Outcomes in patients with muscle-invasive bladder cancer treated with neoadjuvant chemotherapy followed by (chemo) radiotherapy in the BC2001 trial

Running title: Neoadjuvant chemotherapy in muscle-invasive bladder cancer.

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Abstract:

Background: BC2001 demonstrated improved local control with the addition of chemotherapy to radiotherapy in 360 patients with muscle-invasive bladder cancer.

Objective: To establish whether such benefit remained in BC2001 patients who received prior neoadjuvant chemotherapy.

Design, setting and participants: 117 patients (33%) received neoadjuvant chemotherapy and were randomised to radiotherapy with (48%) or without (52%) concomitant chemotherapy. Patients were recruited between August 2001 and April 2008 from 28 UK centres.

Intervention: Platinum-based neoadjuvant chemotherapy, followed by radiotherapy with (cRT) or without (RT) synchronous 5-fluorouracil and mitomycin-C.

Outcome measures and statistical analysis: Toxicity, loco-regional control (LRC), overall survival (OS) and quality of life (QoL).

Results and limitations: 74% patients received gemcitabine plus cisplatin or carboplatin (GC). Compliance rates with full dose radiotherapy were cRT 93% and RT 92%. An excess of grade 3 or above toxicities while on (chemo)radiation occurred in cRT 33% vs RT 22%, although non statistically significant (p=0.16). With 110 months median follow-up for survival (IQR 96-123), cRT showed improved LRC though not statistically significant (adjusted hazard ratio aHR = 0.64, 95CI% 0.33-1.23, p = 0.18). No differences in OS (aHR = 0.95, 95CI% 0.57-1.57, p = 0.8) were observed. No significant detriment in QoL was observed between cRT and RT in this subgroup of patients.

Conclusions: Neoadjuvant chemotherapy does not compromise the delivery of radical curative treatment. Although underpowered due to small sample size, the

benefit of chemoradiotherapy to improve local control in this group of patients receiving neoadjuvant chemotherapy is consistent with that observed in the main trial. Although a non-significant excess of toxicity was observed, there was no evidence of impaired QoL.

Patient Summary: Chemotherapy before radical chemo(radiotherapy) is feasible and well tolerated.

Introduction

Worldwide, approximately 550,000 people are diagnosed with bladder cancer each year and 200,000 patients die of the disease[1]. Management for muscle-invasive bladder cancer (MIBC) is either radical cystectomy and pelvic lymph node dissection (with cisplatin-based neoadjuvant chemotherapy in fit patients) or chemoradiotherapy; the latter providing a possibility of bladder preservation[2]. The BC2001 trial (CRUK/01/004) demonstrated, in patients receiving bladder preservation treatment, that chemoradiotherapy (with concomitant fluorouracil (5-FU) and mitomycin C (MMC)) was superior to radiotherapy alone in achieving local disease control[2].

While these treatments may be curative, a significant proportion of patients develop distant recurrence and will ultimately succumb to metastatic disease[3]. Several studies have explored the role of initial chemotherapy with the aim of eradicating micrometastatic disease[4]. Two large randomised trials and a meta-analysis have demonstrated an improvement in survival with the addition of neoadjuvant cisplatin-based combination chemotherapy to surgery or radiotherapy[5-7]. The use of neoadjuvant chemotherapy is recommended as a standard for patients with MIBC in national and international guidelines[8-10].

Most data on the use of neoadjuvant chemotherapy derives from patients managed by subsequent cystectomy. There is limited data on its impact in patients undergoing bladder preservation therapy. Most available data comes from a subset of patients in the EORTC/MRC trial[6] who received CMV (cisplatin, methotrexate, vinblastine), a regimen now rarely used. The small randomised trial RTOG89-03 did not show benefit of two CMV cycles before chemoradiation with cisplatin[11]. A Canadian retrospective study recently showed encouraging results for the use of neoadjuvant

gemcitabine and cisplatin before chemoradiotherapy[12] though other studies have been less supportive[13]. This report documents the toxicity, disease control outcomes, and quality of life (QoL) in the subgroup of patients randomised to a (chemo)radiation intervention in the BC2001 trial that also received neoadjuvant chemotherapy.

Patients and Methods

Study Design

BC2001 is a phase III trial with a partial 2x2 factorial design conducted at 45 UK centres. Patients with localised MIBC were randomised 1:1 to (i) the chemotherapy comparison, to receive radiotherapy with (cRT) or without (RT) synchronous chemotherapy, and could also be randomised to (ii) the radiotherapy comparison, to receive standard whole bladder radiotherapy (stRT) or reduced high dose volume radiotherapy (RHDVRT) with tumour boost. Recruitment to the double randomisation was encouraged but optional according to patient eligibility and preference. Independent randomisation via telephone used computer-generated random permuted blocks, stratifying by treating centre, planned neoadjuvant chemotherapy use and entry to one or both randomisations. Full details have been reported previously[2,14]. In this report, we describe only patients included in the chemotherapy randomisation who received neoadjuvant chemotherapy prior to the randomised intervention.

