Title: Patient reported quality of life outcomes in patients treated for muscle invasive bladder cancer with radiotherapy +/- chemotherapy in the BC2001 phase III randomised controlled trial

Brief title: Quality of life after bladder preserving treatment for MIBC

Authors:

Robert Huddart*[a] PhD, Emma Hall*[a] PhD, Rebecca Lewis[a] BSc, Nuria Porta[a] PhD, Malcolm Crundwell[b] MD, Peter J Jenkins[c] PhD, Christine Rawlings[d] MSc, Jean Tremlett[e] MSc, Leila Campani[f] BSc, Carey Hendron[f] MSc, Syed A Hussain**[g] MD, Nicholas D James**[f,h] PhD on behalf of the BC2001 Investigators

*RH, EH Joint first authors

** SH, NJ joint last authors

TOTAL AUTHOR COUNT: 12

a. The Institute of Cancer Research, London, UK
b. Royal Devon & Exeter NHS Foundation Trust, Exeter, UK
c. Gloucestershire Oncology Centre, Cheltenham General Hospital, Cheltenham, UK;
d. Torbay and South Devon NHS Foundation Trust, Torquay, UK;
e. Brighton & Sussex University Hospitals NHS Trust, Brighton, UK;
f. University of Birmingham, Birmingham, UK
g. University of Sheffield, Academic unit of Oncology, Department of Oncology and metabolism, Medical School, Sheffield, UK;

h. University Hospitals Birmingham NHS Foundation Trust, UK

Corresponding author:

Professor Robert Huddart

The Institute of Cancer Research, London, SM2 5NG, UK

Tel: 0208 661 3457

Fax: 02086613142

Robert.Huddart@icr.ac.uk

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Abstract

Background

BC2001, the largest randomised trial of bladder sparing treatment for muscle invasive bladder cancer, demonstrated improvement of local control and bladder cancer specific survival from the addition of concomitant 5-fluorouracil and mitomycin C to radiotherapy.

Objective

To determine the impact of treatment on the health related quality of life (HRQoL) of BC2001 participants.

Design, setting and participants

458 UK patients with T2-T4a N0 M0 transitional cell cancer of the bladder.

Intervention

Patients were randomised to radiotherapy (178) or chemo-radiotherapy (182) (chemotherapy comparison) and/or to standard (108) or reduced high-dose volume radiotherapy (111) (radiotherapy comparison).

Outcome measurements and statistical analysis

Patients completed Functional Assessment of Cancer Therapy-Bladder (FACT-BL) questionnaires at baseline, end of treatment (EoT), 6, 12, 24, 36, 48 and 60 months (m) post-radiotherapy. The primary endpoint was change from baseline in the bladder cancer subscale (BLCS) at 12m.

Results and limitations

Data were available for 331(92%) and 204(93%) participants at baseline and 192(54%) and 114(52%) at 12m for the chemotherapy and radiotherapy

comparisons respectively. HRQoL declined at EoT (BLCS -5.06 [99% confidence intervals (CI) -6.12 to -4.00, p<0.001]; overall FACT-B TOTAL score -8.22 [-10.76 to -5.68, p<0.01]), recovering to baseline at six months and remaining similar to baseline subsequently. There was no significant difference between randomised groups at any timepoint.

Conclusions

Immediately following (chemo)radiotherapy a significant proportion of patients report declines in HRQoL which improve to baseline after six months. Two thirds of patients report stable or improved HRQoL on long-term follow up. There is no evidence of impairment in HRQoL resulting from the addition of chemotherapy.

Patient summary

Quality of life of bladder cancer patients treated with radiotherapy +/- chemotherapy deteriorates during treatment but improves to at least pre-treatment levels within six months. Adding chemotherapy to radiotherapy does not affect patient reported quality of life.

Introduction

The BC2001 trial is the largest randomised trial of radiotherapy in muscle invasive bladder cancer (MIBC) conducted to date. We previously reported that addition of chemotherapy to radiotherapy significantly improves clinical outcomes without significant increase in clinician reported toxicity and that reducing the bladder volume exposed to high dose radiotherapy does not impact disease control or clinician reported toxicity.[1,2] Here we present the five-year, patient reported, health related quality of life (HRQoL) outcomes of the trial.

There are few papers describing long-term toxicity or patient reported outcomes following bladder preservation treatment for MIBC. Previously published studies of bladder cancer patient reported outcomes, though reassuring, are limited by being retrospective in nature and there is a paucity of data from randomised controlled trials.[3-6] We therefore planned a prospective assessment of patient reported outcomes within BC2001, using the Functional Assessment of Cancer Therapy - Bladder (FACT-BL) questionnaire.[7] The main objective was to document the longitudinal quality of life experience of patients undergoing radical radiotherapy and to compare it by randomised treatment groups.

