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Clinical and patient reported outcomes of SPARE - a randomised feasibility study of selective bladder preservation versus radical cystectomy

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Abstract

Objectives:

To test the feasibility of a randomised trial in muscle invasive bladder cancer (MIBC)

and compare outcomes in patients who receive neoadjuvant chemotherapy followed by

radical cystectomy or selective bladder preservation, where definitive treatment

(cystectomy or radiotherapy) is determined by response to chemotherapy.

Patients and methods

SPARE is a multicentre randomised controlled trial comparing radical cystectomy and

selective bladder preservation in patients with MIBC staged T2-3 N0 M0, fit for both

treatment strategies and receiving three cycles of neoadjuvant chemotherapy.

Patients were randomised between radical cystectomy and selective bladder

preservation prior to a cystoscopy after cycle three of neoadjuvant chemotherapy.

Patients with ≤T1 residual tumour received a fourth cycle of neoadjuvant chemotherapy

in both groups, followed by radical radiotherapy in the selective bladder preservation

group and radical cystectomy in in the radical cystectomy group; non-responders in both groups proceeded immediately to radical cystectomy following cycle three. Feasibility study primary endpoints were accrual rate and compliance with assigned treatment strategy. The phase III trial was designed to demonstrate non-inferiority of selective bladder preservation in terms of overall survival in patients whose tumours responded to neoadjuvant chemotherapy. Secondary endpoints included patient reported quality of life, clinician assessed toxicity, loco-regional recurrence free survival and rate of salvage cystectomy after bladder preservation.

Results

Trial recruitment was challenging and below the predefined target with 45 patients recruited in 30 months (25 radical cystectomy; 20 selective bladder preservation). Non-compliance with assigned treatment strategy was frequent, 6/25 patients (24%) randomised to radical cystectomy received radiotherapy.

Long term bladder preservation rate was 11/15 (73%) in those who received radiotherapy per protocol. Overall survival was not significantly different between groups.

Conclusions:

Randomising MIBC patients between radical cystectomy and selective bladder preservation based on response to neoadjuvant chemotherapy was not feasible in the UK health system. Strong clinician and patient preferences for treatments impacted willingness to undergo randomisation and acceptance of treatment allocation. Due to the small number of participants, firm conclusions about disease and toxicity outcomes cannot be drawn.

Key words:

Muscle invasive bladder cancer; radical cystectomy; selective bladder preservation; radiotherapy; randomised controlled trial

Introduction

Achieving local disease control is a critical step in treating muscle invasive bladder cancer (MIBC). A common approach is surgical removal of the bladder and adjacent organs - radical cystectomy. Despite being a successful approach to cancer control, this is a major operation, in an often unfit and/or elderly population. It requires formation of a urinary diversion and has substantial associated morbidity and mortality rates (1, 2).

Radical radiotherapy (RT) is an alternative to cystectomy (3, 4). It preserves a functioning bladder and avoids the risks of major surgery, but does not achieve local control for all patients and, if unsuccessful, requires subsequent salvage cystectomy, which can be challenging (5). The relative efficacy of radiotherapy and cystectomy has been debated extensively but, as randomised data are lacking, comparisons have been largely based on retrospective series where inherent biases can make interpretation difficult (4, 6, 7). UK bladder cancer treatment guidelines released in 2015 recommend that patients with muscle invasive bladder cancer are offered a choice of radical cystectomy or radiotherapy with a radiosensitiser (8).

There also exists a paucity of comparative data on the effects of both treatment options on patients' quality of life. Radical cystectomy has been found to have a substantial negative impact on health related quality of life in the first year postoperatively (9),

whilst patients who have received radiotherapy experience greater gastrointestinal dysfunction (10).

Several groups have hypothesised that radiotherapy would be more attractive as a treatment option if it were possible to select patients with tumours most likely to respond. This would minimise the need for salvage cystectomy by undertaking immediate radical cystectomy for patients predicted to have less chance of cure with radiotherapy.

Neoadjuvant chemotherapy before radical treatment improves survival in MIBC (11, 12) and studies have suggested that tumours which respond to neoadjuvant chemotherapy may achieve higher rates of local control with radiotherapy than those which don't (12, 13). Utilising chemotherapy in this way to select patients for radiotherapy achieved high levels of long term bladder preservation and avoided the need for surgery in most patients (14, 15). To test the efficacy of this approach we planned a randomised trial, with an initial feasibility study to compare, after neoadjuvant chemotherapy, a selective bladder preservation strategy with patients undergoing radical cystectomy.

Patients and methods

Study design

SPARE (CRUK/07/011) was a multicentre phase III randomised controlled trial with an initial feasibility study (Figure 1). The aims of the feasibility study were to determine viability of accrual for the phase III trial and assess compliance with the assigned treatment strategy. There was an embedded qualitative research programme, which has

been previously reported (16, 17). The phase III trial was designed to determine if overall survival (OS) following bladder preservation is non-inferior to that following radical cystectomy for patients whose tumours respond to neoadjuvant chemotherapy.

Patients were recruited at UK NHS Trusts. All Trusts providing trial treatment had to provide details of surgical activity including morbidity and mortality rates for central review and confirmation of completion of a radiotherapy quality assurance program prior to activation. Randomisation was by telephone to the Clinical Trials and Statistics Unit, Institute of Cancer Research (ICR-CTSU). Participants were assigned 1:1 between selective bladder preservation and radical cystectomy using computer generated random permuted blocks (size 6 and 8), stratified by centre. Treatment allocation was not masked.

Patients

Eligible patients provided written informed consent, were receiving neoadjuvant chemotherapy and fit for radiotherapy and surgery, at least 18 years old, had T2-T3 N0 M0 transitional cell carcinoma of the bladder and WHO performance status 0-1, with satisfactory haematological profile and kidney function. Key exclusion criteria were widespread carcinoma in situ (CIS), simultaneous upper tract, urethral or prostatic urethral TCC, untreated hydronephrosis and invasive malignancy in the previous 5 years.

Initially treatment allocation took place during cycle two of neoadjuvant chemotherapy. Based on findings of the qualitative recruitment investigation (17), this timeframe was amended in August 2009 to allow randomisation at any time prior to a cystoscopy following cycle three (C3) of neoadjuvant chemotherapy.

Treatments:

All participants received neoadjuvant chemotherapy. Gemcitabine (1000mg/m^2 day 1 and day 8) and cisplatin (70mg/m^2) repeated every 21 days was recommended. All patients had a cystoscopy and tumour bed biopsy under general anaesthetic after cycle 3 of neoadjuvant chemotherapy, with subsequent treatment dependent on response.

Patients with pT2 or greater disease in both randomised groups proceeded immediately to radical cystectomy within 6 weeks of cycle 3. Patients with histological downstaging (pT1 or less), or a macroscopically normal bladder were classified as responders and received cycle 4 of neoadjuvant chemotherapy with subsequent treatment determined by randomised allocation. Patients receiving radiotherapy were permitted to receive concomitant radiosensitising chemotherapy.

Selective bladder preservation group

Patients whose tumours responded to neoadjuvant chemotherapy started radiotherapy to the bladder 4-6 weeks after cycle 4. Two fractionation schedules in standard use in the UK were permitted (55Gy/20 fractions or 64Gy/32 fractions). The planning target volume was the bladder plus 1.5cm margin, delivered by 3D conformal techniques.

