A RANDOMISED PHASE III STUDY OF RADIOTHERAPY WITH AND WITHOUT SYNCHRONOUS CHEMOTHERAPY IN MUSCLE INVASIVE BLADDER CANCER *

(ISRCTN 68324339

EUDRACT 2004-000164-26)

PROTOCOL

An NCRI trial supported by the Cancer Research UK

www.bc2001.bham.ac.uk

*This trial was previously: A 2x2 Factorial randomised phase III study comparing standard versus whole bladder radiotherapy with tumour boost with and without synchronous chemotherapy in muscle invasive bladder Cancer

Protocol version 5 dated 10/08/2006

Administration

This clinical trial protocol is intended to provide guidance and information for the conduct of the Bladder Cancer Trial (BC2001) in participating centres. It is not for use as a guide for the management of other patients outside of the trial. Every care was taken in the protocols drafting, but corrections and amendments may be necessary and these will be circulated to known participants in the trial.

Urgent Clinical enquiries should be directed to Dr Robert Huddart (Radiotherapy) and Prof Nick James (Chemotherapy).

Please contact your trial co-ordinator with any general or administrative queries.

Trial Co-ordination/ Data Management:

Ms Carey Hendron
Clinical Trials Unit
Cancer Research UK Institute for Cancer Studies
Cancer Trial Unit
The University of Birmingham, Vincent Drive
Edgbaston, Birmingham B15 2TT
Tel: 0121 414 7559 Fax: 0121 414 3263
Email:C.Hendron@bham.ac.uk

Ms Kathryn Briggs/ Ms Sheetal Patel
Clinical Trials and Statistics Unit
Institute of Cancer Research
Sir Richard Doll Building
15 Cotswold Road
Sutton, Surrey SM2 5NG
Tel: 020 8722 4058/ 020 8643 8901 Ext 4514
Fax: 020 8770 7876
Email: Kathryn.Briggs@icr.ac.uk
Sheetal.Patel@icr.ac.uk

Chief Investigators:

Prof Nicholas James
Cancer Research UK Institute for Cancer Studies
The University of Birmingham, Vincent Drive
Edgbaston, Birmingham
B15 2TT
Tel: 0121 414 7584/4097 Fax: 0121 414 3263
Email:N.D.James@bham.ac.uk

Dr Robert A Huddart
Institute of Cancer Research
Royal Marsden Hospital
Downs Road
Sutton, Surrey SM2 5PT
Tel: 020 8661 3457/3529 Fax: 020 8643 8809
Email: Robert. Huddart@icr.ac.uk

Co-Investigator

Dr. Syed A. Hussain
Cancer Research UK Institute for Cancer Studies
The University of Birmingham
Vincent Drive
Edgbaston, Birmingham
B15 2TT
Tel: 0121-4721311- Q.E Hospital
Email: S.A.Hussain@bham.ac.uk

Statistician

Dr Emma Hall
Clinical Trials and Statistics Unit
Brookes Lawley Building
Institute of Cancer Research
15 Cotswold Road
Sutton, Surrey SM2 5NG
Tel: 020 8722 4292 Fax: 020 8770 7876
Email: emma.hall@icr.ac.uk

Randomisation Only: 020 8643 7150 Fax: 020 8770 7876

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SUMMARY OF VERSION 5

1. The radiotherapy comparison has closed to further recruitment. Therefore there are now only 2 randomised treatment options. These are:

    - Standard volume radiotherapy with synchronous chemotherapy
    - Standard volume radiotherapy alone

    Patients may be treated with standard volume radiotherapy or whole bladder radiotherapy and tumour boost at the discretion of the treating clinician; however choice of radiotherapy will need to be stated before the patient is randomised.

    Details of the radiotherapy comparison remain in the protocol for information only; this can be identified by the dark grey font.

    The planned follow-up for all patients in the trial remains unchanged.

2. The power of the trial has been reduced to 80%. The target accrual has therefore been reduced to 350 patients randomised to synchronous chemotherapy versus no chemotherapy.

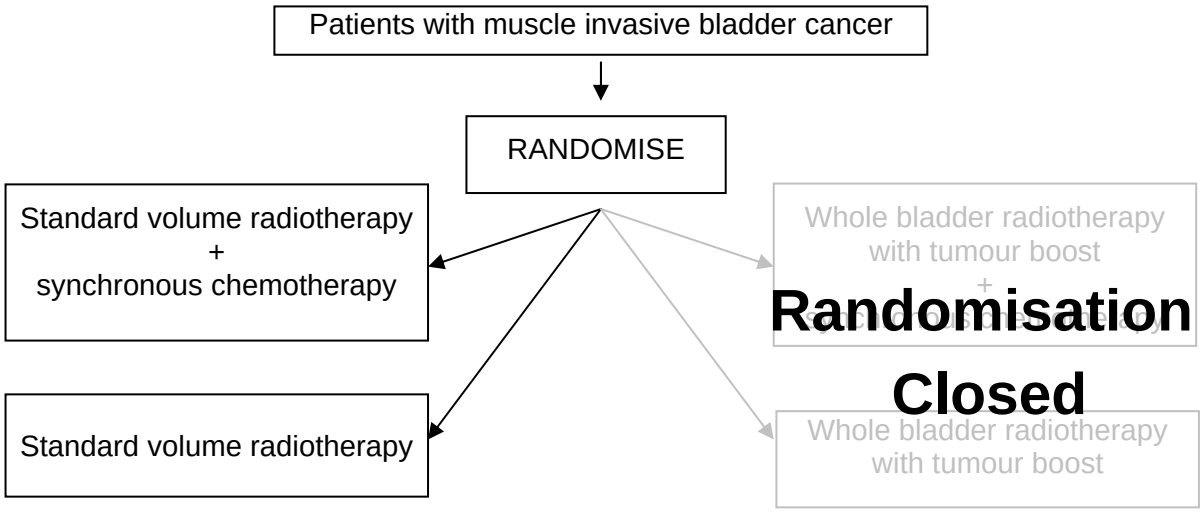
3. Two further secondary endpoints have been added. These are:

    - Disease free survival
    - Metastases free survival

4. Guidance on recording toxicity, dose modifications and discontinuation of treatment is included.

1 SUMMARY

A randomised phase III study of radiotherapy with and without synchronous chemotherapy in muscle invasive bladder cancer*



Aims	**To determine the efficacy and toxicity of synchronous chemo-radiotherapy in conservative management of invasive bladder cancer compared to radiotherapy alone**
Study Design	**Randomised, multicentre study**
Patients	**350 patients, with histologically proven invasive bladder cancer, fit to undergo the protocol**
End points	**Primary: Loco-regional (pelvic nodes & bladder) disease free survival** **Secondary: Disease free survival, metastases free survival, Late toxicity at 1 and 2 years as assessed by: RTOG/ Lent Som toxicity score, Bladder capacity, Fact-BL Quality of Life scores** **Tertiary: Acute toxicity, Cystoscopic local control at 3 months, 1 year and 2 years, Rate of salvage cystectomy, Overall survival**
Stratification	**Centre** **Neo-adjuvant chemotherapy (yes/no)**
Follow-up	**Weekly during, and at the end of treatment,** **6 months, 9 months post randomisation and annually thereafter**

*This trial was previously: A 2x2 Factorial randomised phase III study comparing standard versus whole bladder radiotherapy with tumour boost with and without synchronous chemotherapy in muscle invasive bladder Cancer

2. OBJECTIVES

a. To investigate the efficacy and toxicity of synchronous chemo-radiotherapy in conservative management of invasive bladder cancer compared to radiotherapy alone.

The following objective relates to the radiotherapy comparison which has now closed:

b. To investigate whether modifying the volume of bladder irradiated by the full dose of radiotherapy can reduce toxicity of radiotherapy in the conservative treatment of invasive bladder cancer, without impacting on local control.

3. BACKGROUND

Bladder cancer, with over 13,000 new cases in 1995, is the 5th most common cause of cancer in the UK (cancer fact sheet). Approximately 20% of newly diagnosed cases are invasive. Sixty percent of patients with T2 bladder cancer survive 5 years whilst for T3N0 patients 5 year survival is about 40%. Patients with more advanced or nodal disease do significantly worse. To improve outcome, neoadjuvant and adjuvant chemotherapy has been tested in numerous phase II and a few phase III studies. To date this approach has not had a significant impact on overall survival (1-4).