Patient eligibility and selection

Eligible patients were aged at least18 years with histologically confirmed stage T2-T4aN0M0 bladder cancer (adenocarcinoma, transitional or squamous cell carcinoma). Main inclusion criteria were: WHO performance status $\leqslant$2, leucocytes

>4.0x10^9/L, platelets >100x10^9/L, GFR >25ml/min and serum bilirubin, ALT or AST <1.5 x upper limit of normal. Main exclusions were prior malignancy, previous pelvic radiotherapy, bilateral hip replacements likely to interfere with protocol treatment, pregnancy and, inflammatory bowel disease.

Treatment

Platinum-based neoadjuvant chemotherapy was permitted but not mandatory for patients entering the trial; the treatment regime was chosen as per local practice. Following neoadjuvant chemotherapy, two radiotherapy dose/fractionation schedules were permitted (55Gy in 20 fractions(f) over 4 weeks or 64Gy in 32f over 6.5 weeks), determined by centre at study outset. Patients allocated concomitant chemotherapy also received 5-FU (500mg/m^2/24hours continuous infusion during 1-5&16-20f) and MMC (12mg/m^2 intravenous bolus dose on day 1).

Dose modifications for concomitant chemotherapy and radiotherapy were permitted; the protocol recommended reducing or omitting chemotherapy prior to interrupting radiotherapy in an effort to minimise the risk of compromising delivery of the “core” therapy.

Trial Assessments

At baseline, all patients underwent physical examination, hematologic and biochemical analyses, assessment of bladder capacity, computed tomography (CT) of the abdomen and pelvis, chest radiography or CT, and examination under anesthesia plus cystoscopic resection of tumor and biopsy.

Tumour control was assessed by physical examination, chest radiographs and cystoscopy (rigid or flexible) at 6, 9, and 12 months post-randomisation and annually thereafter for five years. Biopsy of the tumour bed and normal bladder was

mandated at 6 months and repeated if clinically indicated. CT imaging of the abdomen and pelvis was performed at 1 and 2 years post-randomisation and subsequently based on clinical indication.

Toxicities were graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2[15] throughout study treatment. Subsequent toxicity assessment was performed at 6, 9 and 12 months post-randomisation and annually thereafter up to five years according to the Radiation Therapy Oncology Group (RTOG)[16] and Late Effects of Normal Tissue (Subjective, Objective, Management) (LENT/SOM)[17,18] scales. QoL was assessed at 6 and 12 months post-randomisation and then annually to 5 years using the Functional Assessment of Cancer Therapy-Bladder cancer module (FACT-BL)[19].

Endpoints

Key outcomes in this subgroup analysis included both safety and efficacy measures. Analyses of acute (on-treatment) toxicity focused on any NCI-CTC grade 3 or higher events and on events in the gastrointestinal (GI) and genitourinary (GU) domains. Late toxicity event rates are reported at 1 and 2 years and overall up to five years as reported on RTOG and LENT/SOM scales. Efficacy endpoints were (i) loco-regional control (LRC), defined as time to first recurrence in pelvic nodes or bladder (either muscle or non-muscle invasive), censored at the first of metastasis (if $\geqslant$30 days before loco-regional recurrence), second primary or death; (ii) invasive loco-regional control (ILRC), defined as time to first recurrence in pelvic nodes or muscle-invasive bladder, censored at the first of metastasis (if $\geqslant$30 days before loco-regional recurrence), second primary or death; (iii) metastasis-free survival (MFS), time to

first metastasis or bladder cancer death, censored at second primary or non-bladder cancer death; and (iv) overall survival (OS).

Statistical Analysis

Only patients who received neoadjuvant chemotherapy and were randomised to the chemotherapy comparison are included in this subgroup analysis. The same statistical methods used to report the main chemotherapy comparison are followed[20].

Randomised treatment comparisons (cRT vs RT) of efficacy outcomes are based on the intention-to-treat (ITT) population, whilst toxicity comparisons are based on the as-treated population. For time-to-event endpoints, Kaplan-Meier survival curves are presented and randomised groups compared by stratified log-rank tests (adjusting by the factorial radiotherapy intervention group, stRT vs. RHDVRT). Hazard ratios (HR) are calculated from a Cox proportional hazards model (adjusting for radiotherapy intervention group only) and presented with 95% confidence intervals (CI). An adjusted model is used to account for radiotherapy intervention group, age at entry, radiotherapy fractionation, presence of multiple tumours, pathological stage, WHO performance status and tumour grade (as pre-specified in the BC2001 statistical Analysis Plan). Proportional hazards assumption was tested using Schoenfeld residuals and held for all endpoints. Median follow-up for each endpoint is calculated by the reverse Kaplan-Meier method.