Radical cystectomy group

Patients whose tumours responded to neoadjuvant chemotherapy received radical cystectomy 4-6 weeks after cycle 4. Radical cystectomy consisted of resection of the bladder, prostate and seminal vesicles in men and bladder, uterus, ovaries and upper vagina in women. Pelvic lymphadenectomy, removing a minimum of 10 lymph nodes, was mandated and recommended to include dissection of obturator nodes and external

iliac nodes to the level of the iliac bifurcation and internal iliac nodes from the right and left side of pelvis. The lateral limit of the dissection was the genito-femoral nerve on the psoas muscle and medial and posterior limits represented by the obturator nodes. Orthotopic reconstruction using small or large bowel was encouraged however standard ileal conduit formation was also permitted .

Trial assessments

Prior to neoadjuvant chemotherapy, patients underwent physical examination, haematological and biochemical assessment, CT scan of pelvis, chest X-ray or CT, and maximal cystoscopic resection of tumour. Tumour control was assessed by physical examination, chest x-ray and cystoscopy (if applicable) with follow up as shown in Figure 1. Adverse events were graded using Common Toxicity Criteria (CTC) version 3 (18). Patient reported outcomes were collected, using paper EORTC general cancer and MIBC modules (QLQ-C30 and QLQ-BLM30). (19)

Statistical considerations

Endpoints

The primary endpoints of the feasibility study were accrual rate, bladder preservation rate in the selective bladder preservation arm and cystectomy rate in the radical cystectomy arm. For the phase III component, the primary endpoint was 5 year survival. Secondary endpoints were treatment compliance, rate of salvage cystectomy, toxicity, patient-reported quality of life and loco-regional recurrence free (LRFS) and metastasis free (MFS) survival. For this analysis OS was treated as a secondary endpoint.

Sample size

The phase III trial was powered to evaluate non-inferiority in the proportion of patients alive at five years between selective bladder preservation and radical cystectomy in those patients whose tumours responded to neoadjuvant chemotherapy. Seventy percent 5-year survival was assumed (14) with the aim of excluding a decrease of 8% or more in the selective bladder preservation group (corresponding to a critical hazard ratio (HR) for non-inferiority of 1.34). Assuming an 80% neoadjuvant chemotherapy response rate, 1015 patients would have been required to conclude non-inferiority (80% power, one-sided $\alpha=0.05$). For the phase III study to be considered feasible it was recommended that 110 patients be randomised during the first two years, however this was amended to three years, or a sustainable accrual rate of at least 6 patients per month, in August 2009 with the endorsement of the independent Trial Steering Committee (17). An analysis of the feasibility stage was planned to assess compliance with the bladder preservation strategy with the aim of excluding an initial bladder preservation rate of less than 60%. This stop/go criterion was based on a single arm phase II design and required 39/55 patients in the SBP arm to undergo radiotherapy following response to neoadjuvant chemotherapy to warrant continuation to phase III.

Statistical analysis

All randomised participants are included. The number of neoadjuvant chemotherapy responses was compared between groups using Fisher's exact test. Compliance with allocated treatment strategy was assessed by the proportion of patients: (i) with response after cycle 3 who received cycle 4 neoadjuvant chemotherapy and (ii) undergoing allocated treatment as their definitive treatment overall (i.e. cystectomy in the radical cystectomy arm, bladder preservation in selective bladder preservation arm

responders and cystectomy in selective bladder preservation arm non-responders). In the selective bladder preservation group, bladder preservation rate (BPR) was the proportion of patients who did not require cystectomy following radiotherapy both overall and in the subset who received RT according to protocol guidelines, ie in the population who responded to chemotherapy and received cycle 4. Unless otherwise stated, proportions are presented with exact binomial 95% confidence intervals (CI).

Worst grade adverse events were compared by definitive treatment received and time to grade 3-4 event was estimated using Kaplan-Meier methods.

Time to event endpoints were assessed using Kaplan-Meier methods in the population of responders in both groups, and repeated according to both intention to treat (ITT) and definitive treatment received. Treatment effects were estimated using unadjusted Cox regression models with a HR<1 indicating benefit for selective bladder preservation in the ITT analysis or radiotherapy for the treatment received analysis. OS was defined as time to death from any cause; time to loco-regional recurrence (LRR) was calculated to first non-muscle invasive (NMIBC) or muscle invasive (MIBC) recurrence in the bladder or recurrence in the pelvic nodes; MFS was time to the first of distant recurrence or death; disease specific survival (DSS) was time to death following nodal or metastatic recurrence or unsalvageable local recurrence. All times are calculated from randomisation.

Quality of life data was analysed by treatment received and data were scored and missing data handled in accordance with the EORTC QLQ-C30 scoring manual (20). For each QLQ-C30 subscale, mean change from baseline was calculated, with 99% CI, for

each group at each time point and longitudinal plots of change from baseline were produced. Differences between groups in mean change from baseline to 12 months were assessed using ANCOVA, adjusting for baseline score.

Analyses are based on a snapshot of the database taken on 30th September 2014 and performed using Stata (21).

Research Governance

SPARE was funded by Cancer Research UK (CRUK/07/011, C1491/A9895). The study is registered (ISRCTN61126465), sponsored by ICR and approved by the South East Multicentre Research Ethics Committee. SPARE was managed by a multidisciplinary trial management group and overseen by independent data monitoring (IDMC) and trial steering (TSC) committees.

Results

Patient screening and recruitment

The first participant was recruited on 20/07/2007 and the trial closed to recruitment on 12/02/2010 with 45 patients accrued on the advice of the IDMC and TSC due to failure to achieve target (stop/go) accrual rates .

Participating sites were requested to submit anonymised screening logs to the central coordinating centre on a regular basis throughout recruitment, to report patients with T2/T3 N0 M0 bladder cancer who may be eligible for the trial. 796 patients were reported, of whom 490 were ineligible, the majority of whom were not fit enough to receive all three SPARE treatment modalities – chemotherapy, cystectomy and

radiotherapy. A further 141 potentially eligible patients were not approached regarding participation, largely due to the complexity of the patient referral pathway which meant that they were not identified as potentially eligible by the participating centre prior to radical treatment commencing (22).

45/165 patients approached to participate consented, with 25 allocated to the radical cystectomy group and 20 to selective bladder preservation. Of the 120 patients approached who declined, radiotherapy was preferred by 51 and surgery by 25 (unknown 44) (Figure 2).

Baseline characteristics and compliance with allocated treatment (Table 1)

23/23 (100%) radical cystectomy patients (2 missing) and 17/20 (85%) selective bladder preservation patients responded to neoadjuvant chemotherapy (P=0.092). 35 of these 40 patients with a response to neoadjuvant chemotherapy received cycle 4 in accordance with the protocol.

Deviations from protocol defined treatment were frequent (Figure 2). 36/45 (80.0%, 95% CI:, 65.4% to 90.4%) received definitive treatment according to allocated group. 19/25 (76%, 95% CI: 54.9% to 90.6%) patients allocated radical cystectomy underwent cystectomy with 6 (24%) receiving radiotherapy.

In the selective bladder preservation group, 17/20 (85.0%, 95% CI: 62.1% to 96.8%) received protocol defined treatment; 15/20 selective bladder preservation patients (75%, 95% CI: 50.9% to 91.3%) responded to neoadjuvant chemotherapy and received radiotherapy per protocol and 2/20 patients (10%, 95% CI: 1.2% to 31.7%) did not respond to chemotherapy and proceeded to cystectomy per protocol. The other three

patients were not treated in accordance with the selective bladder preservation strategy: 1 non-responder had radiotherapy after 3 cycles of neoadjuvant chemotherapy rather than proceeding to radical cystectomy; 2 responded yet had radical cystectomy (1 after 3 and 1 after all 4 cycles of neoadjuvant chemotherapy).