The optimum management strategy for control of local disease remains to be determined. Surgical removal of the bladder may attain local control but 20-30% of patients may develop a local relapse (5-7) and all will need either reconstructive bladder surgery (which is either not available or not applicable to the majority of UK patients) or an ileal diversion. Radical radiotherapy has been commonly used as an alternative especially in the UK. This approach suffers from a relatively high rate of incomplete response or local recurrence (up to 50%) with salvage cystectomy being used for failures (8). Even in the absence of more effective systemic therapy, improving bladder preservation is likely to lead to an improved quality of life (QoL) for patients with this disease.

There are indications from other primary sites that synchronous chemo-radiotherapy may produce local control and survival advantages (9-12). In particularly the UKCCCR study comparing radiotherapy with synchronous chemotherapy in anal cancer shows a substantial advantage in local control to the synchronous therapy arm (13). This approach is being explored in other primary sites for example in head and neck cancer in the UKHAN 1 trial.

A variety of phase II studies have studied the efficacy and toxicity of this approach in bladder cancer generally with results better than that seen with radiotherapy alone (see table 1 and (14-36). Recently four large randomised studies on the use of synchronous chemo-radiotherapy for cervical cancer (37-40) showed reductions in odds of death or recurrence of around 50% with the addition of synchronous chemotherapy. This prompted the National Cancer Institute to issue a rare clinical announcement that strong consideration should be given to the incorporation of concurrent cisplatin therapy in women who require radiation therapy for treatment of cervical cancer.

Table 1 Overview of phase II studies utilising concomitant chemotherapy and radiotherapy in the treatment of invasive bladder cancer.

First author (Year)	N	Type of chemotherapy	Concomitant chemotherapy schedule	Median follow-up	CR	Survival
Jakse[16] (1985)	22	Cisplatin 70mg/m^2	Wk 1,4,7	14 months	77%	NS
Coppin[17] (1986)	29	Cisplatin100mg/m^2	Wk 1,3		76%	82% (3yr)
Jakse[18] (1987)	11	Cisplatin 70mg/m^2 Adriamycin 10mg/m^2		8 months	82%	NS
Jakse[19] (1989)	8 16	Adriamycin 10mg/m^2 OR Adriamycin 20mg/m^2			75% 75%	NS
Rotman[22] (1990)	19	5 FU 25mg/kg/day for 5 days Mitomycin C 10mg/m^2 day 1 (5pts)	3 weekly	38 months	74-89%	54% (5yr)
Russell[23] (1990)	34	5-FU 1000mg/m^2/day x4	Wk 1,4	18 months	81%	64% (45 months)
Rebischung[24] (1992)	69	5-FU 200mg/m^2 days 1-4 Cisplatin 20mg/m^2 days 1-4			78.5%	56%
Utsunomiya[25] (1992)	15	Cisplatin 20mg/m^2 days 1-5	Wk 1,4		20%	NS
Housset[26] (1993)	54	Cisplatin 15mg/ms/day 5-FU 400mg/m^2/day days 1-3	Wk 1,3	27 months	74%	59% (3yr)
Matshushima[27] (1993)	50	Cisplatin 20mg/m^2 days 1-5	Wk 1,4		59%	NS
Tester[28] (1993)	47	Cisplatin 100mg/m^2	Wk 1,3		66%	64% (3yrs)
Benoit[29] (1995)	17	5-FU Cisplatin (dose NS)			53% (N+ only)	NS
Chauvet[31,32] (1996/8)	109	Cisplatin 20-25mg/m^2 days 1-5	Wk 2,5	73 months	79%	36% (5 yrs)
Chauvet[33] (1998)	46	Cisplatin 80mg/m^2 day 1 5-FU 800mg/m^2 days 2-5 (23 got extra 2 courses of MCV)	Wk 1,5	38 months	65%	53% (3 yrs)
Sauer[34] (1998)	115 + 69	Cisplatin 25mg/m^2 days 1-5 or Carboplatin 65mg/m^2 days 1-5	Wk 1, 5 Wk 1, 5	7.5 years	85% 70%	69% (5 yrs) 57%
Birkenhake[35] (1999)	25	5-FU 600mg/m^2 for 5 days Cisplatin 20mg/m^2 days 1-5	Wk 1,5	38 months	88%	NS
Radosevic[36]	67	Carboplatin 150mg day 5 (to total 900mg)	Weekly		92.5%	55% (5 yrs)

CR complete response rate; NS not stated
In some studies a proportion of patients received elective cystectomy.
Studies utilising neoadjuvant chemotherapy in addition are not included.
* In the 12 patients treated conservatively

Currently, the only randomised evidence in bladder cancer comes from a small trial by the National Cancer Institute of Canada (41). This study randomised 99 patients to receive cisplatin 100mg/m^2 with radiotherapy or radiotherapy alone to a dose of 40Gy followed by elective cystectomy or further radiotherapy. The chemo-radiotherapy arm showed statistically non-significant improvements in complete response rate to radiotherapy (24/51 v 14/48; difference 16% [95% CI: -5 to 37%], p=0.11) and in overall survival (47% v 33% at 3 years, log rank p=0.34). Significant differences were seen in the pattern of relapse. The risk of pelvic failure was significantly reduced in the chemo-radiotherapy arm (15/51 v 36/48, p=0.026) with a corresponding improvement in pelvic-progression free survival (67% v 47% at 2 years, log rank p=0.038) and bladder preservation (70% v 36%, log rank p=0.16). The small numbers treated suggest the power of the study was limited and further investigation of this area is therefore justified.

Cisplatin is not the ideal drug in a chemo-radiotherapy of bladder cancer as significant proportions of patients have impaired renal function and administration would require inpatient stay and hydration. It is therefore proposed to use the combination of 5-Fluorouracil (5-FU), Mitomycin C and radiotherapy using a similar schedule to that adopted in the UKCCCR anal carcinoma study (13). This regimen has thus been extensively assessed in terms of feasibility and toxicity and has the advantage that it is not limited by renal function problems. 5-FU is systemically active in bladder cancer (42-44). Mitomycin C is used in the treatment of superficial disease and is of value as a radiosensitiser. Low dose 5-FU and Mitomycin C were tested in a small phase II study of predominantly T3/T4 patients and achieved a 74% clinical complete response (CR) rate and long-term survival of 54% (22). In our pilot study undertaken in Birmingham we evaluated Mitomycin C 12mg/m^2 day 1 and 5-FU 500mg /m^2 /day days 1-5 and 16-20 plus radiotherapy 55Gy in 20 fractions. Ten out of 20 (50%) patients had hydronephrosis and seven had a GFR<50 ml/min. Pathological CR rate in the bladder at 3 months was 70% (45). Dose escalation to 14 days total infusion led to grade III bladder and bowel toxicity proving 10-day infusion as the maximum tolerated dose.

Endpoints of this trial will be loco-regional disease-free survival (i.e. pelvic-progression free survival, with pelvic relapse/control judged by cystoscopy and CT scan), overall disease free survival, metastases free survival, toxicity, assessed using standard scales (RTOG and Lent Som), and overall quality of life (QoL) as measured by the patient completed Fact-BL questionnaire (52-54).

The following relates to the radiotherapy comparison which has now closed:

An alternative approach to improve local control is to escalate the radiation dose. Conventional radiation dose is limited by the incidence of late side effects, predominantly in the treatment of bladder cancer, involving the bladder. Generally, the whole bladder has been included in the radiotherapy fields as it has been thought that the development of bladder cancer is associated with a mucosal field change. However the need to treat the whole bladder rather than the tumour alone has not been clearly established. Indeed the lack of efficacy of radiation in the treatment of superficial disease and the success of interstitial radiotherapy which gives a high but localised dose questions this belief (46-47).

