)		72.7 (67.1, 79.4)	
Gender												
Male	34	77	37	93	3	100	19	70	38	78	131	80
Female	10	23	3	8	0	0	8	30	11	22	32	20
Neoadjuvant chemotherapy												
Yes	23	52	36	90	0	0	13	48	13	27	85	52
No	21	48	4	10	3	100	14	52	36	73	78	48
Grade												
G1	0	0	0	0	0	0	0	0	0	0	0	0
G2	2	5	1	3	1	33	0	0	3	6	7	4
G3	42	95	39	98	2	67	27	100	44	90	154	95
Unobtainable	0	0	0	0	0	0	0	0	2	4	2	1
CIS present												
Yes	5	11	12	30	0	0	5	19	11	22	33	20
No	39	89	28	70	3	100	22	81	36	74	128	79
Unobtainable	0	0	0	0	0	0	0	0	2	4	2	1
Residual disease present												
Yes	10	23	8	20	2	67	9	33	13	27	42	26
No	30	68	28	70	1	33	17	63	34	69	110	67
Unobtainable	4	9	4	10	0	0	1	4	2	4	11	7
WHO performance status												
0	25	56	30	75	2	67	12	44	16	33	85	52
1	17	39	10	25	1	33	11	41	23	48	62	38
2	2	5	0	0	0	0	4	15	9	19	15	9
Missing	0	0	0	0	0	0	0	0	1	1	1	1
Clinical stage												
T2	37	84	27	68	2	67	20	74	40	83	126	78
T3a	4	9	8	20	0	0	2	7	3	6	17	10
T3b	2	5	5	13	0	0	4	15	5	10	16	10
T4a	1	2	0	0	1	33	1	4	0	0	3	2
Nodal staging												
N0	44	100	40	100	3	100	27	100	48	100	162	100
Metastatic staging												
M0	44	100	40	100	3	100	27	100	48	100	162	100

Table 2: Treatment emerging acute toxicities summary table

32f cohort	5FU/MMC (N=94)		GEM (N=22)		CON (N=11)		G2+ p-value (between regimens)	RT alone (N=52)		G2+ p-value (Concomitant therapy vs RT alone)
CTCAE G2+ toxicity	N	%	N	%	N	%		N	%	
GI	20	21	12	54	4	27	0.006	11	21	0.355
GU	33	35	9	41	3	27	0.779	16	31	0.605
Any pre-specified toxicity*	47	50	15	69	5	45	0.281	24	47	0.510
20f cohort	5FU/MMC (N=44)		GEM (N=40)		CON (N=27)		G2+ p-value (between regimens)	RT alone (N=49)		G2+ p-value (Concomitant therapy vs RT alone)
CTCAE G2+ toxicity	N	%	N	%	N	%		N	%	
GI	18	41	25	63	11	40	0.099	7	14	<0.001
GU	17	39	13	33	11	41	0.771	11	22	0.099
Any pre-specified toxicity*	27	61	30	76	17	63	0.484	17	35	<0.001

*This includes GI toxicities (anorexia, nausea, vomiting, constipation, diarrhoea, abdominal pain, dehydration, proctitis, GI fistula, obstruction, weight loss, haemorrhage and mucositis); GU toxicities (frequency/urgency, cystitis, incontinence, bladder spasm, urinary retention, urinary tract obstruction, nocturia and haematuria); other pre-specific recorded on the Case Report Forms were fatigue, febrile neutropenia, chest pain and Palmar-plantar syndrome.