22 participants overall (16 selective bladder preservation; 6 radical cystectomy) received radiotherapy, two with concomitant radiosensitisation. 5 of the 22 (22.7%; 95% CI: 7.8% to 45.4%) radiotherapy recipients subsequently underwent salvage cystectomy, all due to recurrent bladder cancer (3 MIBC, 2 NMIBC). The long term bladder preservation rate in the selective bladder preservation group was 12/20 (60%) and was 11/15 (73%) in those SBP patients who received RT per protocol.

Toxicity

More patients undergoing radical cystectomy had CTC grade 3-4 toxicity (16/23 (70%) for cystectomy; 8/22 (36%) for radiotherapy: P=0.038) (12/23 (52%) and 6/22 (27%) respectively if erectile dysfunction is excluded) (Table 2, Figure 3). The most common CTC G1-4 toxicity in patients undergoing cystectomy was fatigue (15/23 (65%)); and in patients receiving radiotherapy was fatigue and nocturia (both 12/22 (55%)).

Cancer control and survival

Median follow up is 58.0 months (IQR 44.3–61.3). The HR for the randomised comparison of overall survival was 3.05; 95% CI: 0.92 to 10.15) (Figure 4). Considering groups defined by definitive treatment received gave a HR of 1.83 (95% CI: 0.55 to 6.07) (Figure S1). Given the wide confidence intervals of the estimate, a survival difference

between groups can be neither confirmed nor excluded and non-inferiority cannot be claimed.

LRR rate at two years was lower in patients randomised to radical cystectomy at 15.3% (95% CI: 5.2% to 40.5%) versus 68.9% (95% CI: 42.5% to 91.5%) in the selective bladder preservation group (Figure 4). Seven patients in the selective bladder preservation group developed NMIBC recurrence of whom five are long term survivors after salvage treatment. There was no evidence of difference in MFS (Figure 4) or DSS between randomised groups.

Quality of life

Baseline subscale scores were similar between groups. After 12 months patients who received radiotherapy showed improvement in mean global health status and social functioning whilst these declined in the cystectomy group (Table 3). However, the confidence limits of the estimates of differences between groups are wide (Figure 5). Changes over time in BLM30 single items scores suggest a decline in body image and male sexual problems after radical cystectomy that is less evident in radiotherapy patients (Figure 6). With both treatments there is an improvement in future perspectives with time.

Discussion

SPARE closed due to failure to meet the predefined minimum target recruitment rate, even though there had been extensive efforts and qualitative research to support recruitment (16, 17, 22).

One key criterion for assessing feasibility of phase III was to demonstrate acceptability of the randomised treatment strategies and viability of use of chemotherapy response to select patients for radiotherapy. At least 60% of those in the selective bladder preservation group were anticipated to receive radiotherapy per protocol. Whilst an initial bladder preservation rate of 75% was observed in those receiving radiotherapy per protocol in the selective bladder preservation arm, the small number of patients recruited resulted in wide CIs spanning 60% such that the threshold to warrant continuation to phase III was not met. A 90% cystectomy rate was anticipated in the radical cystectomy group but cystectomy was only performed in 76% of patients in this group.

Low randomisation rates and frequent deviations from allocated treatment suggest patients have a reluctance to allow randomisation to determine which of two contrasting treatment strategies they should receive. In accordance with the principles of good clinical practice, patients were made aware prior to randomisation that they could change their mind about participation in the trial at any stage without affecting the level of care they would receive. They were, however asked not to join the trial unless they believed they would be willing for their treatment to be determined by the SPARE protocol. Despite this request a high proportion of treatment deviations, largely driven by patient choice, were observed.

An additional contributor to early closure of the study was the smaller than anticipated number of patients eligible for all treatment modalities. This, in addition to a lack of equipoise amongst clinicians (17), had a major impact. Undoubtedly a proportion of patients approached for this study demonstrated an appetite for bladder preservation;

many selecting radiotherapy when declining randomisation and a substantial proportion of participants receiving radiotherapy when not mandated by the protocol. This suggests that patients' wishes for bladder preservation should be considered when discussing treatment options.

Robust conclusions cannot be made due to the limited sample size and are further complicated by poor compliance with assigned treatment strategy and differences in neoadjuvant chemotherapy response rates between the two randomised groups. Overall response to neoadjuvant chemotherapy was consistent with pilot work (15) and was higher than the pathological complete response rates in cystectomy specimens reported in trials of neoadjuvant chemotherapy followed by radical cystectomy (11, 23). This would suggest that cystoscopic examination understages some patients and supports the rationale for recommending additional treatment even for a clinically normal looking bladder.

LRR free survival was worse after radiotherapy, mainly due to the incidence of NMIBC which was more frequent than invasive recurrence. This is reported in other bladder preserving series(15, 24, 25) and suggests the bladder remains at high risk of developing second primary disease. This may indicate a role for preventative therapy such as that undertaken for NMIBC. Many cases of NMIBC can be salvaged with local treatment thus the bladder preservation rate remained high as reported elsewhere (15, 25).

When comparing radical radiotherapy to radical cystectomy, considering the frequency of 'non-salvageable' recurrences may be more appropriate than overall recurrence rates. In this study, the rate of non-salvageable recurrences in responders to neoadjuvant chemotherapy is similar for radical cystectomy (4/23) and selective bladder preservation (5/17), as are OS and MFS. Observations from this randomised trial are consistent with the results of population based studies(7, 26-28), non-randomised single institution studies (6) and cross study comparisons (4), demonstrating little evidence of inferior survival following bladder preservation when compared to cystectomy. A recent review of chemo-radiotherapy studies for MIBC reported bladder cancer specific and overall survival rates of 50%-82% and 36%-74% respectively (29), similar to those seen in like-for-like cystectomy series. If, as our results suggest, radiotherapy has less impact on quality of life than radical cystectomy, this would provide additional rationale for consideration of bladder sparing therapy.

Few radiotherapy recipients had concomitant chemo-radiotherapy which has since been shown to significantly improve clinical outcomes (24). The technical delivery of radiotherapy has also improved with the advent of adaptive and image guided techniques (30-32), so one may expect improved outcomes with radiotherapy in the future. Likewise developments in surgery with increasing use of bladder reconstruction, enhanced recovery pathways(33) and minimally invasive techniques (34, 35) should result in benefits for patients.

The poor outcome of participants whose tumours did not respond to neoadjuvant chemotherapy, whether or not they underwent cystectomy, remains a concern and has been seen in other studies(15). Alternative systemic or palliative treatment options should perhaps be explored in this population.

Identification of predictive markers to help select patients for whom organ preservation may be a suitable option remains important. Recent work suggests that bladder cancer may consist of a variety of genetic sub-types. It would be of interest to understand if certain of these subtypes are more or less likely to respond to chemotherapy or radiotherapy (36). Alternative candidates may be markers of DNA repair, with recently published work on MRE11 and TIP60 showing promising initial results(37, 38). These markers will need to be validated and then tested prospectively. Given experiences in SPARE, design of any such study will need to consider the powerful influence of patient and clinician preferences and issues of equipoise.