Recent data, including a randomised-controlled trial in prostate cancer (48) has shown that shielding normal tissue can reduce late effects and perhaps allow dose escalation. This raises the question of whether reducing the volume irradiated in bladder cancer radiotherapy could also allow dose escalation. Data on the relative tolerances of the whole versus part of the bladder to radiotherapy is sparse (49,

50). In a review of partial versus whole organ effects of radiotherapy by Emani et al. (49) data were pooled from a number of sources and suggested that the TD 5/5 (5% side-effect at 5 years) for a contracted bladder was 65Gy for the whole organ versus 80 Gy for 2/3 organ irradiation. In a similar study Marks *et al*. calculated the tolerance of the bladder to global radiotherapy to be between 50-55 Gy but calculated the tolerance of parts to be in order of 65-75Gy (50).

Initial experience at the Royal Marsden Hospital with 2 phase treatment of the bladder (52Gy to the whole bladder and a 12 Gy tumour boost) has shown a 50% reduction of RTOG grade 3 and 4 complication rate compared to consecutively treated patients receiving conventional whole bladder treatment to the same dose (41% for conventional whole bladder radiotherapy versus 22% for those treated in 2 phases p=0.034) (51). Though much of this difference may be due to selection bias this result encourages exploration of partial bladder treatments in more detail. Overall survival (39.9% conventional versus 42.2% 2-phase 5 year median survival, p=0.86) and relapse free survival (29.9% versus 22.9% 5 year RFS, p=0.235) were equivalent.

Reduction in bladder toxicity and volumes irradiated would be advantageous in the context of using synchronous chemo-radiotherapy and could allow for subsequent radiation dose escalation or addition of further chemotherapy. As these two approaches would be complimentary; it is proposed to test both the use of synchronous 5-FU and Mitomycin C and reduced bladder irradiation in a randomised phase III trial using a 2x2 factorial design.

4 TRIAL DESIGN

A multicentre randomised phase III trial comparing synchronous 5-FU/Mitomycin C with radiotherapy versus radiotherapy alone

Previously: A 2x2 factorial randomised phase III study comparing standard versus Whole bladder radiotherapy with tumour boost with and without synchronous chemotherapy in muscle invasive bladder cancer

5 ENDPOINTS

5.1 Primary endpoint

Loco-regional (i.e. pelvic nodes & bladder) disease free survival. The particular time point of interest is 2 years post randomisation.

5.2 Secondary endpoint

Disease free survival, Metastases free survival, Late toxicity at 1 and 2 years as assessed by RTOG and Lent Som toxicity scores, bladder capacity and Fact-BL QoL score. This endpoint is of particular importance in the radiotherapy comparison.

5.3 Tertiary endpoints

- Acute toxicity
- Cystoscopic local control at 6 months, 1 year and 2 years post randomisation.
- Rate of salvage cystectomy
- Overall survival

6 ELIGIBILITY

6.1 Inclusion criteria

- Aged 18 or over
- Histologically proven invasive bladder carcinoma (adenocarcinoma, transitional or squamous cell carcinoma)
- Localised muscle invasive carcinoma either surgically or by imaging (T2-T4a N0 M0).
- WHO performance status of grade 0 to 2
- Leucocytes > $4.0x10^9$/L, platelets > $100x10^9$/L
- GFR > 25ml/min
- Serum bilirubin < 1.5 upper limit of reference range (ULRR) ALT or AST < 1.5 x ULRR
- Patient available for long term follow up, and in the opinion of investigator, able to receive a radical course of radiotherapy
- Patient's written informed consent
- For the QoL part of the study, able to understand and complete the QoL questionnaire

6.2 Exclusion criteria

Patients with any of the following are not eligible for the trial:

- Uncontrolled systemic disease which would preclude the patient from the study
- Pregnancy
- Other malignancy within the previous 2 years (other than adequately treated BCC of the skin or adequately treated in situ carcinoma of the cervix uteri)
- Previous malignancy that is likely to interfere with protocol treatment
- Inflammatory bowel disease
- Previous pelvic radiotherapy
- Bilateral hip replacements compromising accurate radiotherapy planning

7 PRETREATMENT EVALUATION

All patients are required to undergo the following pre-treatment investigations:

- Cystoscopy and tumour biopsy or resection with random biopsies of normal bladder mucosa (as complete a transurethal resection of the bladder tumour as possible is encouraged)
- Completion of bladder map
- Physical examination (including height, weight and surface area) to assess fitness and WHO performance status
- Full blood count (FBC), Urea and electrolytes (U+E's), Liver function tests (LFTS) to include Alkaline phosphates, ALT or AST, bilirubin, albumin. Calculated GFR by Cockcroft formula
- MRI or CT of Pelvis (MRI preferred where possible)
- Chest X-Ray
- Bone scan and liver CT/US for raised ALP or AST
- Bladder capacity (ideally assessed by urodynamic examination. Assessment by cystoscopy or ultrasound are suitable alternatives, however the same technique should be used for pre treatment and follow up assessments)
- Baseline scores of:
- RTOG toxicity
- Lent Som toxicity score
- Fact-BL QoL score

FBC, U+Es, LFTs, MRI/CT of pelvis and chest X-ray should be done no more than 4 weeks prior to randomisation unless the patient is to receive neo-adjuvant chemotherapy. In the case of patients receiving neo-adjuvant chemotherapy these investigations should be done no more than 4 weeks prior to the start of neo-adjuvant chemotherapy.

8 CENTRE ENTRY REQUIREMENTS

Centres must register intended radiotherapy dose schedule prior to entry of first patient.

9 RANDOMISATION

Randomisation will be undertaken by the Institute of Cancer Research, Clinical Trials and Statistics Unit (ICR-CTSU).

To randomise a patient:

- Obtain patient's written informed consent to participate in the study
- Complete the Randomisation Form and telephone:

☎ 020 8643 7150

(Monday - Friday 9am - 5pm)

The patient will be allocated their treatment and a trial number, which must be noted on the randomisation form.

The two possible randomisation options are:

- Synchronous 5-FU and Mitomycin with radiotherapy
- Radiotherapy alone

10 TREATMENT PROTOCOLS

For patients who have received neo-adjuvant chemotherapy it is advised that a gap of 4 weeks be left between the final dose of chemotherapy and the first fraction of on-trial radiotherapy.

Randomised treatment should commence within 6 weeks of randomisation. Patients undergoing neoadjuvant chemotherapy can be consented for BC2001 during this treatment but should not be randomised until they are nearing their final cycle of treatment.

10.1 Synchronous chemotherapy arm

10.1.1 5-Fluorouracil

5-FU will be given as a continuous infusion at 500mg/m^2/24 hours for 5 days corresponding to fractions 1-5 and 16-20 of radiotherapy (corresponding to week 1 and week 4 of treatment). This may involve inpatient care using a suitable infusion pump. Alternatives include the placement of a Hickman Line for the duration of the therapy or the temporary use of a long peripheral line such as a PICC line, which will be inserted by suitably trained nurses under local anaesthetic. This would allow the use of outpatient therapy with a disposable infusion pump (costing around £30 x 2 per patient) in most cases, particularly as they would be attending the radiotherapy department daily during chemotherapy. Experience with the use of outpatient mode of management has been encouraging with minimal complications related to the

line. The majority of patients (31/36) in the Birmingham pilot study (45) preferred the outpatient mode of management which is therefore encouraged.

Patients should not be prescribed Metronidazole while receiving 5-FU.

10.1.2 Mitomycin

Mitomycin will be given as an intravenous bolus dose of 12mg / m^2 on day 1 of radiotherapy.

10.2 Radiotherapy treatments

10.2.1 CT scanning for radiotherapy

(Please refer to the Radiotherapy Planning Document version 1.2 16/05/2002, this is also available on the web site www.bc2001.bham.ac.uk)

Tumour, clinical and planning target volumes will be defined on CT slices taken at 4-5mm intervals (4-5mm slice thickness). Patients will be scanned from bottom of ischial tuberosities to 3cm above the dome of the bladder or bottom of L5 (which ever is higher). Patients will be CT planned with an empty bladder.

The rectum should be empty of flatus and faeces.

Patients will be asked to empty their bladder 15 - 30 minutes immediately prior to scan.

Target outlining should be performed according to local practice.

10.2.2 Radiotherapy technique

Patients should be treated with an empty bladder. Physicians entering patients may choose to treat patients according to either of the techniques used in the now closed radiotherapy randomisation namely either the whole bladder throughout or treat with whole bladder radiotherapy and tumour boost.