The proportion of patients experiencing a grade 3 or above (G3+) toxicity is compared using a Mantel-Haenszel test (stratified chi-squared test), adjusted for the radiotherapy intervention group. Median haemoglobin while on treatment is compared by a Mann-Whitney test.

FACT-BL scores are summarised for the total score, bladder cancer specific subscale (BLCS) and Trial Index Outcome score (TOI, sum of BLCS plus physical and functional sub-scales). Mean difference in change from baseline at one year between randomised groups was estimated by analysis of covariance (ANCOVA) regression models, adjusting for radiotherapy intervention group, radiotherapy fractionation, and baseline score.

Exploratory non-randomised comparisons of toxicity, metastasis-free and overall-survival between patients receiving gemcitabine -cisplatin or gemcitabine-carboplatin (GC) to those receiving other cisplatin-based regimens were performed using methods as described above.

A p-value of 0.05 indicated statistical significance except for QoL endpoints, where a p-value of 0.01 and corresponding 99% CI were used to account for multiple sub-scales and timepoints. Analyses were based on a data snapshot taken on July 11, 2016, and were performed using STATA version 13[21].

Results

Study Population

Overall, 458 patients from 45 UK centres were recruited to the study between August 2001 and April 2008, with 360 patients included in the chemotherapy randomisation. Among these, 117 patients (33%) from 28 centres received neoadjuvant chemotherapy. Fifty-six (48%) patients were randomised to cRT. Randomisation was stratified by planned neoadjuvant treatment, resulting in fairly well-balanced study groups, with any difference due to chance (Table 1). Compared to the main trial population (chemotherapy comparison, N=360[20]), this subgroup of patients were younger, with better WHO performance status (see Supplementary Table S1).

Neoadjuvant Chemotherapy Regimens

Eighty-six (73.5%) patients received gemcitabine plus either cisplatin (n=81) or carboplatin (n=5) (GC, Table 2). GC was received in 12/21 (57%) patients with impaired renal function (GFR<60ml/min), and in 65/87 (76%) patients with adequate renal function (GFR⩾60ml/min). In nine patients baseline GFR value was missing. All but two of the 31 non-GC patients were treated with CMV or MVAC (methotrexate, vinblastine, adriamycin and cisplatin). Of 16 MVAC patients, 11 received the dose-dense schedule.

Toxicity and Compliance with Definitive Treatment

In the cRT group, 53 patients (95%) received 80% or more of the target MMC; 50 (89%) and 43 patients (77%) received ⩾ 80% of the planned 5-FU dose in weeks 1&4, respectively. These were similar to the whole trial population (respectively 96%, 94% and 80% in all cRT patients[2]). Toxicity was the reason most reported for non-compliance.

Compliance rates with full dose radiotherapy were cRT 93% vs RT 92% (compared with cRT 95% and RT 95% in the whole trial population[2]). Significant delays (⩾1 day) in planned radiotherapy were reported for 11 patients (9.4%) with a median delay of 3 days.

Although not statistically significant, an excess of G3+ acute toxicity was noted in the cRT group, with 18 cRT (33%) vs 14 RT (22%) patients (p= 0.16, Table 3). The two groups exhibited similar rates of G3+ GI or GU acute toxicities. Median haemoglobin while on treatment was cRT 11.9 g/dL (IQR 11-12.3) vs RT 12.6 g/dL (IQR 11.8-13.6) (p<0.001). During follow-up, G3+ RTOG late toxicity was reported in 5 cRT (14%) and 2 RT (5.1%) patients (p= 0.16). G3+LENT/SOM toxicities were reported

in 21 cRT (60%) and 18 RT (49%) patients (p= 0.4). The reported toxicity rates in each treatment group were comparable to those observed in the main trial (Supplementary Table S2).

No significant differences were seen between GC or non-GC neoadjuvant regimens. Acute G3+ toxicities were reported by 23/86 GC (27%) and 9/31 non-GC (29%) patients (p=0.8). During follow-up, RTOG G3+ late toxicities were reported in 6/86 (11%) GC patients and 1/31 (4.8%) non-GC patients (p=0.18). LENT-SOM G3+ toxicities were equally common in both groups: GC 28/86 (55%) vs non-GC 11/31 (52%) (p=0.3).

Efficacy

With median 77 months follow up (IQR 23-109), the treatment effect in LRC between cRT and RT in the neoadjuvant chemotherapy patient cohort was: HR 0.64, (95%CI 0.33-1.23; p= 0.18) (Figure 1A). Two-year LRC rates were cRT 65% (95%CI 49-77) vs RT 51% (95%CI 37-63); five-year rates were cRT 62% (95%CI 46-75) and RT 46% (95%CI 32-59).