Conclusions

A randomised phase III trial comparing selective bladder preservation and cystectomy after neoadjuvant chemotherapy was not feasible. Due to the small number of participants, firm conclusions about disease and toxicity outcomes following these interventions cannot be drawn, although high rates of bladder preservation appear to be achievable in chemotherapy responders without compromising OS.

Acknowledgements

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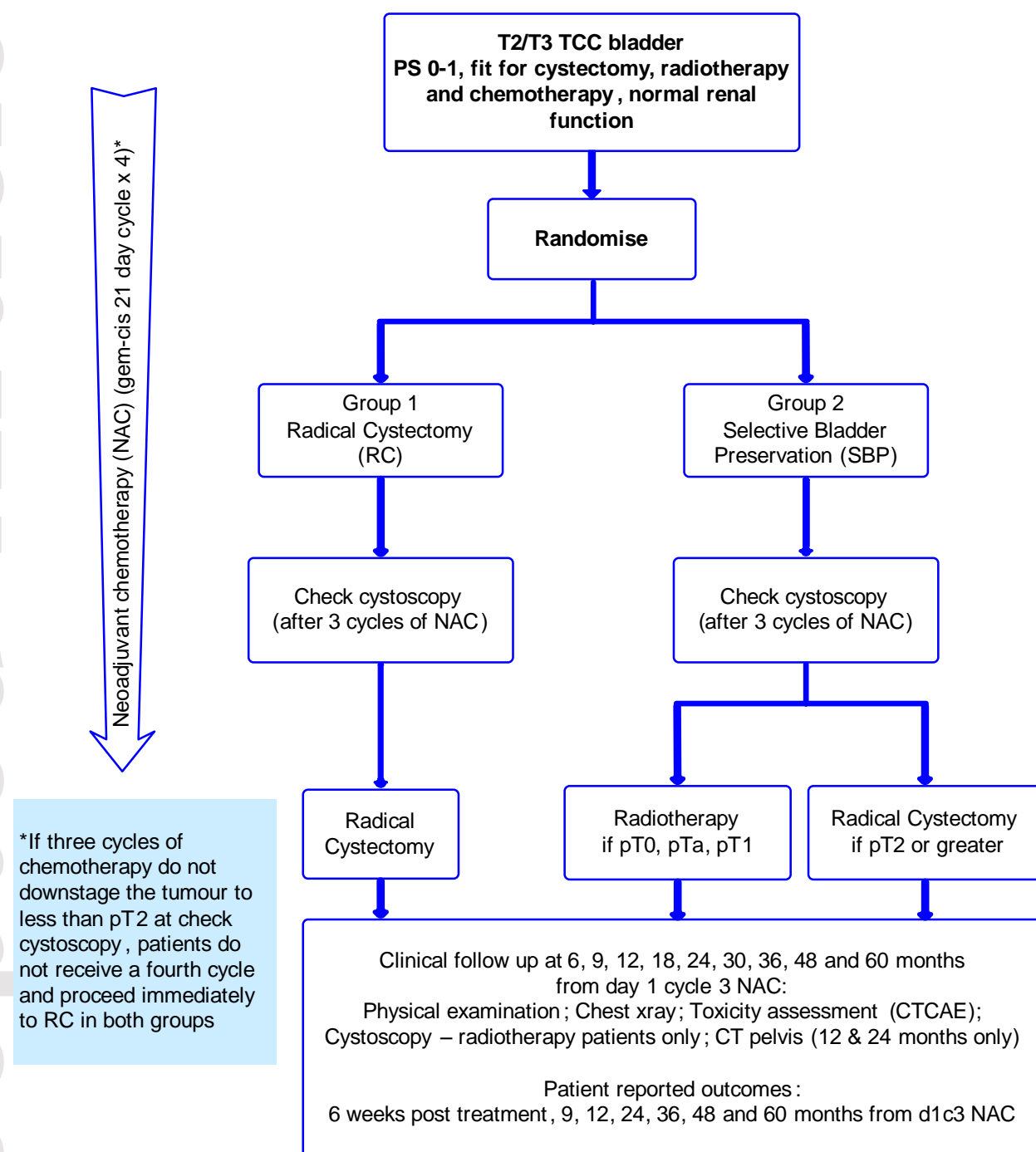
Figure 1 Trial schema

Figure 2 Patient flow through trial

Patients screened
796
From 27 centres

Ineligible
490

Eligible
306

Not approached
141

Approached
165

Declined 120
Did not want to be randomised (18)
Did not want chemotherapy (5)
Preferred RT (51)
Preferred surgery (25)
Other reason / reason unknown (21)

Randomised
45

Radical cystectomy (RC)
25

Selective bladder preservation (SBP)
20

Response to neo-adjuvant chemotherapy (23)

Response data missing (2)

Response to neo-adjuvant chemotherapy (17)

No response to neo-adjuvant chemotherapy (3)

CT4 prescribed (20)

CT4 not prescribed (3)

CT4 not prescribed (2)

CT4 prescribed (15)

CT4 not prescribed (2)

CT4 not prescribed (3)

RC (16) | RT (4) | RC (2)[1] | RT (1)[2] | RC (1) | RT (1) | RC (1) | RT (14) | RC (1)[3] | RT (1)[4] | RC (2) | RT (1)

BC:
1 MIBC | 1 NMIBC | 1 MIBC | 1 MIBC | 1 MIBC | 7 NMIBC | 1 MIBC

SCX:
1 | 1 | 2 | 1

MR:
1 | 1 | 1 | 1 | 2 | 2 | 1 | 1

Alive (12) | Dead (2)[B,C] | Dead (1)[A] | Dead (1)[A] | Alive (3) | Alive (1) | Alive (1) | Dead (1)[A] | Alive (1) | Dead (1)[A] | Dead (1)[A] | Alive (1) | Dead (1)[A] | Alive (2) | Dead (2)[A] | Alive (3) | Dead (2)[D,E] | Alive (2) | Dead (2)[A] | Alive (1) | Dead (1)[A] | Dead (1)[F] | Alive (1) | Dead (1)[A]

Note: pathways highlighted in green indicate per-protocol pathways (i.e. definitive treatment received is correct according to allocated treatment strategy).

Abbreviations: RC: radical cystectomy, SBP: selective bladder preservation, CT4: chemotherapy cycle 4, RT: radiotherapy, MIBC: muscle invasive bladder cancer, NMIBC: non-muscle invasive bladder cancer, BC: bladder cancer recurrence, SCX: salvage cystectomy, MR: metastatic recurrence

Reasons chemotherapy cycle 4 was not prescribed in responders: [1]patient refusal, proceeded to surgery (2); [2]no reason specified but cycles 2 & 3 both reduced and delayed due to on treatment toxicity; [3]joint decision between surgeon, oncologist & patient to proceed straight to RC; [4]patient discontinued during cycle 2 due to myocardial infarction

Causes of death: [A]bladder cancer; [B]pulmonary; [C]aspirated pneumonia, critical illness, neuropathy; [D]small cell lung cancer; [E]myocardial infarction, ischaemic heart disease; [F]carcinomatosis

Table 1 Baseline characteristics and compliance with allocated treatment

	Cystectomy (N=25)	SBP (N=20)	Total (N=45)
	N (%)	N (%)	N (%)
Tumour characteristics			
Gender			
Male	22 (88)	18 (90)	40 (89)
Female	3 (12)	2 (10)	5 (11)
Age			
Mean (SD)	67.6 (6.1)	63.3 (8.5)	65.7 (7.5)
Median (min, max)	67 (58.2, 81.1)	63.2 (37.9, 75.2)	65.3 (37.9, 81.1)
Patient characteristics			
Clinical stage			
T2	22 (88)	14 (70)	36 (80)
T3a	0 (0)	2 (10)	2 (4)
T3b	1 (4)	2 (10)	3 (7)
Missing	2 (8)	2 (10)	4 (9)
Pathological stage			
pT1	1 (4)	1 (5)	2 (4)
pT2	24 (96)	19 (95)	43 (96)
Tumour grade			
G2	1 (4)	3 (15)	4 (9)
G3	24 (96)	17 (85)	41 (91)
Type of chemotherapy			
Gem-Cis	24 (96)	20 (100)	44 (98)
Other (Gem-Carbo)	1 (4)	0 (0)	1 (2)
Compliance with allocated treatment			
Responder	**23 (92)**	**17 (85)**	**40 (89)**
Cystectomy	*18 (72)*	*2 (10)*	*20 (44)*
Radiotherapy	*5 (20)*	*15 (75)*	*20 (44)*
Non-responder	**0 (0)**	**3 (15)**	**3 (7)**
Cystectomy	*- (-)*	*2 (10)*	*2 (4)*
Radiotherapy	*- (-)*	*1 (5)*	*1 (2)*
Response data missing	**2 (8)**	**0 (0)**	**2 (4)**
Cystectomy	*1 (4)*	*- (-)*	*1 (2)*
Radiotherapy	*1 (4)*	*- (-)*	*1 (2)*

Greyed cells indicate correct definitive treatment based on allocation and response to chemotherapy.

Table 2a Worst overall toxicity grade by treatment received for all participants

	Cystectomy (N=23)	Radiotherapy (N=22)	Total (N=45)
CTCAE v3 grade	N (%)	N (%)	N (%)
0	0 (0)	0 (0)	0 (0)
1	2 (9)	6 (27)	8 (18)
2	5 (22)	8 (36)	13 (29)
3	10 (43)	8 (36)	18 (40)
4	6 (26)	0 (0)	6 (13)
Total G0-2	7 (30)	14 (64)	21 (47)
Total G3-4*	16 (70)	8 (36)	24 (53)

*2-sided Fisher's exact test comparing number G3-4 events between the two groups P=0.038

Table 2b as table 2a, excluding erectile dysfunction

	Cystectomy (N=23)	Radiotherapy (N=22)	Total (N=45)
CTCAE v3 grade	N (%)	N (%)	N (%)
0	0 (0)	0 (0)	0 (0)
1	4 (17)	7 (30)	11 (48)
2	7 (30)	9 (39)	16 (70)
3	6 (26)	6 (26)	12 (52)
4	6 (26)	0 (0)	6 (26)
Total G0-2	11 (48)	16 (70)	27 (117)
Total G3-4*	12 (52)	6 (26)	18 (78)

*2-sided Fisher's exact test comparing number G3-4 events between the two groups P=0.130

Figure 3a Time to first G3-4 toxicity by definitive treatment received
Patients in the radiotherapy group are censored at time of salvage cystectomy if this
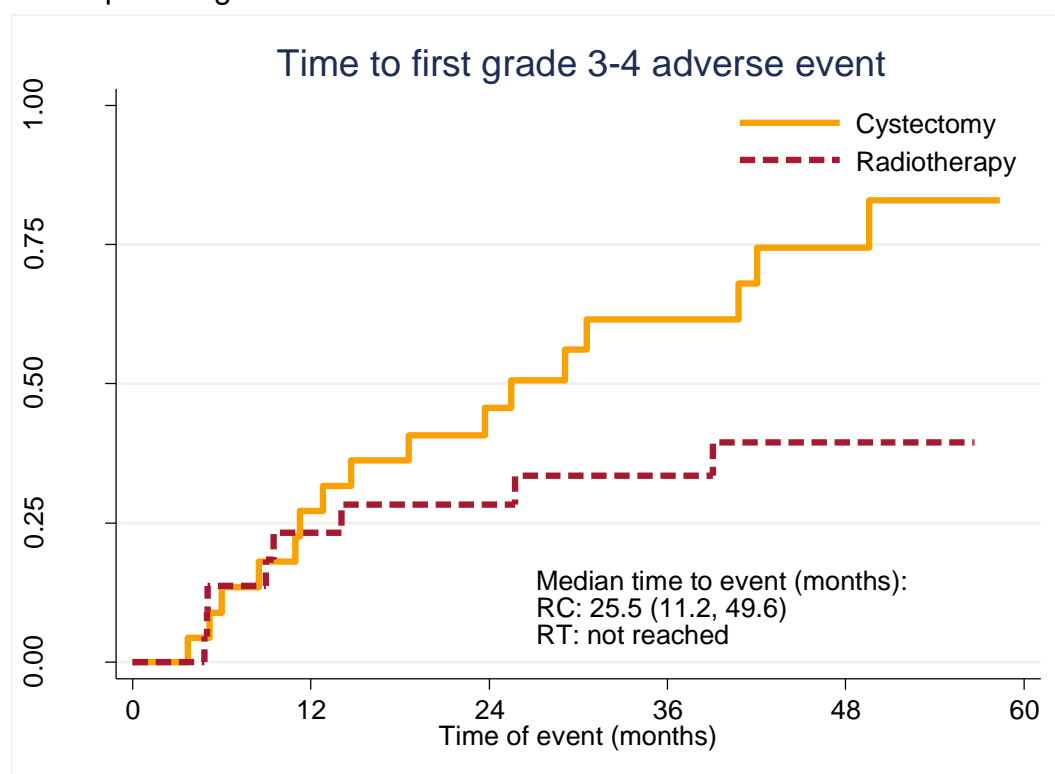occurs prior to grade 3-4 adverse event

Figure 3b (excluding erectile dysfunction)
Patients in the radiotherapy group are censored at time of salvage cystectomy if this
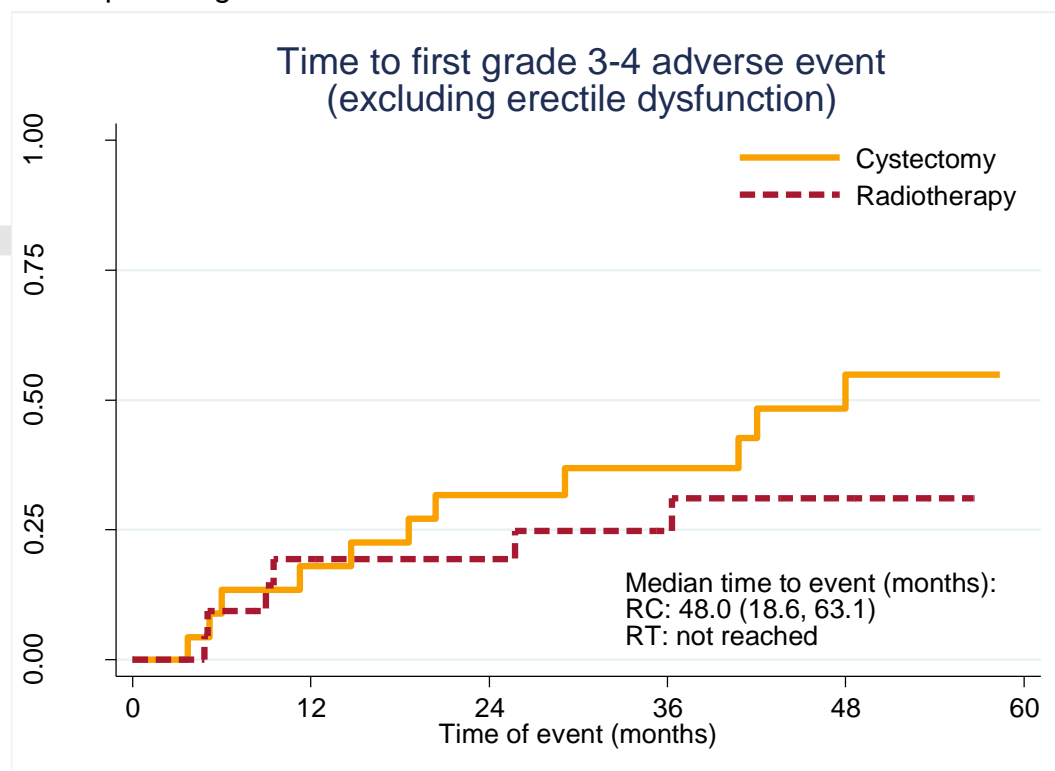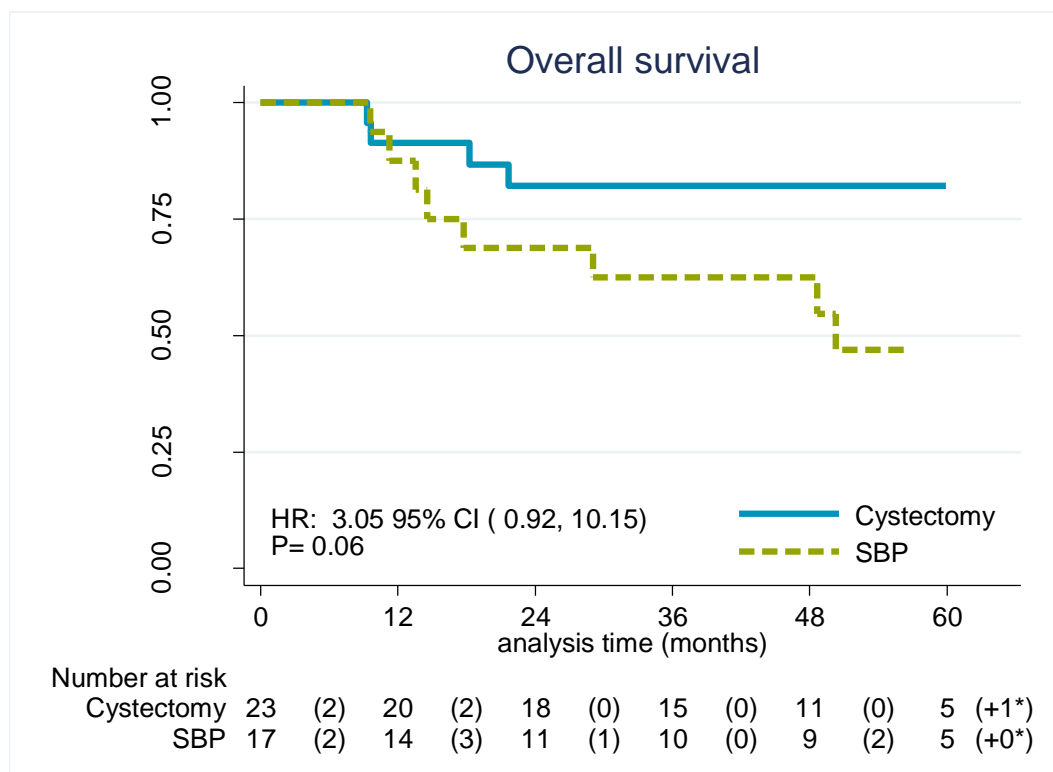occurs prior to grade 3-4 adverse event

Figure 4
Time to event endpoints
Presented by allocated treatment for the population of patients who responded to chemotherapy

In all cases, patients with a second primary without a prior event were censored at the date of second primary and patients without an event were censored at the date last seen.
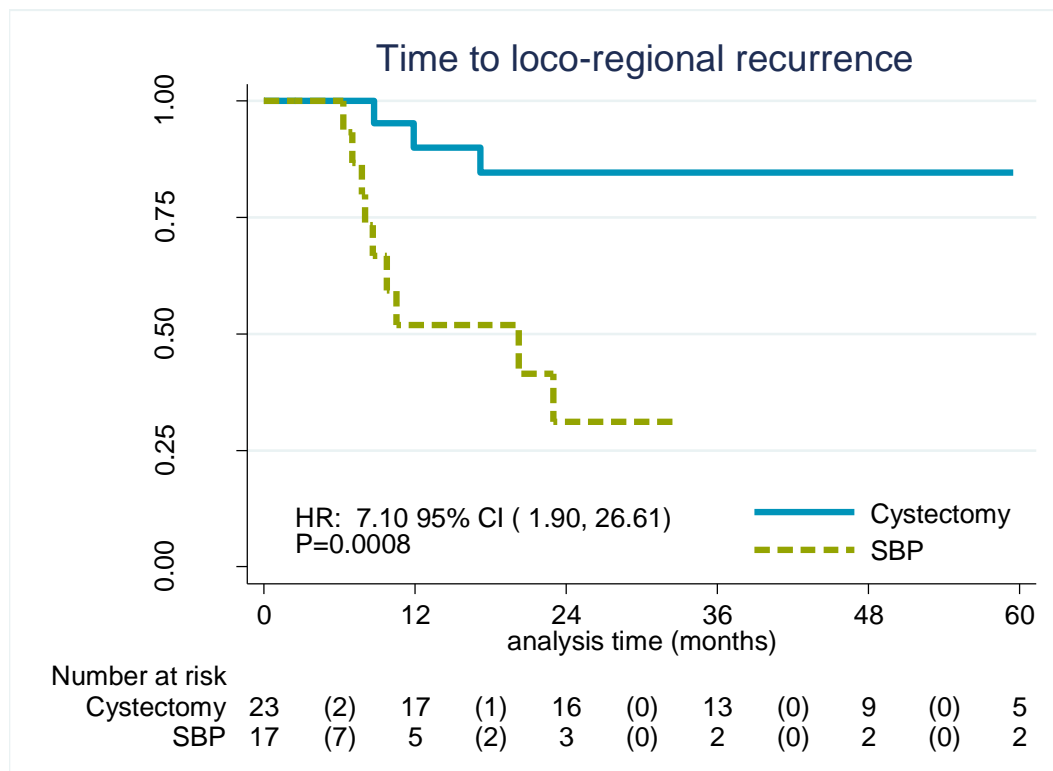
Comparisons between groups were made using the Log Rank test.
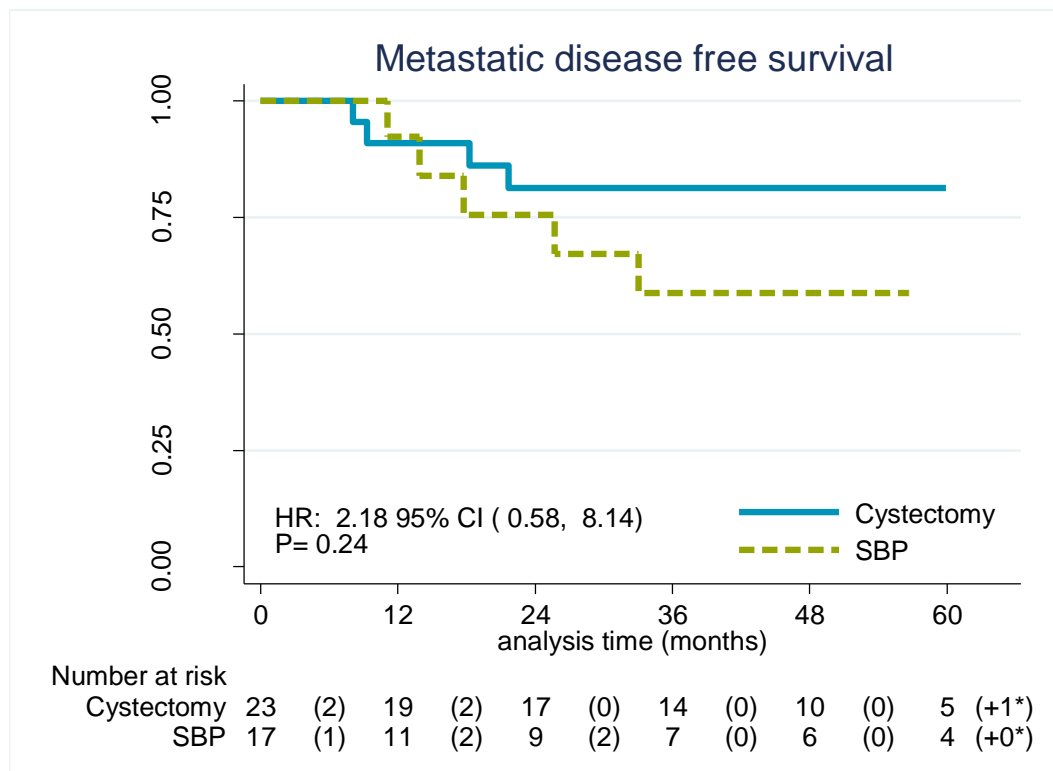
Overall survival

*events occurred after 60 months

LRR

Time to loco-regional recurrence

HR: 7.10 95% CI (1.90, 26.61)
P=0.0008

— Cystectomy
--- SBP

analysis time (months)

Number at risk

	0		12		24		36		48		60
Cystectomy	23	(2)	17	(1)	16	(0)	13	(0)	9	(0)	5
SBP	17	(7)	5	(2)	3	(0)	2	(0)	2	(0)	2

LRR: patients diagnosed with distant recurrence without a prior loco-regional recurrence were censored at the date of diagnosis of distant recurrence and patients who underwent a cystectomy for reasons other than recurrence were censored at the date of cystectomy

Note: of the 7 patients in the SBP group who underwent radiotherapy per protocol and had NMIBC recurrence, 5 are long term survivors while 2 have died following metastatic recurrence. 1 SBP patient underwent radiotherapy per protocol, had MIBC and metastatic recurrence and died despite undergoing salvage cystectomy.

MFS

Metastatic disease free survival

HR: 2.18 95% CI (0.58, 8.14)
P= 0.24

——— Cystectomy
- - - SBP

analysis time (months)

Number at risk

	0		12		24		36		48		60	
Cystectomy	23	(2)	19	(2)	17	(0)	14	(0)	10	(0)	5	(+1*)
SBP	17	(1)	11	(2)	9	(2)	7	(0)	6	(0)	4	(+0*)

*events occurred after 60 months

Table 3
Change in EORTC QLQ C30 subscale scores from baseline to month 12

|	Cystectomy			Radiotherapy			Cystectomy vs Radiotherapy	
	n	Mean change from BL	99% CI	n	Mean change from BL	99% CI	Difference* (Radiotherapy-Cystectomy)	99% CI
Global health status	18	-11.6	-31.9 to 8.7	12	7.64	-11.9 to 27.1	14.2	-11.1 to 39.5
Physical function	18	-10	-23.9 to 3.9	10	-2.67	-22.9 to 17.6	7.76	-13.9 to 29.4
Role function	18	-8.3	-32.8 to 16.1	12	0	-25.5 to 25.5	15.27	-16.3 to 46.9
Emotional function	18	6.5	-6.4 to 19.4	12	6.25	-7.3 to 19.8	3.03	-11.9 to 18.0
Cognitive function	18	6.5	-4.7 to 17.6	12	-2.78	-16.8 to 11.2	-2.59	-14.5 to 9.3
Social function	18	-7.4	-35.1 to 20.3	12	4.17	-25.8 to 34.1	16.62	-16.6 to 49.9
Fatigue	16	-4.9	-28.4 to 18.7	12	-11.11	-35.5 to 13.3	-9.28	-33.2 to 14.7
Nausea / vomiting	18	-7.4	-17.2 to 2.3	12	0	-14.3 to 14.3	5.46	-8.3 to 19.2
Pain	18	1.9	-13.7 to 17.4	11	0	-14.2 to 14.2	-2.71	-19.4 to 14.0
Dyspnoea	18	0	-17.5 to 17.5	11	-3.03	-12.6 to 6.6	-3.47	-23.7 to 16.8
Insomnia	18	-5.6	-34.0 to 22.9	12	-2.78	-26.5 to 20.9	-7.72	-38.0 to 22.5
Appetite loss	18	0	-13.5 to 13.5	12	-2.78	-26.5 to 20.9	-3.53	-23.5 to 16.4
Constipation	18	-7.4	-30.3 to 15.4	12	2.78	-29.6 to 35.2	-2.86	-32.5 to 26.8
Diarrhoea	18	0	-7.8 to 7.8	12	0	-12.7 to 12.7	-0.69	-11.2 to 9.8
Financial problems	18	-3.7	-14.4 to 7.0	12	0	0 to 0	1.68	-10.8 to 14.1

Note: Confidence intervals were constructed using Student's t-distribution. No P-values were calculated.
Note: High scores indicate better function for functional subscales, and high scores indicate worse symptoms / more problems for all other scales.
*ANOVA difference in the change in 12 month subscale score from baseline between patients receiving radiotherapy and patients receiving cystectomy as definitive treatment, adjusting for baseline subscale score.

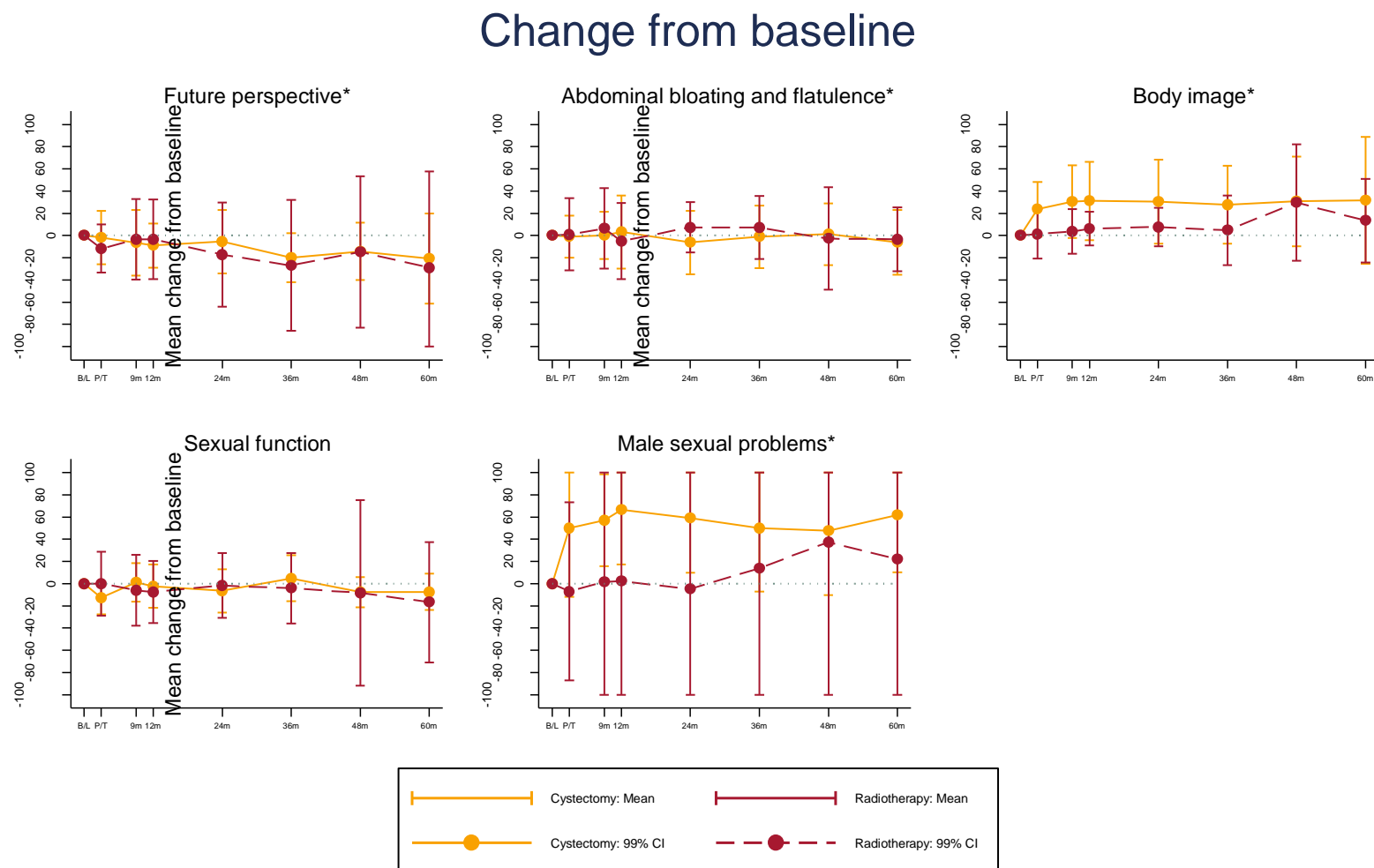Figure 5: Mean change from baseline in EORTC QLQ-C30 subscales

Change from baseline

Figure 6: Mean change from baseline in EORTC QLQ-BLM30 subscales

Change from baseline
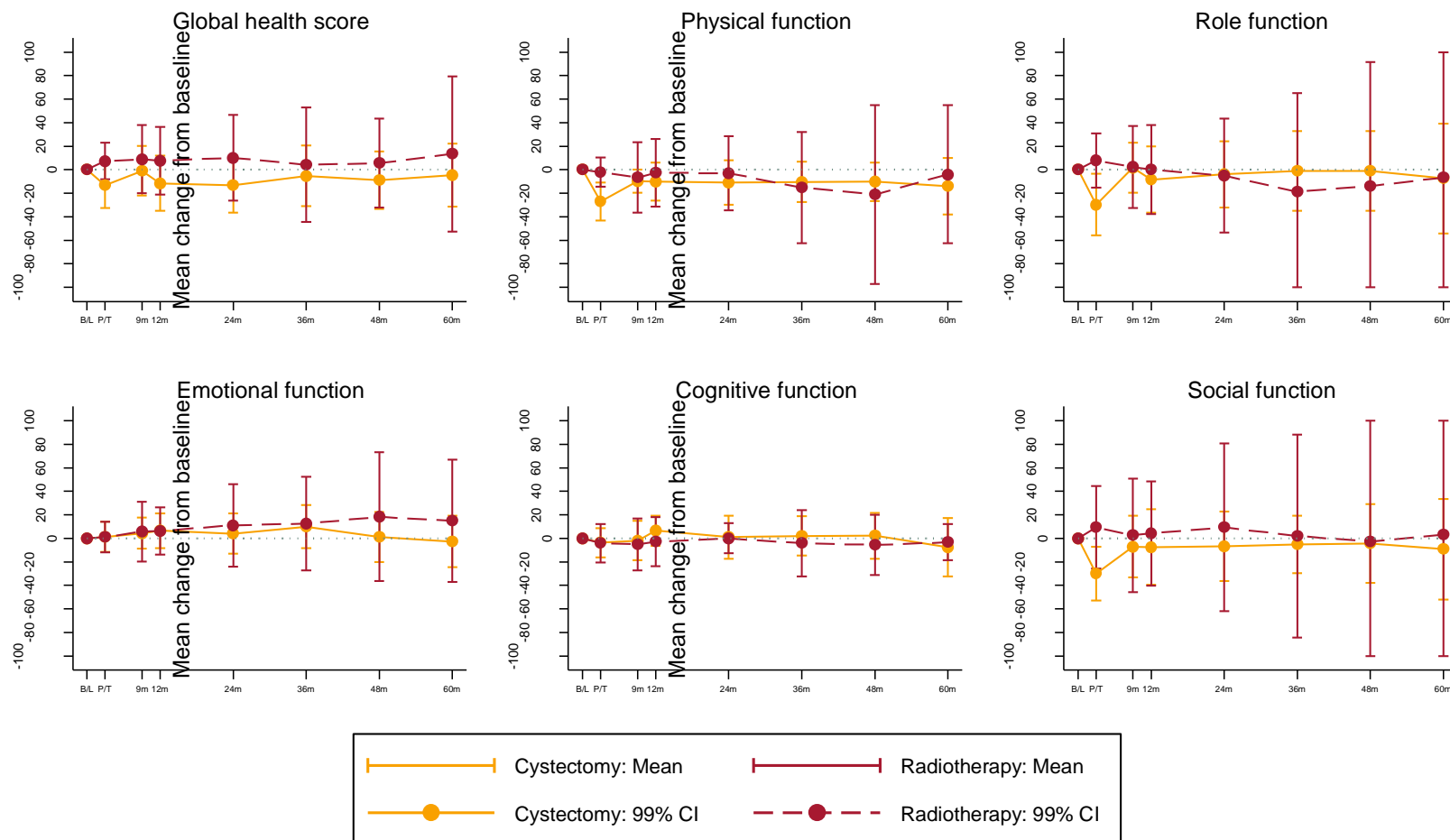
B/L: baseline; P/T: post-treatment
Note: High scores indicate better function for functional subscales (sexual function), and high scores indicate worse symptoms / more problems for all other scales (denoted *).

Note: While the EORTC QLQ-BLM30 module is available for use it had not yet been validated at the time of analysis (i.e. the module had been carefully developed and tested for acceptability with patients, but had not undergone psychometric testing in a large international group of patients). The suggested subscales for this module are still under review and may change after psychometric analysis. The scoring procedure for the sexual function subscale was guided by the validated EORTC QLQ-NMIBC24 questionnaire.