For whole bladder radiotherapy treatment the planning target volume (PTV) is the outer bladder wall with a 1.5 cm margin plus extravesical extent of tumour with a 1.5cm margin. PTV should be covered using an anterior and 2 lateral fields to encompass the PTV in the 95% isodose.

Non-target tissue may be excluded at the discretion of treating physician.

For patients being treated with whole bladder radiotherapy with tumour boost **the PTV gross tumour volume (GTV) plus a 1.5 cm margin. GTV is tumour seen on MRI/CT with guidance of surgical bladder map. PTV should be covered by 3 or 4 coplanar fields. The aim is to achieve 100% (± 5%) of the reference dose to the reduced volume PTV and 80% (± 5%) of the reference dose to the opposite bladder wall.**

The maximum rectal dose to the posterior wall is 80% of reference dose.

Non-target normal tissues may be excluded at discretion of treating physician.

At the discretion of the physician, patients may receive radiotherapy treatments in 1 or 2 phases.

10.2.3 Radiotherapy dose

The total radiotherapy dose will be either

i. 64Gy in 32 fractions over 6.5 weeks or
ii. 55Gy in 20 fractions over 4 weeks.

Trial participants will use the same standard fractionation schedule for all patients entered and inform the Trials Office of their preferred option **before** randomising their first patient. At any centre, all patients should receive the same total dose of radiotherapy.

11 ASSESSMENTS AND FOLLOW UP

11.1 Toxicity

Side effects of radiotherapy and chemotherapy should be recorded on the treatment assessment forms. Toxicity will be assessed initially, during treatment, at 6 and 12 months and annually thereafter according to the CTC, RTOG and Lent/Som scales. Quality of life will be assessed using the Fact BL questionnaire (appendix 4). Please see section 14 on Serious Adverse Events if appropriate.

11.2 Local control

Local control will be primarily assessed by cystoscopy and cystoscopic biopsy, together with chest x-rays and CT scans of the abdomen and pelvis as outlined or as indicated clinically. Both regional failure (i.e pelvic nodes) detected on CT scans and local (i.e bladder) failure would constitute loco-regional failure, however these events will be recorded separately on case report forms for analysis. Data will also be collected on distant failure and all patients will be followed up annually to assess both distant and local control until death. UICC criteria will be used (see appendix 2).

11.3 Assessments schedule

<u>All investigations (FBC, U+Es, LFTs, MRI/CT of pelvis, chest X-ray and cystoscopy) should be done within 4 weeks of the date of patient assessment.</u>

During treatment

Patients should be seen weekly throughout treatment and the following assessments recorded:

- FBC, and U&E's
- Toxicity assessment by CTC toxicity scoring

At completion of treatment (planned or early):

- Physical examination
- FBC, U&E's and LFTs
- FACT BL QoL assessment *(to be completed prior to consultation with Clinician)*
- Toxicity assessment by CTC toxicity scoring

Assessment at 6 months post randomisation (3 months after treatment)

- Physical examination
- FBC, U&E's and LFTs
- FACT BL QoL assessment *(to be completed prior to consultation with Clinician)*
- Toxicity assessment by RTOG and Lent Som
- Chest X-Ray
- Rigid cystoscopy and cystoscopic biopsy (tumour bed and normal bladder)

Assessment at 9 months post randomisation (6 months after treatment)

- Physical examination
- Toxicity assessment by RTOG
- Chest X-Ray
- Cystoscopy (flexible or rigid)

Annual assessment (QoL and Lent / Som to year 5 only)

- Fact BL QoL assessment *(to be completed prior to consultation with Clinician)*

- Physical examination
- Toxicity assessment by RTOG and Lent Som
- Chest X-Ray
- Cystoscopy (flexible or rigid)

Years 1 and 2 only:

- Assessment of bladder capacity (At cystoscopy or by ultrasound or urodynamics)
- CT Abdomen and pelvis

12 TOXICITY AND DOSE MODIFICATIONS

12.1 Radiotherapy

Radical radiotherapy to the bladder has both short and long-term side effects. The immediate side effects include cystitis, acute small bowel reactions and proctitis. Later side effects include telangiectasia of the bladder and bowel, chronic proctitis and tiredness. Loss of bladder volume, reduction in urethral closure pressure and detrusor instability occur also in association with frequency, urgency and urge incontinence (54, 55). Damage to the rectal mucosa can cause long-term rectal blood loss.

12.2 5-Fluorouracil

The principle toxicities of 5-FU are diarrhoea and mucositis. Mild diarrhoea can be controlled with a low residue diet or with suitable anti-diarrhoeals such as Codeine or Loperamide. Less common is plantar palmar (Hand-Foot syndrome) (erythema and desquamation of the skin of the hands and feet) is unlikely given the short duration of therapy but can be managed with Pyridoxine 50mg o.d. if it occurs. In the context of synchronous therapy, the diarrhoea is the most likely toxicity that may be dose limiting. Grade 4 toxicity should be rare at the doses proposed and should be reported to the clinical chemotherapy co-ordinator* immediately. Proposed dose modifications are summarised in table 2.

Table 2 5 FU dose modifications for grade 3 or 4 diarrhoea or mucositis toxicity

Grade 1	*Grade 2*	*Grade 3*	*Grade 4*
		Diarrhoea	
No Change	❖ Reduce infusion dose by 125mg/m^2/day. ❖ Continue radiotherapy.	❖ Discontinue infusion permanently. ❖ Consider interrupting radiotherapy (until symptoms resolve to grade I).	❖ Stop all therapy. ❖ Inform Clinical Coordinator*, reassess weekly.
		Mucositis	
No Change	❖ Reduce infusion dose by 125 mg/m^2/day. ❖ Continue radiotherapy.	❖ Discontinue infusion permanently. ❖ Continue radiotherapy unless diarrhoea also present.	❖ Stop all therapy. ❖ Inform Clinical Coordinator*, reassess weekly.

Clinical Chemotherapy Coordinator: Nicholas James - Tel: 0121 414 7584 or 0121 697 4097

Occasionally, angina may be precipitated. 5-FU infusion should stop immediately if this occurs and the clinical co-ordinator informed. Myelosuppression, nausea and vomiting are unusual. However, with synchronous radiotherapy they may be more pronounced. Simple anti-emetics such as oral Metoclopramide should be used for control.

12.3 Mitomycin

The major toxic effect of Mitomycin is myelosuppression. Pulmonary toxicity has also been reported. Please inform the clinical co-ordinator if this occurs.

13 WITHDRAWAL CRITERIA

Chemotherapy should be stopped for any **grade 4** toxicity. Radiotherapy should be stopped for any **grade 4** toxicity until toxicity is resolved to grade 2 or less.

5-FU infusion should be discontinued if there is any **grade 3** toxicity. In addition, consider interrupting radiotherapy in the presence of **grade 3** diarrhoea (please refer to the Table 2).

If treatment is withdrawn, please complete an end of treatment assessment. All patients withdrawn from treatment should continue to be followed-up. If a serious adverse event has occurred an SAE form should be completed (see section 16).

14 RECORDING TOXICITY, DOSE MODIFICATIONS AND DISCONTINUATION OF TREATMENT

On treatment toxicity should be recorded on the on treatment forms (green forms in CRF booklet). If treatment is reduced, stopped or delayed details should be recorded on the green Radiotherapy and Chemotherapy forms. Radiotherapy treatment over bank holidays should conform to RCR guidelines; any dose compensation for a bank holiday does not need to be recorded on the CRF. If treatment is permanently discontinued a Trial Deviation form should be completed.

15 STATISTICAL CONSIDERATIONS

14.1 Stratification

Randomisation will be stratified by:

1. Centre (to ensure balance in centre related differences including dose selected)
2. Use of Neo-adjuvant chemotherapy (Yes / No)

The following stratification was used when the radiotherapy comparison was open:

3. Intention to enter only 1 of the possible 2 randomisations

14.2 Sample size

The trial by Coppin et al. (41) identified an improvement in 2 year pelvic relapse rate from 53% with radiotherapy alone to 33% with chemo-radiotherapy. To detect a 15% improvement in loco-regional (pelvic) disease-free survival (DFS) (from 50% to 65%) with 80% power and two-sided α=0.05 will require 170 patients per arm. This equates to a hazard ratio of 1.61 (70 critical events per comparison arm). To allow for ineligible patients we will aim to randomise a total of 350.