With median 61 months follow up (IQR 20-100), the chemoradiotherapy benefit observed in ILRC (Figure 1B) was HR 0.58 (95% CI 0.22-1.54; p= 0.3). Two-year invasive locoregional control rates were cRT 90% (95%CI 77-96) and RT 77% (95%CI 63-86); five-year rates were cRT 86% (95%CI 72-94) and RT 74% (95%CI 59-84).

Salvage cystectomies were performed in 27 patients (23%) (supplementary Table S3); 24/27 of those were due to disease recurrence.

With median 96 months follow up (IQR 71-112), five-year MFS rates were cRT 54% (95%CI 40-67) vs RT 48% (95%CI 35-61) (Figure 1C), with HR 0.93 (95% CI 0.52-1.65; p=0.8).

With median 110 months follow up (IQR 96-123), median overall survival (Figure 1D) was 50.4 months for cRT patients and 46.7 months for RT (HR 0.95, 95% CI 0.57-1.57; p= 0.8). Five-year survival rates were cRT 48% (95%CI 34-61) and RT 46% (95%CI 33-58).

Although no statistically significant differences were found in any of the above endpoints, the magnitude of treatment effect observed in the neoadjuvant cohort was comparable to the main trial across all outcomes (see number of events and five-year estimates in supplementary Table S3). Interestingly, the rates of ILRC at five years observed in either treatment group in the neoadjuvant cohort where larger than the respectively observed in the main trial.

No significant differences in MFS or OS were found between GC and non-GC regimens (Figure 2).

Quality of life

FACT-BL scores were equally common at baseline in the neoadjuvant subgroup to the scores observed in the whole population[22] (Supplementary Table S4). Although there seems to be a detrimental impact over time on the TOI subscale by the addition of cRT vs RT alone in this subgroup of patients (Figure 3), these differences did not reach conventional levels of statistical significance. At one year, there was no statistically significant difference between randomised groups in change from baseline in the BLCS (-0.35; 99% CI: -4.41 to 3.71, p=0.8), TOI (-4.73, 99% CI: -13.31, 3.85, p=0.15) or TOTAL (-6.27; 99% CI: -18.03, 5.50, p=0.16) subscales.

Discussion

We have described outcomes in a large prospective cohort of 117 MIBC patients treated with neoadjuvant chemotherapy followed by organ-sparing definitive treatment. The aim of this study was to establish whether the benefit of chemoradiotherapy remained in patients who had received neoadjuvant chemotherapy. As this is an exploratory subgroup analysis of a larger trial, there is insufficient statistical power to detect significant differences between cRT and RT groups. Nevertheless, observed effect sizes are comparable to those reported in the main trial[2,23], and suggest that chemoradiotherapy adds benefit compared to radiotherapy alone even in patients pre-treated with cisplatin based neoadjuvant chemotherapy. In line with data from selective bladder preservation series[12], our data show excellent invasive cancer control rate can be achieved after neoadjuvant chemotherapy followed by concomitant (chemo)radiotherapy, with only 10% of patients developing invasive recurrence within 2 years of diagnosis. Furthermore, there was no significant increase in acute or late toxicity or detriment in QoL amongst patients who received chemoradiotherapy compared to radiotherapy alone following neoadjuvant chemotherapy.

Within the BC2001 trial, neoadjuvant chemotherapy was given at the discretion of the clinician and was used as a stratification factor ensuring those receiving chemoradiotherapy are comparable to those receiving radiotherapy alone. This subgroup may not be directly comparable to the overall trial group as it is likely that neoadjuvant chemotherapy would be considered in patients with a better performance status with fewer comorbidities and overall better prognosis. An impact of possible selection for organ preservation according to response to neoadjuvant chemotherapy also cannot be excluded[24]. We have not reported non-randomised

comparisons of patients treated with or without neoadjuvant chemotherapy as such a comparison would be impacted by inherent biases.

It is notable that among patients in this cohort who received radical radiotherapy only, the 5-year overall survival rate was 46% whilst that reported for radiotherapy alone in the main trial (including patients treated with or without neoadjuvant chemotherapy) was only 37%, a numerical difference that was not seen for chemoradiotherapy (48% neoadjuvant cohort; 49% main trial). These data are comparable to those from the neoadjuvant chemotherapy arm of the BA06 trial where there was a 5-year overall survival rate of 49% with either definitive radiotherapy or surgery[6]. This would suggest a probable survival benefit from the addition of neoadjuvant chemotherapy to organ-preservation. However, the absence of benefit reported in one recent retrospective study,[13] together with our data, suggests that confirmation of benefit in chemoradiotherapy patients would require formal testing in a sufficiently-powered randomised clinical trial.