Patients and Methods

Trial design and participants

BC2001 is a phase III trial with a partial two-by-two factorial design conducted at 45 United Kingdom (UK) hospitals. Patients with localised MIBC were randomised 1:1 to receive (i) radiotherapy with (cRT) or without (RT) chemotherapy (chemotherapy comparison) and (ii) standard whole-bladder radiotherapy (stRT) or reduced high-dose volume radiotherapy (RHDVRT) with tumour boost (radiotherapy comparison)

(Supplementary Figure S1). Recruitment to both randomisations was encouraged but optional according to patient eligibility and preference. All participants received conformal radiotherapy on consecutive weekdays according to the local hospital's standard regimen (either 55Gy/20 fractions or 64Gy/32 fractions). Patients randomised to chemotherapy received intravenous mitomycin C (MMC) (12mg/m^2) on day one of radiotherapy and continuous infusion 5-fluorouracil (5-FU) 500mg/m^2/24 hours for five days during radiotherapy fractions 1-5 &16-20. Full details have been previously reported.[1,2]

The trial was registered (ISRCTN68324339), approved by the North West Multicentre Research Ethics Committee (00/8/075), sponsored by the University of Birmingham and conducted in accordance with the principles of good clinical practice. Participants all provided written informed consent. The Cancer Research UK Clinical Trials Unit at the University of Birmingham and the Clinical Trials and Statistics Unit at the Institute of Cancer Research (ICR-CTSU; London, UK) shared study coordination and data management. ICR-CTSU conducted central statistical data monitoring and statistical analyses.

Health related quality of life study

All BC2001 participants were asked to consent to the optional HRQoL study. Questionnaires were completed in clinic on paper at baseline, end of treatment, six months from end of treatment and annually to five years.

The Functional Assessment of Cancer Therapy - Bladder (FACT-BL) questionnaire incorporates 39 items with five point Likert scale answers and five subscales: physical well-being (PWB), social well-being (SWB), emotional well-being (EWB), functional well-being (FWB), bladder cancer subscale (BLCS).[7] For questions

phrased negatively, scoring was reversed so high scores are indicative of better HRQoL throughout. Scoring and management of missing items were dealt with in accordance with the FACIT Administration and Scoring Guidelines.[8] See Supplementary Appendix 1 for further details.

Outcomes

The primary endpoint for both the chemotherapy and radiotherapy comparisons was the change from baseline score in BLCS. The primary timepoint of interest was one year.

Secondary endpoints included changes from baseline in (i) FACT-BL total score (TOTAL), generated as the sum of all items in the FACT-BL questionnaire; (ii) the separate component subscales (PWB, SWB, EWB, FWB); (iii) the Trial Outcome Index (TOI) score (sum of PWB, FWB and BLCS subscales); and (iv) specific items within the BLCS relating to urinary function, bowel function and male sexual function.

Two exploratory analyses were conducted: firstly, we explored the impact of treatment on HRQoL at an individual level, through a comparison of the percentage of participants experiencing a minimal clinically significant positive or negative change from baseline. This was defined as a three-point change in BLCS, a five-point change in TOI and seven-point change in TOTAL score, thresholds based on previous work on FACT questionnaires.[9-11] Secondly, the effect of pre-treatment with neo-adjuvant chemotherapy was also explored in a non-randomised comparison between patients pre-treated vs not pre-treated.

Statistical Analysis

BC2001 was powered around the primary endpoint of loco-regional control; HRQoL analyses were prospectively planned as a sub-study of the trial.

Analyses were performed for 1) the overall trial population 2) the chemotherapy comparison population, and 3) the radiotherapy comparison population. All analyses were performed on the intention to treat population, with sensitivity analyses to assess robustness of the results. All analyses were done with Stata version 13.1.[12]

For each randomised comparison, ANCOVA regression models were used to formally test for a difference in mean change from baseline, after adjusting for alternate randomisation, radiotherapy fractionation and baseline score. Only patients with paired baseline and follow-up data were included in the analysis. A significance level of 5% was used to test for the principal outcome measure (difference in BLCS mean between treatment groups within each comparison at one year, with 95% CI for the estimated difference). Interaction between the two randomised interventions was tested using an ANCOVA model fitted in patients included in both randomisations. A 1% significance level (and corresponding 99% CI) was used for all other endpoints to make allowance for multiplicity in testing.

See Supplementary Appendix 1 for further details on study methods.

Results

Patients

Between August 2001 and April 2008, 458 BC2001 participants were recruited from 45 UK centres; 452 completed at least one HRQoL assessment. Of these, 216 patients entered the radiotherapy comparison (107 sRT/109 RHDVRT) and 355 patients entered the chemotherapy comparison (179 cRT/176 RT). 119 patients entered both comparisons. At one year, 114 (53%) and 192 (54%) patients in the radiotherapy and chemotherapy comparisons, respectively, provided HRQoL data; this represented 68% and 70% of expected questionnaires (Supplementary Table S1). Amongst patients without 1-year or later HRQoL questionnaires, 55% had an invasive recurrence or cystectomy before 12 months, while for patients with completed 1-year questionnaires, only 11% had had an invasive event before 12 months (Supplementary Figure S2). Baseline features of patients with and without HRQoL data at 1 year are given in Supplementary Table S2. Patients without HRQoL data were similar to those with data apart from a greater frequency of residual mass and incomplete resection.

Change from baseline scores

Overall trial population

Table 1 describes the median and quartile scores for each subscale in the FACT-BL at baseline, end of treatment, one year and five years.

For the whole BC2001 population, a fall in HRQoL is seen immediately following radiotherapy in the majority of domains (Figure 1 and Supplementary Figure S3). For the primary endpoint, there is a mean change in BLCS score of -5.06 (99% CI: -6.12 to -4.00; $p<0.001$); for the TOTAL score a mean change of -8.22 (99% CI: -10.76 to -

5.68; p<0.001); for the TOI score, the mean change is -9.34% (99% CI: -11.47 to -7.20; p<0.001). By six months after radiotherapy, HRQoL scores have improved and returned to baseline levels.

By one year all subscales have recovered to at least baseline levels (p>0.01), and this is maintained or improved on subsequent follow-up. The EWB score significantly improves above baseline at the end of treatment, with a mean change of 1.14 (99% CI: 0.68 to 1.61, p<0.001), and remains above baseline throughout follow-up.