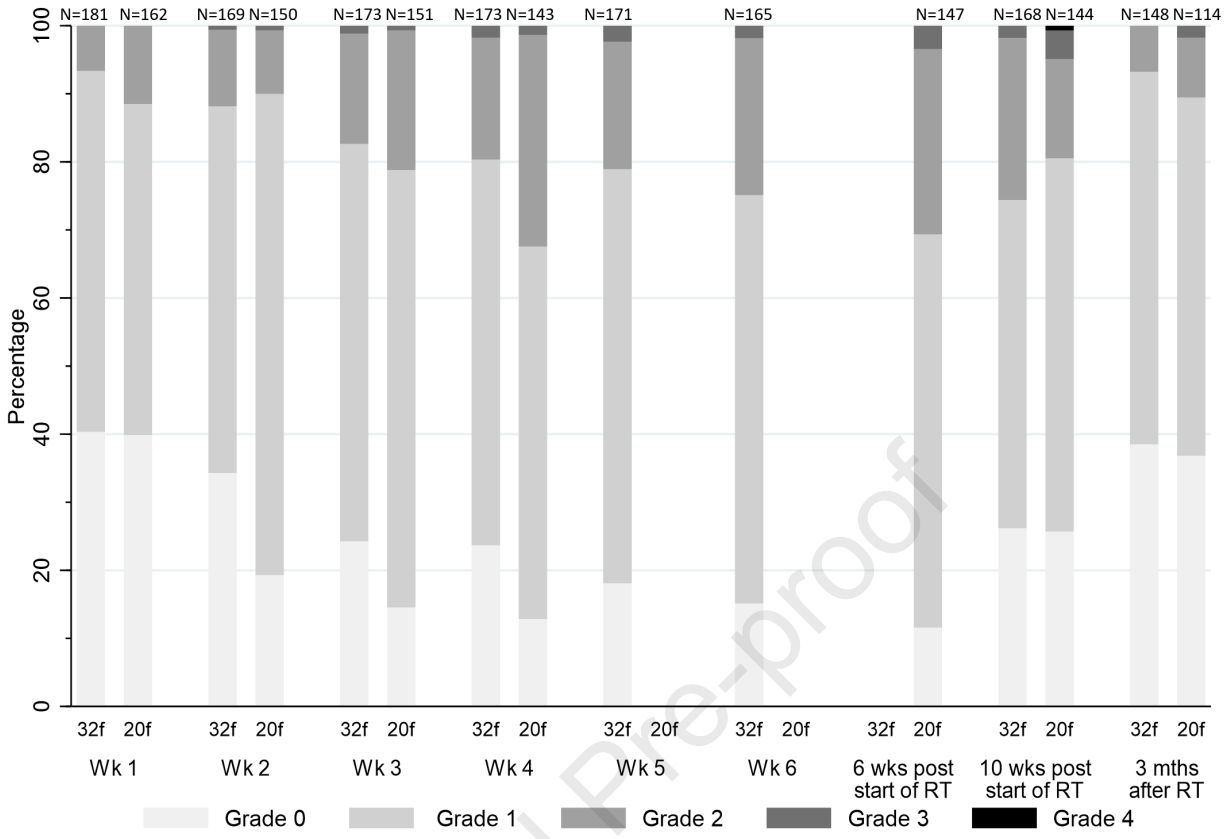
Table 3: Treatment emergent individual gastrointestinal toxicities with >10% grade 2+

20f		5FU/MMC (N=44)		GEM (N=40)		CON (n=27)		G2+ p-value	RT alone (n= 49)	
	Grade	N	%	N	%	N	%		N	%
Anorexia	0/1	40	81	35	87	23	85	0.755	42	86
	2+	4	9	5	13	4	15		0	0
	Missing	0	0	0	0	0	0		7	14
Nausea	0/1	41	93	38	95	20	74	0.022	40	82
	2+	3	7	2	5	7	26		2	4
	Missing	0	0	0	0	0	0		7	14
Vomiting	0/1	44	100	40	100	24	89	0.013	42	76
	2+	0	0	0	0	3	11		0	0
	Missing	0	0	0	0	0	0		7	14
Constipation	0/1	40	91	36	89	27	100	0.267	41	84
	2+	4	9	4	11	0	0		1	2
	Missing	0	0	0	0	0	0		7	14
Diarrhoea	0/1	39	89	24	60	24	89	0.003	38	78
	2+	5	11	16	40	3	11		4	8
	Missing	0	0	0	0	0	0		7	14
Abdominal pain	0/1	39	89	37	92	27	100	0.212	41	84
	2+	5	11	3	8	0	0		1	2
	Missing	0	0	0	0	0	0		7	14
Proctitis	0/1	39	88	29	72	26	96	0.027	41	84
	2+	5	11	11	28	1	4		1	2
	Missing	0	0	0	0	0	0		7	14

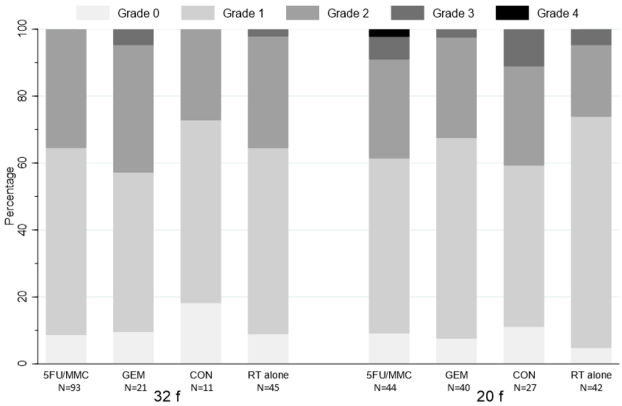
32f		5FU/MMC (N=94)		GEM (N=22)		CON (n=11)		G2+ p-value	RT alone (n= 52)	
	Grade	N	%	N	%	N	%		N	%
Anorexia	0/1	90	96	17	77	9	82	0.011	43	67
	2+	3	3	4	18	2	18		2	4
	Missing	1	1	1	5	0	0		7	13
Nausea	0/1	89	95	19	86	9	82	0.086	44	85
	2+	4	4	2	9	2	18		1	2
	Missing	1	1	1	5	0	0		7	13
Diarrhoea	0/1	85	91	16	72	10	81	0.091	37	71
	2+	8	8	5	23	1	9		8	16
	Missing	1	1	1	5	0	0		7	13

Table 4: Descriptive statistics for the KHQ Symptom Severity Scale (0-30) by concomitant therapy, fractionation cohort and acute time point assessed

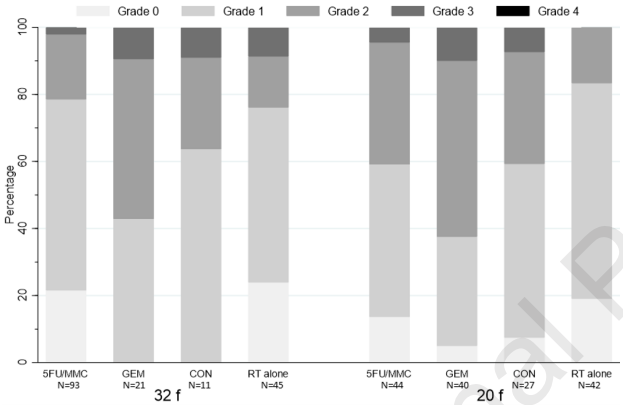
KHQ Symptom severity scale	5FU/MMC	GEM	CON	RT alone
	N Median (IQR)	N Median (IQR)	N Median (IQR)	N Median (IQR)
20f				
Pre-radiotherapy	39 6.0 (4.0, 9.0)	36 4.0 (2.5, 6.0)	26 5.5 (3.0, 9.0)	31 6.0 (3.0, 13.0)
End of Treatment	36 6.0 (4.0, 9.0)	36 5.5 (3.5, 10.0)	21 8.0 (6.0, 10.0)	17 7.0 (6.0, 8.0)
3months post-radiotherapy	30 3.5 (2.0, 8.0)	32 4.0 (1.0, 7.0)	12 5.0 (4.0, 8.0)	24 6.0 (2.0, 8.5)
32f				
Pre-radiotherapy	73 4.0 (2.0, 9.0)	17 6.0 (3.0, 9.0)	10 6.0 (4.0, 14.0)	37 5.0 (3.0, 9.0)
End of Treatment	65 6.0 (4.0, 10.0)	10 8.0 (6.0, 10.0)	8 7.5 (3.0, 10.0)	28 7.0 (3.5, 10.0)
3months post-radiotherapy	66 4.0 (2.0, 7.0)	13 6.0 (4.0, 9.0)	8 11.0 (3.0, 16.5)	30 5.0 (3.0, 10.0)



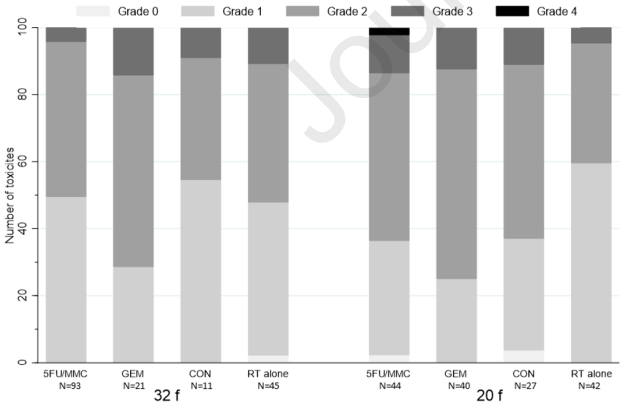
(A) Genitourinary



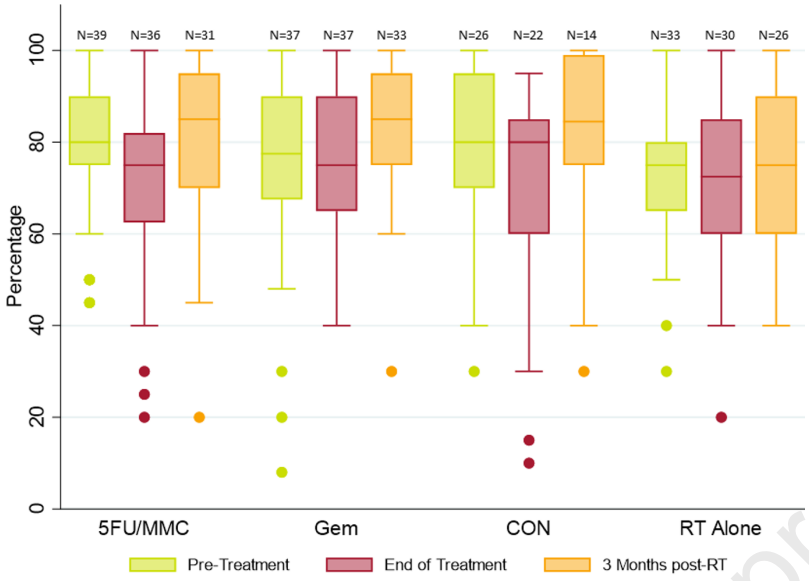
(B) Gastrointestinal



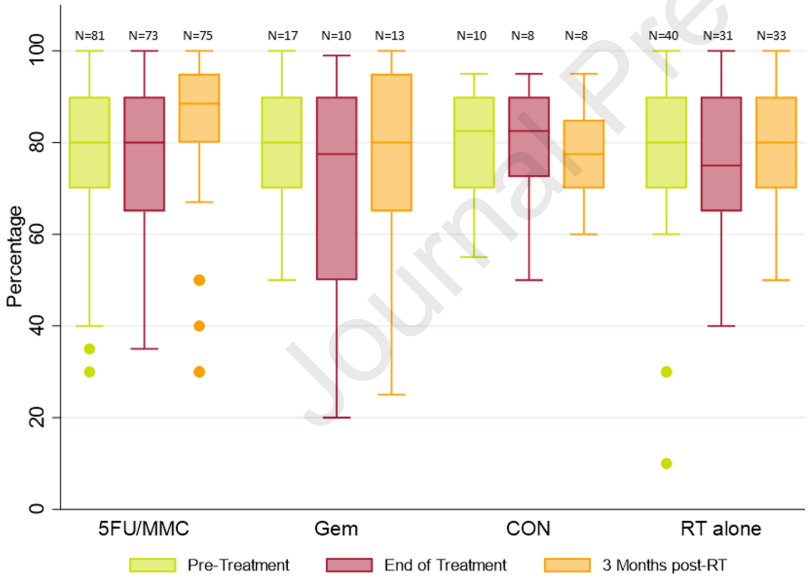
(C) Overall toxicity



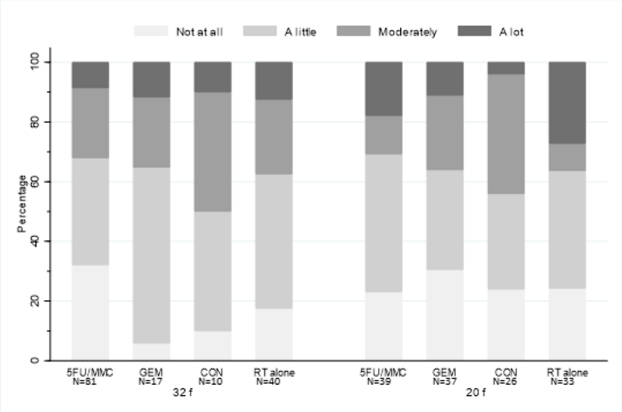
(A) 20f cohort



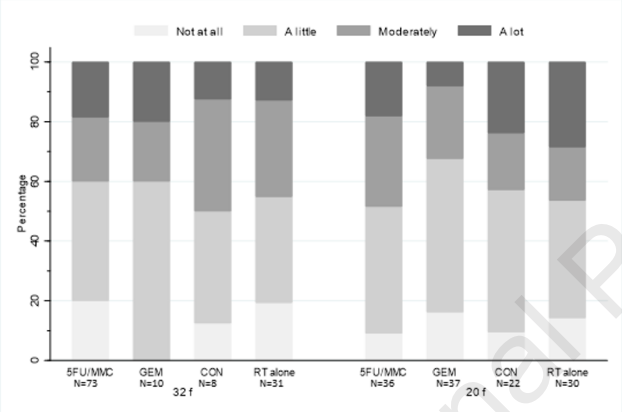
(B) 32f cohort



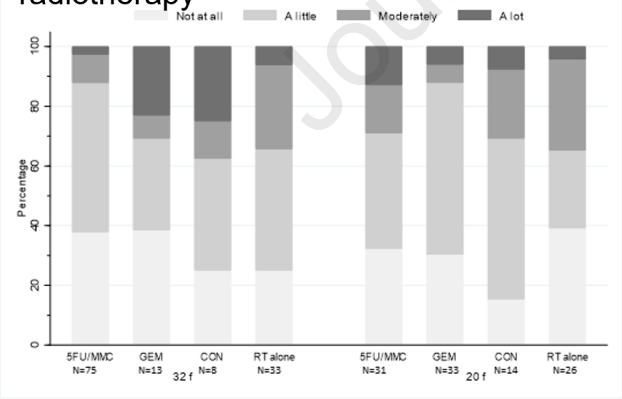
(A) Pre-radiotherapy



(B) End of radiotherapy



(C) 3 months after completing radiotherapy



Highlights

- Grade 2+ acute toxicity was common and similar for 32- and 20-fraction radiotherapy
- Observed grade 3+ acute toxicity in RAIDER was lower than reported in previous trials
- Acute toxicity following bladder radiotherapy returns to baseline levels by 3 months
- The acute toxicity profile varied by concomitant radiosensitising treatment
- Bowel (but not urinary) toxicity appears higher in those receiving gemcitabine

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Robert Huddart reports a relationship with Roche that includes: consulting or advisory, funding grants, and non-financial support. Robert Huddart reports a relationship with Merck Sharp & Dohme UK Ltd that includes: consulting or advisory and funding grants. Robert Huddart reports a relationship with Elekta that includes: funding grants. Robert Huddart reports a relationship with Janssen Pharmaceuticals Inc that includes: consulting or advisory. Robert Huddart reports a relationship with Nektar Therapeutics that includes: consulting or advisory. Robert Huddart reports a relationship with Astellas Pharma Inc that includes: consulting or advisory. Shaista Hafeez reports a relationship with Elekta AB that includes: non-financial support. Shaista Hafeez reports a relationship with Roche that includes: consulting or advisory and non-financial support. Shaista Hafeez reports a relationship with Merck Sharp & Dohme UK Ltd that includes: non-financial support. Ananya Choudhury reports a relationship with Elekta Ltd that includes: consulting or advisory and funding grants. Ananya Choudhury reports a relationship with Roche that includes: consulting or advisory. Ananya Choudhury reports a relationship with Bayer AG that includes: consulting or advisory. Ananya Choudhury reports a relationship with Janssen Pharmaceuticals Inc that includes: consulting or advisory. Emma Hall reports a relationship with Accuray Inc that includes: funding grants. Emma Hall reports a relationship with Varian Medical Systems Inc that includes: funding grants.