Despite the administration of neoadjuvant chemotherapy, the delivery of radical curative treatment with either chemoradiotherapy or radiotherapy was possible even if the compliance rates were marginally lower than the overall population. This is important in the context of previous evidence that demonstrated a clear benefit (20% reduction in the risk of death) with the addition of neoadjuvant CMV chemotherapy to radical radiotherapy[6].

The majority of BC2001 patients treated with neoadjuvant chemotherapy received GC based on evidence of comparable efficacy and less toxicity than MVAC[25], and our results showed no difference in survival based on the neoadjuvant chemotherapy regimen used. Our results are supported by a retrospective study that found that MVAC and GC were associated with comparable pCR rates when given prior to

surgery[26]. Comparison between cisplatin-based and non-cisplatin-based combination neoadjuvant chemotherapy was not possible as only 6/117 received non-cisplatin-based therapy.

There are inherent limitations in this study. Use of neoadjuvant chemotherapy was determined by the treating physician before entry into the trial so, as noted before, there are likely biases in terms of patient characteristics between those receiving or not receiving neoadjuvant chemotherapy. We collected limited information on the neoadjuvant regimes, so are unable to provide any insight into the compliance with neoadjuvant treatment. This subgroup analysis has limited power to show treatment effects of chemoradiation. Furthermore, as a subgroup of the original trial population, unaccounted for selection biases and confounding factors may be present. Another limitation was the large percentage (81%) of patients in our study with T2 disease. Despite these limitations, we believe the current analysis further strengthens the role of neoadjuvant chemotherapy in standard clinical care of patients with MIBC though it is clear there remains scope to improve therapy through e.g. better case selection through biomarker prediction, addition of targeted therapies or immune checkpoint inhibitors[27-29].

Conclusions

Overall, this study confirms that neoadjuvant chemotherapy prior to organ-preserving radical radiotherapy with or without concurrent chemotherapy is feasible and does not confer significant additional treatment-related toxicity nor negatively impact patient reported quality of life. Neoadjuvant chemotherapy canbe considered in any organ-preserving radical treatment strategy in appropriate patients with muscle-

invasive bladder cancer. The role of neoadjuvant chemotherapy before chemoradiotherapy warrants further research in randomised controlled trials.

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Tables

Table 1. Baseline patient characteristics for the BC2001 neoadjuvant patient cohort

		Chemo-radiotherapy 56 (100.0%)	Radiotherapy alone 61 (100.0%)
Sex	Male	50 (89.3%)	50 (82.0%)
Age (years)	N	56	61
	Median (Q25-Q75)	66.8 (62.1-72.5)	64 (59.3-72.9)
	Min-Max	52.3-83.9	50.5-82.1
WHO Performance Status	0	39 (69.6%)	46 (75.4%)
	1	16 (28.6%)	15 (24.6%)
	2	1 (1.8%)	0 (0.0%)
Pathological stage - primary tumour	2	48 (85.7%)	47 (77.0%)
	3a	2 (3.6%)	4 (6.6%)
	3b	5 (8.9%)	6 (9.8%)
	4a	1 (1.8%)	4 (6.6%)
Grade primary tumour	2	2 (3.6%)	13 (21.3%)
	3	54 (96.4%)	48 (78.7%)
TCC histology		54 (96.4%)	60 (98.4%)
Multiple tumours	Yes	8 (14.3%)	14 (23.0%)
Extent of tumour resection	Not resected/Biopsy	11 (19.6%)	5 (8.2%)
	Complete Resection	32 (57.1%)	32 (52.5%)
	Incomplete Resection	13 (23.2%)	23 (37.7%)
	Resected (extent unknown)	0 (0.0%)	1 (1.6%)
Tumour size group	<30mm	15 (26.8%)	11 (18.0%)
	≥30mm	21 (37.5%)	27 (44.3%)
	Unknown	20 (35.7%)	23 (37.7%)
Residual mass post resection	Yes	11 (19.6%)	17 (27.9%)
Radiotherapy randomisation	stRT	6 (10.7%)	12 (19.7%)
	RHDVRT	7 (12.5%)	8 (13.1%)
	Elective stRT	43 (76.8%)	41 (67.2%)
Radiotherapy schedule	55Gy/20F	30 (53.6%)	29 (47.5%)
	64Gy/32F	26 (46.4%)	32 (52.5%)

TSCC: Transitional cell carcinoma; stRT: standard whole bladder radiotherapy; RHDVRT: reduced high dose volume radiotherapy; Q25: 1st quartile (25th percentile), Q3: 3rd quartile (75% percentile); Gy: gray, F: fractions

Table 2: Neoadjuvant chemotherapy regimens reported in BC2001

	Chemo-radiotherapy 56 (100.0%)	Radiotherapy alone 61 (100.0%)	p-value*
GC	**39 (69.6)**	**47 (77.1)**	**0.36**
Gemcitabine+cisplatin	*38 (67.9)*	*43 (70.5)*	
Gemcitabine+carboplatin	*1 (1.8)*	*4 (6.6)*	
Non-GC	**17 (30.4)**	**14 (22.9)**	
MVAC/Acc.MVAC	*7 (12.5)*	*9 (14.8)*	
CMV	*8 (14.3)*	*5 (8.2)*	
ACE	*1 (1.8)*	*0 (0)*	
MOP q10	*1 (0.9)*	*0 (0)*	

* Chi-square p-value type of NAC (GC/ Non GC) with randomised treatment

GC: gemcitabine + cisplatin or gemcitabine+carboplatin; MVAC: methotrexate, vinblastine, doxorubicin and cisplatin; Acc: accelerated; CMV: cisplatin, methotrexate, vinblastine; ACE: doxorubicin, cyclophosphamide, etoposide ; MOPq10: methotrexate, cisplatin, vincristine

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Table 3: Grade 3 or greater toxicity rates by randomised treatment group observed in the BCC001 neoadjuvant chemotherapy cohort

Worst ⩾ grade 3	Chemoradiotherapy		Radiotherapy alone		p-value*
	n/N	%	n/N	%	
Acute toxicity (NCI-CTC grade)					
On treatment (overall)	18/54	33.3%	14/63	22.2%	0.16
Genito-urinary	8/54	14.2%	8/63	13.6%	0.9
Gastro-intestinal	4/54	6.2%	3/63	5.1%	0.6
Late toxicity (RTOG)					
At 1 year	1/30	3.3%	0/30	0	0.4
At 2 years	1/19	5.3%	0/21	0	0.4
Up to 5 years	5/35	14.3%	2/39	5.1%	0.16
Late toxicity (LENT/SOM)					
At 1 year	9/27	33.3%	10/28	35.7%	0.7
At 2 years	5/17	29.4%	6/19	31.6%	0.7
Up to 5 years	21/35	60.0%	18/37	48.6%	0.4

Stratified Mantel-Haenzel test p-value.

NCI-CTC: National Cancer Institute Common Toxicity Criteria version 2; RTOG: Radiation Therapy Oncology Group; LENT/SOM: Late Effects of Normal Tissue (Subjective, Objective, Management)

N=total number of patients with available toxicity assessment; n=number of patients with grade 3+ toxicity

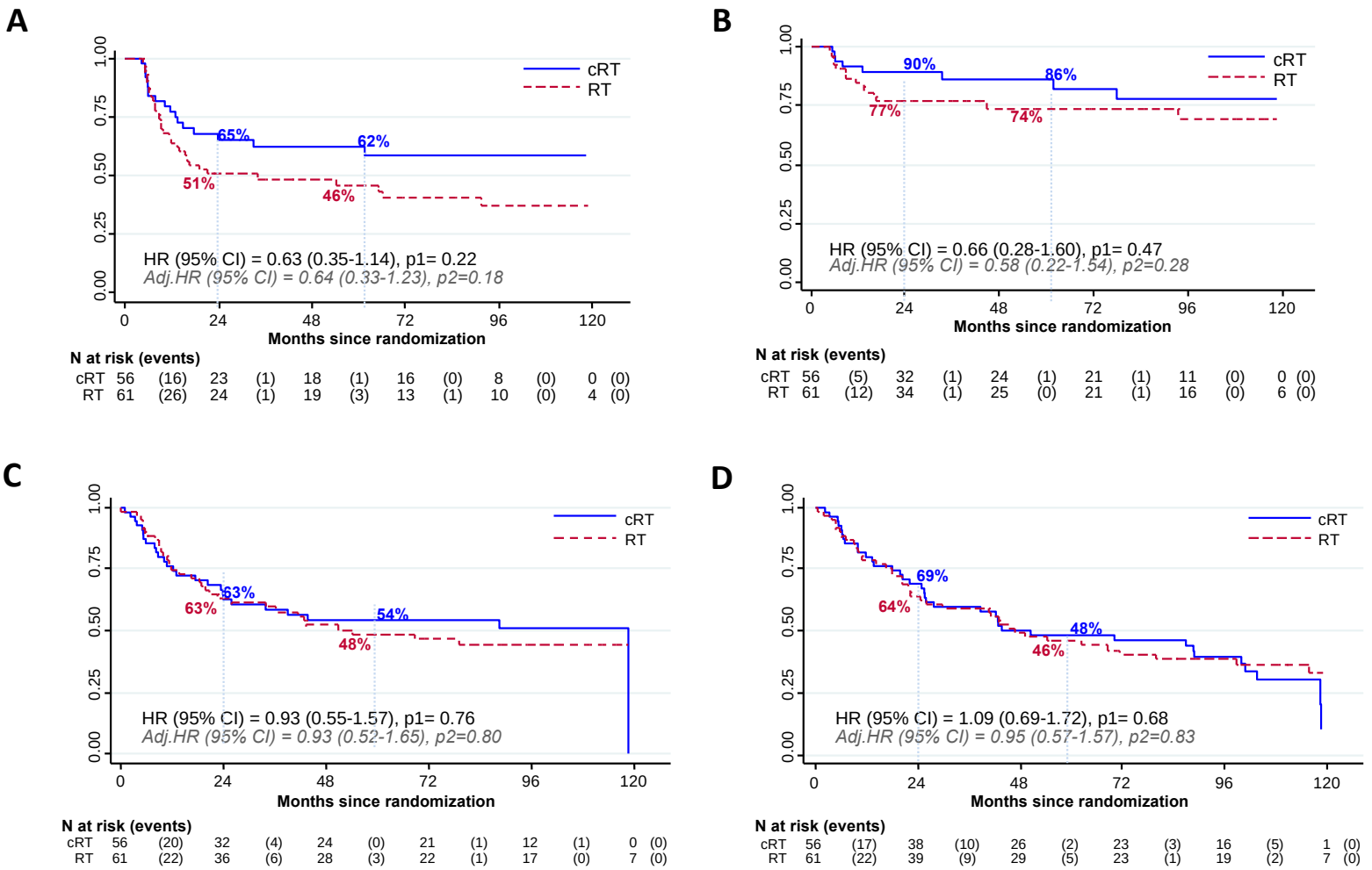
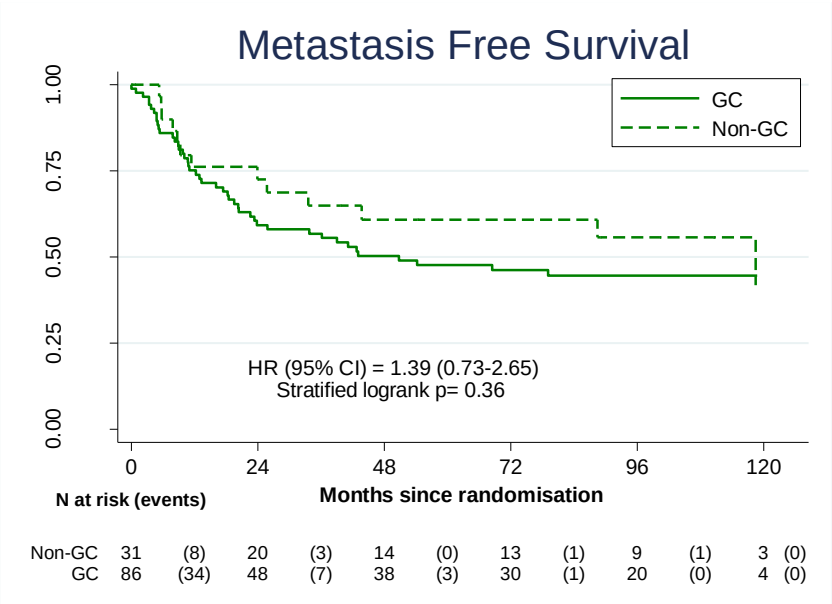


Figure 1: Time to event outcomes in the BC2001 neoadjuvant cohort

Shown are the patients' rates of loco-regional control (Panel A), invasive loco-regional control (Panel B), metastasis free survival (Panel C) and overall survival (Panel D) during 110 months of follow-up. P-values comparing chemoradiotherapy (cRT) and radiotherapy alone (RT) were calculated by log-rank test stratified by radiotherapy treatment group.

HR: hazard ratio, Adj. HR: adjusted hazard ratio; CI: confidence interval.



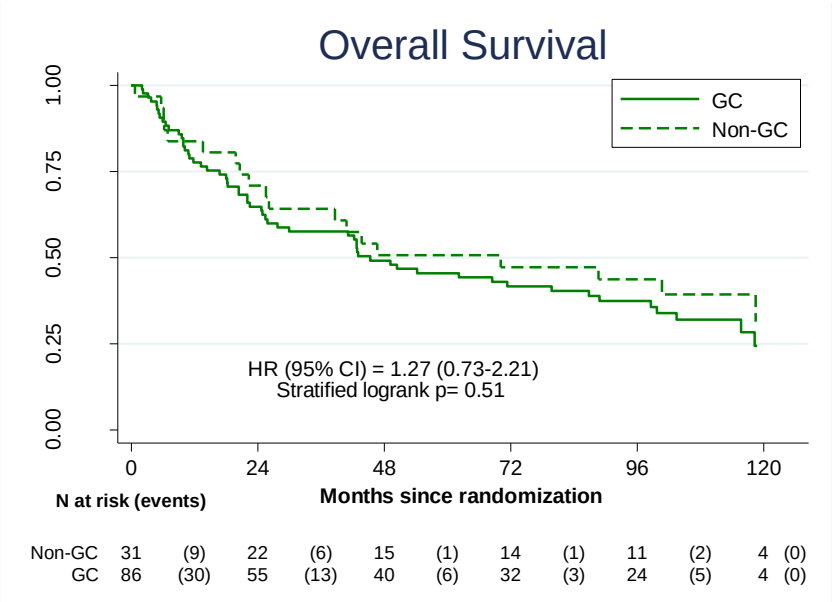


Figure 2: Metastasis-free and overall survival by type of neoadjuvant chemotherapy

Patients are grouped according to chemotherapy regime: gemcitabine + cisplatin or gemcitabine+carboplatin (GC) vs Other regimes (Non GC). Shown are the patients' rates of metastases free survival (Panel A) and overall survival (Panel B). P-values to compare neoadjuvant chemotherapy type were calculated by log-rank test stratified by randomised treatment groups.

HR: hazard ratio, CI: confidence interval

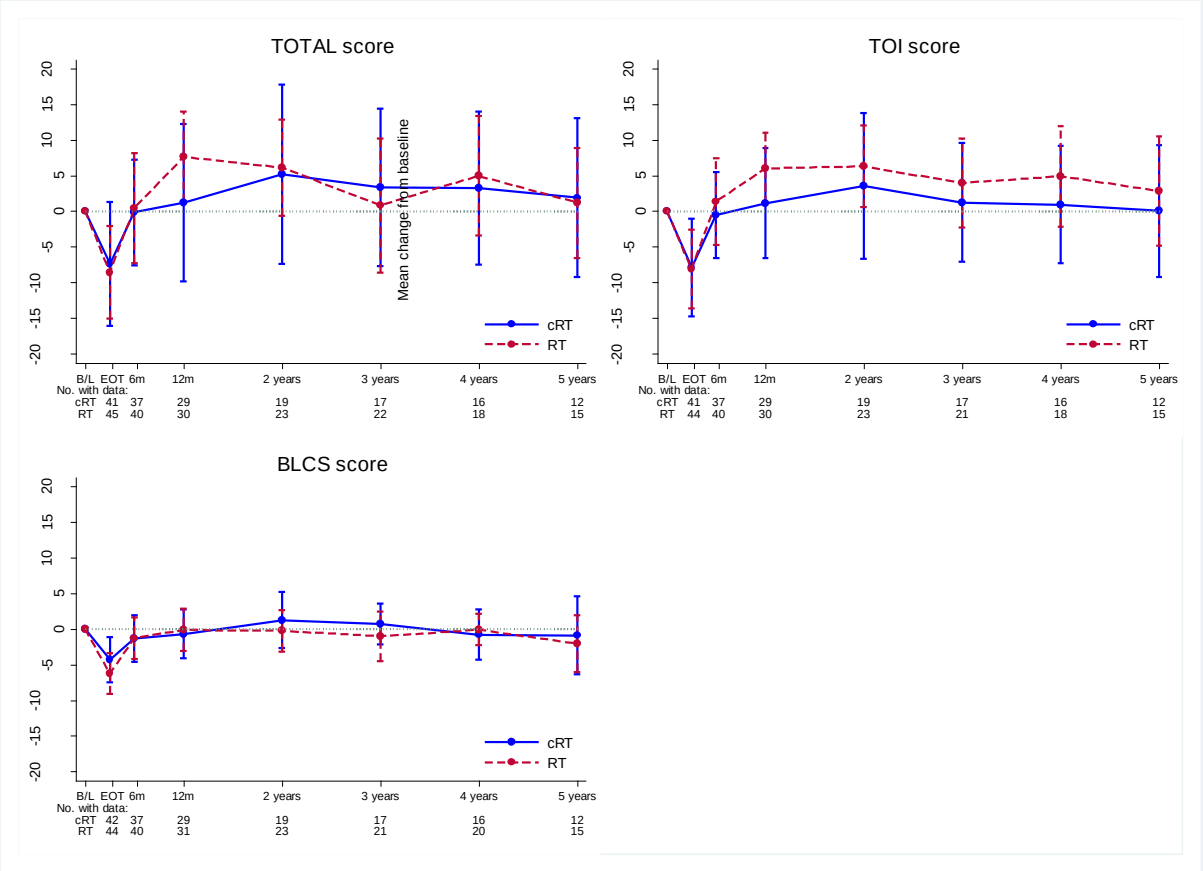


Figure 3. Patient reported outcomes in the subgroup of patients who received neoadjuvant chemotherapy

FACT-BL Mean change from baseline (with 99% confidence intervals) in FACT-BL bladder cancer specific subscale (BLCS), Trial Outcome Index (TOI= BLCS plus physical and functional subscales) and TOTAL scores in patients who received neoadjuvant chemotherapy prior to BC2001 randomisation to chemoradiotherapy (cRT) vs radiotherapy alone (RT).

B/L=Baseline, EOT: end of treatment