Chemotherapy comparison

The primary endpoint for the chemotherapy comparison is shown in Figure 2(A). Table 2 provides the treatment differences at one year for change from baseline in all subscales. For BLCS, the adjusted difference between cRT and RT at one year was 0.18 (95% CI: -1.60 to 1.96, p=0.8). No significant differences were found in any subscale or at any timepoint (Supplementary Figure S4).

Radiotherapy comparison

For the radiotherapy comparison reported in Figure 2(B) and Table 2, the difference between stRT and RHDVRT at one year in change from baseline BLCS score is 2.0 (95% CI: -0.31 to 4.33, p=0.089). No significant differences were found in any subscale or at any timepoint (Supplementary Figure S5).

For patients included in both randomisations, there was no evidence of an interaction effect between the two randomised interventions in either BLCS (p=0.3), TOTAL (p=0.3) or TOI (p=0.4) change at one year.

Pre-treated patients

No detrimental impact on HRQoL was observed in those patients who had received neo-adjuvant chemotherapy prior to trial entry (Supplementary Tables S3-S4 and

Figure S6). Baseline scores were similar between the patients who received neo-adjuvant and those who did not. There was no statistically significant difference in change from baseline BLCS (0.93; 99% CI: -1.39 to 3.25, p=0.3) or TOTAL (6.17; 99% CI: -0.50, 12.85, p=0.017) subscales though the estimated difference in the TOTAL score favoured patients receiving neo-adjuvant chemotherapy compared to those with no prior therapy.

Individual items on the bladder cancer subscale

At one year, the percentage of participants stating they had “quite a bit” or “very much” trouble controlling their urine was 12% (baseline 15%); urinating more than usual was 25% (baseline 34%); not having control of their bowels was 14% (baseline 12%); and having diarrhoea was 2.1% (baseline 1.2%). Amongst males, the percentage being able to have or maintain an erection (“quite a bit” or “very much”) was 20% (baseline 24%). Figure 3 reports the percentages for all items and all timepoints in the overall population. Similar proportions were found in the treatment arms of the randomised comparisons (Supplementary Figure S7).

Impact of treatment on individuals

As expected from the mean scores, in the overall population a substantial proportion of participants reported worsening of HRQoL at the end of treatment (Figure 4A). On the BLCS score, 59% reported worsening of symptoms at the end of treatment, similar to the pattern seen with the TOI score, while 49% reported worsening symptoms in the TOTAL score. Improved HRQoL was reported by 13%, 15% and 17% participants on the BLCS, TOI and TOTAL scores respectively.

By six months the proportion reporting worsening had fallen to 35%, 30% and 29% in the BLCS, TOI and TOTAL scores respectively, with improvement reported in 29%,

34% and 33% respectively. On further follow-up, these relative proportions remain fairly constant, with between 32% to 36% of patients reporting worsening on the BLCS score (Figure 4B), 28% to 36% on the TOI score, and 25% to 30% on the TOTAL score, with similar numbers reporting improvement.

No significant difference was found between randomised groups within each comparison in the proportions of patients reporting clinically relevant improvement/worsening on any scale or at any timepoint (Supplementary Tables S5-S10).

For all endpoints, the pre-planned sensitivity analyses confirmed the results reported (results not shown).

Discussion

We report the largest study of patient reported outcomes after bladder preserving treatment for muscle invasive bladder cancer. A key strength is that this is, to our knowledge, the only such data prospectively collected within a randomised controlled trial. A drawback, however, is that not all patients returned HRQoL questionnaires at the key defined timepoint, most frequently due to prior recurrence or cystectomy, so it is likely the impact of recurrence is not fully captured in these data. However approximately 70% of patients did return questionnaires at one year, which is similar to the 77% return rate in the cohort HRQoL study of Mak et al[13]. Response rates declined further over time though ~60% of expected questionaires were received at 5 years. It is likely that co-morbidities and competing risks (including death) would contribute to non-response in this elderly population.

The results as expected show an early reduction in HRQoL at the end of treatment consistent with treatment related toxicity; by six months this has largely improved so

that mean scores return to baseline. The addition of chemotherapy to radiotherapy did not affect the reported HRQoL outcomes, providing evidence that the large beneficial effect on loco-regional control with chemo-radiotherapy using 5FU and mitomycin C is achieved without an appreciable adverse impact on HRQoL. Likewise there is no evidence that neo-adjuvant chemotherapy impairs HRQoL. If anything, there was a trend towards improved HRQoL in these patients, though as baseline is taken after neo-adjuvant treatment, this may have impaired baseline scores and improvement could represent recovery of chemotherapy related toxicity. Alternatively, the debulking effect of the prior chemotherapy may have left a better functioning bladder than one that has recently undergone TURBT, leaving better radiation tolerance.

These results are in line with the limited previous data available. Lagrange et al investigated HRQoL using the EORTC QLQ-C30 tool in 51 patients in a phase II non-randomised trial of 5FU and cisplatin given during whole pelvic radiotherapy.[14] Similarly to our study, they demonstrated a fall in HRQoL immediately after treatment which slightly improved above baseline across subscales after six months. This is supported by other smaller studies that report long-term HRQoL outcomes similar to population averages.[4-6,15] The exception to this was emotional wellbeing which improved at EOT and beyond perhaps emphasizing the positive psychological impact of receiving radical treatment and the support of care providers despite potential side effects.