Closed Radiotherapy Comparison

Early closure of this randomisation has meant that we will not be able to achieve the original aims in terms of the differences we set out to detect. However, with the current 212 patients (end July 2006) evaluable for the comparison of standard volume RT with whole bladder RT and boost, there will be 83% power (two-sided α=0.05) to detect a 20% difference in loco-regional (pelvic) disease-free survival (DFS) (from 50% to 70%).

Given 212 patients have been randomised and allowing for 25% inevaluable patients at 1 year, 160 patients would be expected to be assessable for toxicity at 1 year. This will allow detection of a 20%

reduction from 40% to 20% in RTOG grade 3 or 4 toxicity with 73% power and 5% significance (two-sided).

The following information relates to the original radiotherapy comparison which has now closed

Pilot data showed modifying the volume of bladder irradiated with the full dose of radiotherapy reduced RTOG grade 3 or 4 bladder toxicity from 43% to 23% (51). If 480 patients are randomised and allowing for 25% inevaluable patients at 1 year, 360 patients will be assessable for toxicity at 1 year. This will allow detection of a 15% reduction from 40% to 25% in RTOG grade 3 or 4 toxicity with 86% power and 5% significance.

Recruitment will continue until there are at least 460 patients in each comparison (i.e. 460 randomised to chemotherapy v no chemotherapy and 460 randomised to standard v whole bladder radiotherapy with tumour boost). The trial is powered to detect a difference of 15% in DFS. If the reduced radiotherapy arm is inferior to the standard radiotherapy arm by 20% or more (in terms of local control, CR rate or salvage cystectomy rate) then whole bladder radiotherapy with tumour boost will not be recommended. Inferiority of 10% or less would be tolerated if there was a corresponding reduction in toxicity. If the 2-year DFS is 50% in the standard radiotherapy arm, 460 patients will allow us to show that the whole bladder radiotherapy with tumour boost arm is at worst 10% inferior with 70% power (1-sided α=0.05). A total of 620 patients would be needed to detect inferiority of 10% with 80% power.

The monitoring process outlined below should ensure that the radiotherapy randomisation is stopped if the whole bladder radiotherapy with tumour boost arm is greatly inferior (say by 20%). The IDMC may also recommend an increase in sample size should it become important to rule out inferiority of 10% or more.

14.3 Analysis strategy

The study will be analysed by 'intention to treat' according to randomised allocation therefore all patients should be followed for outcome data whether or not they complete the study treatment phase. Baseline characteristics, quality of life scores and response rates will be described by randomised treatment group. The failure/relapse pattern of the arms will be compared using chi-squared tests. Disease-free and overall survival will be assessed using Kaplan-Meier methods. Survival differences between groups will be estimated with the log rank test. Cox proportional hazards models (57) will be used to adjust for prognostic factors. Tests for interactions between the two treatment modalities will be performed though it is recognised that the power to detect anything but large interactions will be limited. Analyses comparing chemo-radiotherapy to radiotherapy alone will be stratified by radiotherapy treatment standard radiotherapy or whole bladder radiotherapy with tumour boost (randomisation now closed)

The proportion of patients reporting any grade 3 or 4 toxicity will be compared between the treatments arms using chi-square tests. Questionnaire specific algorithms will be used to define QoL parameters of interest (53, 54). Missing QoL items will be handled according to pre-defined standard rules. Treatment groups will be compared at individual time-points and overall for differences in the parameters. T-test and non-parametric methods, such as the Mann-Whitney test, will be used as appropriate. A nominal significance of 1% will be used to give some allowance for multiple testing of quality of life and toxicity endpoints.

14.4 Data monitoring committee

An Independent Data Monitoring Committee (IDMC) will be set up to monitor the progress of the trial. They will meet at regular intervals as they see fit but at least annually. Following each meeting they will report their findings and recommendations to the chair of the Trial Management Group and the chair of the Trial Steering Committee. All interim analyses will be supplied in confidence by the trial statistician to the IDMC together with any other analyses the IDMC request. The IDMC will advise on the frequency of reviews of the data on the basis of accrual and event rates.

Close monitoring of toxicity will be performed throughout the trial and any potential problems indicated to the IDMC. The IDMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials justifies continuing recruitment of further patients. A preliminary analysis will be undertaken after 25 patients have been entered to assess within patient variability and to provide some indication of whether the assumptions underlying the power calculations are reasonable.

The first full interim analysis will be at 1 year, after 100 patients have been entered or after >50 salvage cystectomies have been undertaken (whichever is sooner). Emphasis will be placed on checking for excessive toxicity in the synchronous chemotherapy arm or excess local recurrence rates in the whole bladder radiotherapy with tumour boost arm.

No results on survival or recurrence will be released until at least one year after the last patient is randomised unless the IDMC determine it is unethical to withhold interim results. A website will be set up for the trial covering information about the study and its progress.

16 ADVERSE EVENTS

An ‘adverse event’ is any untoward medical occurrence in a subject to whom a medicinal product has been administered within the last 30 days, including occurrences which are not necessarily caused by or related to that product. This definition also includes ‘adverse reactions’, which are any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

For the purposes of this trial we will extend this definition to include patients whom have not been administered a medicinal product but who have received radiotherapy within the last 30 days.

A Serious Adverse Event (SAE) is any adverse event that

- results in death
- is life threatening
- requires hospitalisation or prolongs an existing hospitalisation
- a new cancer
- results in persistent or significant disability/incapacity

Suspected unexpected serious adverse reactions (SUSARS)

SUSARs are serious adverse reactions, which occur whilst a patient is on, or has received, treatment in the last 30 days, which are unexpected and are suspected to be related to the investigational medicinal product (Mitomycin C and 5-Fluorouracil). The summary of product characteristics for the drugs will be used to determine expectedness.

Relevant and complete information on all adverse events (serious and non-serious) occurring during the course of the study must be recorded in the appropriate section of the study forms.

The Investigator should report the following SAEs within 24 hours of becoming aware of it, by completing an SAE form and faxing it to:

ICR-CTSU
SAE Safety Desk
FAX: 020 8722 4368

i) DEATHS as follows:

- regardless of cause, which occur within 30 days from the last cytotoxic drug administration.
- occurring after 30 days as a complication of a non disease-related event occurring during treatment or as a result of delayed toxicity of the study drugs
- unexpected, during planned follow-up

ii) ALL SERIOUS ADVERSE EVENTS with the ***following exceptions***:

- SAEs representing only a sign/symptom, an expected change, or progression of the neoplastic condition that was the cause of treatment.
- any grade of mylosuppression/ cytopenia, and emesis, not requiring inpatient hospitalisation for specific treatment.

In addition to SAEs defined above we will also collect information on any SAEs that the Investigator judges to have occurred as a result of late radiotherapy toxicity.

The Chief Investigator (CI), or designated Co-Investigator will review all reported SAEs and independently assess them for relatedness to the chemotherapy and radiotherapy. The causality assessment given by the investigator will not be overruled. If the CI disagrees with the investigator's causality assessment, both the opinions of the investigator and the CI will be provided Serious adverse events assessed as "possibly", "probably" or "definitely" related to the chemotherapy by the investigator will be assessed for expectedness.

If either the Investigator or the CI consider the reaction to be a SUSAR (i.e. "possibly", "probably" or "definitely" related to the chemotherapy and unexpected) it will be reported to the MHRA and relevant ethics committee as described below.

Reporting of SUSARs

If an SAE is defined as a SUSAR and is fatal or life threatening, ICR-CTSU will report this to the MHRA and the relevant ethics committee (main REC) within 7 days from the date the SAE is confirmed as a SUSAR by the CI or designated Co-Investigator. Additional relevant information may be requested and

this should then be sent to ICR-CTSU within 8 days.

If an SAE is defined as a SUSAR and is not fatal or life threatening, ICR-CTSU will report this to the MHRA and the relevant ethics committee (main REC) within15 days.

Principal Investigators at centres actively recruiting patients will be informed of any SUSARs which occur in relation to the investigational medicinal products used in the trial at least once a year.