Analysis of clinically relevant changes in HRQoL on an individual basis perhaps provides a richer understanding of the impact of treatment on patients. It is clear from this analysis that the majority of patients experience some deterioration in symptoms at the end of radiotherapy, though many subsequently recover and a

substantial proportion have HRQoL similar to, or better than, baseline over subsequent follow-up. The observation of a mean overall score similar to baseline is thus achieved as roughly similar numbers of patients have improvement and deterioration in quality of life. Similar findings have been shown in previous studies. For example, Zietman et al reported in a retrospective study of 48 patients treated with bladder conserving therapy that patients had similar or higher than population average scores[4]. However, seven did have reduced bladder compliance, two reported bladder hypersensitivity and seven were distressed by bowel urgency. Likewise, Henningsohn et al reported that 74% of patients had 'little or no' urinary distress in a cohort study of 58 patients post radiotherapy.[3] In this study, 32% of radiotherapy patients had some gastrointestinal symptoms compared to 9% of population controls. Lagrange et al again reported that over 70% had 'satisfactory' urinary function after six months; a similar proportion to our study.[14]

We can thus conclude from these data that though most patients can expect satisfactory health related quality of life after radiotherapy; a subgroup will have a decline. Understanding the drivers of this deterioration should be a priority in future HRQoL research in bladder cancer. Can those patients likely to experience a persistent decline in HRQoL be predicted from baseline characteristics, tumour related characteristics, prior therapies (e.g. BCG for NMIBC) or even their baseline germ line genetics? Recently a number of common genetic variants have been associated with toxicity in prostate and breast radiotherapy;[16] a study in bladder cancer patients would be of interest. We also need to consider if there are any interventions that can be undertaken to moderate the impact of radiotherapy treatment on HRQoL. For instance there are limited data suggesting that instillation of hyaluronic acid may reduce radiation cystitis in gynaecological patients.[17]

It is disappointing that we could not demonstrate any evidence of symptomatic or HRQoL improvement in the group of patients treated with a modified radiotherapy volume. This treatment approach was developed on the basis that restricting the high dose volume may reduce bladder shrinkage/fibrosis that is sometimes seen with whole bladder radiotherapy, supported by retrospective studies suggesting that global bladder radiation tolerance was less than focal tolerance.[18] Our study of this issue was undermined by early closure of the radiotherapy comparison randomisation due to slow recruitment and a substantial number of protocol violations resulting in low power to assess treatment effects. Additionally this study was performed in the era before intensity modulated and image guided radiotherapy, with the use of large margins around the tumour so the amount of bladder sparing will have been limited. Based on a successful pilot study[19] we are currently revisiting this issue in conjunction with dose escalation in a randomised phase II trial (RAIDER ISRCTN26779187).

Chemo-radiotherapy is a widely used bladder conserving alternative to radical cystectomy. This study does not directly address the relative HRQoL benefits of surgery and (chemo)-radiotherapy. Indeed given the very different treatment modalities making such a comparison is challenging, for instance, a patient who has a radical cystectomy and utero-ileal bypass does not pass urine and therefore reporting of urinary symptoms has a very different interpretation. Several retrospective or cohort studies suggest that HRQoL after radiotherapy is at least equivalent and possibly superior to that following cystectomy.[5,20-24]. The largest of these is a cohort study of 173 survivors of bladder cancer 7-9 years after cystectomy or chemo-radiotherapy reported better HRQoL in most domains after chemo-radiotherapy, though this study is limited by lack of baseline data. [13] One aspect of

this study was the better sexual function after chemo-radiotherapy, which is supported by our data that show at worst a modest decline in sexual function after radiotherapy with or without chemotherapy. We previously published a small randomised feasibility study of selective bladder preservation and radical cystectomy (SPARE).[15] The patients who had radiotherapy had similar HRQoL scores to those reported here, which, although not statistically significant, tended to be higher than those achieved by patients having cystectomy.

Conclusions

This study shows that overall, after an initial fall immediately post treatment HRQoL recovers to baseline levels and is maintained at this level out to five years for bladder cancer patients treated with radiotherapy. Adding concomitant chemotherapy or using neoadjuvant chemotherapy has no significant impact on HRQoL, further supporting the routine use of 5FU and mitomycin C in this setting. Although the majority of patients maintain HRQoL similar to or better than baseline, around one third experience some persistent detriment. This has to be considered in the context of the significant quality of life impact of the alternative treatment of cystectomy.

Acknowledgements

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FIGURES

Figure 1. Mean change from baseline (with 99% confidence intervals) in FACT-BL BLCS, TOI and TOTAL scores – overall population