Follow-up of SAEs and SUSARs

The subject must be followed-up until clinical recovery is complete and laboratory tests have returned to normal, or until disease has stabilised. Information on final diagnosis and outcome of SUSARs which may not be available at the time the SUSAR is initially reported should be forwarded to the ICR-CTSU, within the timeframe requested.

Annual Reporting of SAEs

An annual report will be provided to the MHRA and the main REC after the end of the reporting year. This will be defined as one year after the date when the CTA was obtained. This will be in the form of a line listing and will include all Serious Adverse Reactions.

17 QUALITY OF LIFE STUDY

QoL will be assessed using the FACT BL patient completed questionnaire (Appendix 4). All eligible patients will be asked to consent to the QoL part of the study. Questionnaires will be completed at baseline, end of treatment, 6 months post randomisation, at 1 year and then annually to 5 years. The patient should be asked to complete the questionnaire prior to consultation with the clinician.

It is essential to explain to the patient that all parts of the questionnaire should be completed as fully as possible. An information pack about the QoL aspect of the study will be sent to all participating centres. This will include procedures and guidelines for administering the questionnaires. Each centre will need to identify and name a person responsible for administering the questionnaires.

18 PATHOLOGICAL TISSUE COLLECTION

Consent for access to paraffin blocks and frozen tissue (if available) will be sought to allow prospective collection of tissue sections for analysis at a later date. Stored tissue and urine samples may be used to research biological predictors or markers of therapeutic response including Bcl-2, Bax and p53 expression. Consent will also be sought to use excess tissue, removed at staging and during follow-up cystoscopy for research purposes.

19 QUALITY ASSURANCE

On commencing the trial, all trial investigators will receive educational material with example outline plans. Investigators will be required to send CT scans, (film or paper copies), outlined with copy of the plan on the first three patients entered. A cross sectional radiotherapy plan on all patients along with beam data is also required. An additional outlining exercise will be organised when MRC data transfer system is operational.

At a future date we may undertake more detailed dose / volume analysis. In such instances Investigators may be asked to send more detailed data relating to the radiotherapy plans (capturing dose/volume cubes) and should notify the Trials' Offices before deleting any relevant data.
A QA review visit is planned at least once during the life of the trial.

20 ETHICAL CONSIDERATIONS

MREC approval will be sought by the Clinical Co-ordinators. Centres will need to contact Clinical Co-ordinators for a copy of the MREC approval letter and LREC application form. Each centre will need to obtain LREC approval of the trial protocol before entering any patients.

Written patient information about the objective and procedures of the trial and the possible risks involved must be given to each patient before randomisation. Signed informed consent must be obtained from all patients prior to inclusion in the trial. A suggested patient information leaflet and patient consent form are included (Appendix 1),.

National Health Service Guidelines for storage, transmittal and disclosure of patient information will be followed at all times. After randomisation, all data on patients collected in the course of the trial will be documented anonymously, i.e. they will be identified only by patient number and initials.

21 TRIAL MANAGEMENT

20.1 Trial Management Group

A Trial Management Group (TMG) will be set up and will include the principal investigators (Prof N. James (chemotherapy) and Dr RA. Huddart (radiotherapy)), co-investigators (Dr. SA. Hussain), the trial statistician and the trial co-ordinators / data managers. The TMG have overall responsibility for the conduct of the trial. The Clinical Trials and Statistics Unit (ICR-CTSU) at the Institute of Cancer Research, Sutton, and The Clinical Trials Unit at The Institute for Cancer Studies, University of Birmingham, will undertake day to day management and co-ordination of the trial. Patients will be entered into the study by individual participating centres and will follow the inclusion/exclusion criteria outlined in the protocol. Patients will be randomised by the CTSU using a well-established dedicated telephone randomisation service. In cases where there are doubts regarding the patient suitability for the trial, one of the principal investigators will be contacted. Protocols and CRFs will be printed and distributed to participating centres by the co-ordinating trials offices. Data managers/ co-ordinators will be situated at the CTSU and at the Clinical Trials Unit in Birmingham and the trial will build on collaboration between the two groups. The co-ordinators will liaise with a principal contact at each centre to ensure timely and accurate completion of CRFs and patient reported QoL. The co-ordinators will aim to visit the centres 1-2 times a year to perform data audit and promote trial activity. The Birmingham Trials Unit will provide CTSU with data collected from the centres under their day to day management at regular intervals in an agreed format and timely fashion. Data will be managed at the CTSU using database facilities available within the Unit.

A website will be established in collaboration with the Cancer Help UK to disseminate information about the trial related issues both to clinicians and to patients.

20.2 Trial Steering Committee

A Trial Steering Committee will monitor and supervise the progress of the trial. The role of the TSC is to provide overall supervision of the trial on behalf of the funding body. In particular, the TSC will

concentrate on the progress of the trial, adherence to the protocol, patient safety and the consideration of new information. Day-to day management of the trial is the responsibility of the Chief Investigators and Trial Management Group.

Membership will be limited and include an independent Chairman (not involved directly in the trial other than as a member of the TSC), not less than two other independent members and one or two Principal Investigators. Where possible membership will include a lay/consumer representative. Trial co-ordinators, statisticians etc will attend meetings as appropriate. Observers from the funding body and, if applicable, Host Institutions or sponsors will be invited to all meetings. The TSC will meet at least annually

20.3 Sponsorship

The University of Birmingham is the Sponsor of this study in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 and in line with the Research Governance Framework for Health and Social Care and ICH GCP.

22 PUBLICATION POLICY

All publications and presentations relating to the trial should be approved by the TMG. The clinical co-ordinators, trial statistician and investigators contributing 10% or more of patients to the trial will write any publications. No investigator will present subsets of the data without prior permission of the TMG.

Results from different centres will be analysed together and published in a peer-reviewed journal after a minimum of 1 year follow up on all patients.

23 END OF STUDY

For the purposes of Clinical Trial Authorisation (CTA) under the European Union Directive 2001/20/EC, the study is deemed to have ended 30 days after the last patient receives the last dose of the investigational medicinal product (IMP) (adjuvant chemotherapy).

The trial will then enter a follow-up phase.

For the purposes of Research Ethics Committee approval, the study end date is deemed to be the date of last data capture.

24 MONITORING

A clinical risk assessment will be undertaken and this will be used to inform the approach taken to monitoring including the focus and intensity of the monitoring process. Particular consideration will be given to the following:

- Consent
- Eligibility
- Capturing and reporting information on Serious Adverse Events
- Capturing, processing and coding of study endpoints

It is likely that source document verification (SDV) will be undertaken for key variables on a random sample of patients entered from each participating centre.

25 ARCHIVING

Essential documents are documents that individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced, for example CRFs, patient consent forms. These will be maintained at both the Trials Unit (ICR-CTSU and/or CRCTU) and at the Investigator Sites in a way that will facilitate the management of the trial, audit and inspection. They will be retained for a sufficient period (at least 5 years) for possible audit and inspection by the regulatory authority. The sponsor or trial organisers will notify the investigator sites of their responsibility for archiving essential documents. Documents will be securely stored and access will be restricted to authorised personnel. An archive log will be maintained to track archived documents.

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APPENDIX 1 – PATIENT INFORMATION AND CONSENT FORM

These are provided as separate documents.

APPENDIX 2 - WHO PERFORMANCE STATUS, RTOG GRADINGS FOR LATE SIDE EFFECTS AFTER RADIOTHERAPY & UICC CRITERIA FOR ASSESSMENT OF RESPONSE

WHO performance status:

0 Able to carry out all normal activity without restriction.

1 Restricted in physically strenuous activity but ambulatory and able to carry out light work.

2 Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.

3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.

4 Completely disabled; cannot carry on any self-care: totally confined to bed or chair.

RTOG Gradings for Late Side Effects After Radiotherapy

0	1	2	3	4	5
No symptoms	Minor symptoms requiring no treatment	Symptoms responding to simple out patient management, lifestyle (performance status) not affected	Distressing symptoms altering the patient's lifestyle (performance status) Hospitalisation for diagnosis or minor surgical intervention (such as urethral dilation) may be required	Major surgical intervention (such as laparotomy colostomy, cystectomy) or prolonged hospitalisation required	Fatal complica-tions

UICC criteria for assessment of response

Compete response (CR)
The disappearance of all known disease, determined by two observations not less than 4 weeks apart

Partial response (PR)
50% or more decrease in total tumour size of the lesions which have been measured to determine the effect of therapy by 2 observations not less than 4 weeks apart. In addition there can be no appearance of new lesions or progression of any lesion.

Progressive disease (PD)
A 25% or more increase in size of one or more measurable lesions, or the appearance of new lesions.

No change (NC)
Neither a CR, PR nor a progression has been demonstrated at least 4 weeks after treatment start.

APPENDIX 3 – LENT SOM QUESTIONNAIRE

BC2001 LENT / SOM

Trial No. ☐☐☐☐☐ Patients initial's ☐☐☐

Hospital _____ Hospital no. ☐☐☐☐☐☐☐☐☐☐

Date of this assessment:

☐☐ ☐☐ ☐☐☐☐ (dd mm yyyy)

Which Assessment? Baseline ☐ 6 mth FU ☐ 1 Year FU ☐ 2 Years FU ☐

3 Years FU ☐ 4 Years FU ☐ 5 Years FU ☐

Please complete each section. If there is no toxicity for a whole section, tick the no toxicity box; if there is toxicity in some areas grade the whole box using the grade 0 for none or the appropriate grades 1-4 printed in the proforma.

Rectum No toxicity (tick) ☐

Subjective	Grade	**Objective**	Grade	**Management**	Grade
Stool frequency		Bleeding		Pain	
Sphincter control		Stricture		Tenis / stool freq	
Pain		Ulceration		Bleeding	
Tenesmus				Stricture	
Mucosal loss				Ulceration	
				Sphincter control	

Bladder / Urethra No toxicity (tick) ☐

Subjective	Grade	**Objective**	Grade	**Management**	Grade
Dysuria		Haematuria		Dysuria	
Frequency		Endoscopy		Frequency	
Haematuria		Maximum volume		Haematuria/ Telangiectasia	
Incontinence		Residual volume		Incontinence	
Decreased stream				Decreased stream	

Ureter No toxicity (tick) ☐

Subjective	Grade	**Objective**	Grade	**Management**	Grade
Pain		Obstruction		Pain	
		Renal function		Obstruction	

Male Sexual Dysfunction No toxicity (tick) ☐

Subjective	Grade	**Objective**	Grade	**Management**	Grade
Erectile function for vag penetration		Frequency		Impotence	
Dryness		Orgasm			
Desire					

Satisfaction					

Female Sexual Dysfunction

No toxicity (tick) ☐

Subjective	Grade	**Objective**	Grade	**Management**	Grade
Dyspareunia		Vaginal stenosis / length		Dryness	
Dryness		Synechiae		Stenosis / Synechiae	
Desire		Frequency		Dyspareunia	
Satisfaction		Orgasm			

Small Intestine / Colon No toxicity (tick) ☐

Subjective	Grade	**Objective**	Grade	**Management**	Grade
Stool frequency		Melena		Pain	
Stool consistency		Wt loss from RT		Stool consist/freq	
Pain		Ulceration		Bleeding	
Constipation				Ulceration	

Skin / Subcutaneous No toxicity (tick) ☐

Subjective	Grade	**Objective**	Grade	**Management**	Grade
Scaliness / Roughness		Oedema		Dryness	
Sensation		Alopecia (scalp)		Sensation	
		Pigmentation change		Ulcer	
		Ulcer / Necrosis		Oedema	
		Telangiectasia		Fibrosis / Scar	
		Fibrosis / Scar			
		Atrophy / Contraction (depression)			

Mature Bone (Excluding Mandible)

No toxicity (tick) ☐

Subjective	**Grade**	**Objective**	Grade	**Management**	Grade
Pain		Fracture		Pain	
Function		Mucosa soft tissue		Function	
Joint movement		Skin over bone		Joint movement	
		Joint movement			

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Lent Som Gradings

Rectum

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Stool frequency	2-4 per day	5-8 per day	>8 per day	Uncontrolled Diarrhoea
Sphincter control	Occasional	Intermittent	Persistent	Refractory
Pain	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating
Tenesmus	Occasional urgency	Intermittent urgency	Persistent urgency	Refractory
Mucosal loss	Occasional	Intermittent	Persistent	Refractory
Objective				
Bleeding	Occult	Occasional >2/week	Persistent/daily	Gross Haemorage
Stricture	>2/3 normal diameter with dilatation	1/3 - 2/3 normal diameter with dilation	< 1/3 normal diameter	Complete obstruction
Ulceration	Superficial <= 1cm^2	Superficial > 1cm^2	Deep ulcer	Perforation, fistulae
Management				
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Tenismus and stool frequency	Occasional, <= 2 antidiarrhoeals/week	Regular, > 2 antidiarrhoeals/week	Multiple, <= 2 antidiarrhoeals/day	Surgical intervention / permanent colostomy
Bleeding	Stool softener, iron therapy	Occasional transfusion	Frequent transfusions	Surgical intervention / permanent colostomy
Stricture	Diet modification	Occasional dilatation	Regular dilatation	Surgical intervention / permanent colostomy
Ulceration	Diet modification, stool softener	Occasional steriods	Steroids per enema, hyperbaric oxygen	Surgical intervention / permanent colostomy
Sphincter control	Occasional use of incontinence pads	Intermittent use of incontinence pads	Persistent use of incontinence pads	Surgical intervention / permanent colostomy

Bladder / Urethra

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Dysuria	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractor & excruciating
Frequency	3 - 4 hour intervals	2 - 3 hour intervals	1 - 2 hour intervals	Hourly
Haematuria	Occasional	Intermittent	Persistent with clot	Refractory
Incontinence	< weekly episodes	< daily episodes	< 2 pads / undergarments / day	Refractory
Decreased stream	Occasionally weak	Intermittent	Persistent but incomplete obstruction	Complete obstruction
Objective				
Haematuria	Microscopic, normal haemoglobin	Intermittent macroscopic, <10% decrease in haemoglobin	Persistent macroscopic, 10% - 20% decrease in haemoglobin	Refractory, > 20% decrease in haemoglobin
Endoscopy	Patchy atrophy or Telangiectasia without bleeding	Confluent atrophy or Telangiectasia with gross bleeding	Ulcerations into muscle	Perforation, fistula
Maximum volume	>300 cc - 400 cc	>200 cc - 300 cc	>100 cc - 200 cc	< 100 cc
Residual volume	25 cc	>25 cc - 100 cc	> 100 cc	
Management				
Dysuria	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Frequency	Alkalisation	Occasional anti-spasmodic	Regular narcotic	Cystectomy
Haematuria/ Telangiectasia	Iron therapy	Occasional transfusion or single cauterisation	Frequent transfusion or coagulation	Surgical intervention
Incontinence	Occasional use of incontinence pads	Intermittent use of incontinence pads	Regular use of pad or self-catheterisation	Permanent catheter
Decreased stream		< Once-a-day self-catheterisation	Dilatation, > once-a-day self catheterisation	Permanent catheter, surgical intervention

Ureter

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Pain	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating
Objective				
Obstruction	Ureteral narrowing without hydronephrosis	Ureteral narrowing with hydronephrosis	Unilateral obstruction	Bilateral obstruction
Renal function	1+ proteinuria	2+ proteinuria	4+ proteinuria	
Management				
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Obstruction			Unilateral stent or nephrostomy	Bilateral nephrostomy or diversion

Male Sexual Dysfunction

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Erectile function for vaginal penetration	Occasionally insufficient	Intermittently insufficient	Not sufficient	Impotent
Dryness	Occasional	Intermittent	Persistent	Refractory
Desire	Occasional	Intermittent	Seldom	Never
Satisfaction	Occasional	Intermittent	Seldom	Never
Objective				
Frequency		Decreased from normal	Rare	Never
Orgasm	Occasional	Intermittent	Seldom	Never
Management				
Impotence		Medical intervention	Surgical intervention	