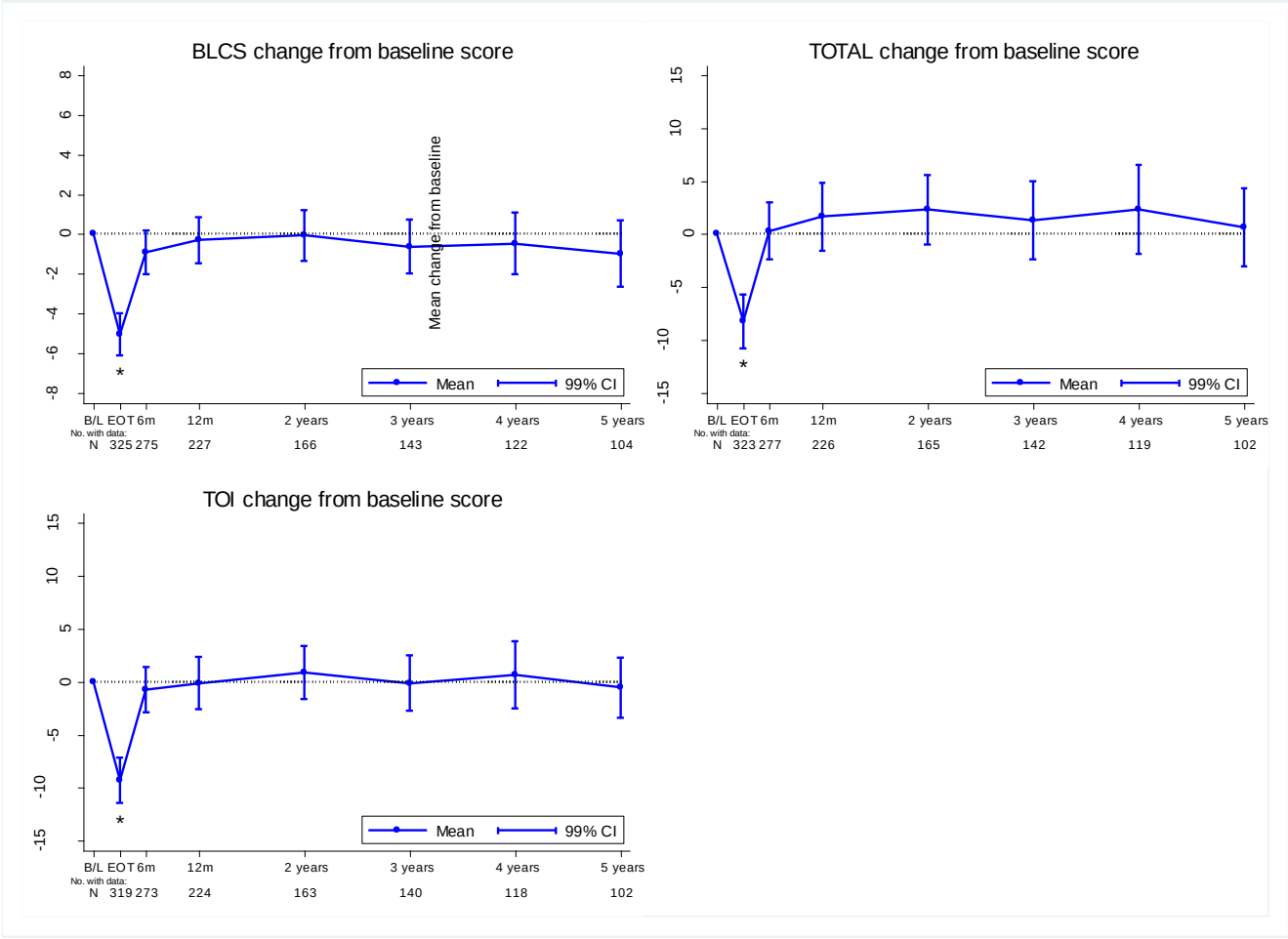
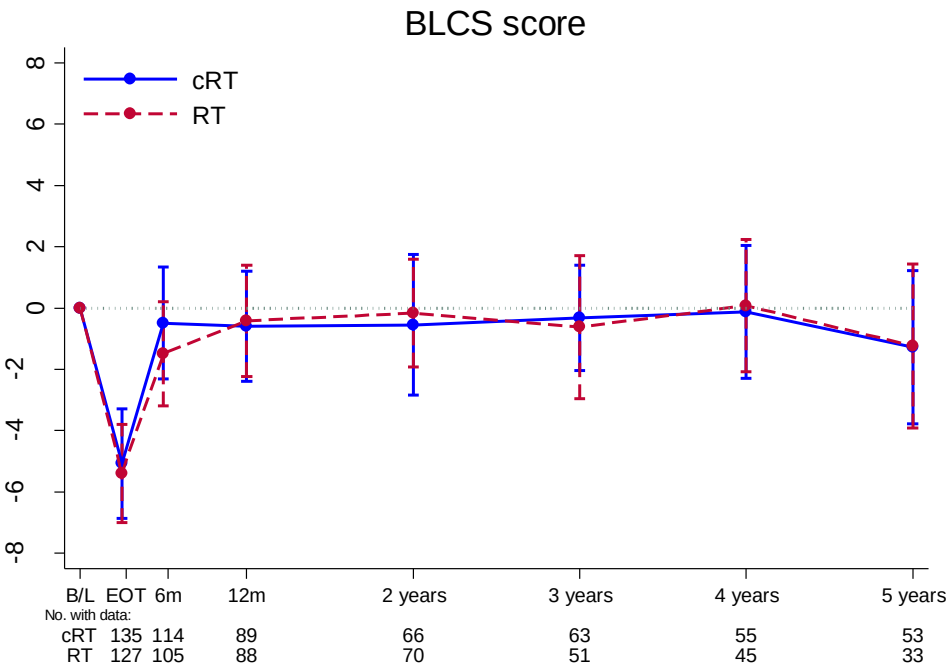


Figure 2. Mean change from baseline (with 99% confidence intervals) in BLCS score in the treatment comparisons

(A) CT comparison



(B) RT comparison

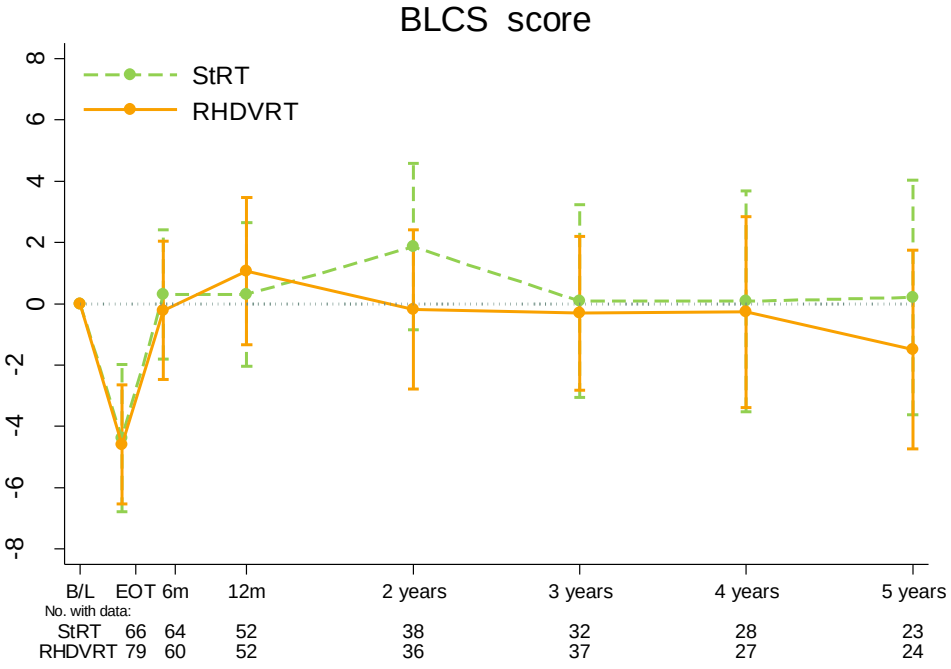


Figure 3. Individual items in the bladder cancer subscale of FACT-BL

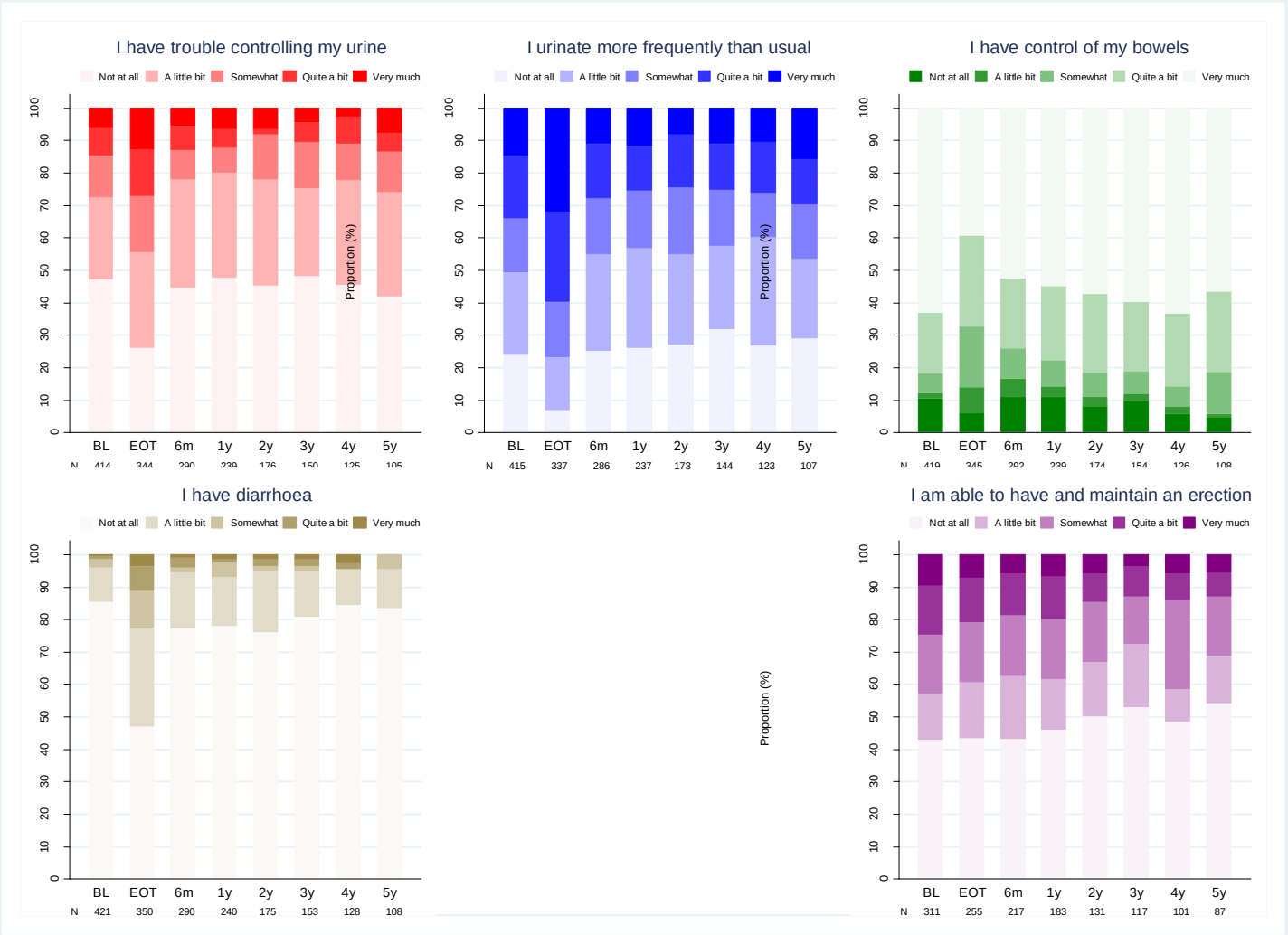
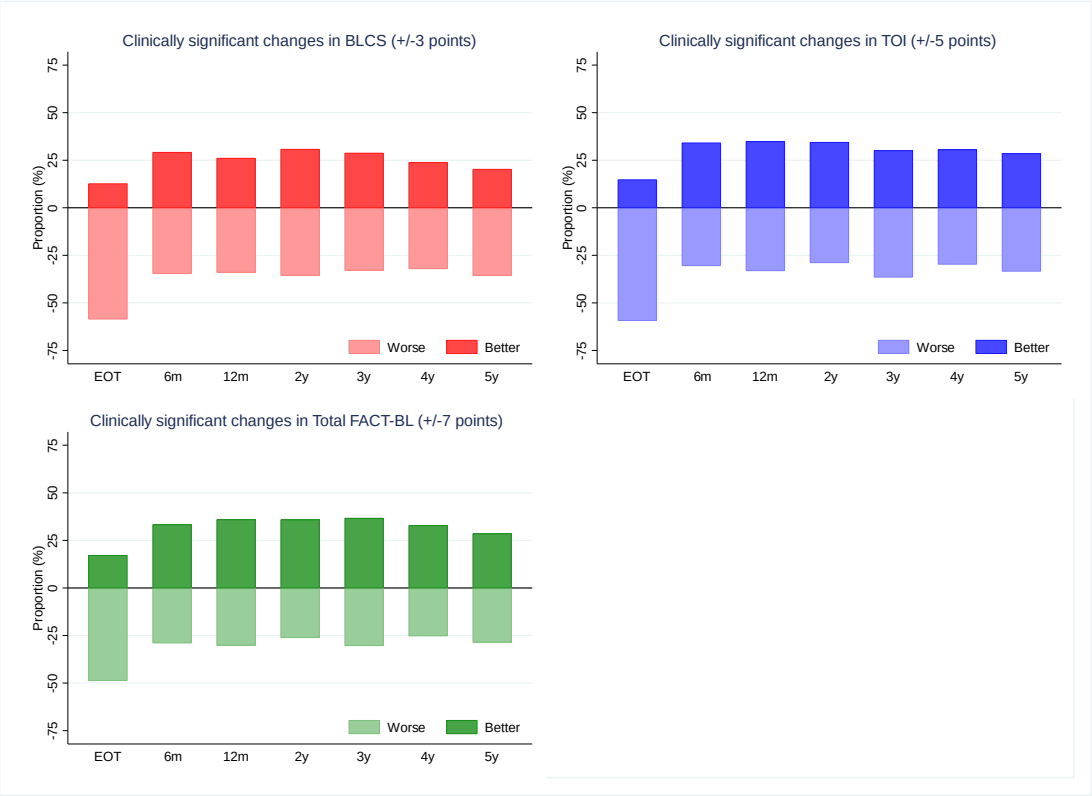


Figure 4. Impact of treatment on individuals

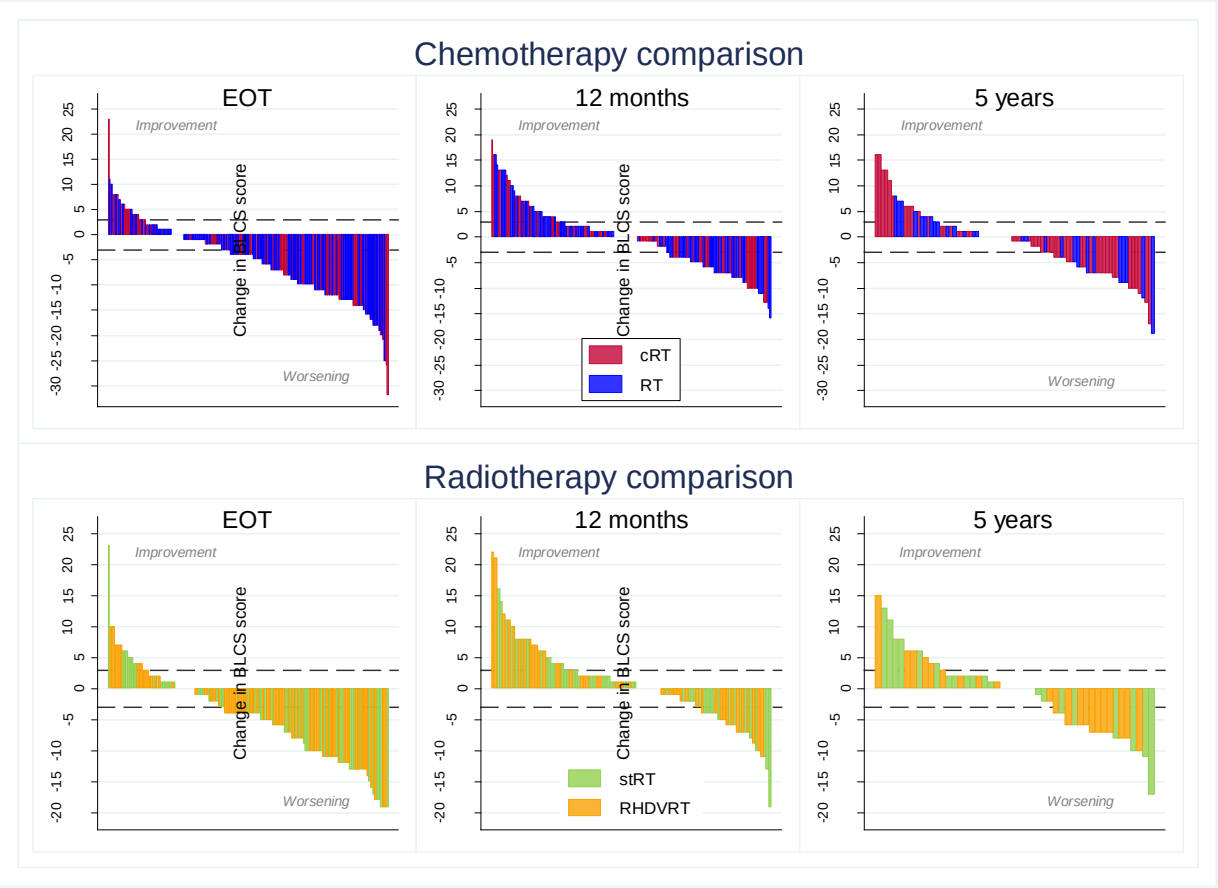
(A) Proportion of patients with clinically significant changes in BLCS, TOI and TOTAL - overall population

Clinically significant changes are defined as changes from baseline above (better) or below (worse) the subscale threshold (BLCS +/-3 points, TOI +/-5 points, TOTAL +/- 7 points) at each timepoint. Patients without clinically significant changes are not shown in the figure.



(B) Waterfall plot of the absolute change in BLCS score from baseline at each time point, per randomised comparison

Each bar represents a patient. Dashed line - clinical significance (±3)



TABLES

Table 1. General FACT-BL scores per subscale and timepoint – overall population

	Baseline			EOT			1 year			5 years		
	N	Median	Q1-Q3	N	Median	Q1-Q3	N	Median	Q1-Q3	N	Median	Q1-Q3
BLCS	421	34	29-39	349	29	24-35	242	35	30-37	109	34	31-38
TOTAL	421	124	108-133	349	115	97-130	240	126	113-137	107	127	116-136
TOI	418	80	70-88	346	71	57-83	240	82	72-90	107	83	74-89
EWB	420	20	17-22	352	21	19-23	242	21	19-23	108	22	20-24
FWB	421	21	17-25	350	19	14-24	242	22	17-26	109	22	18-26
SWB	415	25	22-28	345	25	21-27	242	25	21-28	105	24	20-27
PWB	423	25	22-27	351	24	20-26	242	26	23-27	108	26	24-27

Q1: 1st quartile (25% percentile), Q3: 3rd quartile (75% percentile)

BLCS= Bladder cancer subscale; TOI=Trial Outcome Index; EWB=Emotional well-being; FWB= Functional well-being;

SWB=Social well-being; PWB= Physical well-being.

Table 2. Change from baseline at one year for the randomised comparisons

	cRT			RT			Difference cRT-RT§		
1 year	N	Mean¥	99% CI	N	Mean¥	99% CI	Mean†	99% CI*	p-value
BLCS	89	-0.59	-2.42, 1.24	88	-0.42	-2.27, 1.44	0.18	-1.60, 1.96*	0.8
TOTAL	89	0.67	-4.56, 5.89	86	2.67	-2.46, 7.80	-1.79	-8.3, 4.72	0.5
TOI	88	-0.50	-4.45, 3.45	86	0.94	-3.08, 4.96	-1.07	-6.21, 4.07	0.6
EWB	91	0.90	-0.26, 2.06	88	1.48	0.46, 2.51	-0.47	-1.68, 0.75	0.3
FWB	89	0.25	-1.54, 2.04	88	0.99	-0.69, 2.67	-0.67	-2.77, 1.44	0.4
SWB	88	-0.16	-1.80, 1.47	88	0.22	-1.12, 1.55	-0.30	-2.07, 1.48	0.7
PWB	91	-0.11	-1.33, 1.10	88	0.38	-0.89, 1.66	-0.54	-2.14, 1.07	0.4
	stRT			RHDVRT			Difference stRT-RHDVRT§		
	N	Mean	99% CI	N	Mean	99% CI	Mean	99% CI*	p-value
BLCS	52	0.31	-2.13, 2.74	52	1.06	-1.43, 3.55	2.01	-0.31, 4.33*	0.089
TOTAL	53	2.09	-5.58, 9.75	53	5.71	-0.66, 12.07	6.29	-2.54, 15.12	0.064
TOI	52	0.01	-5.96, 5.98	52	1.79	-2.79, 6.38	4.05	-2.75, 10.85	0.12
EWB	54	1.27	-0.22, 2.76	52	1.98	0.78, 3.18	0.86	-0.52, 2.24	0.11
FWB	53	-0.12	-3.19, 2.94	53	0.26	-1.61, 2.14	1.21	-1.98, 4.39	0.3
SWB	53	0.21	-2.34, 2.76	51	0.41	-1.33, 2.16	1.21	-1.60, 4.02	0.3
PWB	54	-0.19	-2.13, 1.75	53	0.69	-0.54, 1.91	1.16	-0.84, 3.16	0.13

¥ Mean change from baseline at 1 year, within each group

§Positive differences favour experimental group (cRT or RHDVRT, respectively)

†Mean difference between groups, computed by ANCOVA and adjusted by alternate randomisation, radiotherapy fractionation schedule and baseline score.

*95% CI for comparison of primary endpoint change in BLCS at one year

BLCS= Bladder cancer subscale; TOI=Trial Outcome Index; EWB=Emotional well-being; FWB= Functional well-being; SWB=Social well-being; PWB= Physical well-being.

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