Female Sexual Dysfunction

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Dyspareunia	Occasional	Intermittent	Persistent	Refractory
Dryness	Occasional	Intermittent	Persistent	Refractory
Desire	Occasional	Intermittent	Seldom	Never
Satisfaction	Occasional	Intermittent	Seldom	Never
Objective				
Vaginal stenosis / length	>2/3 normal length	1/3 - 2/3 normal length	<1/3 normal length	Obliteration
Synechiae			Partial	Complete
Frequency		Decreased from normal	Rare	Never
Orgasm	Occasional	Intermittent	Seldom	Never
Management				
Dryness	Hormone replacement	Artificial lubrication		
Stenosis / Synechiae	Occasional dilation	Intermittent dilation	Persistent dilation	Surgical reconstruction
Dyspareunia	Occasional hormone cream	Intermittent hormone cream	Persistent hormone cream	

Small Intestine / Colon

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Stool frequency	2-4 per day	5-8 per day	>8 per day	Refractory Diarrhoea
Stool consistency	Bulky	Loose	Mucous, dark, watery	
Pain	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory / Rebound
Constipation	3-4 per week	Only 2 per week	Only 1 per week	No stool in 10 days
Objective				
Melena	Occult/Occasional	Intermittent & tolerable, normal Hb	Persistent, 10-20% decrease in Hb	Refractory or frank blood > 20% decrease in Hb
Weight loss from time of treatment	>=5% - 10%	>10% - 20%	>20% - 30%	>30%
Stricture	>2/3 normal diameter with dilatation	1/3 - 2/3 normal diameter with dilation	< 1/3 normal diameter	Complete obstruction
Ulceration	Superficial <= 1cm^2	Superficial > 1cm^2	Deep ulcer	Perforation, fistulae
Management				
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Stool consistency / frequency	Diet modification	Regular use of non-narcotic antidarrhoea	Continuous use of narcotic antidiarrhoea	
Bleeding	Iron therapy	Occasional transfusion	Frequent transfusions	Surgical intervention
Stricture	Occasional diet adaptation	Diet adaptation required	Medical intervention, NG suction	Surgical intervention
Ulceration			Medical intervention	Surgical intervention

Skin / Subcutaneous Tissue

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Scaliness / Roughness	Present / asymptomatic	Symptomatic	Require constant attention	
Sensation	Hypersensitivity, pruritus	Intermittent pain	Persistent pain	Debilitating dysfunction
Objective				
Oedema	Present / asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction
Alopecia (scalp)	Thinning	Patchy, permanent	Complete, permanent	
Pigmentation change	Transitory, slight	Permanent, marked		
Ulcer / Necrosis	Epidermal only	Dermal	Subcutaneous	Bone exposed
Telangiectasia	Minor	Moderate <50%	Gross >50%	
Fibrosis / Scar	Present / asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction
Atrophy / Contraction (depression)	Present / asymptomatic	Symptomatic / <10%	Secondary dysfunction / 10% - 30%	Total dysfunction / >30%
Management				
Dryness			Medical intervention	
Sensation		Intermittent medical intervention	Continuous medical intervention	
Ulcer			Medical intervention	Surgical intervention / amputation
Oedema			Medical intervention	Surgical intervention / amputation
Fibrosis / Scar			Medical intervention	Surgical intervention / amputation

Mature bone (Excluding Mandible)

	Grade 1	Grade 2	Grade 3	Grade 4
Subjective				
Pain	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating
Function	Interferes with athletic recreation	Interferes with work	Interferes with daily activity	Complete lack of function
Joint movement	Stiffness interfering with athletic recreation	Stiffness interfering with work	Stiffness interfering with daily activity	Complete fixation, necrosis
Objective				
Fracture			Partial thickness	Full thickness
Mucosa soft tissue			Sequestration	
Skin over bone	Erythema	Ulcer	Sinus	Fistula
Joint movement	<10% decrease	>10% - 30% decrease	>30% - 80% decrease	>80% decrease
Management				
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Function	Occasional physiotherapy	Intermittent physiotherapy	Persistent physiotherapy or medical intervention	Surgical intervention
Joint movement	Occasional physiotherapy	Intensive physiotherapy	Corrective surgery	

APPENDIX 4 – FACT – BL QUESTIONNAIRE

Today's Date ☐☐ ☐☐ ☐☐☐☐
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FACT-BI (Version 4)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea.....	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family.....	0	1	2	3	4
GP4	I have pain.....	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends.....	0	1	2	3	4
GS2	I get emotional support from my family.....	0	1	2	3	4
GS3	I get support from my friends.....	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness.....	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support).....	0	1	2	3	4
Q1	Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box ☐ and go to the next section.					
GS7	I am satisfied with my sex life	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness ..	0	1	2	3	4
GE4	I feel nervous.....	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun.....	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days.</u>

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
BL1	I have trouble controlling my urine.....	0	1	2	3	4
C2	I am losing weight.....	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
C5	I have diarrhea.....	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BL3	It burns when I urinate	0	1	2	3	4
BL4	I am interested in sex.....	0	1	2	3	4
BL5	(For men only) I am able to have and maintain an erection	0	1	2	3	4
Q2	Do you have an ostomy appliance? No___ Yes___ If ***yes***, answer the following two items: ↓					
C8	I am embarrassed by my ostomy appliance	0	1	2	3	4
C9	Caring for my ostomy appliance is difficult.....	0	1	2	3	4

APPENDIX 5 – CTC TOXICITY SCORING

CTC Version 2.0 Publish Date: April 30, 1999 – Please note version 2

Cancer Therapy Evaluation Program 15 Revised March 23, 1998 Common Toxicity Criteria, Version 2.0
DCTD, NCI, NIH, DHHS March 1998

	1	2	3	4
GASTEROINTESTINAL				
Diarrhoea patients without colostomy:	increase of <4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or haemodynamic collapse
Diarrhoea patients with a colostomy:	mild increase in loose, watery colostomy output compared with pre-treatment	moderate increase in loose, watery colostomy output compared with pre-treatment, but not interfering with normal activity	severe increase in loose, watery colostomy output compared with pre-treatment, interfering with normal activity	physiologic consequences, requiring intensive care; or haemodynamic collapse
Stomatis / pharyngitis (oral/pharyngeal mucositis)	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, oedema or ulcers but can eat or swallow	painful erythema, oedema, or ulcers preventing swallowing or requiring IV hydration	severe ulceration or requires hydration or parenteral (or enteral) nutritional support or prophylatic intubation
Nausea	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Vomiting	1 episode in 24 hours over pre-treatment	2-5 episodes in 24 hours over pre-treatment	≥6 episodes in 24 hours over pre-treatment; or need for IV fluids	requiring parenteral nutrition; or physiologic consequences requiring intensive care; haemodynamic collapse
RENAL/GENITOURINARY				
Dysuria (painful urination)	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	-
Urinary frequency/ urgency	increase in frequency or nocturia up to 2 x normal	increase >2 x normal but < hourly	hourly or more with urgency, or requiring catheter	-
Urinary Retention	hesitancy or dribbling, but no significant residential urine; retention occurring during the immediate postponement period	hesitancy requiring medication or occasional in/out catheterisation (<4 x per week), operative bladder atony requiring indwelling catheter beyond immediate postponement period but for <6 weeks	requiring frequent in/out catheterisation (≥ 4 x per week) or urological intervention (e.g. TURP, suprapubic tube, urethrotomy)	bladder rupture
OTHER				
Haematuria (in the absence of vaginal bleeding)	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterisation or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Plantar palmer syndrome	skin changes or dermatitis without pain (e.g., erythema, peeling)	skin changes with pain, not interfering with function	skin changes with pain, interfering with function	-
Dyspnea (shortness of breath)	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support
Pneumonitis / pulmonary infiltrates	radiographic changes but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation
Cardiovascular **Cardiac-ischemia** / infarction	non-specific T-wave flattening or changes	asymptomatic, ST - and T wave changes suggesting ischemia	angina without evidence of infarction	acute myocardial infarction
Cardiovascular / **Arrhythmia**	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment of underlying cause	life-threatening (e.g. arrhythmia associated with CHF, hypotension, syncope, shock)
Mucositis due to radiation	erythema of the mucosa	patchy pseudomembra-nous reaction (patches generally ≤1.5 cm in diameter & non-contiguous)	confluent pseudomem-branous reaction (contiguous patches generally >1.5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion