

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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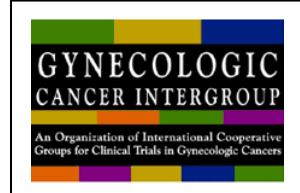
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INTERLACE

A phase III multicentre trial of weekly induction chemotherapy followed by standard chemoradiation versus standard chemoradiation alone in patients with locally advanced cervical cancer

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Please note: This trial protocol must not be applied to patients treated outside the INTERLACE trial. UCL CTC can only ensure that approved trial investigators are provided with amendments to the protocol.

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1 PROTOCOL SUMMARY

1.1 Summary of Trial Design

Title:	A phase III multicentre trial of weekly induction chemotherapy followed by standard chemoradiation versus standard chemoradiation alone in patients with locally advanced cervical cancer
Short Title/acronym:	INTERLACE
EUDRACT no:	2011-001300-35
Sponsor name & reference:	University College London -11/0034
Funder name & reference:	Cancer Research UK – C37815/A12832
Clinicaltrials.gov no:	NCT01566240
Design:	Randomised, controlled, phase III, multicentre trial
Overall aim:	To investigate in a randomised trial whether additional short-course chemotherapy given on a weekly schedule immediately before standard chemoradiation leads to an improvement in overall survival
Primary endpoints:	Overall survival Progression free survival
Secondary endpoints:	Adverse events Quality of life Patterns of relapse Time to first subsequent treatment
Target accrual:	500 patients
Inclusion & exclusion criteria:	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Histologically confirmed FIGO stage Ib2- IVa (using adapted 2009 FIGO staging, see appendix V) squamous, adeno or adenosquamous carcinoma of the cervix (except those with disease extending to lower third of vagina). Patients with FIGO stage IB1 <u>and</u> positive lymph nodes are also eligible • Deemed suitable and fit for radical chemoradiation • Medically fit to receive carboplatin and paclitaxel • ECOG performance status 0 – 1 • No evidence of active TB • Aged 18 and over • Adequate renal function, defined as a GFR ≥ 60 ml/min calculated using the Wright

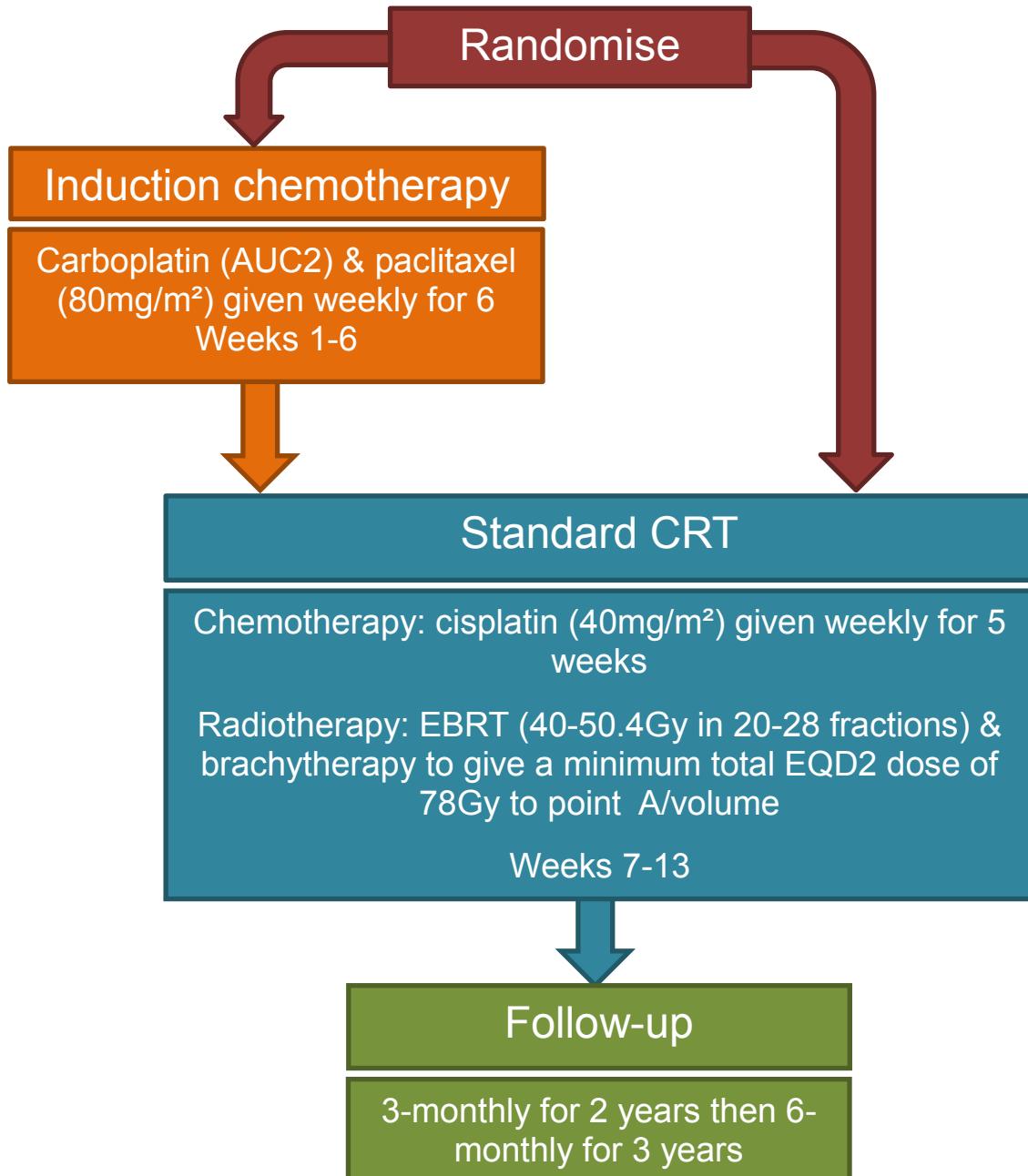
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	<p>equation (or ≥ 50 ml/min for radioisotope GFR assessment)</p> <ul style="list-style-type: none"> • Adequate liver function, as defined by ALT or AST < 2.5 ULN and bilirubin < 1.25 ULN • Adequate bone marrow function as defined by ANC $\geq 1.5 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$ • Using adequate contraception precautions if relevant • A documented negative HIV test (patients recruited from high risk countries or who have moved within the past 10 years from high risk countries) • A documented negative pregnancy test (if applicable) • Capable of providing written or witnessed informed consent <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Previous pelvic malignancy (regardless of interval since diagnosis) • Previous malignancy not affecting the pelvis (except basal cell carcinoma of the skin) where disease free interval is less than 10 years • Positive lymph nodes (imaging or histological) above the aortic bifurcation • Hydronephrosis which has not undergone ureteric stenting or nephrostomy except where the affected kidney is non-functioning • Evidence of distant metastasis i.e. any non-nodal metastasis beyond the pelvis • Previous pelvic radiotherapy • Prior diagnosis of Crohn's disease or Ulcerative colitis • Uncontrolled cardiac disease (defined as cardiac function which would preclude hydration during cisplatin administration and any contraindication to paclitaxel) • Pregnant or lactating
Planned number of sites:	40-50
Target countries:	United Kingdom, Mexico, Italy, India, Brazil
Treatment summary:	Patients with locally advanced cervical cancer will be randomised to receive either induction chemotherapy with weekly carboplatin AUC2 and paclitaxel 80mg/m ² for six weeks, followed by standard chemoradiation (investigational arm) or chemoradiation alone (standard arm). The radiation in both arms will comprise external beam 40-

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	50.4Gy in 20–28 fractions plus intracavity brachytherapy to achieve a minimum total EQD2 dose of 78-86Gy with weekly cisplatin 40mg/m ² for 5 weeks
Anticipated duration of recruitment:	8 years
Duration of patient follow up:	3 monthly for 2 years and 6 monthly until the end of the trial from the end of treatment.
Definition of end of trial:	30 days after the last patient has completed 3 years of follow up visits at which point the 'declaration of end of trial' form will be submitted
Translational component (optional):	Paraffin embedded cervical tissue block from original diagnosis for future translational studies
Other related research:	Economic evaluation – Various costs associated with trial treatment and patient care will be recorded in the Case Report Forms, allowing for a formal economic evaluation comparing the two arms of the study to be conducted

1.2 Trial Schema



2 INTRODUCTION

2.1 Background

More than 500,000 new cases of cervical cancer are diagnosed worldwide each year with approximately 270,000 deaths annually¹. In the UK there were 2828 cases in 2007 and 957 deaths from cervical cancer in 2008 (Cancer Research UK)². Despite the fall in the overall incidence of cervical cancer in the UK since the introduction of screening, many patients diagnosed with invasive cancer have locally advanced disease at presentation. Although such patients receive initial treatment with curative intent, a significant proportion subsequently relapse and die from metastatic disease. There is an urgent need to improve first-line systemic treatment in locally advanced disease.

In 1999, following the publication of 5 large randomised trials^{3,4,5,6,7} the US National Cancer Institute (NCI)⁸ issued a clinical alert, recommending that women with locally advanced cervical cancer receiving radical radiotherapy (RT) with curative intent also receive concomitant platinum chemotherapy. From then on, chemoradiotherapy (CRT) was adopted in the UK and elsewhere as the new standard of care for women with locally advanced cervix cancer. Nonetheless, interpretation of its benefits were complicated by differences in trial design so an individual patient data (IPD) meta-analysis was undertaken to assess the effect of CRT on all outcomes. That analysis, based on 18 trials from 11 countries (including the 5 pivotal studies which triggered the NCI alert) confirmed the benefit of adding chemotherapy to radiation. However, it showed that the improvement in 5-year overall survival (OS) was only 6% (i.e. from 60 to 66 %, HR 0.81)⁹. The 5-year disease free survival (DFS) rate was 58%. The benefit of adding chemotherapy to RT was seen across subgroups defined by age, histology, and grade but appeared to be less in patients with tumours of higher stage. The estimated absolute survival benefit from CRT, compared to RT alone at 5 years was 10% for those with stage I/Illa disease but only 3% for those with stage III/IVa disease. In the decade since the introduction of CRT there have been no further advances in the management of locally advanced cervical cancer. A single trial has reported a survival advantage from the addition of adjuvant chemotherapy after CRT¹⁰ but its findings await confirmation in additional randomised trials and it is not considered standard of care.

We propose to explore the role of additional weekly dose-dense chemotherapy given immediately prior to CRT, based on the rationale that such induction chemotherapy might reduce tumour volume while controlling micrometastatic disease. The use of weekly dose-dense chemotherapy in cervical cancer treatment is novel and could overcome tumour regrowth between cycles while limiting the proliferation of tumour cells resistant to both chemotherapy and radiotherapy. Our strategy is further supported by the findings of a meta-analysis⁹ of 18 trials of neoadjuvant chemotherapy (NACT) prior to radiotherapy in women with locally advanced cervical cancer, a meta-analysis undertaken because of conflicting results of individual trials of NACT in these patients. Heterogeneity in chemotherapy cycle length, platinum dose intensity and interval between NACT and start of radiotherapy precluded a unified analysis. However, the authors identified chemotherapy cycle length and platinum dose intensity as important factors in determining the impact of neoadjuvant chemotherapy on outcome. The trials that delivered short cycle chemotherapy (<14 days) gave a pooled HR of 0.83, equivalent

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to a 7% improvement in 5 year survival. In contrast, for trials with longer chemotherapy cycles (>14days) the pooled HR was 1.25, equivalent to an absolute detriment in survival of 8% at 5 years. Accelerated repopulation of resistant cancer cells during prolonged intervals (in some trials > 6 weeks) between NACT and CRT may also account for the detrimental effect on survival observed in some of the studies. Our study design is therefore based on maximizing dose density and intensity, while allowing no delay between NACT and CRT.

Further findings to support the role of additional dose-dense chemotherapy come from a phase II study of weekly NACT followed by radical CRT in 46 patients (median age 43 years) with locally advanced cervical cancer was performed at 3 trial sites in the UK¹¹. The majority (83%) of patients had FIGO stage II/III disease; 71% had squamous carcinoma, 22% adenocarcinoma and 7% adenosquamous carcinoma. Compliance with NACT was very good with 76% (35/46) of patients completing all six cycles and 89% (41/46) completing five cycles. 80% (37/46) of patients completed the mandated 4-6 cycles of concomitant cisplatin with radiation. Of the remaining 10 patients, 5 completed 3 cycles and 3 patients did not start cisplatin (1 progressive disease, 1 unwell and 1 hypersensitivity reaction). Almost all patients (96%) completed external beam radiation and 98% of these completed brachytherapy as well. The entire course of radiation was delivered within 50 days in 80% (37/46) of patients. Only 11% of patients experienced Grade 3/4 toxicity during the NACT phase. During CRT, 47% experienced grade 3/4 haematological toxicity; in 30% this was grade 3 neutropenia. Grade 3/4 non-haematological events occurred in 22% of patients. Nearly 70% of patients obtained a partial or a complete response (as assessed by MRI) at the end of NACT. 12 weeks after completion of CRT the response rate was 84.5%. At the time of analysis (median follow-up 34 months) the PFS and OS at 3 years are both 65%. This data confirms that weekly, dose-dense NACT is feasible and does not compromise the radiation dose or the overall treatment time.

3 TRIAL DESIGN

This is a phase III multicentre randomised controlled trial of weekly induction chemotherapy followed by standard chemoradiation (investigational arm) versus standard chemoradiation alone (control arm) in patients with locally advanced cervical cancer.

Patients in the investigational arm will receive six weekly IV infusions of paclitaxel 80mg/m² and carboplatin AUC2 during weeks 1-6 inclusive and commence standard chemoradiation in week 7 consisting of external beam 40-50.4Gy in 20-28 fractions plus intracavitary brachytherapy to achieve a total EQD2 dose of 78-86Gy with five weekly IV infusions of cisplatin 40mg/m² for five weeks.

The trial will enrol 500 patients with follow up three monthly for the first two years and then six monthly for three years. Survival data will then be collected for all patients on a six monthly basis until the end of the trial.

3.1 Trial objectives

INTERLACE will investigate in a randomised trial whether additional short-course chemotherapy given on a weekly schedule immediately before standard chemoradiation leads to an improvement in overall survival.

3.2 Trial Endpoints

The primary endpoints:

- Overall survival (OS)
- Progression free survival (PFS)

Secondary endpoints:

- Adverse events (AE) as assessed by the Common Terminology Criteria for Adverse Events v4.03
- Quality of Life as assessed by EORTC QLQ-C30, QLQ-CX24 and EQ-5D-5L
- Patterns of first relapse (local and/or systemic)
- Time to first subsequent treatment

3.3 Trial Activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Health Research Authority (HRA) approval, including Research Ethics Committee approval
- Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) (and other relevant national regulatory authorities)

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- ‘Adoption’ into NIHR portfolio
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

4 SELECTION OF SITES/SITE INVESTIGATORS

4.1 Site Selection

In this protocol trial 'site' refers to the hospital where trial-related activities are conducted. Sites must be able to comply with:

- Trial treatments, imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority and the Medicines for Human Use (Clinical Trials) Regulation (SI 2004/1031) and all amendments
- Data collection requirements, including adherence to CRF submission timelines as per section [10.3 – Timelines for Data Return](#).
- Sample collection, processing and storage requirements
- Monitoring requirements, as outlined in protocol [Section 13 – Trial Monitoring and Oversight](#). Prior to site activation, centres will be required to complete the Radiotherapy Quality Assurance Programme, an overview of which is presented in section 16 (Radiotherapy Quality Assurance Programme).

In addition, non-UK sites must be able to comply with:

- Identification of specialists providing care for locally advanced cervical cancer
- All local legislative requirements and all regulations governing clinical trials
- Non UK sites should refer to their group specific appendix for additional detailed instructions

4.1.1 Selection of Principal Investigator and other investigators at sites

Each site must appoint an appropriate Principal Investigator (PI), i.e. a consultant oncologist authorised by the site to lead and coordinate the work of the trial on behalf of the site. Co-investigators must be trained and approved by the PI. All PIs and co-investigators must be medical doctors and have experience treating locally advanced cervical cancer. In the UK, the Principal Investigator must be a core or extended member of the designated Gynae Network MDT. Other investigators at site wishing to participate in the trial must be medical doctors who are trained and approved by the PI. The PI must ensure that all other investigators have adequate knowledge and experience to perform the duties delegated to them.

The PI is responsible for the conduct of the trial at their site and for ensuring that any amendments are implemented in a timely fashion. If a PI plans to take a leave of absence, UCL CTC must be informed promptly. For absences greater than three months or where the PI is no longer able to perform his/her duties at the site UCL CTC may terminate recruitment at site. A new suitable replacement PI must be identified by the site and UCL CTC notified.

UCL CTC may terminate recruitment at a site where a suitable replacement PI has not been identified within three months.

4.1.2 Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). An up-to-date, signed copy of the CV with evidence of GCP training (or copy of the GCP certificate) for the PI must be forwarded to UCL CTC upon request.

GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

4.2 Site initiation and Activation

4.2.1 Site initiation

Before a site is activated, the UCL CTC trial team will arrange a site initiation with the site which the PI, the pharmacy lead and site research team must attend. The site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed for each site by site visit or teleconference. Re-initiating sites may be required where there has been a significant delay between initiation and enrolling the first patient.

4.2.2 Required documentation

The following documentation must be submitted by the site to UCL CTC prior to a site being activated by UCL CTC trial team:

- Trial specific Site Registration Form (identifying relevant local staff)
- Relevant institutional approvals
- A completed site delegation log that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately)
- Completed site contacts form (with contact information for all members of local staff)
- A copy of the PI's current CV that is signed and dated (with documented up to date GCP training, or copy of GCP training certificate)
- A copy of the trial specific prescription
- Completed Radiotherapy Quality Assurance Documents submitted to and approved by INTERLACE Chief Investigator and the Radiotherapy QA Lead

In addition, the following agreements must be in place:

- For UK sites: a signed Clinical Trial Site Agreement (CTSA) between the Sponsor and the relevant institution (usually an NHS Trust/Health Board)
- For non-UK sites: a signed International Clinical Trials Site Agreement (ICTSA).
- For countries with a country coordinating centre (CCC):
 - a signed International Country Coordinating Centre Agreement
 - a signed clinical trial agreement between the CCC and the relevant institution.

4.2.3 Site activation letter

Once the UCL CTC trial team has received all required documentation and the site has been initiated, a site activation letter will be issued to the PI, at which point the site may start to approach patients.

Following site activation, the PI is responsible for ensuring:

- adherence to the most recent version of the protocol;
- all relevant site staff are trained in the protocol requirements;
- appropriate recruitment and medical care of patients in the trial;
- timely completion and return of CRFs (including assessment of all adverse events);
- prompt notification and assessment of all serious adverse events;
- that the site has facilities to provide **24 hour medical advice** for trial patients

4.2.4 Non-UK Sites

Non UK sites should refer to their group specific guidance document for additional detailed instructions.

5 INFORMED CONSENT

Sites are responsible for assessing a patient's capacity to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheet(s), are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved consent form(s).

UK sites must assess a patient's ability to understand verbal and written information in English and whether or not an interpreter would be required to ensure fully informed consent. If a patient requires an interpreter and none is available, the patient should not be considered for the trial.

Sites must assess a patient's ability to understand verbal and written information in English (or the local language, if consented at a non-UK site) and whether or not an interpreter would be required to ensure fully informed consent. If a patient requires an interpreter and none is available, the patient should not be considered for the trial.

The PI, or where delegated by the PI, other appropriately trained site staff are, required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions the current approved patient information sheet(s) for the trial should be discussed with the patient.

A **minimum of twenty four hours** must be allowed for the patient to consider and discuss participation in the trial.

Written informed consent on the current approved version of the consent form(s) for the trial must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient notes.

Patients will also be asked to give permission for their biopsy tumour tissue to be used in future translational studies. A separate patient information sheet and consent form will be provided to inform patients about this voluntary aspect of the study.

Site staff are responsible for:

- Checking that the correct current approved version(s) of the patient information sheet(s) and consent form(s) are used
- Checking that information on the consent form(s) are complete and legible
- Checking that the patient has completed/initialled all relevant sections and signed and dated the form
- Checking that an appropriate member of staff has countersigned and dated the consent form(s) to confirm that they provided information to the patient
- Checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.)
- Following randomisation, adding the patient trial number to all copies of the consent form(s) which should be filed in the patient's medical notes and investigator site file and a copy should be sent to UCL CTC

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- Giving the patient a copy of the signed consent form, patient information sheet and patient contact card
- Following randomisation sending the INTERLACE GP letter to the patient's GP.

The right of the patient to decline to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time (see [Section 14.0 – Withdrawal of Patients](#)).

Non-UK sites should consent patients for trial participation according to local practice and regulatory and/or ethical requirements. Non-UK sites should refer to their group specific appendix for additional detailed instruction.

6 SELECTION OF PATIENTS

6.1 Pre-randomisation Evaluation

The following assessments or procedures are required to evaluate the suitability of patients for the trial. The following assessments will be made to confirm eligibility to enter the study. These are standard for any patient undergoing investigation and treatment of cervical cancer: Patients must start treatment < 28 days from randomisation.

Within 50 days of randomisation

- CT or PET CT chest/abdomen
- MRI Pelvis (+/- abdomen) – please note diffusion enhanced imaging is preferable though not essential, please see Appendix III for preferred patient preparation and scan sequencing
CT Pelvis and clinical examination by two study investigators is acceptable in non-European countries/non-UK sites only
- Physical examination

Within 31 days of randomisation

- Clinical examination: blood pressure, pulse, ECOG performance status (see Appendix II)
- Height and weight
- Calculate tumour volume using volume of an ellipsoid $\frac{1}{2} \times D1 \times D2 \times D3$ where D is the diameter of the tumour in the three different axes
- Negative HIV test in patients recruited from high risk countries or who have moved within the past 10 years from high risk countries. (Please see [Section 6.5 – HIV Testing](#))
- Glomerular filtration rate $\geq 60\text{ml/min}$ calculated using the Wright equation (see Appendix IV) or $\geq 50\text{ ml/min}$ for radioisotope GFR assessment
- Full blood count – WBC, neutrophils, haemoglobin, platelets
- Biochemistry – sodium, potassium, urea, creatinine, bilirubin, albumin, magnesium, calcium, ALP, AST or ALT, LDH, gamma GT

Within 14 days of randomisation

- Pregnancy test for any woman of child bearing potential (WOCBP). For more details and definition of WOCBP see [Section 6.4.1 – Definitions](#)
- Pregnancy and Birth Control.
- Quality of Life questionnaires

Within 14 days of starting treatment

- Full blood count – as above
- Biochemistry – as above
- Squamous Cell Carcinoma Antigen (if available) - [Section 6.6 – Squamous Cell Carcinoma Antigen](#)
- Toxicity/Adverse events

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A summary of the screening procedures are shown in Table 1.

Table 1 – Screening Procedures

All Arms	Screening Procedures				
	At screening prior to any study procedure	Within 50 days prior to Randomisation	Within 31 days prior to Randomisation	Within 14 days prior to Randomisation	Within 14 days prior to starting treatment
Informed Consent	X				
Medical History	X				
Examination with Biopsy & Cytoscopy as appropriate	X				
Physical Examination	X				
Clinical Examination: BP, Pulse, ECOG PS			X		
Height, Weight			X		
CT or PET CT Chest Abdomen		X			
MRI Pelvis (+/- abdomen)		X			
CT Pelvis if MRI not available ^a		X			
Tumour Volume ^b			X		
Negative HIV Test ^c			X		
Pregnancy Test (if applicable) ^d				X	
Adequate Renal Function ^e			X		
FBC ^f			X		X
Biochemistry ^g			X		X
Squamous Cell Carcinoma Antigen ^h					X
Toxicity/Adverse Events					X
Q of L Questionnaire ⁱ				X	

a MRI pelvis in Europe and UK; CT pelvis and clinical examination by two study investigator is acceptable in non-European countries/non- UK sites only

b Calculate tumour volume using volume of an ellipsoid $\frac{1}{2} \times D1 \times D2 \times D3$ where D is the diameter of the tumour in the three different axes

c Patients recruited from high risk countries or who have moved within the past 10 years from high risk countries. For more details see [Section 6.5 – HIV Testing](#).

d Pregnancy test for women of childbearing potential (WOCBP). For more details and definition of WOCBP see [Section 6.4.1 – Definitions](#).

e GFR $\geq 60\text{ml/min}$ calculated using Wright equation or $\geq 50\text{ml/min}$ for radioisotope GFR assessment (see Appendix IV)

f WBC, neutrophils, haemoglobin, platelets

g Sodium, potassium, urea, creatinine, bilirubin, albumin, magnesium, calcium, ALP, AST or ALT, LDH, gamma GT

h Squamous Cell Carcinoma Antigen (if available). For more details see [Section 6.6 – Squamous Cell Carcinoma Antigen](#)

i Baseline Q of L questionnaire to be completed after informed consent and before patient randomisation

6.2 Screening Log

A screening log should be maintained by the site and kept in the Investigator Site File. This should record all patients identified with disease stage appropriate for INTERLACE and for those not randomised record the reasons why not. The log should be sent to UCL CTC when requested with patient identifiers removed prior to sending where applicable.

6.3 Patient Eligibility

There will be no exception to the eligibility requirements at the time of randomisation. Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). Queries in relation to the eligibility criteria must be addressed prior to randomisation. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria apply.

6.3.1 Inclusion criteria

A patient with all the following characteristics may be included in the study:

- Histologically confirmed FIGO stage Ib2-IVa squamous, adeno or adenosquamous carcinoma of the cervix (except where the disease extends to the lower third of the vagina). Patients with histologically confirmed FIGO stage IB1 and positive lymph nodes are also eligible. Adapted 2009 FIGO staging is used for the trial please see Appendix V
- Deemed suitable and fit for radical chemoradiation
- Medically fit to receive carboplatin and paclitaxel
- ECOG performance status 0 – 1 see Appendix II
- No evidence of active TB
- Aged 18 and over
- Adequate renal function, defined as a GFR \geq 60 ml/min calculated using the Wright equation (or \geq 50 ml/min for radioisotope GFR assessment (see Appendix IV)
- Adequate liver function, as defined by ALT or AST $<$ 2.5 ULN and bilirubin $<$ 1.25 ULN
- Adequate bone marrow function as defined by ANC \geq 1.5 \times 10⁹/L, platelets \geq 100 \times 10⁹/L
- Using adequate contraception precautions if relevant
- A documented negative HIV test (patients recruited from high risk countries or who have moved within the past 10 years from high risk countries). For more details see [Section 6.5 – HIV Testing](#).
- A documented negative pregnancy test (if applicable)
- Capable of providing written or witnessed informed consent

Patients with positive (pelvic/para-aortic/both) nodes (either histologically/PET positive \geq =15 mm on CT/MRI) at or below the level of the aortic bifurcation may be included in the study provided none of the exclusion criteria apply.

6.3.2 Exclusion criteria

A patient with any of the following characteristics is excluded from the study:

- Previous pelvic malignancy (regardless of interval since diagnosis)
- Previous malignancy not affecting the pelvis (except basal cell carcinoma of the skin) where disease free interval is less than 10 years
- Positive lymph nodes (imaging or histological) above the aortic bifurcation*
- Hydronephrosis which has not undergone ureteric stenting or nephrostomy except where the affected kidney is non-functioning
- Evidence of distant metastasis i.e. any non-nodal metastasis beyond the pelvis
- Previous pelvic radiotherapy
- Prior diagnosis of Crohn's disease or Ulcerative colitis
- Uncontrolled cardiac disease (defined as cardiac function which would preclude hydration during cisplatin administration and any contraindication to paclitaxel)
- Women who are pregnant or lactating

* i.e. PET AVID any size, CT/MRI $\geq 15\text{mm}$

6.4 Pregnancy and birth control

6.4.1 Definitions

Definition of women of childbearing potential (WOCBP)

A woman of childbearing potential (WOCBP) is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who:

- Has not undergone a hysterectomy or bilateral oophorectomy/salpingectomy
- Is not postmenopausal (a post-menopausal woman is a female who has not had menses at any time in the preceding 12 consecutive months without an alternative medical cause)
- Has not had premature ovarian failure confirmed by a specialist gynaecologist

6.4.2 Risk of exposure to trial treatment during pregnancy

The risk of exposure to trial treatment has been evaluated using the safety information available in individual SPCs for Carboplatin, paclitaxel and cisplatin. A literature review has taken place to evaluate the safety information for radiotherapy. All trial treatments may cause foetal harms when administered to a pregnant woman.

6.4.3 Pregnancy testing

All women of childbearing potential who are at risk of becoming pregnant (currently sexually active) must undergo a pregnancy test within 14 days of randomisation; site testing procedure will be according to local practice.

6.4.4 Contraceptive advice

Acceptable methods of effective contraception for this trial are:

Due to the effects of carboplatin, paclitaxel and cisplatin during pregnancy and lactation, WOCBP (currently sexually active) must consent to use two of the following acceptable methods of contraception for the duration of their induction chemotherapy and during chemoradiation and any other treatment on the trial.

Acceptable methods of effective contraception for this trial are:

- Established use of oral, injected or implanted hormonal methods of contraception (either combined estrogen and progestogen or progestogen only).

- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps with spermicidal foam/gel/film/cream/suppository). The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:
 - Failure rates indicate that when used alone, the diaphragm and condom are **not** highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection.
 - However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and must not be used alone.
- bilateral tubal occlusion¹
- ***vasectomised partner***¹²
- Sexual abstinence ³:
 1. Contraception methods that are considered to have low user dependency.
 2. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
 3. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Please note: intrauterine device/systems cannot be used as they must be removed prior to chemoradiation.

The method(s) of contraception used must be stated in the patient medical notes and case report forms.

If a patient becomes pregnant during the trial, see [Section 11 - Pharmacovigilance](#).

6.4.5 Action to be taken in the event of pregnancy

If a patient becomes pregnant:

- prior to initiating treatment, the patient will not receive trial treatment unless they elect to have a termination (please note, in such instances, termination must be the patient's own choice)
- during treatment, clinicians should consider whether the possible benefits of receiving treatment with these drugs outweigh the potential risks to the foetus. and, if they consent to pregnancy monitoring, followed up until 6 weeks after the end of the pregnancy
- after the end of the treatment, until the end of trial the patient will be followed up until 6 weeks after the end of the pregnancy if they consent to pregnancy monitoring

Notification to UCL CTC – refer to Pregnancy Report Processing (see [Section 11 - Pharmacovigilance](#))

6.4.6 Long term infertility

After chemoradiation, the uterus will be unable to sustain a pregnancy. Any requirement for egg cryo-preservation by individual patients should be considered as per local site policy prior to entry to the trial, and collection undertaken prior to commencing treatment.

6.4.7 Lactation

Mothers should be advised against breast-feeding while receiving trial treatment.

Patients being treated with carboplatin, paclitaxel or cisplatin should discontinue breastfeeding for the duration of their treatment.

6.5 HIV Testing

A documented negative HIV test is required from patients recruited from high risk countries or who have moved within the past 10 years from high risk countries. The following countries are considered as high risk¹²:

- All countries within the African continent
- United States of America
- Russian Federation
- India

All patients recruited from the above group of countries must have a HIV test within 31 days prior to randomisation.

6.6 Squamous Cell Carcinoma Antigen

The squamous cell carcinoma (SCC) antigen is the most commonly used tumour marker for cervical cancer¹³. This antigen is elevated in approximately 75-90% of patients with advanced stage (FIGO IIB and higher) disease and correlates with the extent of disease¹⁴⁻¹⁶, response to radiotherapy¹⁷, response to chemotherapy^{18, 19} and can be used to predict survival and tumour recurrence during follow-up. With the development of a sensitive radioimmunoassay, this marker can be readily detected in the serum and is now considered a valuable tool for monitoring cervical cancer²⁰.

If during follow-up the level is elevated beyond the normal range, repeat the test again in 4 weeks and if still elevated investigate.

The SCC antigen is tested by performing blood test, which is to be processed locally by the biochemistry department at the recruiting site. It is entirely optional – sites are not required to do it. However if available we ask for sites to measure it and provide where required.

If sites are unfamiliar with the test and its interpretation, we advise that this test is not performed.

7 RANDOMISATION PROCEDURES

7.1 Randomisation

Patient randomisation will be performed remotely at site by authorised site staff via an online UCL CTC website and this must be completed prior to commencement of any trial treatment. Pre-randomisation evaluations should be carried out at sites as detailed in [Section 6.1 – Pre-randomisation evaluation](#). Instructions for the online randomisation will be provided at the time of study activation.

Patients will be stratified according to the following factors: FIGO stage and tumour volume; positive (pelvic/para-aortic/both)/negative nodes; squamous vs non-squamous histology; IMRT vs no IMRT; age and recruiting site.

Following pre-treatment evaluations, confirmation of eligibility and consent of a patient at a site, the paper randomisation form must be fully completed before progressing to online randomisation. The eligibility criteria will be reviewed during online randomisation using the data entered on the paper CRF.

Once the patient has been randomised:

- An automatic email and fax confirmation will be sent to the main contact detailing the patient's inclusion in the trial, their trial number and treatment allocation.
- UCL CTC INTERLACE team will forward a copy of this email to pharmacy (UK sites only).
- The site contact must forward email to the site PI, and any other members of site team involved in patient's care.
- The site contact must fax a copy of the randomisation form to UCL CTC immediately.
- A separate email containing the case report forms will be sent to the main contact at site.

Non-UK sites should refer to their group specific guidance document for additional detailed instructions.

INTERLACE telephone number:	+44 (0)20 7679 9866
INTERLACE fax number:	+44 (0)20 7679 9871
INTERLACE randomisation website:	http://online.ctc.ucl.ac.uk
UCL CTC Office hours:	09:00 to 17:00 (UK time) Monday to Friday, excluding Bank Holidays

Once a patient has been randomised onto the trial they must be provided with the following:

- A copy of their signed consent form(s) and patient information sheet(s)
- A patient contact card. Site on-call contact details for 24 hour medical care must be added to this card and patients advised to carry this with them at all times while participating in the trial.

The INTERLACE GP letter should also be sent to the patient's GP.

8 TRIAL TREATMENT

Investigational Medicinal Products (IMPs)

For the purpose of this protocol, the IMPs are:

- Carboplatin
- Paclitaxel

Investigational treatments:

The investigational treatment is:

- Radiotherapy

Non Investigational Medicinal Products (NIMPs):

The following drug is administered as part of standard care and is therefore considered a NIMP:

- Cisplatin

**Note: the above information relates to the status of drugs in the UK and EU.
Countries outside the UK and EU should refer to their country-specific Summary
of Drug Arrangements (SoDA) for local information.**

8.1 Investigational Medicinal Products

Carboplatin and paclitaxel are currently not licensed for use in this disease area. They **will not** be provided for the trial and so hospital commercial stock should be used.

Please refer to the Summary of Drug Arrangements (SoDA) for full arrangements for the trial.

8.2 Treatment Summary

Patients with locally advanced cervical cancer will be randomised to receive either:

- induction chemotherapy with IV carboplatin AUC2 [(GFR + 25) x 2mgs] and IV paclitaxel 80mg/m² followed by standard chemoradiation (investigational arm)
- standard chemoradiation alone (standard arm)

The radiation in both arms will comprise external beam 40–50.4Gy in 20–28 fractions daily over 4-5.5 weeks plus intracavity brachytherapy to achieve a total EQD2 ($\alpha/\beta=10$) dose of 78-86Gy to point A /volume with weekly cisplatin 40mg/m² IV for 5 weeks. Radiotherapy will be delivered 5 days per week (Monday - Friday or 5 consecutive days as per local practice) one fraction per day unless where compensation for treatment gaps/delays are required where 2 fractions of external beam radiation may be delivered in one day with a minimum of a six hour gap. External beam and brachytherapy must not be delivered on the same day.

Please note:

- FBC and biochemistry are required within 14 days of the first cycle of chemotherapy (both trial arms).
- For second and subsequent chemotherapy cycles, FBC and biochemistry ideally must be done within 36 hours of treatment but biochemistry may be done up to 72 hours beforehand providing all indices are stable and not significantly different from baseline.
- At baseline, ANC and platelet count will be ANC $\geq 1.5 \times 10^9/L$ and platelets $\geq 100 \times 10^9/L$.
- Once on treatment (experimental or control arm) patients can continue with treatment as long as ANC count $\geq 1.0 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$.
- It is mandatory to give 5 cycles of cisplatin

8.2.1 Induction chemotherapy – carboplatin & paclitaxel

Weekly treatment for six weeks.

Week	1	2	3	4	5	6
Preferred start day	Mon, Tues or Wed					
Paclitaxel 80 mg/m ²	•	•	•	•	•	•
Carboplatin AUC2	•	•	•	•	•	•
Radiotherapy Planning				•		

It is preferable that induction chemotherapy should start on the Monday, Tuesday or Wednesday of week 1 of treatment and should be delivered on the same day each week. Minor deviations for logistical reasons are permitted as outlined in 8.3.1 below. Cisplatin should continue on the same day of the week if possible.

It is suggested that patients receiving induction chemotherapy should have their radiotherapy planning conducted between weeks 3 to 5 of their weekly induction treatment to ensure the patient is ready to start radiotherapy in week 7.

The interval from the last dose of induction chemotherapy to the first dose of cisplatin should be at least 7 days.

A minimum interval of 5 days between the last dose of induction chemotherapy and the first fraction of radiotherapy is required.

8.2.2 Chemoradiation – cisplatin & radiotherapy

Weekly treatment for five weeks regardless of fractionation schedule

Week	7	8	9	10	11	12
	Days 1-5	Days 8-12	Days 15-19	Days 22-26	Days 29-33	Days 36-40
Radiotherapy: 40-50.4Gy in 20-28 fractions	• • • • •	• • • • •	• • • • •	• • • • •	• • • • •	• • • •
Cisplatin 40mg/m ² Mon, Tues or Wed	•	•	•	•	•	

A brachytherapy boost is delivered to all patients where technically possible, according to local protocol (approved by TMG). However all treatment must be completed within 50 days (or 56 days with prior approval from the TMG) therefore it may be necessary to commence brachytherapy during external beam radiation.

Please note: brachytherapy and external beam radiation may not be given on the same day. Two brachytherapy treatments may be given on the same day, as long as there is a gap of 6 hours between treatments. Cisplatin should not be given on the same day as brachytherapy.

8.3 Trial Treatment Details

The IMPs for this trial are **carboplatin and paclitaxel**. Please note that for the purposes of this trial, **cisplatin** is classified as a non-investigational medicinal product (NIMP). Carboplatin, paclitaxel and cisplatin are to be supplied from Hospital Commercial Stock as detailed in the pharmacy file “Summary of Drug Arrangements” document.

Sites are not required to use a fixed brand of drug preparation.

The below table shows the dose calculation and maximum permitted dose for each of the trial drugs:

Drug	Dose calculation	Maximum dose
Carboplatin	2 x (GFR + 25)	270mg
Paclitaxel	BSA x 80	162mg
Cisplatin	BSA x 40	70mg

8.3.1 Induction chemotherapy

Weekly induction chemotherapy should be given on the same day each week i.e. at 7 day intervals. Minor deviations for logistical reasons, such as an 8 or 9 day interval followed by a 6 day interval, are permitted but should be avoided if possible. Weekly paclitaxel and carboplatin chemotherapy must not be given when the interval is less

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than 6 days from the previous treatment. The interval from the last dose of induction chemotherapy to the start of cisplatin should be a minimum of 7 days to allow blood counts to recover.

Paclitaxel

- Paclitaxel: 80 mg/m² in 250 ml of 5% dextrose or 0.9% sodium chloride IV over one hour (or prepared according to the SmPC for the brand used at site or as per local procedures if different; if preparation based on local procedures these should be supported by published data and approved by QA pharmacy or equivalent), followed by carboplatin AUC 2.
- This treatment is delivered weekly for 6 weeks i.e. on days 1, 8, 15, 22, 29 & 36.
- For patients who have BSA (calculated using actual body weight) more than 2.0m², the paclitaxel dose should be calculated using BSA = 2.0m². i.e. maximum total dose =162mg.
- The BSA should be recalculated if weight changes by >10% and the method for calculating BSA should follow local practice.
- Paclitaxel must be given before the carboplatin infusion.
- Nano-particle albumin bound paclitaxel must not be used.
- Dose banding for paclitaxel and carboplatin is as per local policy.
- Paclitaxel should be administered using non-PVC tubing and in-line filters (please refer to manufacturer's guidelines).

Carboplatin

- Carboplatin: AUC 2 IV infusion in 250-500 ml of 5% dextrose or 0.9% sodium chloride IV over 30 minutes (or prepared according to the SmPC for the brand used at site or as per local procedures if different; if preparation based on local procedures these should be supported by published data and approved by QA pharmacy or equivalent),
- Treatment is delivered weekly for 6 weeks i.e. on days 1, 8, 15, 22, 29, & 36.
- Dose calculated according to Calvert formula: Dose (mg) = 2 x (GFR + 25). GFR calculated using Wright formula (see Appendix IV) or radioisotope GFR assessment.
- The absolute dose of carboplatin will be capped at 270mg (corresponding to a GFR of 110ml/min).

The same dose of carboplatin should be prescribed each week unless the creatinine increases by 10%. The recalculated dose should be used even if creatinine decreases.

8.3.2 Chemoradiation

All centres must give 5 cycles of weekly cisplatin.

Cisplatin

- 40 mg/m² (capped at 70mg total dose) in 1 litre of sodium chloride 0.9% IV over one hour (or prepared according to the SmPC for the brand used at site or as per local procedures if different; if preparation based on local procedures these should be supported by published data and approved by QA pharmacy or equivalent), weekly for five weeks maximum, commencing in the first week of radiotherapy or as soon as blood counts have recovered from induction chemotherapy.
- Pre chemotherapy hydration with IV magnesium with or without potassium supplementation should be given according to the following schedule or as per local practice: Sodium chloride 0.9% 1 litre with 10mmol magnesium sulphate and 20mmol potassium chloride IV over 60 minutes, followed by 100ml of mannitol 10% IV over 15 minutes.
- IV post hydration is not required for cisplatin as long as the patient can drink approximately 8 glasses of water. If a patient is unable to drink this quantity then 1 litre of sodium chloride 0.9% with potassium and magnesium supplementation should be given.
- Cisplatin is given concurrently with radiotherapy. Cisplatin chemotherapy should not start before the first day of radiotherapy. See section 8.8 for further details on the radiotherapy treatment.
- Cisplatin infusion should ideally commence prior to daily radiotherapy fraction.
- The interval from the last dose of induction chemotherapy to the start of cisplatin should be a minimum of 7 days to allow blood counts to recover. Where daily radiotherapy is being delivered (Monday – Friday), it is suggested that cisplatin is given on a Monday, Tuesday or Wednesday of each week to maximise the potential radiosensitizing effect. Cisplatin must not be given on the same day as brachytherapy.
- Dose banding for cisplatin is as per local policy.

8.3.3 Anti-emetics and pre-medication

Induction chemotherapy

Premedication and antiemetic therapy before chemotherapy according to local policy or as follows:

- Steroid premedication for weekly paclitaxel: Dexamethasone 8 mg IV bolus at least 30 minutes before the start of the infusion.
- Antihistamine premedication: Chlorphenamine 10 mg IV bolus and ranitidine 50 mg IV bolus 30 minutes before each dose of paclitaxel.
- Granisetron 1 mg IV or other 5HT3 antagonist IV bolus 30 minutes before paclitaxel.

Antiemetics post treatment according to local protocol or as follows:

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- Domperidone 10mg oral qds prn for 3 days.

Cisplatin

Anti-emetics and premedication given according to local protocol or as follows:

- Dexamethasone 8 mg IV bolus and granisetron 1 mg IV (or other 5HT3 antagonist) bolus prior to cisplatin infusion.

Suggested antiemetics post treatment according to local protocol or as follows:

- Dexamethasone 4 mg bd oral for 2 days.
- Domperidone 10mg qds oral prn for 3 days.

If significant emesis, consider the use of appreptitant starting prior to the cisplatin infusion in addition to the above.

8.4 Dose Modifications

8.4.1 Haematological toxicity

Induction Chemotherapy

Full doses of both drugs will be given weekly if neutrophil count $\geq 1.0 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$.

FBC and biochemistry ideally must be done within 36 hours of treatment but biochemistry may be done up to 72 hours beforehand providing all indices are stable and not significantly different from baseline.

The following dose adjustments are recommended:

Table 4 - Dose modifications for haematological toxicity during induction chemotherapy

Haematological toxicity	Paclitaxel Day 1	Carboplatin Day 1
No toxicity during cycle	100% dose (80mg/m ²)	100% dose (AUC 2)
On day of treatment ANC <1 and or platelets ≤ 50	Omit this week's treatment - future doses will be at 80% of absolute dose	Omit this week's treatment
On day of treatment Platelets < 75 but > 50	100% dose	Omit this week's treatment
If weekly treatment with one or both drugs omitted on 1 occasion	80% of absolute dose (at next & all subsequent cycles)	AUC 1.6 (at next & all subsequent cycles)
Febrile neutropenia (\geq grade 3)	80% of dose (at next & all subsequent cycles)	AUC 1.6 (at next & all subsequent cycles)
Further occurrence of ANC <1 or platelets ≤ 50 despite dose reduction or second occurrence of febrile neutropenia	Discontinue further induction chemotherapy. Proceed to chemoradiation as soon as is possible as per trial protocol	Discontinue further induction chemotherapy. Proceed to chemoradiation as soon as is possible as per trial protocol

Chemoradiation

Full dose of cisplatin will be given concomitantly with radiotherapy starting in week 7 for those patients on the investigational arm providing ANC count $\geq 1.0 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$ within 36 hours of treatment.

If these levels are not reached the following dose modifications (based on the absolute drug dose) are recommended:

Table 5 – Dose modifications for haematological toxicity during chemoradiation

Haematological toxicity	Cisplatin – weekly
No toxicity during cycle	100% dose (40mg/m ²)
Day 1 ANC <1.0 or platelets <75	Delay for 24 hours. If still no recovery omit for 1 week.
If cisplatin omitted on 2 occasions	Continue at 80% of the absolute dose
If further delays despite dose modification	Discontinue cisplatin
Febrile neutropenia (\geq grade 3) or ANC <0.5 lasting >7 days	Hold for 1 week, if ANC resolves to grade 1 resume at 80% dose. If ANC does not resolve to grade 1 discontinue cisplatin
2 nd occurrence of febrile neutropenia or ANC <0.5 lasting >7 days	Discontinue cisplatin

All reasonable efforts must be made to ensure that the radiotherapy treatment continues without interruption.

Use of GCSF

The use of GCSF is permitted at the investigator's discretion to ensure that patients can complete the prescribed course of chemotherapy.

GCSF should not be given within 24 hours pre or post chemotherapy treatment.

8.4.2 Hypersensitivity reactions

Induction Chemotherapy

Patients who have a clinically significant hypersensitivity reaction to paclitaxel will discontinue induction chemotherapy and should proceed to chemoradiation as per trial protocol as soon as possible.

A clinically significant hypersensitivity reaction is one which meets the criteria for a CTCAE Grade 3 or 4 allergic reaction or for a CTCAE Grade 3 or 4 anaphylaxis. A patient may also discontinue induction chemotherapy if she has a hypersensitivity reaction to paclitaxel which does not meet the criteria but which, in the opinion of the investigator, poses a significant risk on re-challenge.

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Patients who develop a significant hypersensitivity reaction to carboplatin may continue on paclitaxel alone.

For Grade 1 or 2 reaction to carboplatin only, treatment may continue at the Investigator's discretion with increased steroid, antihistamine and slower infusion time.

Caution should be exercised with cisplatin administration during the CRT phase of the treatment as additional premedication may be required due to the potential for an allergic reaction to cisplatin in a patient allergic to carboplatin. However an allergic reaction to carboplatin is not a contraindication to the use of cisplatin.

Chemoradiation

Patients who experience a Grade 3 or 4 allergic reaction to cisplatin should discontinue cisplatin and continue with radiation alone.

8.4.3 Renal toxicity

Induction Chemotherapy

During treatment if there is a >10% rise in serum creatinine from baseline, or if the serum creatinine comes into the abnormal range for the first time, recheck GFR (calculated according to Wright equation (see Appendix IV) or radioisotope GFR assessment).

If calculated GFR has fallen below 60mls/min (or measured GFR has fallen below 50ml/min) or has deteriorated by 25% or more from baseline omit carboplatin for that week.

If calculated GFR recovers to above 60mls/min (or measured GFR above 50ml/min) or to within 25% of baseline, recalculate the carboplatin dose and continue at that dose for all subsequent weeks.

Discontinue carboplatin if withheld on more than 1 occasion.

Table 6 - Dose modifications for Renal Toxicity during induction chemotherapy

Renal toxicity	Paclitaxel	Carboplatin
No toxicity during cycle	100% dose	100% dose
On day of treatment/within 72hours Serum Creatinine ≤ 110% of baseline value	100% dose	Same dose based on baseline GFR
On day of treatment/within 72hours Serum Creatinine > 110% of baseline value; redetermined GFR > 50 ml/min if measured (or >60 ml/min if calculated) and > 75% of baseline GFR	100% dose	Recalculate dose of carboplatin AUC2 on redetermined GFR and administer if patient otherwise well, with additional hydration as appropriate
On day of treatment Serum Creatinine > 110% of baseline value; redetermined GFR < 50 ml/min if measured (or <60ml/min if calculated) OR < 75% of baseline GFR	100% dose	Omit carboplatin
If weekly carboplatin treatment omitted on 1 occasion but GFR recovers to > 50 ml/min if measured (>60 ml/min if calculated) and > 75% of baseline GFR	100% dose	Recalculate dose of carboplatin AUC2 on redetermined GFR on day of treatment and administer if patient otherwise well, with additional hydration as appropriate
If weekly carboplatin treatment omitted on 2 occasions OR GFR does not recover to > 50 ml/min if measured (>60ml/min if calculated) and > to 75% of baseline GFR	100% dose	Discontinue carboplatin and continue with Paclitaxel alone

Chemoradiation**Table 7 - Dose modifications for Renal Toxicity during Chemoradiation**

GFR (ml/min)	Dose of cisplatin
≥50 ml/min if measured or ≥60ml/min if calculated	100%
≥50 ml/min if measured or ≥60 if calculated but < 75% of baseline GFR	100% but consider slower infusion and extra hydration
<50 ml/min if measured or <60ml/min if calculated	Omit
If omitted on 1 occasion but recovers to > 50 ml/min if measured or >60ml/min if calculated within 7 days	80% dose, consider slower infusion and extra hydration
If omitted on 1 occasion and no recovery to > 50 ml/min if measured or >60ml/min if calculated within 7 days of initial fall	Discontinue permanently, continue radiation only

During delays or breaks in cisplatin patients should continue with radical radiotherapy alone.

8.4.4 Hepatic toxicity***Induction Chemotherapy***

If bilirubin level during treatment rises to >1.25 x ULN but < 2 x ULN and transaminases are < 10 x ULN, suggest 25% dose reduction of the paclitaxel.

Any further rise in bilirubin and /or transaminases despite dose modification above, discontinue paclitaxel.

Paclitaxel should be re-challenged if bilirubin decreases to <1.25 x ULN and transaminases decrease to < 10 x ULN.

If the bilirubin level exceeds 2 x ULN and /or transaminases ≥ 10 times ULN then omit that dose of paclitaxel and rechallenge (with 25% dose reduction) if the bilirubin level falls to <1.25 x ULN and /or transaminases fall to less than 10 x ULN within 7 days.

If bilirubin <1.25 x ULN and transaminases >ULN but less than 10x ULN continue without dose modification.

8.4.5 Peripheral neuropathy***Induction Chemotherapy***

Peripheral neuropathy > Grade 2, omit paclitaxel for one week. If recovers to grade 1 continue with paclitaxel at 80% of the dose. If there is a further occurrence despite dose reduction, discontinue induction chemotherapy and proceed to radiation with or without concomitant cisplatin at the investigators discretion and according to patient wishes.

Chemoradiation

Peripheral neuropathy > Grade 2 omit cisplatin for one week. If recovery occurs to Grade 1 continue with cisplatin at 80% of the dose.

If further occurrence despite dose reduction, discontinue cisplatin and continue with radiation alone.

8.4.6 Ototoxicity***Chemoradiation***

Tinnitus or impaired hearing \geq Grade 2 hold until recovery to Grade 1. Then continue at 80% of the absolute dose.

Where possible audiology should be performed to document hearing loss.

8.4.7 Gastrointestinal toxicity***Induction Chemotherapy***

Patients with Grade 3 or 4 anorexia, nausea, vomiting, constipation, diarrhoea or other gastrointestinal events should be managed according to local guidelines.

Hold treatment until symptoms resolve to Grade 1 and then either continue with 100% dose and increase the antiemetic cover or continue with paclitaxel at 80% of the absolute dose and carboplatin at AUC 1.6 (at investigator's discretion).

If there is a further occurrence despite dose modifications and maximum antiemetic therapy, discontinue induction chemotherapy and proceed to chemoradiation as soon as possible.

Chemoradiation

Patients with Grade 3 or 4 anorexia, nausea, vomiting, constipation, diarrhoea or other gastrointestinal events should be managed according to local guidelines. Hold cisplatin until toxicity resolves to Grade 1 and then either continue with full dose cisplatin with increased antiemetic cover or at 80% of the absolute dose (at investigator's discretion) If further occurrence despite dose reduction then discontinue cisplatin and continue radiation alone. Every effort must be made to continue the radiation therapy without interruption.

8.5 Management of Overdoses, Trial treatment error, or Occupational Exposure***Overdose***

An overdose is the administration of a quantity of a trial treatment, either per administration or cumulatively, which is in excess of the protocol specified dose. The dose can either be evaluated as overdose by the trial team at site or by the Sponsor upon review.

All accidental or intentional overdoses, whether or not they result in adverse events, must be recorded in the patient notes and CRFs.

INTERLACE

Overdoses should be reported on an incident report (see [section 12.1](#)). Any adverse events resulting from an overdose should be reported as an SAE (see [section 11.2.3](#) for reporting procedures). The fact that an overdose has occurred must be clearly stated on the SAE Report.

Sites must inform UCL CTC immediately when an overdose has been identified. Also refer to [Section 12 – Incident Reporting and Serious Breaches](#).

Trial treatment error

Any unintentional error in prescribing, dispensing, or administration of a trial treatment while in the control of a healthcare professional or consumer. The error can be identified either by the trial team at site or by the Sponsor upon review.

Include details from IB/SPC on the clinical management of trial treatment errors, where available. Trial Treatment errors should be reported on in incident report (see [section 12.1](#)). Any adverse events resulting from a medication error should be reported as an SAE (see [section 11.2.3](#) for reporting procedures).

Occupational exposure

Exposure to a trial treatment as a result of one's professional or non-professional occupation. Occupational exposure should be reported on an incident report form (see section 12.1).

8.6 Supportive Care

Additional medication for intercurrent illness or to manage the side effects of chemotherapy and /or radiotherapy may be prescribed at the investigator's discretion. However patients should not receive any other anti-cancer therapy or other investigational drugs whilst on the trial.

The treatment of venous thromboembolism during induction chemotherapy and the entire course of chemoradiation must be with low molecular weight heparin or equivalent and not warfarin.

8.7 COVID-19 Vaccines

As there are currently no live attenuated vaccines licensed, the INTERLACE Trial Management Group approve of the use of COVID-19 vaccines in existing INTERLACE participants in the absence of any other contraindications without treatment interruption. Potential patients who have received a COVID-19 vaccination are also not excluded from entering the trial.

The timing of COVID-19 vaccine administration and Trial treatment should be determined by the Principal Investigator or a Co-investigator at site in the best interests of the patient, however we recommend that for patients receiving cytotoxic chemotherapy/Systemic anti-cancer therapy (SACT) vaccine administration should occur when blood counts have maximally recovered (towards end of cycle) and should be avoided on same day of chemotherapy. Vaccine administration should be recorded

in the medical notes and concomitant treatment CRF. If you have any questions or would like advice from the INTERLACE TMG please contact UCL CTC.

8.8 Contraindications

Caution should be exercised in the choice of supportive medications and antibiotics to minimise the risk of enhancement of drug toxicity, in particular medications which inhibit CYP3A4 and could enhance paclitaxel toxicity.

Traditional and herbal medications may also cause unfavourable interactions and should be discussed specifically with participating patients.

8.9 Radiotherapy

The standardised radiotherapy for this trial is external beam radiation followed by brachytherapy or external beam and concomitant brachytherapy boost. A Radiotherapy QA Pack will be provided to all participating Radiotherapy centres with guidelines on the full radiotherapy and brachytherapy processes (including an outlining atlas) as well as detailed information on the Quality Assurance programme. All participating centres will be required to comply with the RTQA programme outlined.

Radiotherapy QA will be performed by the National Radiotherapy QA group (RTTQA), and will consist of pre-activation QA exercises and on-trial QA, as described below. All QA, as well as the Radiotherapy QA Pack, will be available for download from the “Downloads” section in the RTTQA website: <http://rttrialsqa.org.uk/> Please contact the RTTQA team for a username and password.

All QA must be completed and submitted electronically to Patty Díez at interlaceqa.enh-tr@nhs.net. Any queries please call on 020 3826 2323.

Pre-activation QA

- *Pre-trial (facility) questionnaire:* containing questions on a range of aspects relevant to the trial including details of the equipment to be used to plan and treat INTERLACE patients and the staff involved in the QA process.
- *Process document:* to be submitted by the centre detailing all aspects of the tasks required for complete external beam and brachytherapy treatments. This should include all steps from immobilisation, scanning, through planning and verification to treatment. Please note that centres will already have such a document for peer review and this can be submitted without alteration.
- *EBRT Outlining (benchmark) cases:* clinicians will participate in the pre trial QA process through the submission of test outlining cases. These will be available for download from the RTTQA website. In some circumstances sample cases of previously treated patients may be reviewed instead but they must be protocol-compliant.

- *EBRT Planning (benchmark)* cases: QA of 3D conformal, IMRT and rotational planning will be monitored using a similar technique. Pre-outlined 3D test cases will be available for download from the RTTQA website and each participating centre will be expected to submit them for assessment of adherence to trial protocol and plan quality. In some circumstances sample plans from previously treated patients may be submitted for review instead but both outlines and plan must be protocol-compliant.
- *Brachytherapy example case (dummy run)*: each centre will be asked to submit an anonymised example case they have already treated to complete their brachytherapy outlining and planning QA.
- *Brachytherapy TPS check*: centres will need to create a line source on their brachytherapy TPS and note the doses at various points from the sources and submit these to the RTQA team to assess their planning system algorithms.

On-trial QA

- *Brachytherapy dosimetry audit*: all UK centres taking part in INTERLACE will be required to take part in the INTERLACE phantom audit, the IPEM film phantom audit and the IPEM HDR well chamber audit. These can be completed at any time and is NOT required PRE-recruitment.
- *Plan data collection*: On-going QA will be carried out as required (including prospective review of first few patients as well as retrospective review of a proportion of all randomised patients). Data will be collected for all patients treated in the INTERLACE trial. Data should be sent in DICOM format and include:
 - 3D EBRT and brachytherapy: patient history, CT and MR datasets, registration objects, structure, plan and dose-cube files.
 - 2D brachytherapy: printouts from the TPS and imaging.

In addition patient history and imaging reports as well as both EBRT and brachy PAFs should be emailed to the trial contact.

8.10 Pharmacy Responsibilities

All pharmacy aspects of the trial at participating sites are the responsibility of the PI, who may delegate this responsibility to the local pharmacist or other appropriately qualified personnel, who will be the Pharmacy Lead. The delegation of duties must be recorded on the site staff delegation log.

8.10.1 Drug accountability

The Pharmacy Lead must ensure that appropriate records are maintained.

These records must include accountability of **carboplatin** and **paclitaxel**, including: dispensing, reconciliation and destruction of returned/unused medication. Template accountability forms will be supplied, however, sites may be permitted to use their own drug accountability records provided the same information is captured, as a minimum. Such in-house records must be submitted to UCL CTC for review and authorisation for use prior to patient enrolment.

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Copies of completed drug accountability logs must be submitted to UCL CTC for all trial patients at the end of treatment or upon request. Also refer to [Section 13.2 – Centralised Monitoring.](#)

Please note: for non-UK sites, drug accountability may be required for carboplatin, paclitaxel and cisplatin, depending on the licensing status of the trial drugs. This will be made clear in country-specific SoDA and agreed ahead of site activation.

8.11 Clinical Management after Treatment Discontinuation

If patients withdraw consent or stop treatment due to adverse events, subsequent treatment will be at the discretion of the treating clinician.

Also refer to [Section 14 – Withdrawal of Patients](#) for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.

9 ASSESSMENTS

Prior to performing any study procedures, the Investigator or his/her designated staff will obtain written informed consent from the subject. After reading the subject information leaflet and having all questions answered, if the subject chooses to give consent, it must be obtained in writing. The subject's consent must be confirmed by a dated signature at the time of the subject's signature by the person conducting the informed consent discussions. A copy of the signed consent document must be given to the subject. The Investigator will retain the original in the subject's clinical notes or source documents and if applicable (per local site procedures), a copy should be kept in the Study Site Trial File as well.

Subjects who have successfully met and continue to meet all the inclusion and exclusion criteria will be considered for randomisation. For detailed screening, please see the entry criteria and see section 6.1 for a summary of pre-randomisation assessments.

9.1 Assessments during Treatment

During treatment the patient should be seen every week and the following assessments/investigations/procedures performed:

- Physical examination
- Clinical examination: BP, pulse, ECOG performance status
- Weight
- Full Blood Count*,** WBC, neutrophils, haemoglobin, platelets
- Biochemistry ** - sodium, potassium, urea, creatinine, bilirubin, albumin, magnesium, calcium, ALP, AST or ALT
- Toxicity/Adverse Events
- Quality of Life (given to patient on day one of induction chemotherapy week 4, if allocated to this group, and then for all patients on day one of chemoradiotherapy and day one of week 3 chemoradiotherapy)

* Every effort should be made to maintain Hb $\geq 11\text{g/dL}$. Patients should be considered for transfusion if level falls below 11g/dL.

** FBC and biochemistry are required within 14 days of the first cycle of chemotherapy (both trial arms). ANC $\geq 1.5 \times 10^9/\text{L}$ and platelets $\geq 100 \times 10^9/\text{L}$.

Please note: For second and subsequent chemotherapy cycles, FBC and biochemistry ideally must be done within 36 hours of treatment but biochemistry may be done up to 72 hours beforehand providing all indices are stable and not significantly different from baseline. ANC count $\geq 1.0 \times 10^9/\text{L}$ and platelets $\geq 75 \times 10^9/\text{L}$.

If a patient is scheduled for treatment on a Monday and it is standard practice to perform haematology and biochemistry on the previous Friday, it is acceptable to confirm treatment and commence hydration based on Friday's results; however, FBC should be conducted again on Monday to ensure platelets and white cell counts (including ANC) are within the correct range for chemotherapy to commence.

A summary of follow-up assessment investigations are shown in Table 11 below.

INTERLACE**Table 11 – Follow-up Assessments**

All Treatment Arms	Baseline	During Treatment	4 Weeks Post all Treatment	12 Weeks Post all Treatment ^l	Follow-up Post Treatment 3 monthly for 2 years, 6 monthly for 3 years	Further data collection
Informed Consent	X					
Medical History	X					
Examination with Biopsy and Cytoscopy	X					
Physical Examination	X		X	X	X	
Clinical Examination: BP, Pulse, ECOG PS	X	X	X	X	X	
Height, Weight ^a	X	X				
CT or PET CT Chest/Abdomen	X					
MRI Pelvis (+/- abdomen)	X			12/52 after completion of CRT treatment		
CT Pelvis if MRI not available ^b	X			12/52 after completion of CRT treatment		
Tumour Volume ^c	X			X		
Negative HIV Test ^d	X					
Pregnancy Test ^e	X					
Adequate Renal Function ^f	X					
FBC ^g	X	X	X			
Biochemistry ^h	X	X	X			
Squamous Cell Carcinoma Antigen ⁱ	X		X		X	
Translational Tissue ^j	X					
Toxicity/Adverse Events	X	X	X	X	X	
Q of L Questionnaire ^k	X	X	X	X	X	
Disease & survival status (from medical notes)						X

a Height only recorded at baseline, weight weekly during treatment

b MRI pelvis in Europe and UK; CT pelvis permitted in non-European countries/non-UK sites if MRI not available and to include clinical examination by two study investigators

c Calculate tumour volume using volume of an ellipsoid $\frac{1}{2} \times D1 \times D2 \times D3$ where D is the diameter of the tumour in the three different axesd Patients recruited from high risk countries or who have moved within the past 10 years from high risk countries. For more details see [Section 6.5 – HIV Testing](#).e Pregnancy test for WOCBP. For more details and definition of WOCBP see [Section 6.4.1 – Definitions](#).f GFR \geq 60ml/min calculated using the Wright equation or \geq 50ml/min for radioisotope GFR assessment (see Appendix IV)

g WBC, neutrophils, haemoglobin, platelets

h Sodium, potassium, urea, creatinine, bilirubin, albumin, magnesium, calcium, ALP, AST or ALT, LDH, gamma GT

i Squamous Cell Carcinoma Antigen (if available). For more details see [Section 9.3 – Assessments During Follow-up](#).j Consent for paraffin embedded cervical tissue block obtained from the original primary tumour (optional)
k Q of L Questionnaire – to be given at baseline, day one of week 4 of induction chemotherapy (if allocated to this group), day one of chemoradiotherapy, day one of week 3 chemoradiotherapy, 4 weeks post chemoradiotherapy and during follow-up clinic visits

l Imaging at 12/52 post treatment only unless clinically indicated thereafter

9.2 Assessments on Completion of Trial Treatment

4 weeks post treatment assessment

The following assessments will be performed 4 weeks after the completion of chemoradiation:

- Physical examination
- Clinical examination: BP, pulse, ECOG performance status
- Full blood count
- Biochemistry
- Squamous Cell Carcinoma Antigen (if available) - see [section 6.6 – Squamous Cell Carcinoma Antigen](#).
- Toxicity/Adverse Events
- Quality of Life questionnaire

12 weeks post treatment assessment

The following assessments will be performed after a minimum of twelve weeks from the date of completion of chemoradiation:

- MRI (non-European/non-UK sites are permitted to perform CT pelvis)
- Physical examination
- Clinical examination: BP, pulse, ECOG performance status
- Full blood count (if clinically indicated)
- Biochemistry (if clinically indicated)
- Squamous Cell Carcinoma Antigen (if available) - [section 6.6 – Squamous Cell Carcinoma Antigen](#)
- Toxicity/Adverse Events
- Quality of Life questionnaire

Please note all patients will be required to undergo MRI pelvis or CT pelvis with clinical examination by two study investigators (non-European countries/non-UK sites only) 12 weeks after completing chemoradiation and response documented according to RECIST (see Appendix VIII – Response Criteria).

In addition tumour volume should be calculated using volume of an ellipsoid $\frac{1}{2} \times D1 \times D2 \times D3$ where D is the diameter of the tumour in the three different axes.

9.3. Assessments During Follow Up

On completion or discontinuation of trial treatment, patients will be followed 3 monthly for the first 2 years and 6 monthly until the end of trial. The trial Follow-up form should be completed for the first 5 years following the end of treatment and, following this, the Survival Data Form should be completed at all subsequent 6-monthly visits.

The below table shows the trial follow-up timepoints and associated forms that should be submitted at each visit:

Timepoint post-treatment	Name of form to complete
4 weeks	4 week post treatment form
12 weeks	12 week post treatment form
6 months	Follow-up form
9 months	Follow-up form
12 months	Follow-up form
15 months	Follow-up form
18 months	Follow-up form
21 months	Follow-up form
24 months	Follow-up form
30 months	Follow-up form
36 months	Follow-up form
42 months	Follow-up form
48 months	Follow-up form
54 months	Follow-up form
60 months	Follow-up form
Month 66 onwards	Survival Data form

If a patient fails to attend a visit or cannot be followed up at site, all efforts should be made by the site to contact the patient's GP to assess their condition.

The following assessments should be performed at each follow-up visit

- Physical examination
- Clinical examination: BP, pulse, ECOG performance status
- Squamous Cell Carcinoma Antigen (if available) - [section 6.6 – Squamous Cell Carcinoma Antigen](#)
- Toxicity/Adverse Events
- Quality of Life questionnaire

9.4 Assessments after Disease Progression

Upon progression, sites should complete the Progression Form, detailing the date of progression, how progression was confirmed and primary and/or metastatic site(s) where applicable.

After progression, patients should continue to be followed up where possible according to the trial follow-up schedule. If a patient is unable to attend trial visits, sites should try to make any reasonable efforts to obtain information about survival status and adverse events via the patient's hospital notes, another treating department in the hospital or by getting in touch with the patient's GP.

As a minimum, survival data should be reported on the Follow-up CRFs. A Death Form should be submitted once the site learns of a trial patient's death.

Please note: adverse event data is still required following patient progression. Please make all reasonable efforts to collect this information.

10 DATA MANAGEMENT AND DATA HANDLING GUIDELINES

Data will be collected from sites on version controlled case report forms (CRFs) designed for the trial and supplied by UCL CTC. Data must be accurately transcribed and must be verifiable from source data at site.

Examples of source documents are hospital records which include laboratory and other clinical reports etc.

Where copies of supporting source documentation (e.g. autopsy reports, pathology reports, CT scan images etc.) are being submitted to UCL CTC, the patient's trial number must be clearly indicated on all material and any patient identifiers removed/blacked out prior to sending to maintain confidentiality.

Please note that for this trial, patients have consented to their names being supplied to UCL CTC. This is to confirm patient's consent to participate in the translational research.

10.1 Completing Case Report Forms

All CRFs must be completed and signed by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. The PI is responsible for the accuracy of all data reported in the CRF.

All entries must be clear, legible and written in ball point pen. Any corrections made to a CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialed. Correction fluid must not be used.

The use of abbreviations and acronyms must be avoided.

Once completed the original CRFs must be sent to UCL CTC (or via the Country Coordinating Centre (CCC) for non-UK sites) and a copy kept at site.

10.2 Missing Data

To avoid the need for unnecessary data queries CRFs must be checked at site (and CCC if applicable) to ensure there are no blank fields before sending to UCL CTC. When data are unavailable because a measure has not been taken or test not performed, enter "ND" for not done. If an item was not required at the particular time the form relates to, enter "NA" for not applicable. When data are unknown enter the value "NK" (only use if every effort has been made to obtain the data).

10.3 Timelines for Data Return

UK sites must complete and return CRFs to UCL CTC as soon as possible after patient visit and within one month of the patient visit.

Non-UK sites with a Country Coordinating Centre must complete and submit CRFs to their CCC within one month of the patient visit. CCCs must forward all CRFs to UCL CTC within 5 business days of receipt.

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Non-UK sites without a Country Coordinating Centre must complete and submit all CRFs to UCL CTC within one month of the patient visit.

Sites who persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and subjected to a 'for cause' monitoring visit. See [section 13.3 – 'For cause' on-site monitoring](#) for details.

10.4 Data Queries

Data arriving at UCL CTC will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values.

Data Clarification Requests will be sent to the data contact at site (or CCC where applicable). When completing these requests, sites should respond to queries in the space provided on the form (unless otherwise indicated within the query). Sites do not need to complete the Data Clarification Request form along with an updated CRF (unless indicated).

Further guidance on how data contacts should respond to data queries can be found on the Data Clarification Requests.

11 PHARMACOVIGILANCE

11.1 Definitions

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting” and ICH GCP E6.

Adverse Event (AE)

Any untoward medical occurrence in a patient treated on a trial protocol, which does not necessarily have a causal relationship with an IMP or investigational treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of an IMP or investigational treatment, whether or not related to that IMP or investigational treatment. See [section 11.2.1 for AE reporting procedures](#).

Adverse Reaction (AR)

All untoward and unintended responses to an IMP or investigational treatment-related to any dose administered. A causal relationship between an IMP or investigational treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that at any dose:

- Results in death
- Is life threatening (the term “life-threatening” refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above)

See [section 11.2.2 for SAE reporting procedures](#).

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which **is not consistent** with the reference safety information (RSI).

i.e. an adverse event that meets all the following criteria:

- Serious – meets one or more of the serious criteria, listed under the definition of SAE above
- Related – assessed by the local PI or designee, or Sponsor as causally related to one or more elements of the trial treatment
- Unexpected – the event is not consistent with the applicable reference safety information

See [section 11.3 for SUSAR reporting procedures.](#)

Overdose, IMP or Investigational treatment error

Refer to section 8.5 for details on reporting of these events.

11.2 Reporting Procedures

Adverse Event Term

An adverse event term must be provided for each adverse event, preferably using the term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v4.03, available online at:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Severity grade

Severity of each adverse event must be determined by using the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 as a guideline, wherever possible. The criteria are available online at:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

In those cases where the CTCAE criteria do not apply, severity should be coded according to the following criteria:

- 1 = Mild (awareness of sign or symptom, but easily tolerated)
- 2 = Moderate (discomfort enough to cause interference with normal daily activities)
- 3 = Severe (inability to perform normal daily activities)
- 4 = Life threatening (immediate risk of death from the reaction as it occurred)
- 5 = Fatal (the event resulted in death)

Causality

The relationship between the treatment and an adverse event will be assessed.

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For AEs (including SAEs), the local PI, or other delegated site investigator, will assess whether the event is causally related to each IMP and investigational treatment.

For SAEs a review will also be carried out by the sponsor's delegate.

Causal relationship to each trial treatment must be determined as follows:

- **None**

There is no evidence of any causal relationship.

- **Unlikely**

There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of a trial treatment). There is another reasonable explanation of the event (e.g. the patient's clinical condition, other concomitant treatments).

- **Possibly**

There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of a trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

- **Probably**

There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

- **Definitely**

There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

UCL CTC will consider events evaluated as possibly, probably or definitely related to be adverse reactions.

11.2.1 Reporting of Adverse Events (AEs)

All adverse events that occur between informed consent until the end of the trial, whether related to trial treatment or not, must be recorded in the patient notes and the trial CRFs.

Adverse events meeting the definition of a Serious Adverse Event (SAE) must also be reported to UCL CTC using the trial specific SAE Report - see [Section 11.2.2 – Reporting of Serious Adverse Events](#).

Pre-existing conditions (i.e. conditions present at informed consent) do not qualify as adverse events unless they worsen.

E.g. an AE could be an exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition (worsening of the event). Another example of an AE is when a pre-existing condition improves during the trial (e.g. from grade 3 to grade 1) and then it worsens again (e.g. from grade 1 to grade 2), even if the event is of severity equal or lower to the original condition (improvement and recurrence of the event).

NB the disease(s) under study and its anticipated day-to-day fluctuations would not be an AE.

11.2.2 Reporting of Serious Adverse Events (SAEs)

All SAEs that occur between the signing of informed consent and 30 calendar days post the last IMP and post last investigational treatment administration (or after this date if the site investigator feels the event is related to a trial treatment) must be submitted to UCL CTC by fax or email within **24 hours** of observing or learning of the event, using the trial specific SAE Report.

All sections on the SAE Report must be completed. If the event is **not being reported within 24 hours** to UCL CTC, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

Non-UK participating sites should refer to their group specific appendix for additional detailed instructions.

Exemptions from SAE Report submission

For this trial, the following events are exempt from requiring submission on an SAE Report **unless considered to be related to the IMP OR investigational treatment(s)**. However, the events must be recorded in the relevant section(s) of the trial CRFs:

- events that occur more than 30 calendar days post last IMP and post last investigational treatment administration that are not considered to be side-effects of the IMP or investigational treatment. Note: this does not include pregnancy related events (see section 11.5)
-
- disease progression (including disease related deaths)

Please note that hospitalisation for elective treatment, palliative care, socio-economic or logistic reasons do not qualify as an SAE.

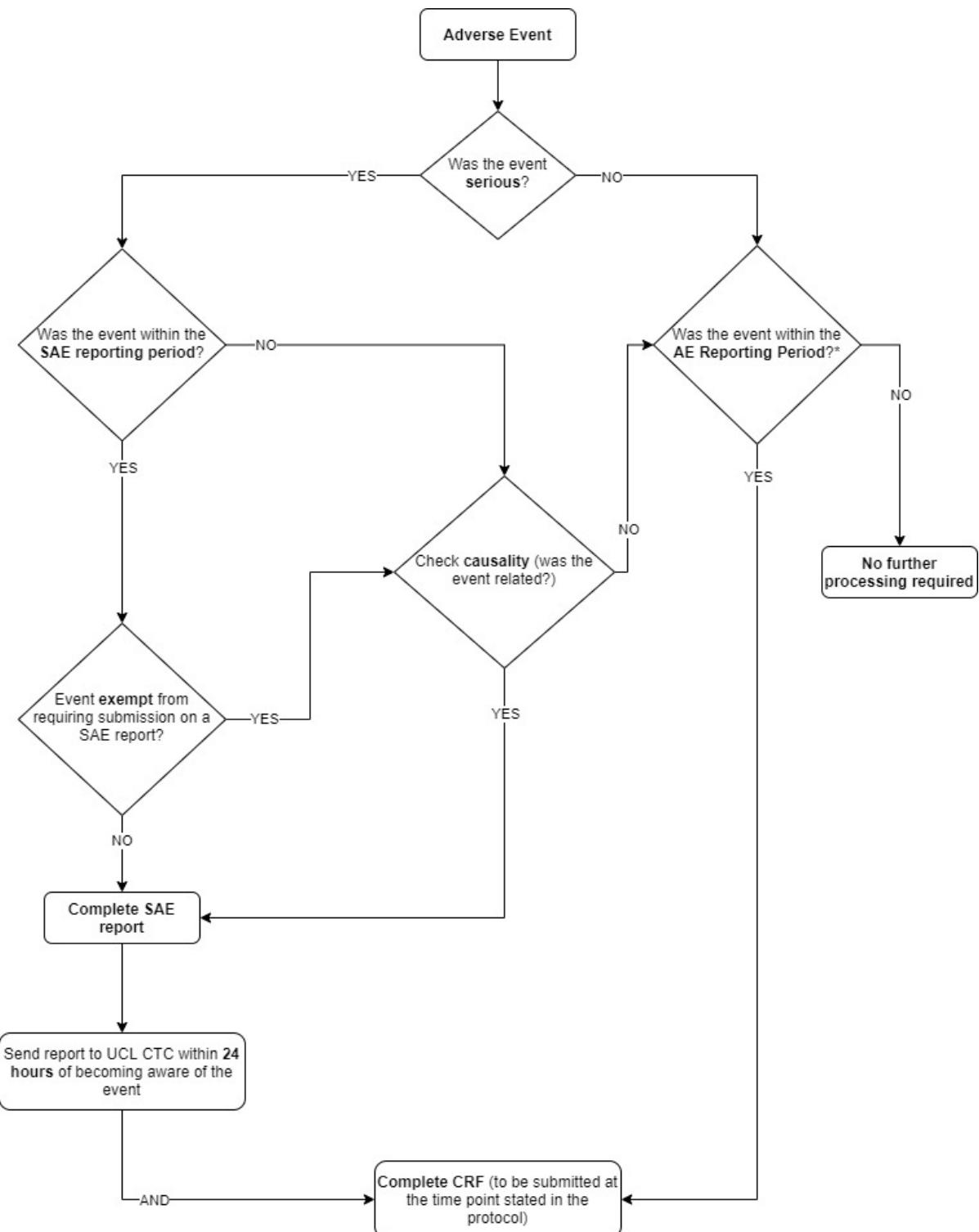
Completed SAE Reports must be faxed or emailed within 24 hours of becoming aware of the event to UCL CTC

Fax: +44 (0)20 7679 9871
Email: ctc.interlace@ucl.ac.uk

SAE Follow-up Reports

UCL CTC will follow up all SAE/SARs until resolution and until there are no further queries.

Sites must ensure any new and relevant information is provided to UCL CTC promptly. If an event term changes or a new event is added, the causality must be re-assessed by an Investigator. If the event is not being reported to UCL CTC within 24 hours, the circumstances that led to the delay must be detailed in the SAE/SAR Report to avoid unnecessary queries.

SAE and AE Reporting Flowchart

*This applies if AE and SAE reporting period differs

SAE Processing at UCL CTC

On receipt of the SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the RSI (the list of expected adverse events in Appendix IX for radiotherapy and the approved SPCs for carboplatin, paclitaxel and cisplatin).

The CI, or their delegate (e.g. a clinical member of the TMG), will be contacted to review the SAE and to perform an evaluation of causality on behalf of the sponsor. If UCL CTC has considered expectedness difficult to determine, the CI, or their delegate, will be consulted for their opinion at this time.

11.3 SUSARs

If the event is evaluated as a Suspected Unexpected Serious Adverse Reaction (SUSAR), UCL CTC will submit a report to the applicable regulatory authority within the EEA within 7 calendar days for fatal/life threatening events (with a follow-up report within a further 8 calendar days) and 15 calendar days for all other events.

SUSARs occurring within the EEA

Where the SUSAR has occurred outside the UK but within the EEA, UCL CTC will enter the case on the EudraVigilance Clinical Trial Module in order to notify the European Medicines Agency and applicable regulatory authorities.

SUSARs occurring within the UK or outside of the EEA

Where the SUSAR has occurred within the UK or outside the EEA, UCL CTC will submit the report directly to the MHRA for them to enter the case on the EudraVigilance Clinical Trial Module. UCL CTC will also report all SUSARs originating in the UK to the UK REC.

Country coordinating centres (CCCs)/ Country Lead Sites (CLSs)

UCL CTC will also send all submitted SUSAR reports to country co-ordinating centres/country lead sites (CCCs/CLSs) within 6 (six) calendar days for initial reports of fatal/life threatening events, with a follow-up report within a further 7 (seven) calendar days if applicable, and 14 (fourteen) calendar days for all other events. CCCs/CLSs must forward all SUSAR reports to their ethics committee(s), as required, and their regulatory authority (for non-EEA countries only), if applicable, within 1 business day. UCL CTC will ensure that consideration is given where the reporting deadline occurs at a weekend to allow reporting within the required timeframes.

Where there are conflicting evaluations of causal relationship by the site and UCL CTC/CI, both opinions will be reported.

Informing Sites of SUSARs

UCL CTC will inform all UK PIs of any SUSARs that occur on the trial. PIs will receive a quarterly line listing which must be processed according to local requirements.

For participating countries outside the UK, UCL CTC will submit line listings to CCCs for forwarding to the PIs in their country within one business day. Where there is no CCC, UCL CTC will submit SUSAR reports directly to sites in that country.

11.4 Safety Monitoring

UCL CTC will provide safety information to the TMG and the IDMC on a periodic basis for review.

Trial safety data will be monitored to identify:

- Whether disease-related events (exempt from SAE reporting as per [section 11.2.2 – Reporting of Serious Adverse Events](#)) appear to be enhanced by the IMP or investigational treatment
- new adverse reactions to the combination therapy or individual IMP or investigational treatment
- a higher incidence in rare adverse events than is stated in the SPC for an IMP or investigational treatment;
- trial related events that are not considered related to the IMP or investigational treatment, but may lead to changes to the trial documents. These would include events related to NIMP.

Should UCL CTC identify or suspect any issues concerning patient safety at any point throughout the trial, the CI or TMG will be consulted for their opinion.

11.5 Pregnancy

Reporting period

If a female patient becomes pregnant at any point during the trial, a completed trial specific Pregnancy Report must be submitted to UCL CTC by fax or email within **24 hours** of learning of its occurrence.

A pregnancy exposure to trial treatment includes:

- Pregnancy in a trial patient occurring between consent and 30 days after the last trial treatment.

Consent to report information regarding the pregnancy must be obtained from the pregnant patient. The trial-specific pregnancy monitoring information sheet and informed consent form for trial patients must be used for this purpose.

If consent is not given, the notification that a pregnancy has occurred will be retained by UCL CTC, however no further action will be taken on the information detailed in the report.

All pregnancies must be reported by faxing or emailing a completed Pregnancy Report within 24 hours of becoming aware of the pregnancy to UCL CTC
Fax: +44 (0)20 7679 9871
Email: ctc.interlace@ucl.ac.uk

Pregnancy Follow-Up Reports

For pregnant patients or partners who consent, their pregnancies must be followed-up **at least monthly** for up to 6 weeks after the end of the pregnancy (or later if there are ongoing issues) to collect information on any ante- and post-natal problems for both mother and child. If significant new information is received, follow-up Pregnancy Reports must be submitted to UCL CTC by email within **24 hours** of learning of the new information. In case of adverse outcome to the pregnancy reports must include an evaluation of the possible relationship of each trial treatment to the pregnancy outcome.

SAEs during pregnancy

Any SAE occurring in a pregnant patient must be reported using the trial specific SAE Report, according to SAE reporting procedures. Refer to section 11.2.2.

Pregnancy Report processing at UCL CTC

UCL CTC will submit a report to the applicable regulatory authority within the EEA, the UK REC and CCCs/CLSs should the pregnancy outcome meet the definition of a SUSAR. Refer to [Section 11.3 – SUSARs](#) for details.

11.6 Development Safety Update Reports (DSURs)

Safety data obtained from the trial will be included in DSURs that UCL CTC **will submit to the MHRA, the UK REC and all CCCs/CLSs**. CCCs/CLSs must forward all reports to the regulatory authority and ethics committee(s) and any other organisations as identified in the agreement between UCL and the CCC/CLS in that country according to the timelines outlined in the agreement between UCL and the CCC/CLS.

12 INCIDENT REPORTING AND SERIOUS BREACHES

12.1 Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. UCL CTC may require a report on the incident(s) and a form will be provided if the organisation does not have an appropriate document (e.g. Trust Incident Form for UK sites).

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

Where the incident has occurred in a site outside the UK, the CCC/CLS in that country must also notify the relevant ethics committee in accordance with local requirements. Where UCL CTC identifies an incident at a site outside the UK, the CCC/CLS in the country where the incident occurred will be informed.

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

UCL CTC will assess all incidents to see if they meet the definition of a serious breach.

Non UK sites should refer to their group specific appendix for additional detailed instructions.

12.2 Serious Breaches

A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research.

Systematic or persistent non-compliance by a site with GCP and/or the protocol, including failure to report SAEs occurring on trial within the specified timeframe, may be deemed a serious breach.

In cases where a serious breach has been identified, UCL CTC will inform the MHRA within 7 calendar days of becoming aware of the breach.

The serious breach report may also be forwarded to CCCs/CLSs for submission to their regulatory authorities and any other organisations as identified in the agreement between UCL and the CCC/CLS, as required.

UK sites must have written procedures for notifying the sponsor of serious breaches (MHRA Guidance on the Notification of Serious Breaches).

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

Non UK sites should see their group specific appendix for additional detailed instructions.

13 TRIAL MONITORING AND OVERSIGHT

All sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Where permitted by site policy, remote access to source data/documents may also be provided by participating sites for remote monitoring by UCL CTC or its representatives.

Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form. UCL CTC staff or its representatives conduct all monitoring in compliance with the participant consent, site policy and data protection requirements.

UCL CTC will determine the appropriate level and nature of monitoring required, based on the objective, purpose, phase, design, size, complexity, endpoints and risks associated with the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly. Details of monitoring activities will be included in the trial monitoring plan and conveyed to sites during initiation. The Monitoring Plan will be under review throughout the trial and updated information provided to sites as necessary.

13.1 On-Site Monitoring

13.2 There is no routine on-site monitoring for UK sites. Monitoring of non-UK sites will be performed in accordance with the monitoring plan and regulatory requirements of each country. Centralised Monitoring

Sites will be requested to submit screening logs and staff delegation logs to UCL CTC at on an annual basis or on request and these will be checked for consistency and completeness. Also refer to [Section 4.2.2 – Required Documentation](#) and [Section 6.2 – Screening Log](#).

In the UK, a copy of the consent form for each patient entered onto the trial must be submitted to UCL CTC. These will be checked for completeness and accuracy i.e. the correct version of the form has been used, patient initials in every box, patient name and signature on the form, patient personally completed date of signing, and the person taking consent has signed/dated and is listed on the delegation log as performing this duty. Also refer to [Section 5 – Informed Consent](#).

In non-UK sites, sites must complete the Consent Form Log, which should be submitted to the CTC upon randomisation of each patient or on request (i.e. during central monitoring).

Copies of completed drug accountability logs must be returned to UCL CTC for all trial patients. Sites will be required to submit logs following the patient's completion of trial treatment or on request. A proportion of these (normally including the first patient enrolled at each site) will be monitored centrally to ensure completeness and correlation with data captured in the CRF. Also refer to [Section 8.9.1 – Drug Accountability](#).

INTERLACE

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File and Pharmacy Site File on an annual basis. Checklists detailing the current version/date of version controlled documents will be provided for this purpose.

Data received at UCL CTC will be subject to review in accordance with [Section 10.4 – Data Queries](#).

13.3 'Triggered' On-Site and Remote Monitoring

On-site/remote monitoring visits may be scheduled following UCL CTC review and/or where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements.

On-site Monitoring

Sites will be sent an email in advance outlining the reason(s) for the visit and confirming when it will take place. The email will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities, who will be performing the visit.

Remote Monitoring

UCL CTC defines remote monitoring as activities conducted at a location remote from the research site which replicate some on-site activities e.g source data review. Remote monitoring may be conducted in response to exceptional circumstances preventing access to participating sites (e.g. global pandemic) or conducted routinely. Details of remote monitoring will be agreed with participating sites, conducted in accordance with applicable guidelines/regulations, site policy and documented in the monitoring plan.

Sites will be sent an email in advance, confirming when remote monitoring is scheduled to take place and how the source documents will be remotely accessed. The email will include a list of the documents to be reviewed, interviews that will be conducted via telephone/videoconference and who will be performing remote monitoring.

Remote monitoring will be conducted by UCL CTC or its representatives via a device with adequate security. Patient confidentiality will be maintained at all times, and monitoring activities will be conducted in an appropriate environment where no unauthorised viewing or overhearing of conversations is possible by third parties. Refer to section 10 Data Management and Data Handling Guidelines for details of how source documentation may be submitted to UCL CTC.

Monitoring Follow Up

Following on-site/remote monitoring, the Trial Monitor/Trial Coordinator will provide a follow up email to the site, which will summarise the documents reviewed and a statement of findings, incidents, deficiencies, conclusions, actions taken and/or actions required. The PI at each site will be responsible for ensuring that monitoring findings are addressed in a timely manner, and by the deadline specified.

13.4 Escalation of monitoring issues

Where monitoring indicates that a patient may have been placed at risk (for example a treatment error or overdose), the matter will be raised urgently with site staff and escalated as appropriate.

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial and whether the incident(s) constitute a serious breach. Refer to section 12 Incident Reporting and Serious Breaches for details.

13.5 Oversight Committees

13.5.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialties and INTERLACE trial staff from UCL CTC. The TMG will be responsible for overseeing the trial. The group will meet regularly approximately twice a year and will send updates to PIs (via newsletters or at Investigator meetings) and to the NCRI Gynaecological Clinical Studies Group.

The TMG will review substantial amendments to the protocol prior to submission to the REC and MHRA and relevant Regulatory Authorities. All PIs will be kept informed of substantial amendments through their nominated responsible individuals.

All TMG members will be required to read and sign the CTC's TMG Charter.

13.5.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder and the Sponsor.

13.5.3 Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held during the trial to review interim analyses, or as necessary to address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

13.5.4 Role of UCL CTC

UCL CTC will be responsible for the day to day coordination and management of the trial and will act as custodian of the data generated in the trial (on behalf of UCL). UCL CTC is responsible for all duties relating to pharmacovigilance which are conducted in accordance with [Section 11 - Pharmacovigilance](#).

14 WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment, assessments, follow-up and data collection.

14.1 Patients who do not start Trial Treatment

If a patient does not start treatment, the reasons for this must be recorded in the patient's notes and on the relevant Case Report Form(s). Reasons that a patient may not start treatment include:

- Deterioration in health
- Patient decision

If a patient does not start treatment, the site should contact CTC immediately explaining why this is the case. CTC will confirm which CRFs should be completed to document the patient's withdrawal from trial treatment.

As INTERLACE is an intent-to-treat trial, we would expect patients to be followed up as per trial protocol. As a minimum, survival and progression information (if applicable) should be collected. The data collected will be used in the trial analysis.

14.2 Discontinuation of Trial Treatment

A patient may be withdrawn from trial treatment whenever continued participation is no longer in the patient's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing treatment may include:

- Disease progression whilst on therapy
- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- Patient choice
- Any alterations in the patient's condition which justifies the discontinuation of treatment in the site investigator's opinion

In these cases patients remain within the trial for the purposes of follow-up and data analysis unless they explicitly withdraw consent for trial follow-up and/or data collection.

If a patient expresses their wish to withdraw from trial treatment, sites should explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes and for allowing existing collected data to be used. If the patient gives a reason for their withdrawal, this should be recorded.

14.3 Future Data Collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected, with the exception of safety data, and recorded on the Lost to Follow-up CRF. In this event, data due up to the date of withdrawal must be submitted but no further data (other than essential safety data) should be sent to UCL CTC (or CCC for non-UK sites).

14.4 Losses to Follow-Up

If a patient moves from the area, every effort should be made for the patient to be followed up at another participating trial site and for this new site to take over the responsibility for the patient, or for follow-up via GP. Details of participating trial sites can be obtained from the UCL CTC trial team who must be informed of the transfer of care and follow up arrangements. If it is not possible to transfer to a participating site, the registering site remains responsible for submission of forms.

If a patient is lost to follow-up at a site every effort should be made to contact the patient's GP to obtain information on the patient's status.

For non-UK sites:

If a patient does not attend several scheduled appointments, and the site has tried to make contact via a primary care physician, then reasonable efforts should be made to follow-up with the patient directly. If the patient is lost to follow-up, the Lost to Follow-up CRF should be completed.

15 TRIAL CLOSURE

15.1 End of Trial

For regulatory purposes the end of the trial will be 30 days after the last patient has completed 3 years of follow up visits. At this point, the 'declaration of end of trial' form will be submitted to participating regulatory authorities and ethical committees, as required.

Following this, UCL CTC will advise sites on the procedure for closing the trial at the site.

Once the end of trial has been declared, no more prospective patient data will be collected but sites must co-operate with any data queries regarding existing data to allow for analysis and publication of results.

15.2 Archiving of Trial Documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the trial held at site are retained for a minimum of 5 years after the end of the trial, in accordance with national legislation.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

15.3 Early Discontinuation of Trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see [Section 13.4.2 – Trial Steering Committee](#) and [Section 13.4.3 – Independent Data Monitoring Committee](#)). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow up of patients.

15.4 Withdrawal from Trial Participation by a Site

Should a site choose to close to recruitment the PI must inform UCL CTC in writing. Follow up as per protocol must continue for all patients recruited into the trial at that site and other responsibilities continue as per CTSA.

Should a non-UK site choose to close to recruitment, the PI must inform UCL CTC in writing. Follow up as per protocol must continue for any patients recruited into the trial at that site and other responsibilities continue as per the agreement with the site and/or CCC.

16 STATISTICS

16.1 Sample size calculation

The 5 year overall survival rate for chemoradiation is between 60-70%⁹. We assume the lower estimate of 60% since a large proportion of patients are expected to come from the UK (this corresponds to a median survival of 6.78 years). We aim to detect a hazard ratio of between 0.65 and 0.70 (80% power and two-sided 5% significance level), with 7 years of recruitment and then a 3 year follow-up period. The table shows the power for various hazard ratios, given a study size of 500 patients, which is expected in the 7 year accrual period (using sample size software):²⁴

Target hazard ratio	Power, given 480 patients (~95% of 500)	Number of events
0.70	70%	192
0.67	79%	194
0.65	84%	198

In the Vale et al meta-analysis⁹, the pooled hazard ratio for comparing chemoradiation (CRT) with radiotherapy alone (RT) was 0.81, from 13 trials in which none used additional chemotherapy. There were 2 further trials involving chemotherapy after CRT versus RT, and the hazard ratio was 0.46. Therefore, an indirect comparison of chemotherapy plus CRT versus CRT alone yields a hazard ratio of 0.57 (0.46/0.81). Therefore, in our trial (of chemotherapy before CRT vs CRT) we consider a hazard ratio of between 0.65 and 0.70 to be feasible and clinically worthwhile, given the extra financial costs that would be incurred if induction chemo were to be recommended.

Sample size is based on OS only as this would require more patients than using PFS. In order to maintain an overall error rate of 5%, we will use a fixed sequence (hierarchical sequential testing) approach based on PFS first then OS. The treatment effect on PFS would need to be statistically significant first ($p<0.05$) to allow a formal statistical analysis of OS afterwards.

16.2 Statistical analyses

Primary endpoints

- Overall survival (OS), measured from the date of randomisation until date of death from any cause. Patients who do not die will be censored at the date last seen alive.
- Progression-free survival (PFS), measured from the date of randomisation until date of first progression or death, whichever occurs first. Patients who do not die or progress will be censored at the date last seen alive.

Secondary endpoints

- Adverse events will be categorised by the CTCAE guidelines (version 4.03).
- Health-related quality of life using EORTC QLQ-C30, and the cervical cancer specific module (QLQ CX-24) and EQ-5D-5L for economic evaluation.
- Patterns of first relapse (local and/or systemic)

- Time to first subsequent treatment

16.2.1 Analyses

All analyses will be by intention-to-treat. Additional analyses would be restricted to patients who completed at least 4 weeks of chemotherapy (prior to radiotherapy).

Overall survival and PFS will be compared between the two arms using a logrank test, and Cox regression modelling, allowing for the randomisation stratification factors (FIGO stage and tumour volume, positive/negative nodes, squamous vs non-squamous histology, IMRT vs no IMRT, age and recruiting site). We will obtain estimates of the hazard ratios and 95% CIs.

Subgroup analyses for OS and PFS would be performed for the stratification factors, and others that may later be shown to be important (i.e. from future publications/evidence).

The highest CTCAE grade will be obtained for each type of adverse event, for each patient. These data will be summarised in each trial group, and compared using chi-squared tests. Focus would be on those with grade 3 or 4 events. The proportion of patients with any grade 3 or 4 event will also be compared.

Quality of life (QoL) will be compared between the two trial groups, using mixed modelling, to allow for the repeated measures nature of the data. Key time points will also be examined: ie QoL at 1, 2 and 3 years; these could be analysed using a general linear model, where the baseline QoL score is used as a covariate. The main effect size for QoL is expected to be the mean difference in scores. The QoL instruments will be used to analyse the data according to the functional and symptom domains (15 using the EORTC QLQ C30 instrument). Please see Appendix XI for further details on Quality of Life study.

Patterns of Relapse will be collected. At relapse all patients will be required to undergo as a minimum CT chest, abdomen and pelvis. Ideally patients would have an MRI pelvis (+/- abdomen) and CT or PET CT of chest and abdomen to document site/s of relapse. This will permit the collection of accurate data on patterns of relapse in both the standard and investigational arms of the trial.

16.2.2 Economic evaluation

Details of the following costs will be collected in the CRF:

- Radiotherapy and Chemotherapy
- Treatment Administration
- Hospitalisations / GP visits including additional follow up visits
- Any adverse events related to the study arm treatment – and specific concomitant medications (supportive treatments)

A stochastic cost effectiveness analysis will be carried out using patient level data. In addition the Quality of life based on EQ-5D-5L (using UK Time Trade Off scores) will be used to derive an EQ-5D-5L index (converted roughly to a 0 to 1 scale). The adjusted Overall Survival times will be generated to provide an estimate of the QALY and to derive the Cost Effectiveness Acceptability Curve (CEAC). The CEAC will provide an estimate

of the probability of the investigational arm (additional chemotherapy + chemoradiation) being cost effective compared to the control arm (chemoradiation alone). Costs which are censored (e.g. because patients were lost to follow up) will be accounted for. A suitable model to predict the survival time probabilities over time may be used, depending on the number of deaths observed.

Probabilistic sensitivity analysis will also be carried out to take into account uncertainty. The analysis will be carried out from an NHS paying perspective.

16.3 Interim analyses

No formal interim analyses of the efficacy endpoint are planned. The IDMC will review data on safety and, when requested, efficacy, in order to determine whether the trial should stop early.

17 ETHICAL AND REGULATORY APPROVALS

In conducting the trial, the Sponsor, UCL CTC and sites shall comply with all laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:

- the principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) and any applicable local GCP laws or regulations in the relevant country(ies)
- Human Rights Act 1998
- Data Protection Act 2018
- General Data Protection Regulation (EU)2016/679 (GDPR)
- Freedom of Information Act 2000
- Human Tissue Act 2004
- Medicines Act 1968
- Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments
- Good Manufacturing Practice
- the Research Governance Framework for Health and Social Care, issued by the Health Research Authority

All non-UK sites shall comply with all their local laws and statutes applicable to the performance of clinical trials and research.

Non UK sites should refer to their Country Specific Guidance Document for additional detailed instruction.

17.1 Ethical Approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial.

The trial has received a favourable opinion from the South Central – Oxford B Research Ethics Committee and Health Research Authority (HRA) approval for conduct in the UK.

UCL CTC will submit Annual Progress Reports to the REC, which will commence one year from the date of ethical approval for the trial.

Favourable opinion will also be obtained in all participating countries outside the UK in compliance with all local laws, statutes and requirements.

17.2 Regulatory Approval

A Clinical Trial Authorisation (CTA) has been granted for the trial.

The trial will be conducted at approved trial sites in accordance with the trial protocol and the terms of the CTA granted by the MHRA and other Regulatory Authorities where applicable.

17.3 Site Approvals

Evidence of assessment of capability and capacity by the Trust/Health Board R&D for a UK trial site must be provided to UCL CTC. Sites will only be activated when all necessary local approvals for the trial have been obtained.

All non-UK sites must provide confirmation of approval of their local institution(s).

17.4 Protocol Amendments

UCL CTC will be responsible for gaining ethical and regulatory approval(s), for amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments.

UCL CTC will forward protocol amendments to non-UK sites via the CCC/CLS for regulatory and ethics approval in that country.

17.5 Patient Confidentiality & Data Protection

Patient identifiable data, including full name, date of birth and NHS number (local equivalent for non-UK sites) will be required for the randomisation process and will be provided to UCL CTC. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 2018 and GDPR, with the Data Protection Officer at UCL.

18 SPONSORSHIP AND INDEMNITY

18.1 Sponsor Details

Sponsor Name: University College London

Address: Joint Research Office
Gower Street
London
WC1E 6BT

Contact: Managing Director, UCLH/UCL Research

Tel: 020 3447 9995/2178 (unit admin)
Fax: 020 3447 9937

Legal Representative in EU UCL Research Limited
70 Sir John Rogerson's Quay
Dublin 2
D01 R296
Ireland

18.2 Indemnity

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

19 FUNDING

Cancer Research UK are supporting the central coordination of the trial through UCL CTC.

Country coordinating centres and/or non-UK sites may be sourcing, obtaining and managing distribution of any additional local funding for the trial outside the UK.

20 PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the Trial Management Group (TMG). The first publication of the trial results will be in the name of the TMG. Authors will be cited by name if published in a journal where this does not conflict with the journal's policy. Contributing site Investigators (PIs plus Co-Investigators) will be included as authors if in the opinion of the TMG, they have contributed to the overall success of the study. Other investigators and research nurses where appropriate will be acknowledged, along with the trial participants. Data from all sites will be analysed together and published as soon as possible. Participating sites may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG. The trial data are owned by the TMG. The ClinicalTrials.gov number (NCT01566240) allocated to this trial will be quoted in any publications based upon its results.

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Appendix I Abbreviations

ABPI	Association of British Pharmaceutical Industry
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
ANT	Anterior
AR	Adverse Reaction
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BD	Twice a Day
BSA	Body Surface Area
CCC	Country Coordinating Centre
CEAC	Cost Effectiveness Acceptability Curve
CI	Chief Investigator
CLRN	Comprehensive Local Research Network
CLS	Country Lead Site
CR	Complete Response
CRF	Case Report Form
CRT	Chemoradiotherapy
CT	Computerised Tomography
CTA	Clinical Trial Authorisation
CTAAC	Clinical Trials Advisory & Awards Committee
CTCAE	Common Terminology Criteria for Adverse Events
CTSA	Clinical Trial Site Agreement
CTV	Clinical Target Volume
CXR	Chest X-Ray
DFS	Disease Free Survival
DPA	Data Protection Act
DSUR	Development Safety Update Report
ECG	Electrocardiogram
EEA	European Economic Area
EudraCT	European Clinical Trials Database
EBRT	External Beam Radiotherapy
FBC	Full Blood Count
FIGO	International Federation of Gynaecology and Obstetrics
G-CSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GTV	Gross Target Volume
Hb	Haemoglobin
HR	Hazard Ratio
HRA	Health Research Authority
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
ICTSA	International Clinical Trials Site Agreement
IDMC	Independent Data Monitoring Committee

IMP	Investigational Medicinal Product
IMRT	Intensity Modulated Radiotherapy
INR	International Normalised Ratio
ISRCTN	International Standard Randomised Controlled Trial Number
IV	Intravenous
LAT	Lateral
LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
LLN	Lower Limit of Normal
MRC	Medical Research Council
MRI	Magnetic Resonance Image
MHRA	Medicines and Healthcare products Regulatory Agency
NACT	Neoadjuvant Chemoradiotherapy
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NRES	National Research Ethics Service
OS	Overall Survival
PA	Posteroanterior
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PO	By Mouth
PRN	As Required
PR	Partial Response
PSW	Pelvic Side Wall
QA	Quality Assurance
QALY	Quality Adjusted Life Years
QDS	Four times a day
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RT	Radiotherapy
RTOG	Radiotherapy Oncology Group
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCC	Squamous Cell Carcinoma
SD	Stable Disease
SPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL CTC	CR UK and UCL Cancer Trials Centre
U&E	Urea and Electrolytes
ULN	Upper Limit of Normal
WBC	White Blood Cells

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Appendix II ECOG Performance Status

Grade 0	Fully active, able to carry out all normal (pre-disease) activity without restriction
Grade 1	Restricted in physically strenuous activity but ambulatory and able to carry out light work, e.g. light house work, office work
Grade 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Grade 3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
Grade 4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair

Ref: Oken, M.M. et al. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix III MRI Scan Protocol

Magnet strength: 1.5T or 3T
Coil: Multichannel e.g. typically 8

Patient preparation:

Routine checks for MR contraindications
Check trial consents
Buscopan/glucagon

Summary of scan sequences:

Appropriate use of parallel imaging and propellor imaging as available. In obese patients, use saturation bands to saturate anterior abdominal fat to reduce ghosting artefact.

Abdomen:

1. Coronal T2 to cover kidneys (gradient echo, breath hold)
2. Axial T1 and T2 through kidneys to aortic bifurcation, mainly to survey for retroperitoneal lymphadenopathy. Use either breathhold or respiratory compensated sequences

Pelvis:

1. Sagittal T2 SE (turbo/Fast etc) through uterus, cervix and parametria, to pelvic side wall.
2. Small FOV axial T2 SE through the uterus, cervix and vagina, tilted perpendicular to the long axis of the cervix.
3. Axial T2 SE to cover pelvis (for nodal disease)
4. Axial T1 SE to cover pelvis
5. Axial diffusion imaging. EPI with 5-6 b values including at least b=0 and b=1000. Preferably b 0, 50, 150, 500, 800, 1000.

Appendix IV Renal Function

Glomerular filtration rate must be $\geq 60\text{ml/min}$ calculated using the Wright equation (**without creatinine kinase**) or $\geq 50\text{ml/min}$ using radioisotope GFR assessment.

For sites using the Wright equation with Enzymatic Serum Creatinine (**without creatinine kinase**), the following formulae should be used to calculate the dose of carboplatin (electronic copy of the spreadsheet will be made available to sites).

$$\text{GFR} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr}}$$

For sites using the Wright equation with Jaffe Serum Creatinine (**without creatinine kinase**), the following formulae should be used to calculate the dose of carboplatin (electronic copy of spreadsheet will be made available to sites).

$$\text{GFR} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \text{Sex})}{\text{SCr}}$$

Appendix V FIGO Staging of Carcinoma of the Cervix Uteri^a

For the purposes of randomisation, centres must continue to use the FIGO staging below, adapted from FIGO Committee on Gynecologic Oncology. Pecorelli S: Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 105 (2): 103-4, 2009.

Stage	
I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded).
IA	Invasive carcinoma, which can be diagnosed only by microscopy with deepest invasion ≤5 mm and largest extension ≥7 mm.
IA1	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm.
IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm.
IB	Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage IA. ^b
IB1	Clinically visible lesion ≤4.0 cm in greatest dimension.
IB2	Clinically visible lesion >4.0 cm in greatest dimension.
II	Cervical carcinoma invades beyond the uterus but not to the pelvic wall or to the lower third of the vagina.
IIA	Without parametrial invasion.
IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension.
IIA2	Clinically visible lesion >4.0 cm in greatest dimension.
IIB	With obvious parametrial invasion.
III	The tumour extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney. ^c
IIIA	Tumour involves lower third of the vagina with no extension to the pelvic wall.
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney.
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV.
IVA	Spread of the growth to adjacent organs.
IVB	Spread to distant organs.

^aAdapted from FIGO Committee on Gynecologic Oncology. Pecorelli S: Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 105 (2): 103-4, 2009

^bAll macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not >7.00 mm. Depth of invasion should not be >5.00 mm taken from the base of the epithelium of the original tissue—superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with "early (minimal) stromal invasion" (~1 mm).

The involvement of vascular/lymphatic spaces should not change the stage allotment.

^cOn rectal examination, there is no cancer-free space between the tumour and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be the result of another cause.

Appendix VI Royal College of Radiologists Guidelines

The timely delivery of radical radiotherapy: standards and guidelines for the management of unscheduled treatment interruption, third edition 2008. Board of Faculty of Clinical Oncology, The Royal College of Radiologists.

For further guidance on treatment delays, please refer to Section 5 – Compensatory Measures.

Appendix VII Simulator 2D Planning

Simulator 2D Planning will only be permitted at centres in developing nations after consultation with the Chief Investigator/TMG. The standard of care will be 3D conformal planning.

Target Localisation

Position	Supine
Immobilization	Ankle and/or knee supports Two lateral and one anterior permanent skin marks

Simulator Imaging of bony anatomy: pelvis

Below are suggested field borders to ensure that tumour and potential sites of disease are within the radiation field. Taking account of extent of tumour on imaging the following field borders may be modified to permit complete coverage of the GTV:

- Superior L3/4 junction.
- Lateral 3cm lateral to side walls of the pelvis.
- Inferior margins should be at the lower margin of the obturator foramina, 3cm below the lowest extent of the tumour, or if there is involvement of the lower 1/3 of the vagina an introital marker should be used and the field should be 2cm below this.
- Anterior border of the pelvic field should be 1cm in front of the symphysis pubis.
- Posterior border should be at the junction of S2/S3 or 3cm posterior to the uterus or any gross disease whichever is greater.

Whilst shielding may be used, care should be taken to review the clinical and radiological findings to ensure that disease is fully covered. The following are suggestions for areas that may be shielded.

Shielding may be used to protect the sacral plexus on the lateral fields and the small bowel on the anterior - superior lateral fields.

On the anterior/posterior fields, shielding may be used to protect the femoral heads and upper femora and small bowel on the superior part of the field at the level of the mid and upper common iliac vessels.

This may be done by shielding from 1cm to the transverse spinous processes to the midpoint of the lateral border.

Extended field (to treat disease beyond the limits of the pelvic field as per inclusion /exclusion criteria) should encompass the highest involved lymph node with a margin of 3cm or one vertebral body above to a maximum upper level of L1/L2 intervertebral space. Lateral margins above L4 vertebral body should be at least 6cm wide or a minimum of 2cm lateral to the lateral border of the involved lymph node whichever is greater. Shielding should be employed to exclude the kidneys where possible.

Field arrangements and verification as per that outlined above for 3D planning.

Appendix VIII Response Criteria

Response Evaluation Criteria in Solid Tumours (RECIST) – Version 1.1

Objective tumour response from 12 weeks post treatment will be measured according to the RECIST (Response Evaluation Criteria In Solid Tumours) criteria (version 1.1).

Response criteria are essentially based on a set of measurable lesions identified at baseline as target lesions, and – together with other lesions that are denoted as non-target lesions – followed until disease progression.

The following paragraphs are a quick reference to the RECIST criteria (version 1.1). The complete criteria are included in the published RECIST document:

Eisenhauer, EA, Therasse, P, Bogaerts, J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247

And also available at: <http://www.eortc.be/RECIST>

Reporting of tumour response

All patients included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation, if they don't complete treatment or if they are ineligible, or not followed/re-evaluated.

Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, not evaluable.

Imaging timepoints for tumour evaluation

An MRI (or CT) will must be performed at the following time points:

- Baseline
- Minimum of 12 weeks post treatment

Measurability of tumour lesions at baseline

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable)
- 20 mm by chest X-ray

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- For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be:
- ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations

Bone scan, PET scan and plain films can be used to confirm the presence or disappearance of bone lesions but not to measure bone lesions. Lytic bone lesions / lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurable lesions. Blastic bone lesions are non-measurable.

Radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable). Cystic metastases can be considered as measurable lesions if they meet the definition of measurability. If non-cystic lesions are present in the same patient, these are preferred for selection of target lesions.

Tumour lesions in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

All measurements should be taken and recorded in metric notation, using calipers if clinically assessed. The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up.

Methods of assessment

An MRI (or CT) scan must be used to assess the tumour at both baseline and the 12 weeks post treatment visit.

Please note: A CT scan is only acceptable in non-European countries/non-UK sites. All European countries (including the UK) must use MRI pelvis.

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and at the 12 weeks post treatment visit.

While on study, all target lesions recorded at baseline should have their actual measurements recorded on the CRF at the 12 weeks post treatment visit, even when very small (e.g. 2 mm).

If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

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For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the “merged lesion”.

Baseline documentation of “Target” and “Non-Target” lesions

All measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs and should be those that lend themselves to reproducible repeated measurements. On occasion, the largest lesion may not lend itself to reproducible measurement, in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

Only the short axis of lymph nodes identified as target lesions contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterise the objective tumour.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases ‘unequivocal progression’ of each should be noted throughout follow-up. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. multiple enlarged pelvic lymph nodes or multiple liver metastases’.

Response Criteria

The measurements noted at baseline will be compared to the measurements taken 12 weeks post treatment as assessed as per the criteria below:

Evaluation of target lesions	
Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as <u>reference the baseline sum diameters</u> .
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as <u>reference the smallest sum on study</u> (this includes the baseline sum if that is the smallest on study). In addition, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as <u>reference the smallest sum diameters while on study</u> .

Evaluation of non-target lesions	
Complete Response (CR):	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Incomplete Response/ Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1).

- (1) Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or trial chair).

INTERLACE***Evaluation of best overall response***

The best overall response is the best response recorded from the start of the study treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since being on the study). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, the case is usually considered NE at that time point unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response.

The best overall response is determined once all the data for the patient is known.

Time point response: patients with target (+/- non-target) disease

Target lesions	Non-Target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all	No	PR
SD	Non-PD or not all	No	SD
Not all	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is

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recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response.

For equivocal findings of progression (e.g. very small and uncertain new lesions, cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded on study. The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Appendix IX Radiotherapy - Expected Adverse Events

The following AEs are commonly associated with radiotherapy and will be considered expected for this treatment:

Blood and lymphatic system disorders

- Anaemia⁵

Gastrointestinal disorders

- Abdominal pain¹¹
- Anal stenosis⁷
- Bloating¹
- Constipation⁹
- Diarrhoea¹
- Enterocolitis¹⁰
- Fecal incontinence¹
- Flatulence¹
- Malabsorption¹
- Nausea⁶
- Proctitis¹⁰
- Rectal fistula²
- Rectal hemorrhage^{1, 4}
- Vomiting⁶
- Other: Anal fissure⁷
- Other: Blood in stool⁷
- Other: Bowel perforation¹⁰
- Other: Bowel obstruction¹⁰
- Other: Mucous stool¹
- Other: Steatorrhoea¹

General disorders

- Fatigue¹
- Fever⁷
- Pain¹
- Obstruction⁴
- Perforation^{3, 5}

Infections and infestations

- Bladder infection⁷
- Urinary tract infection⁷

Investigations

- Weight loss⁷
- White Blood Cell decreased⁷

Metabolism and nutrition disorders

- Anorexia⁶

Musculoskeletal and connective tissue disorders

- Bone pain¹
- Fracture¹
- Osteoporosis¹

Psychiatric disorders

- Anorgasmia¹
- Libido decreased¹

Renal and urinary disorders

- Bladder obstruction³
- Bladder spasm¹
- Cystitis
- Haematuria⁹
- Urinary fistula⁹
- Urinary frequency¹
- Urinary incontinence^{1, 6}
- Urinary tract pain¹
- Urinary urgency¹
- Other: Renal necrosis¹

Reproductive system and breast disorders

- Dyspareunia¹
- Pelvic pain⁷
- Premature menopause¹
- Vaginal dryness¹
- Vaginal fistula²
- Vaginal hemorrhage⁶
- Vaginal stricture¹
- Other: Infertility¹
- Other: Painful orgasm¹
- Other: Vulvovaginal atrophy¹

Skin and subcutaneous tissue disorders

- Pain of skin²

Vascular disorders

- Lymphoedema¹

INTERLACE**RTOG/EORTC Radiation Toxicity Grades⁸**

Shaded text boxes indicate expected radiation toxicities in patients undergoing pelvic radiation treatment in the INTERLACE trial

For all: 0 - no symptoms, 5 - death directly related to radiation effects

ACUTE TOXICITY

RTOG ACUTE Radiation Morbidity				
Tissue	Grade 1	2	3	4
Skin	Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating	Tender or bright erythema, patchy moist desquamation / moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Mucous membrane	Injection / may experience mild pain not requiring analgesic	Patchy mucositis that may produce an inflammatory serosanguinous discharge / may experience moderate pain requiring analgesia	Confluent fibrinous mucositis / may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
Eye	Mild conjunctivitis w/ or w/o scleral injection / increased tearing	Moderate conjunctivitis w/ or w/o keratitis requiring steroids and/or antibiotics / dry eye requiring artificial tears / iritis with photophobia	Severe keratitis with corneal ulceration / objective decrease in visual acuity or in visual fields / acute glaucoma / panophthalmitis	Loss of vision (uni or bilateral)
Ear	Mild external otitis with erythema, pruritus, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline	Moderate external otitis requiring topical medication / serous otitis media / hypoacusis on testing only	Severe external otitis with discharge or moist desquamation / symptomatic hypoacusis / tinnitus, not drug related	Deafness
Salivary gland	Mild mouth dryness / slightly thickened saliva / may have slightly altered taste such as metallic taste / these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness / thick, sticky saliva / markedly altered taste	(none)	Acute salivary gland necrosis
Pharynx & esophagus	Mild dysphagia or odynophagia / may require topical anesthetic or non-narcotic analgesics / may require soft diet	Moderate dysphagia or odynophagia / may require narcotic analgesics / may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss > 15% from pretreatment baseline requiring NG feeding tube, IV fluids, or hyperalimentation	Complete obstruction, ulceration, perforation, fistula

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Larynx	Mild or intermittent hoarseness / cough not requiring antitussive / erythema of mucosa	Persistent hoarseness but able to vocalize / referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic / cough requiring antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic / confluent fibrinous exudate, marked arytenoid edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary
Upper GI	Anorexia with ≤ 5% weight loss from pretreatment baseline / nausea not requiring antiemetics / abdominal discomfort not requiring parasympatholytic drugs or analgesics	Anorexia with ≤ 15% weight loss from pretreatment baseline / nausea and/or vomiting requiring antiemetics / abdominal pain requiring analgesics	Anorexia with > 15% weight loss from pretreatment baseline or requiring NG tube or parenteral support. Nausea and/or vomiting requiring tube or parenteral support / abdominal pain, severe despite medication / hematemesis or melena / abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Ileus, subacute or acute obstruction, perforation, GI bleeding requiring transfusion / abdominal pain requiring tube decompression or bowel diversion
Lower GI / Pelvis	Increased frequency or change in quality of bowel habits not requiring medication / rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g. Lomotil) / mucous discharge not necessitating sanitary pads / rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support / severe mucous or blood discharge necessitating sanitary pads / abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
Lung	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents / dyspnea with minimal effort but not at rest	Severe cough unresponsive to narcotic antitussive agent or dyspnea at rest / clinical or radiological evidence of acute pneumonitis / intermittent oxygen or steroids may be required	Severe respiratory insufficiency / continuous oxygen or assisted ventilation
Genitourinary	Frequency of urination or nocturia twice pretreatment habit / dysuria, urgency not requiring medication	Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g. Pyridium)	Frequency with urgency and nocturia hourly or more frequently / dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic / gross hematuria with/without clot passage	Hematuria requiring transfusion / acute bladder obstruction not secondary to clot passage, ulceration, or necrosis
Heart	Asymptomatic but objective evidence of EKG changes or pericardial abnormalities without evidence of other heart disease	Symptomatic with EKG changes and radiological findings of congestive heart failure or pericardial disease / no specific treatment required	Congestive heart failure, angina pectoris, pericardial disease responding to therapy	Congestive heart failure, angina pectoris, pericardial disease, arrhythmias not responsive to nonsurgical measures

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CNS	Fully functional status (i.e. able to work) with minor neurological findings, no medication needed	Neurological findings present sufficient to require home care / nursing assistance may be required / medications including steroids/antiseizure agents may be required	Neurological findings requiring hospitalization for initial management	Serious neurological impairment that includes paralysis, coma, or seizures > 3 per week despite medication / hospitalization required
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LATE TOXICITY

For all: 0 - no symptoms, 5 - death directly related to radiation effects

RTOG/EORTC LATE Radiation Morbidity				
Tissue	Grade 1	2	3	4
Skin	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Subcutaneous tissue	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture > 10% linear measurement	Necrosis
Mucous membrane	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucous	Marked atrophy with complete dryness	Ulceration
Salivary glands	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
Spinal cord	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadriplegia
Brain	Mild headache; slight lethargy	Moderate headache; great lethargy	Severe headache; severe CNS dysfunction (partial loss of power or dyskinesia)	Coma
Eye	Asymptomatic cataract; minor corneal ulceration or keratitis	Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment	Panophthalmitis / blindness
Larynx	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis
Lung	Asymptomatic or mild symptoms (dry cough); slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); low grade fever; patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; dense radiographic changes	Severe respiratory insufficiency / Continuous oxygen / assisted ventilation
Heart	Asymptomatic or mild symptoms; transient T wave inversion & ST changes; sinus tachy > 110 (at rest)	Moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low ORS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities	Tamponade / severe heart failure; severe constrictive pericarditis
Esophagus	Mild fibrosis; slight difficulty in swallowing	Unable to take solid food normally; swallowing semisolid	Severe fibrosis; able to swallow only liquids; may have pain on	Necrosis / perforation fistula

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	solids; no pain on swallowing	food; dilatation may be indicated	swallowing; dilatation required	
Small/Large intestine	Mild diarrhea; mild cramping; bowel movement 5 times daily; slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement > 5 times daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis / perforation fistula
Liver	Mild lassitude; nausea, dyspepsia; slightly abnormal liver function	Moderate symptoms; some abnormal liver function tests; serum albumin normal	Disabling hepatic insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites	Necrosis / hepatic coma or encephalopathy
Kidney	Transient albuminuria; no hypertension; mild impairment of renal function; urea 25-35 mg/dL; creatinine 1.5-2.0 mg/dL; creatinine clearance > 75%	Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function; urea > 36-60; creatinine clearance 50-74%	Severe albuminuria; severe hypertension; persistent anemia (< 10); severe renal failure; urea > 60; creatinine > 4.0; creatinine clearance < 50%	Malignant hypertension; uremic coma; urea > 100
Bladder	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria	Severe frequency & dysuria; severe telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (<150 cc)	Necrosis/contracted bladder (capacity < 100 cc); severe hemorrhagic cystitis
Bone	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis / spontaneous fracture
Joint	Mild joint stiffness; slight limitation of movement	Moderate stiffness; intermittent or moderate joint pain; moderate limitation of movement	Severe joint stiffness; pain with severe limitation of movement	Necrosis / complete fixation

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Appendix X Quality of Life Sub-Study

Background

In order to best inform patients of the options available for curative treatment of locally advanced cervical cancer, it is important to know, not only the survival benefits of treatments, but the impact of such treatments on patients' symptoms, daily functioning and quality of life. Chemoradiotherapy (CRT) is known to bring additional acute toxicity, but in view of the survival benefit from the treatment, this is regarded as acceptable²⁵. However, there is insufficient data on the late effects of CRT. Systematic reviews recommend all new trials to include parallel quality of life studies and prospective data on both acute and chronic effects, to inform both clinicians and patients.

Rationale for Quality of Life Sub-study in INTERLACE Trial

The investigational treatment, in the form of 6 weeks of induction weekly chemotherapy, will prolong the duration of treatment and is likely to add some short term toxicity, both during the induction chemotherapy itself and during the subsequent CRT. The main trial hypothesis is that adding induction chemotherapy to CRT will result in better overall survival.

The hypothesis for the QoL sub-study is that we will observe more acute toxicity and QoL deterioration in the investigational arm, both during the induction chemotherapy and during the CRT, but patients will recover at a similar rate on completion of treatment in both arms. Patient symptoms/toxicity, functioning and quality of life after six months of follow up is expected to be similar in both arms. It is important to deliver CRT in the investigational arm, therefore we have to show that induction chemotherapy does not compromise the delivery of CRT.

The QoL sub-study will aim to answer the following questions:

- 1 Will there be higher symptomatology, worse functioning and poorer QoL during CRT in the investigational arm?
- 2 Will patients recover at a similar rate after completion of CRT in both investigational and control arms?
- 3 Will long term symptoms, functioning and QoL after 6 and 12 months of follow-up be similar in both arms?

Design and Methodology

Questionnaires

The quality of life questionnaires to be used are

- EORTC QLQ-C30 (version 3)²⁶
- EORTC cervical cancer module, EORTC QLQ-CX24²⁷
- EQ-5D-5L for economic evaluation²⁸

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The EORTC QLQ-C30 is a general cancer questionnaire, consisting of 30 questions, covering common cancer symptoms (such as pain, fatigue, nausea/vomiting, constipation, diarrhoea, lack of appetite, sleep disturbance), patient functioning (physical, role, emotional, cognitive and social) and global quality of life.

The cervical cancer questionnaire has 24 items, including 3 multi-item scales (symptom experience scale, body image and sexual/vaginal functioning) and 6 single items (lymphoedema, peripheral neuropathy, menopausal symptoms, sexual worry, sexual activity and sexual enjoyment).

The EQ-5D-5L is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

Timing of administration of quality of life questionnaires**Baseline assessment**

All patients should complete the baseline questionnaire booklet (including a demographic form) in clinic, after giving informed consent, but before randomised treatment allocation is known. The completed questionnaires will be posted to the UCL Cancer Trials Centre as soon as the patient is randomised and the patient trial number is known.

During treatment

As the duration of the investigational and control treatments is different, the assessment of quality of life during treatment will be based on delivered treatment, rather than chronological time.

The induction chemotherapy group will complete QoL questionnaires on day one of week 4 of chemotherapy.

All patients will complete quality of life questionnaires before commencing CRT (i.e. on day one of CRT).

Further assessment will be completed during CRT (the first treatment day of the third week of the treatment).

During follow-up

All patients to complete the questionnaires four weeks post-CRT, during a follow-up clinic visit, then three-monthly for two years and six-monthly for three years. Patients will be asked to continue completing QoL even if they have recurrent disease.

Table 1- Summary of administration of QoL questionnaires

Time of assessment	Description
Baseline assessment	After giving informed consent, but before randomised treatment allocation is known
During induction chemo	Day one of week 4 for patients allocated to the induction chemotherapy arm
Before CRT	Day one of CRT
During CRT	Day one of week 3 of CRT
Post CRT	4 weeks post-CRT during clinic visit
3 monthly for two years	During clinic visit
6 monthly for three years	During clinic visit

All questionnaires will be given to the patients by the research nurse, who will then check that patients have answered all the questions. The questionnaires will then be posted to the UCL Cancer Trials Centre. If patients miss a questionnaire, the nurse will complete the reason on the relevant Case Report Form.

Statistical Analysis

The proposed primary endpoints for the QoL sub-study are:

- Symptom experience scale EORTC QLQ-CX24
- Pain subscale EORTC QLQ-C30
- Fatigue scale EORTC QLQ-C30
- Physical function subscale EORTC QLQ-C30
- Role function subscale EORTC QLQ-C30

The secondary endpoints are:

- Nausea/vomiting subscale EORTC QLQ-C30
- Diarrhoea item EORTC QLQ-C30
- Peripheral neuropathy item EORTC QLQ-CX24
- Social function EORTC QLQ-C30

In the analysis, we will aim to detect medium differences in the QoL scores between the two treatment groups. Guidelines published by Cocks et al will be used when interpreting the results²⁹. Generally, for the primary outcomes outlined above, a mean difference of between 5-13 points is considered to be small and 13-19 points a medium difference (these also need to be interpreted in relation to the standard deviations, i.e. the standard differences). We expect to recruit between 400 and 600 patients from the UK and Ireland,

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which will allow us to detect standardised differences of between 0.23 and 0.28, with 80% power and 5% two-sided test of statistical significance.

During analysis, the time dependency of the data will be acknowledged by using a generalised linear modelling approach. Missing data will be handled according to recommended standard EORTC procedures.

The economic analysis will be performed using a stochastic cost effectiveness analysis carried out using patient level data. In addition the Quality of life based on EQ-5D-5L (using UK Time Trade Off scores) will be used to derive an EQ-5D-5L index (converted roughly to a 0 to 1 scale). The adjusted Overall Survival times will be generated to provide an estimate of the QALY and to derive the Cost Effectiveness Acceptability Curve (CEAC). The CEAC will provide an estimate of the probability of the investigational arm (additional chemotherapy + chemoradiation) being cost effective compared to the control arm (chemoradiation alone). Costs which are censored (e.g. because patients were lost to follow up) will be accounted for. A suitable model to predict the survival time probabilities over time may be used, depending on the number of deaths observed.

Probabilistic sensitivity analysis will also be carried out to take into account uncertainty. The analysis will be carried out from an NHS paying perspective.

Appendix XI: Protocol Version History

Protocol:		Amendments:		
Version no.	Date	Amendment no.	Protocol Section (no./title)	Summary of main changes from previous version.
1.0	21/11/11	N/A	N/A	N/A
2.0	28/08/12	002	TMG Group 1.1, 5.3.1 - 5.3.2 1.1 & 5.1 2.2, 16.2, 16.2.2 & Appendix XII 5.3.5 5.4 6.1 7.2 7.2 & 7.6.5 7.6.4 7.8 8.1 & Appendix XII 16.2.2 20	Addition of new TMG member Amendments to the eligibility criteria Translational study added as an 'optional' part of the trial. Health Questionnaire version updated and information provided on how the economic analysis will be performed. Clarification of which countries are regarded as high risk for HIV testing. Clarification of the SCC antigen and how it is tested. Randomisations will now be performed electronically by site staff. Guidance added for radiotherapy planning to take place between weeks 3-5. Overall treatment time may be extended to 56 days with prior approval from the TMG. Recommendations inserted for in vivo measurements. Information on brachytherapy planning updated. Additional QoL questionnaire inserted for patients in the induction chemotherapy arm. Information collected for the economic evaluation updated. Publication policy amended.

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Protocol:		Amendments:		
Version no.	Date	Amendment no.	Protocol Section (no./title)	Summary of main changes from previous version.
3.0*	04/09/14	009	TMG Group 1.1, 6.3.2 1.1 5.0 6.1, Table 1, 11, 17.2.1 6.1 7.1 9.1 7.1, 8,16 8.1, 9.1 8.9.2 8.10 16 Appendix VII 18.4, 18.5, 20 Appendix IX 1.1, 1.2, 4.1, 6.3, 6.3.3, 8.6.1, 8.6.3, 9.1	Addition/Deletion of new TMG member. Amendments to the exclusion criteria. Addition/deletion of participating countries. Consent procedure clarified. Pre-randomisation scans now allow PET CT for chest/abdomen and MRI for abdomen. Deletion of requirements for translational tissue within 14 days of starting treatment. Action taken after randomisation clarified. Recommendation for blood transfusion added. IMRT included as part of trial treatment. Requirements for blood tests clarified. CTV and PTV margins amended. Brachytherapy information updated. Radiotherapy QA programme updated. Simulator 2D planning moved from main protocol to the Appendix. Information for non-UK sites added. Radiotherapy - Expected Adverse Events list amended Administrative/ formatting changes. The following has been deleted from the Appendix: - Suggested Bowel and Bladder Protocol - Radiotherapy Nodal Access

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Protocol:		Amendments:		
Version no.	Date	Amendment no.	Protocol Section (no./title)	Summary of main changes from previous version.

*For a full list of v3.0 changes please see INTERLACE Summary Table document – Amendment 003.

4.0*	21/09/2015	013	N/A 1.1 6.1 6.3.1 8.9, 8.10 16 Various	Update to trial management group membership Various changes to correspond with changes in the following, as per below Clarification regarding disease extending to the lower third of vagina Extension of maximum time between randomisation and start of treatment from within 21 days to \leq 28 days Extension of timeline for pre-randomisation imaging, from within 31 days prior to randomisation, to within 50 days prior to randomisation Clarification of regarding disease extending to the lower third of vagina Widening inclusion by FIGO staging to include stage IB1 patients with positive lymph nodes Various updates and clarifications to radiotherapy and brachytherapy planning Updating of standardised radiotherapy QA processes and procedures Changes to clarify follow up period, update trial management group list, and amend protocol in line with current unit-wide template
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*For a full list of v4.0 changes please see INTERLACE Summary Table document – Amendment 013

4.1	16/11/2015	014 Non-substantial	6.3.1	Correction of typographical error
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Protocol:		Amendments:		
Version no.	Date	Amendment no.	Protocol Section (no./title)	Summary of main changes from previous version.
5.0		017	TMG Group 3.2 4.2.2 4.2.4 7.1 8.1.1a 8.1.1b 8.6.4 8.8 13.3 15.1 18.1 18.3 Appendix I Appendix IX	Addition of new member Updated to include HRA approval process and removal of R&D approval requirement Removal of R&D approval requirement Reference updated to 'Group specific guidance document' Reference updated to 'Group specific guidance document' Clarification of dose banding requirements for carboplatin and paclitaxel Clarification of carboplatin dose modification following weight change Clarification of dose banding requirements for cisplatin Clarification of dose modification following renal toxicity Addition of overdose section Updates to procedures for 'for-cause' onsite monitoring visits Change of end of trial definition Updated to include HRA approval Update to site approval requirements to remove reference to R&D approval Update to abbreviations Merged to include appendix X Inclusion of additional expected adverse events
6.0	01/08/2019	025	N/A 1.2 3.1	Re-numbering of sections throughout the protocol Update to the format of the trial schema Addition of trial objective section

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Protocol:		Amendments:		
Version no.	Date	Amendment no.	Protocol Section (no./title)	Summary of main changes from previous version.
			4.1 4.1.1 4.2.1 5 6.1 6.4.1 6.4.2 6.4.5 6.4.7 6.6 7.1 8	<p>Change of requirement to comply with Research Governance Framework to requirement to comply with UK Policy Framework for Health and Social Care Research</p> <p>Further guidance added for selection of principal investigator</p> <p>Addition of requirement to reinitiate sites if there is a significant delay between activation and recruitment of first patient</p> <p>Addition of requirement of sites to assess a patient's ability to understand verbal and written English or the local language (for non-UK sites)</p> <p>Amendment of 'clinical examination' to 'physical examination'</p> <p>Addition of reference to 'Women of Child Bearing Potential (WOCBP)'</p> <p>Addition of the definition of 'Women of Child Bearing Potential (WOCBP)'</p> <p>Addition of details about the risk of exposure to the trial treatment during pregnancy</p> <p>Further guidance provided about the action to be taken in the event of pregnancy</p> <p>Addition of information regarding lactation while receiving trial treatment</p> <p>Further guidance provided about the use of the squamous cell carcinoma antigen</p> <p>Various minor clarifications to the wording within this section</p> <p>Addition of categorisation of the trial treatments</p> <p>Re-ordering of sections throughout to aid understanding of the text</p>

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Protocol:		Amendments:		
Version no.	Date	Amendment no.	Protocol Section (no./title)	Summary of main changes from previous version.
			8.2	Addition of ANC and platelet count requirements at baseline and prior to receiving treatment
			8.3	Removal of permission for sites to give 4 cycles of cisplatin (and from section 8.3.2) Addition of table detailing dose calculation and maximum dose permitted for each drug Increase of maximum permitted dose of paclitaxel from 160mg to 162mg
			8.3.2	Addition of guidance that cisplatin should not start before the first day of radiotherapy
			8.4	Minor formatting changes throughout section 8.4 to enhance understanding
			8.5	Clarification of how to document overdoses in patients notes and SAE reports
			8.8	Removal of the majority of RT guidance due to it no longer being relevant to the trial and guidance is continually changing. Replacement with reference to RTQA pack which is provided as a separate document and brief guidance on pre-trial and on-trial QA requirements.
			8.9	Consolidation of pharmacy responsibilities
			9.1	Addition of guidance on the management of pre-treatment haematology and biochemistry
			9.2	Clarification of the assessments that need to be carried out at 4 weeks post treatment and 12 weeks post treatment
			9.3	Amendment to the length of the follow-up period from 5 years to 'until the end of the trial' Addition of guidance on the CRFs that need to be completed at each follow-up time point
			9.4	Addition of guidance on the assessments that need to be undertaken after disease progression

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Protocol:		Amendments:		
Version no.	Date	Amendment no.	Protocol Section (no./title)	Summary of main changes from previous version.
			10.3 10.4 11.1 11.2 11.4 11.5 11.6 12.2 13 13.2 14.1 14.3 14.4 15.1 15.4	Addition of guidance on data return for non-UK sites Clarification of how sites should complete data clarification requests Addition of definition of SUSAR Update to the link provided for the CTCAE reference document Several additions to how trial safety data will be monitored Addition of sites being able to email pregnancy reports to CTC Addition of definition of pregnancy exposure to trial Clarification that CCCs/CLSs should forward the DSUR to any organisation identified in the agreement, as well as ethics committees/competent authorities Addition of definition of serious breach Clarification of how appropriate monitoring is defined and conducted Addition of the requirement for non-UK sites to complete a consent form monitoring log Addition of guidance for sites for patients who are randomised but do not start trial treatment Clarification of how data should be collected for patients who are lost to follow-up Addition of guidance for non-UK sites about how to handle losses to follow-up Update to the definition of the end of trial Addition of guidance about how non-UK sites should inform CTC of early closure to recruitment and management of future trial activities.

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Protocol:		Amendments:		
Version no.	Date	Amendment no.	Protocol Section (no./title)	Summary of main changes from previous version.
			16 17 Appendix III Appendix V Appendix VIII Appendix IX	Update to sample size calculation following reduction in sample size Addition of requirement for CTC and sites to comply with GDPR regulation Removal of Appendix III Clarification that the 2009 FIGO staging must be used to randomise patients to INTERLACE Update to RECIST guidance Addition of further expected adverse events for radiotherapy and citations
7.0	08JUN21	030	N/A Protocol summary 3 6.4.4 8.7 8.9 11.2.2 13 16.2 17 18	Update to contact details Update to TMG members Updated in line with changes to endpoints PFS updated to primary endpoint. Time to first subsequent treatment added as secondary endpoint. Update to contraceptive advice Section added related to COVID-19 vaccines RTQA contact details updated Update to exemptions from SAE report submission. SAE reporting flowchart updated Details of remote monitoring added PFS updated to primary endpoint. Time to first subsequent treatment added as secondary endpoint. Updated to reference Data protection Act 2018 and General Data Protection Regulation (EU)2016/679 (GDPR) Sponsor contact role updated and address added for UCL's legal representative in the EU

RTQA INTERLACE

Radiotherapy Trials Quality Assurance

INTERLACE: A phase III multicenter trial of weekly induction chemotherapy followed by standard chemoradiation versus standard chemoradiation alone in patients with locally advanced cervical cancer

RTQA Pack v.2.1

Outlining and Planning Guidelines Brachytherapy Guidelines RT QA Programme

Authors: INTERLACE Trial and RTTQA Groups



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FOREWORD

This updated version of the radiotherapy quality assurance (QA) document contains all the necessary information for prospective INTERLACE trial centres to complete the radiotherapy QA process. In combination with the DICOM data sets available for download from the RTTQA website it will allow centres to complete the outlining and planning QA aspects of the trial.

This new updated version of the QA pack covers all the QA aspects of the INTERLACE trial including the brachytherapy QA components.

The use of IMRT and rotational techniques will also be permitted within INTERLACE. Please refer to <http://www.rttqa.org.uk/> for more information.

1. EBRT OUTLINING GUIDELINES

Accurate target volume definition is essential for radiotherapy planning and 3D conformal radiotherapy requires detailed knowledge of CT-based anatomy [1-3]. We have therefore included a step by step pictorial guide for the delineation of the CTV1, CTV2, CTV3 and the OARs.

(a) Target Localisation

Patients should be CT scanned ideally in a supine position (patients may also be scanned in prone position and use of belly boards is permitted) and immobilised with a minimum of ankle and/or knee supports. (Participating centres should submit details on their immobilisation technique as part of the process document). Patients should have two lateral and one anterior permanent skin marks applied.

Centres should have bladder and bowel preparation protocols in place for IMRT. An example is included in the [Appendix](#). Ideally patients should receive IV contrast unless contraindicated. Patients should be scanned usinge 2.5–5mm slices from the top of L2 (T12 if common iliac nodes or nodes at the aortic bifurcation) to 5cm below ischial tuberosities and include the patient's full external body contour.

(b) Organs at Risk Guidelines

Centres are required to volume the following organs at risk:

- Bladder
- Rectum (including anal canal, up to the level of the recto-sigmoid junction)
- Right and Left kidneys (each as a separate structure).
- Spinal canal (from L2/3 intervertebral space to 2cm superior of the PTV)

In addition, when treating with IMRT/ rotational techniques:

- Bowel bag (up to at least 2cm above the superior extent of the PTV)
- Right and left femurs (each as a separate structure)

The next section explains how they should be contoured [4].

(i) Rectum

Outline the outer wall of the rectum (arrowed in figure 1.2a and 1.2b) and anus (arrowed in figure 1.2c and 1.2d) together from the anal sphincter to the transition anteriorly into the sigmoid colon (arrowed in figure 1.2e and 1.2f).

(ii) Bladder

Outline the outer wall of the entire bladder (arrowed in figure 1.1a and 1.1b).

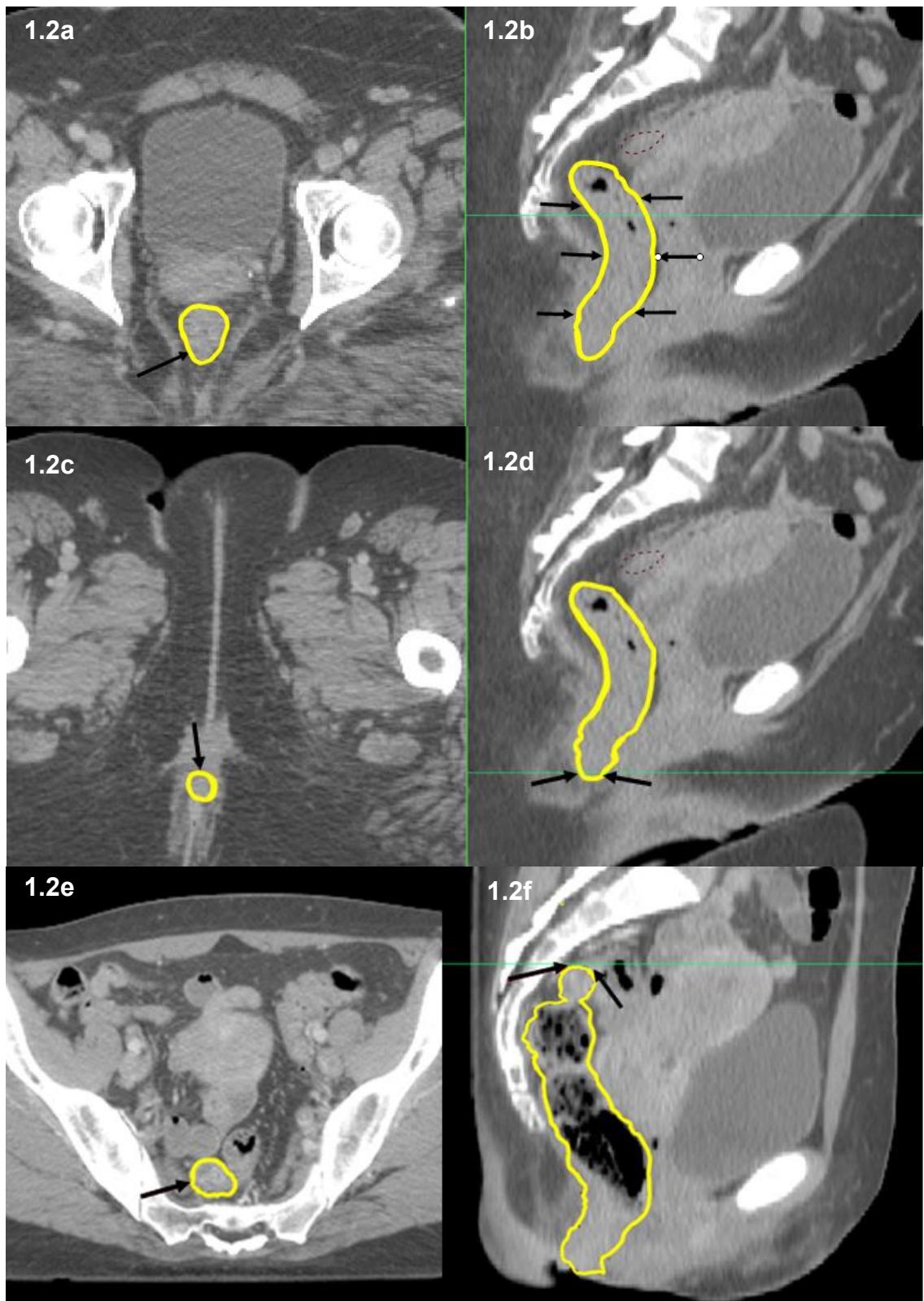


Figure 1.2: Axial (a) and Sagittal (b) CT at level of mid femoral heads with rectum outlined (yellow); Axial (c) and sagittal (d) CT at level of anus; Axial (e) and sagittal (f) CT at level of transition to sigmoid colon (arrowed)



Figure 1.1:Axial (a) and Sagittal (b) CT with bladder outlined as arrowed

(iii) Kidney (Left and Right)

If either kidney is within 2cm of the superior border of the PTV they must be outlined. This will include all patients receiving para-aortic nodal radiotherapy and some patients receiving pelvic RT alone. Outline the outer wall of each kidney individually (left kidney solid arrows, right kidney dashed arrows in figure 1.3a and 1.3b).

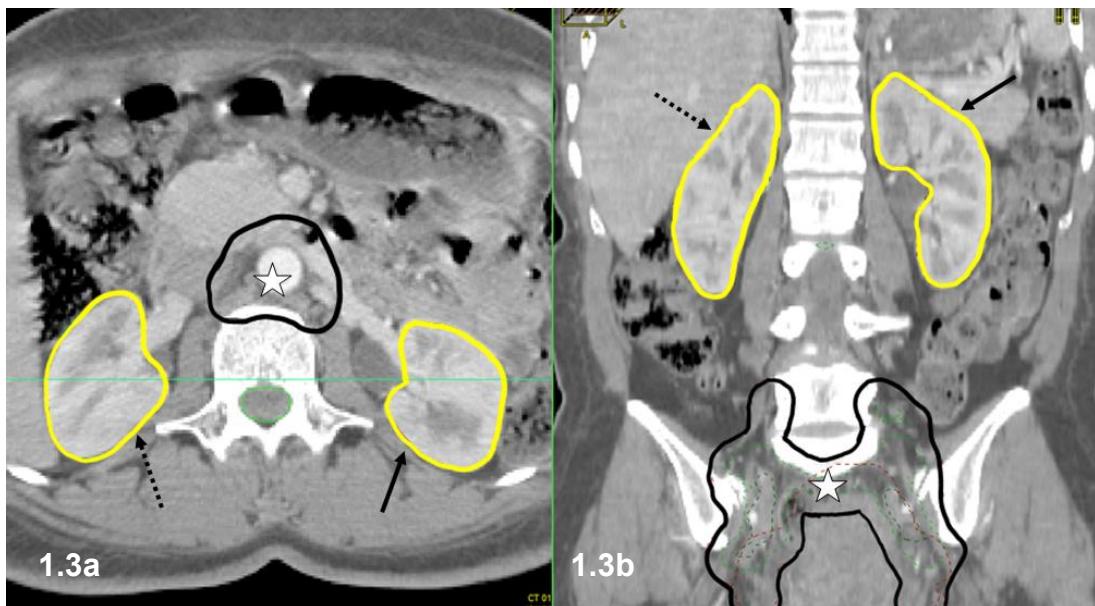


Figure 1.3: Axial (a) and coronal (b) CT of patient receiving para-aortic nodal radiotherapy (PTV starred) with left (solid arrow) and right (dashed arrow) kidneys outlined.

(iv) Spinal canal

If the superior border of the PTV (starred in fig 1.4b) is within 2cm of the L2/3 junction the spinal canal must be outlined. This will include all patients receiving para-aortic nodal radiotherapy and some patients receiving pelvic radiotherapy alone. Outline the whole spinal canal (solid arrow fig 1.4a and 1.4b) from at least 2cm superior to the PTV to the inferior border of L2. The most inferior slice of the spinal canal outline should therefore be level with the inferior border of the L2 vertebra (dashed arrow in fig 1.4b).

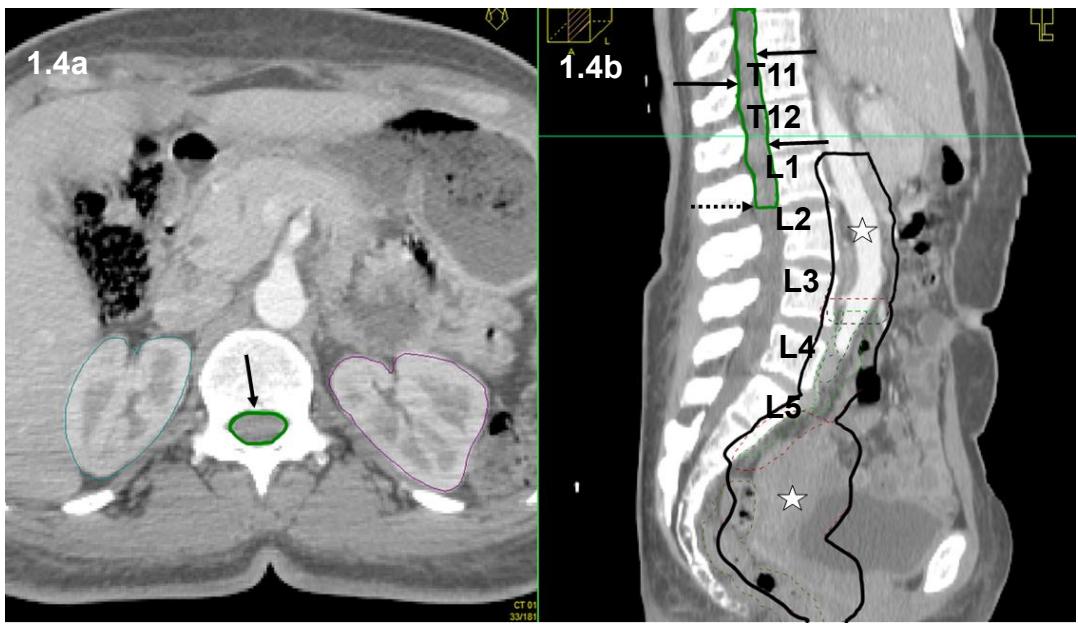


Figure 1.4: Axial (a) and sagittal (b) CT of para-aortic radiotherapy where PTV (star) extends to the superior border of L2. Spinal canal (solid arrows) has inferior level at the lower border of L1 (dashed arrow)

If using IMRT the following Organs At Risk must also be outlined:

(v) Bowel ('Bowel bag' if external beam radiotherapy; bowel loops if Brachytherapy)

RTOG [4] recommends delineation of the 'bowel bag' or 'bowel sac'. The 'bowel bag' is the area within the abdominal cavity (including the retroperitoneal space) in which the bowel loops move around.

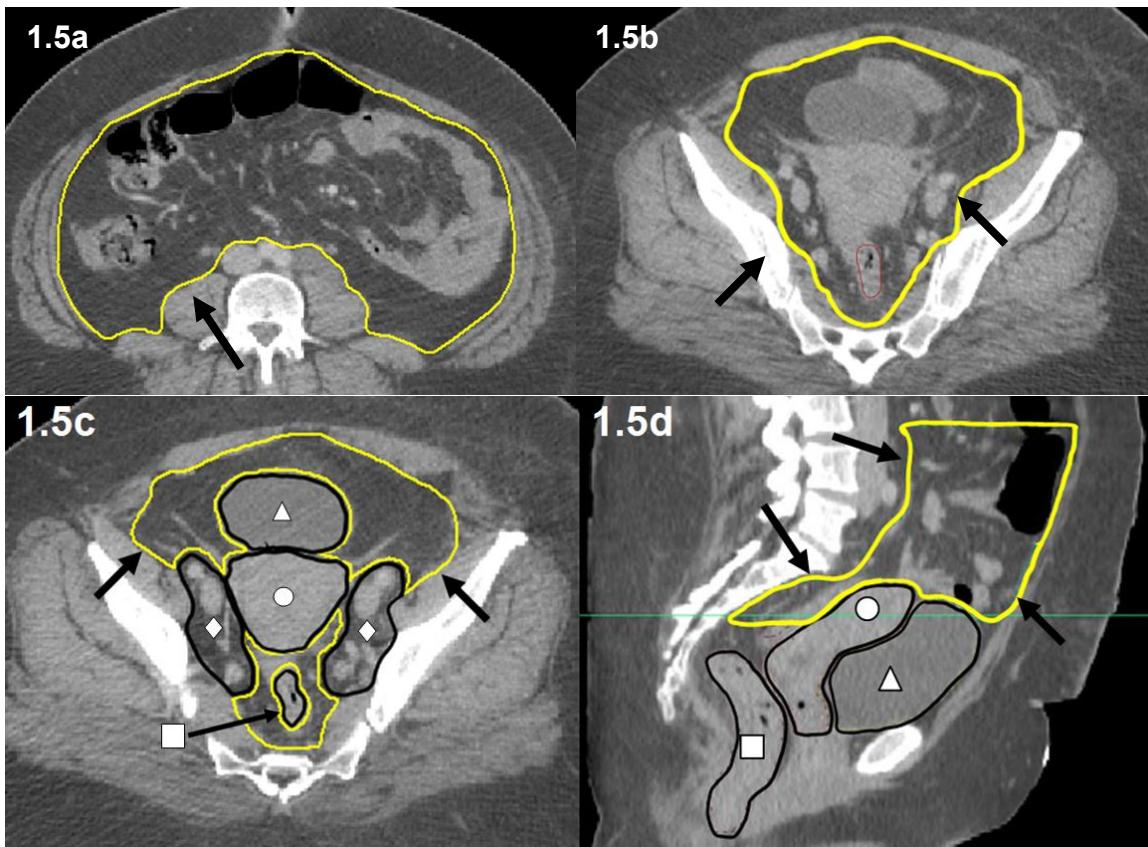


Figure 1.5: Axial (a,b and c) and sagittal (d) CT with bowel bag outlined (yellow) and bladder (triangle), rectum (square), uterus/CTV1 (circle) and CTV2 (diamond) edited out of the initial volume

NB: For brachytherapy we would recommend outlining bowel loops close to the high dose region only.

For the bowel bag, outline the abdominal cavity (excluding muscle, bone and great vessels-aorta and inferior vena cava) as seen in fig 1.5a and 1.5b. On axial imaging, the caudal extent should be at either the level of the anorectum or when no bowel loops are seen; whichever level is most inferior, as in fig 1.5b. The cranial limit should be at least 2cm beyond the superior border of the PTV. Using your treatment planning software (Boolean operations or subtraction) subtract out any overlapping structures including bladder (triangle in fig 1.5c-d), rectum (square in fig 1.5c-d), CTV1 (circle in fig 1.5c-d, includes uterus see section 2) and CTV2 (diamond on 1.5c, see section 3) from the bowel bag to create the final complete outline as seen in fig 1.5c.

TIP: In sections where the abdominal cavity does not change contour significantly alternate axial CT slices can be outlined and subsequent interpolation by the treatment planning software can be performed. It is important to review all CT slices once this has been performed and edit if necessary.

(vi) Femur (Left and Right)



Figure 1.6: Axial (a) and coronal (b) CT with left (solid arrows) and right (dashed arrows) femur outlined.

Outline the left and right femoral head and proximal femur down to the inferior margin of the lesser trochanter as two individual structures (fig 1.6).

(c) Target Volume Definition

Guidelines on target volume delineation for INTERLACE have now been published [5].

The gross tumour volume (GTV) will include all visible tumour seen on staging MRI/CT & found on examination.

The clinical target volume (CTV) will include:

- The entire cervix and local extension of tumour.
- Uterus.
- Parametrium.
- Enlarged visible ovaries.
- Proximal half of the uterosacral ligaments.
- The upper half of the vagina or 2 cm below known vaginal disease.
- The parametrial, medial and lateral external iliac nodes.
- The obturator, internal iliac, subaortic presacral and common iliac nodes.

If there is common iliac nodal involvement the para-aortic nodes should also be treated. It is helpful to outline the following as separate CTVs since the margins differ.

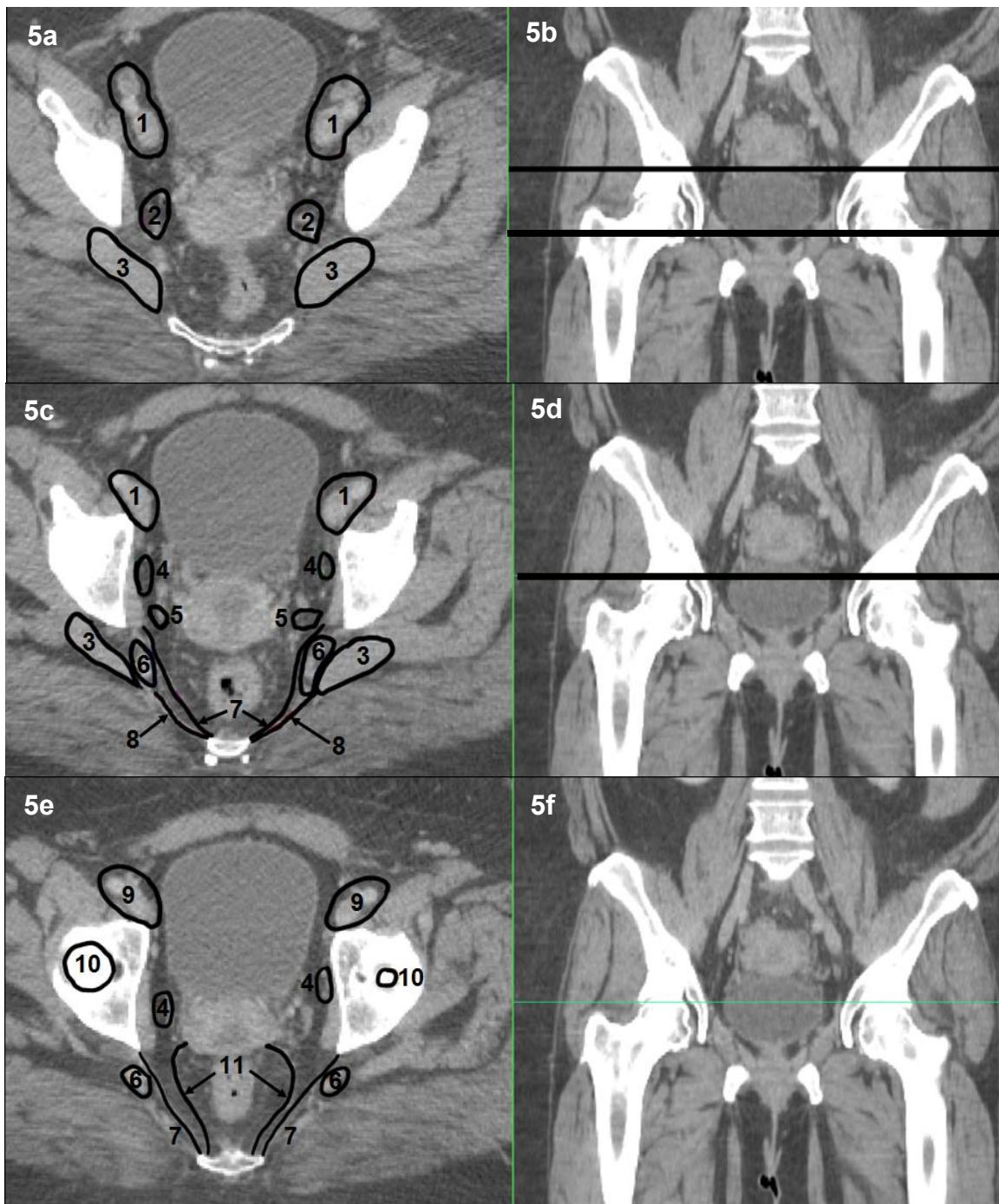


Figure 5: Axial CT images (a,c,e) with line on coronal showing corresponding position (b, d, f, respectively). Anatomical areas: 1=external iliac vessels; 2=junction of gluteal and internal iliac vessels; 3=piriformis muscle; 4=obturator vessels/infra-iliac region; 5=internal iliac vessels; 6=gluteal vessels; 7=sacrospinous ligament; 8=sacrotuberous ligament; 9=inguinal vessels; 10=femoral head; 11=uterosacral ligaments

(i) Clinical Target Volume 1 (CTV1)

CTV1 includes the GTV and its local extent, the entire uterine cervix (fig 7), entire uterine corpus, both parametria, ovaries if seen, proximal half of the uterosacral ligaments and at least the upper half of the vagina, depending upon extent of disease [6, 7]. CTV1 is delineated as a single contiguous volume but for the purpose of these instructions it is separated to aid description.

Step 1 (Figure 2.1): Outline the entire uterine corpus. The sagittal images will help determine the extent of this outline. The uterine cervix (star) and vagina (triangle) can be seen outlined on the sagittal CT.

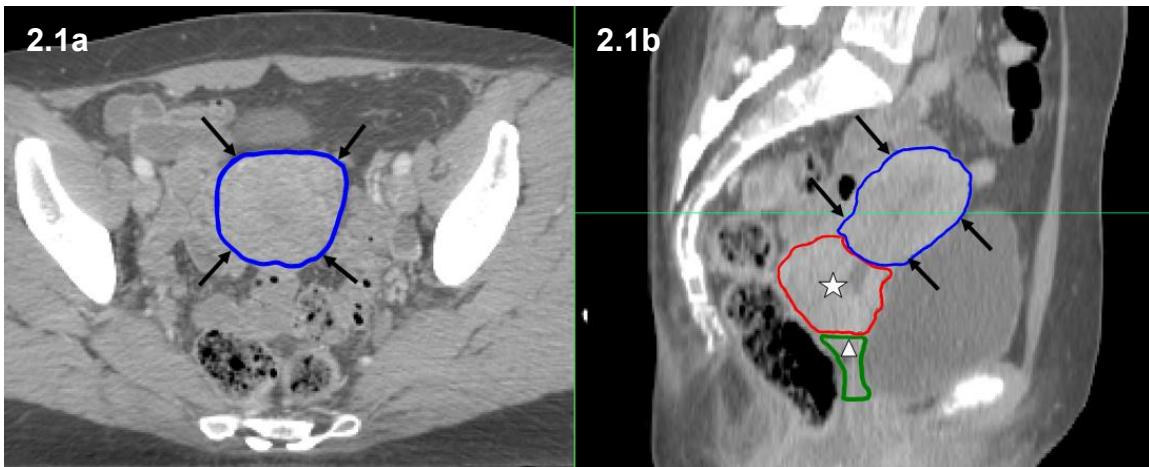


Figure 2.1: Axial (a) and sagittal (b) CT with the uterine corpus (blue), uterine cervix (star) and vagina (triangle)

Step 2 (Figure 2.2): Outline the ovaries (arrowed in fig 2.2a and 2.2b) in continuity with the uterine corpus (circle) if they are visible on the radiotherapy planning CT.

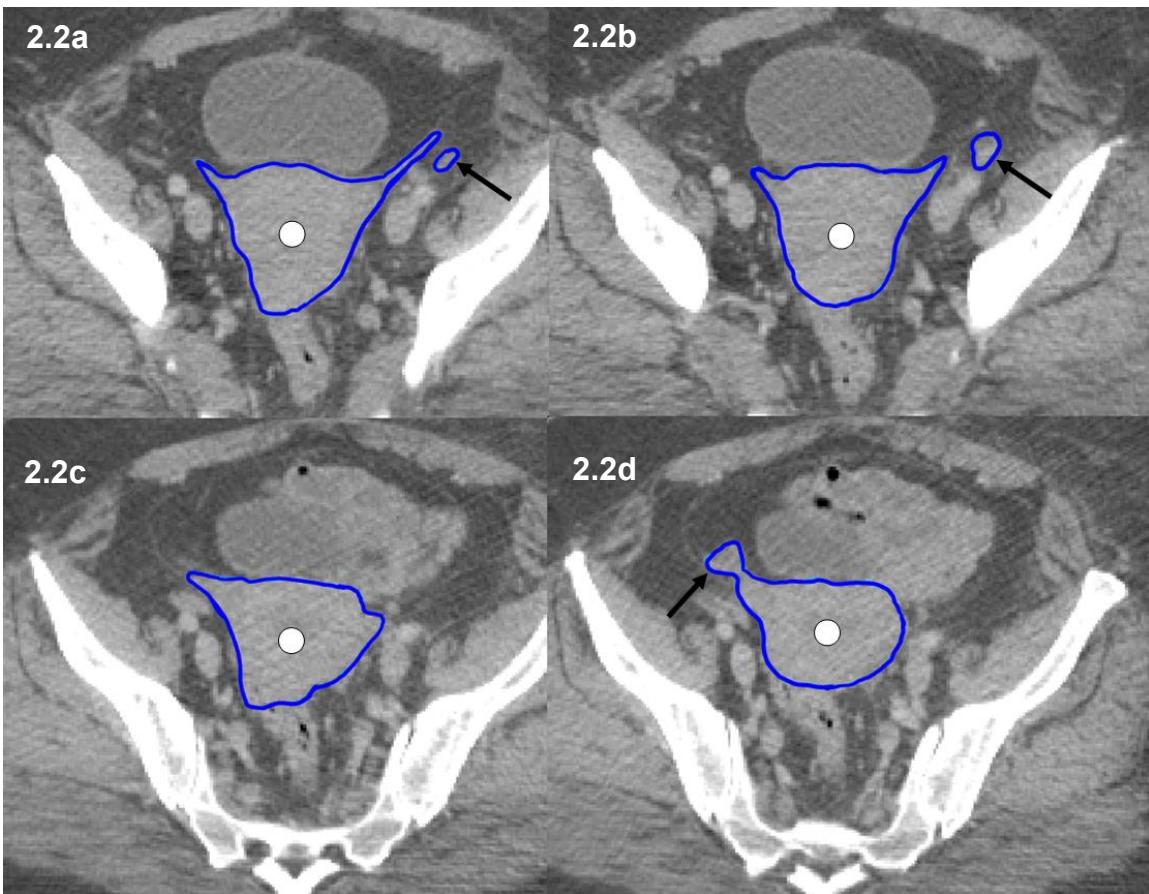


Figure 2.2 a-d: Sequential axial CT images with uterine corpus (circle) & ovaries (arrowed) outlined in continuity

Step 3 (Figure 2.3): Outline the entire uterine cervix including the local tumour extension (gross tumour volume) as arrowed in fig 2.3a and 2.3b. The uterine corpus (circle) and vagina (triangle) are also seen on the sagittal view (fig 2.3b).

TIP: Using diagnostic imaging, especially the T2 weighted MRI if available, and examination under anaesthetic staging information will help to determine the boundaries of the gross tumour, uterine corpus and cervix, and hence CTV1.

TIP: If the uterine arteries can be seen entering the uterus this is the cranial margin of the cervix.

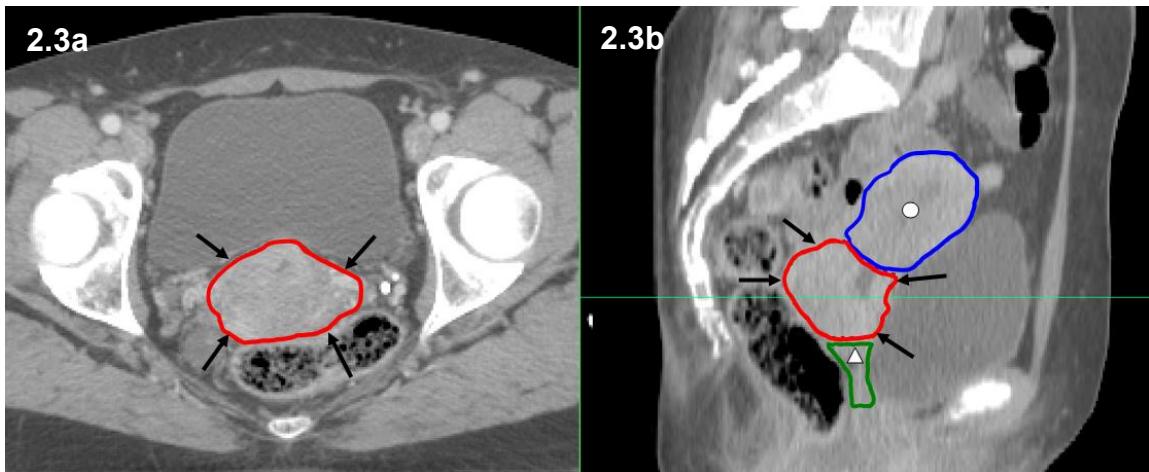


Figure 2.3: Axial (a) and sagittal (b) CT of the cervix and GTV outlined as a single structure (red); uterine corpus (circle) and vagina (triangle)

NB: There will be overlap of CTV1 and CTV2 due to the parametrial volume extending to the lateral pelvic sidewall. This is expected and acceptable and does not need to be edited.

Border	Definition (see figure 2.4)
Superior	Fallopian tube or broad ligament (1)[4] Uterine artery enters uterus (2) [7]
Inferior	Levator ani/pelvic floor muscles (3)
Anterior	Post bladder (4) or posterior border of external iliac vessels (5)
Posterior	Mesorectal fascia and uterosacral ligaments(6)
Lateral	Medial internal obturator(7)/piriformis muscle(8)/ischial ramus(9) ie Pelvic sidewall
Medial	Cervix

Table 1: Definition of the borders of the parametria outlines, which is part of CTV1

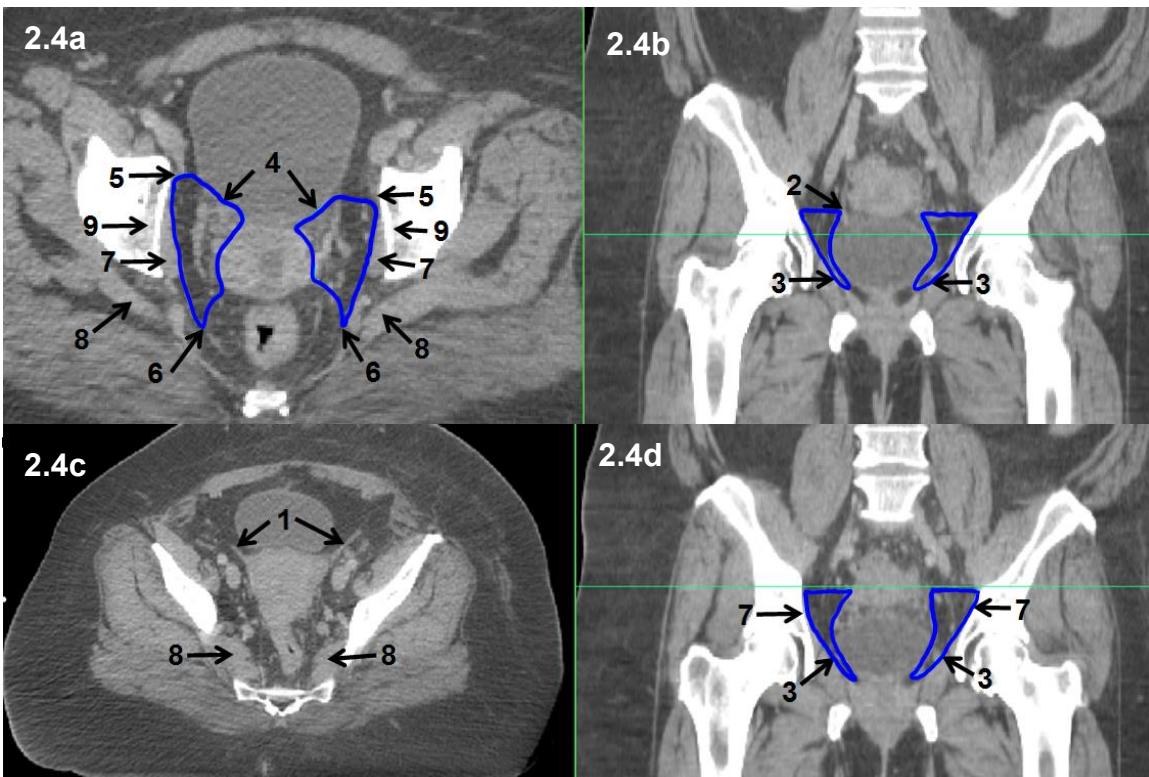


Figure 2.4: Axial (a and c) and coronal (b and d) CT with both parametria borders outlined; see table 1

Step 4: Outline both parametria even if not involved with disease, the borders of which are outlined in table 1 and figure 2.4.

TIP: On axial imaging the level at which bowel is visible adjacent to the uterus is often superior to the parametrial outline, i.e. when outlining the parametria one would not expect to see bowel adjacent to the uterus on the same axial image as the parametrial outline.

Step 5 (Figure 2.5): Outline the proximal half of the uterosacral ligaments (arrowed in fig 2.5 and no 6 in 2.4a). Extend the volume posteriorly along the uterosacral ligaments if they are known to be involved

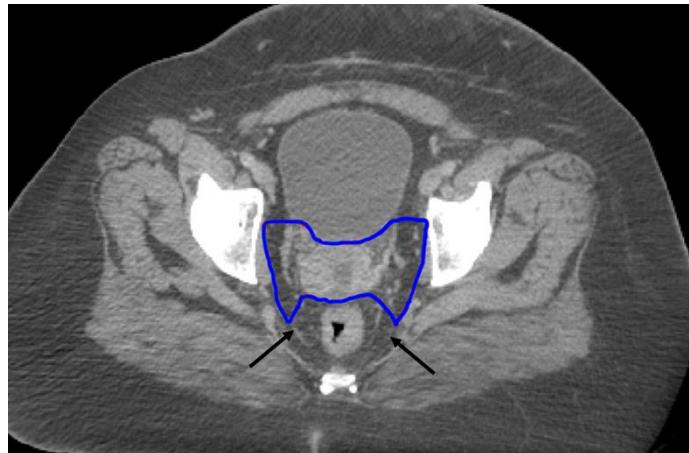


Figure 2.5: Axial CT demonstrating the uterosacral ligaments (arrowed) and CTV1 (outlined)

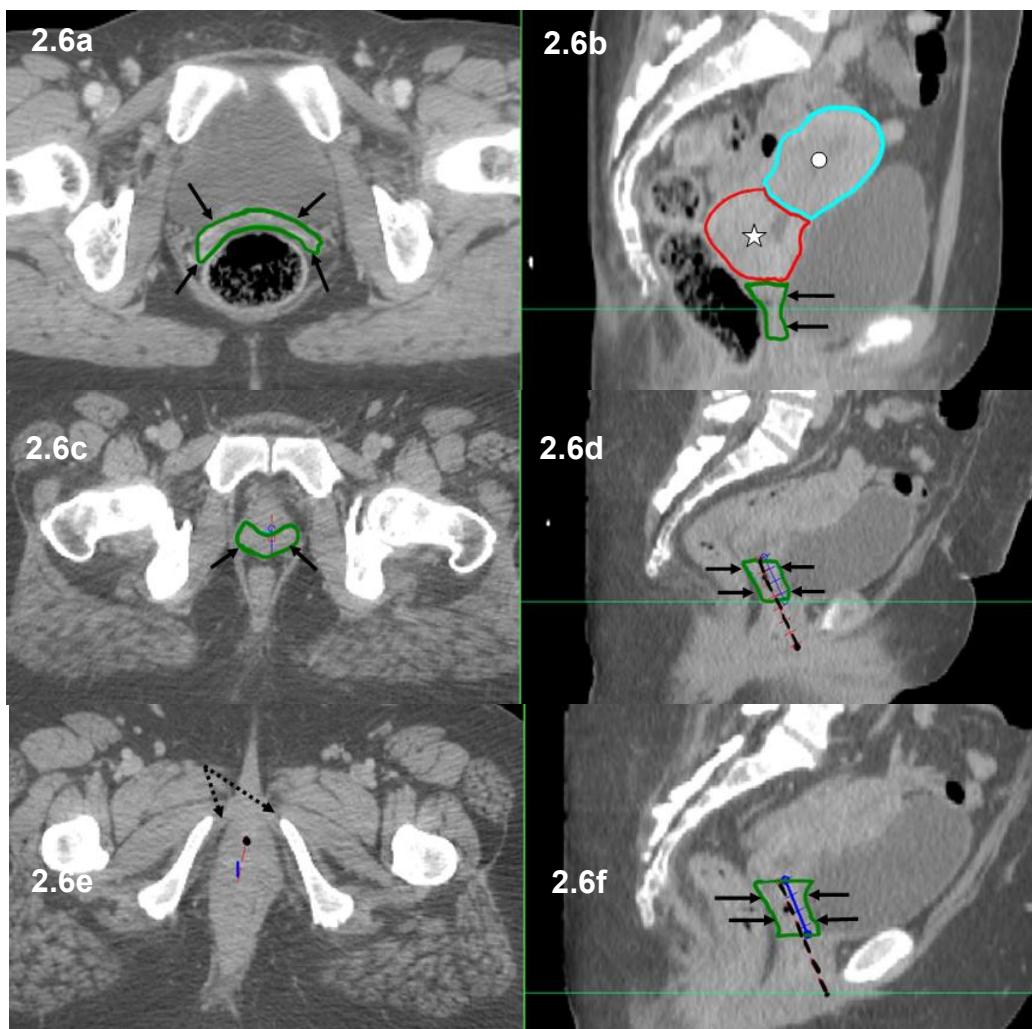


Figure 2.6: Axial (a,c,e) and sagittal (b,d,f) CT showing upper half of vagina (green), uterus (circle) and cervix (star); dashed line follows length of vagina; arrow on e shows clitoral crura at ~ inferior axial slice of vagina

Step 6 (Figure 2.6): Outline the upper half of the vagina (arrowed in fig 2.6a-d and 2.6f) if there is no vaginal involvement or 2cm below known disease. The paravaginal tissue should be included in this outline (fig 2.6a and 2.6c). The introitus is very difficult to see on the planning CT and therefore an introital marker can be used to show this OR the level of the introitus is just proximal to the level of the clitoral crura (arrowed in fig 2.6e) and therefore on CT this can be used as an approximate level.

(ii) CTV2: Pelvic nodal guidelines

Nodal groups at risk of microscopic disease and therefore included in CTV2: common iliac, internal & external iliac, obturator, presacral. Please follow instructions to accurately outline CTV2 [3, 8, 9].

Step 1: Outline the iliac blood vessels (fig 3.1a, 3.2a and 3.6a). The most superior axial outline should be at the aortic bifurcation. The most inferior should be at the superior border of the femoral head which represents the caudal margin of the external iliac vessels.

Step 2: Using the treatment planning software add a 7mm margin to the blood vessels (fig 3.1b, 3.2b and 3.6b) all around except for superiorly where 0mm is added. This ensures the superior border of CTV2 is the level of the aortic bifurcation.

Step 3: Edit this outline using the rollerball, eraser or drawing tools to remove bone and muscle from the outline (fig 3.1c, 3.2c and 3.6c). Also edit the CTV, using the same tools, to include all visible nodes or lymphoceles if applicable. Involved nodes should be included in CTV2 with a 3-5mm margin. Do not edit to exclude bladder or bowel.

Step 4: Extend the outline posterolaterally, using the same tools, at the level of the common iliac vessels to ensure the space between the psoas muscle and vertebral body is included (fig 3.1d).

Step 5: Add a presacral strip by adding a 10mm strip joining the left and right outlines over the anterior sacrum (dashed arrow in fig 3.2d) to the lower level of S2. You do not need to extend into the sacral foramina (arrowed in fig 3.3) but do include the sacral notch.

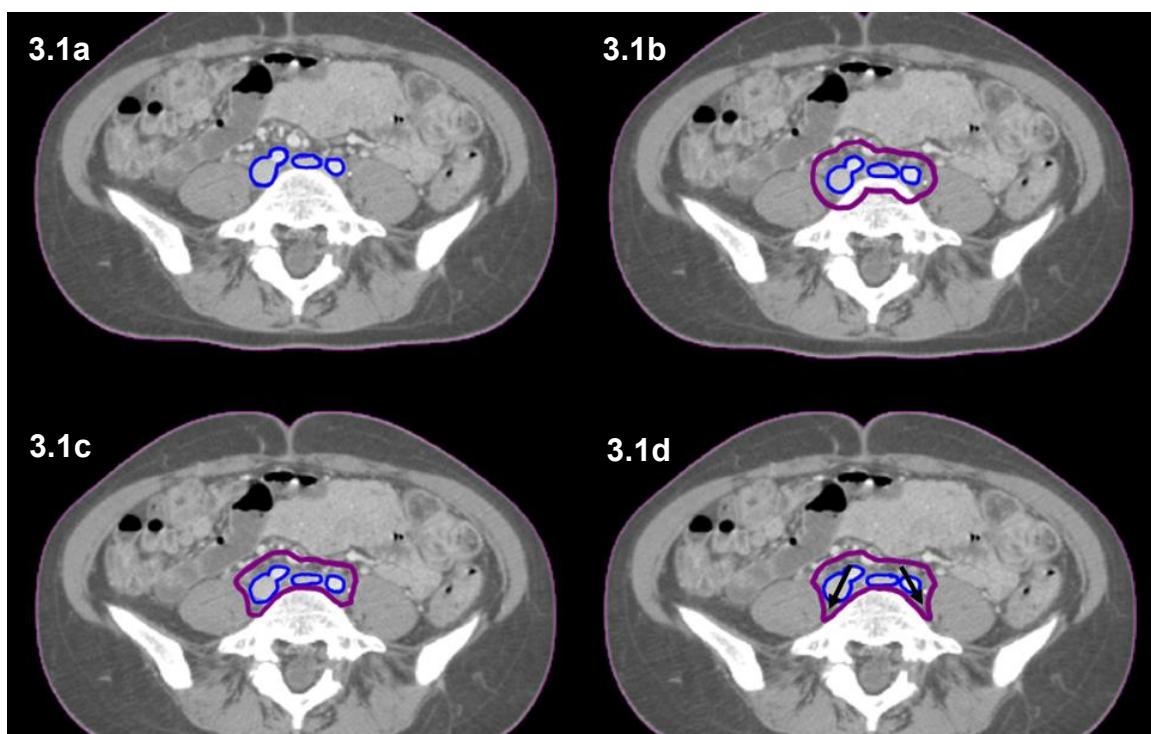


Figure 3.1: (a) Axial CT image 1cm inferior to aortic bifurcation with common iliac vessels (blue). (b) 7mm margin added (purple). (c) edited to exclude muscle and bone. (d) extended posterolaterally to include area between psoas muscle and vertebral body (arrowed)

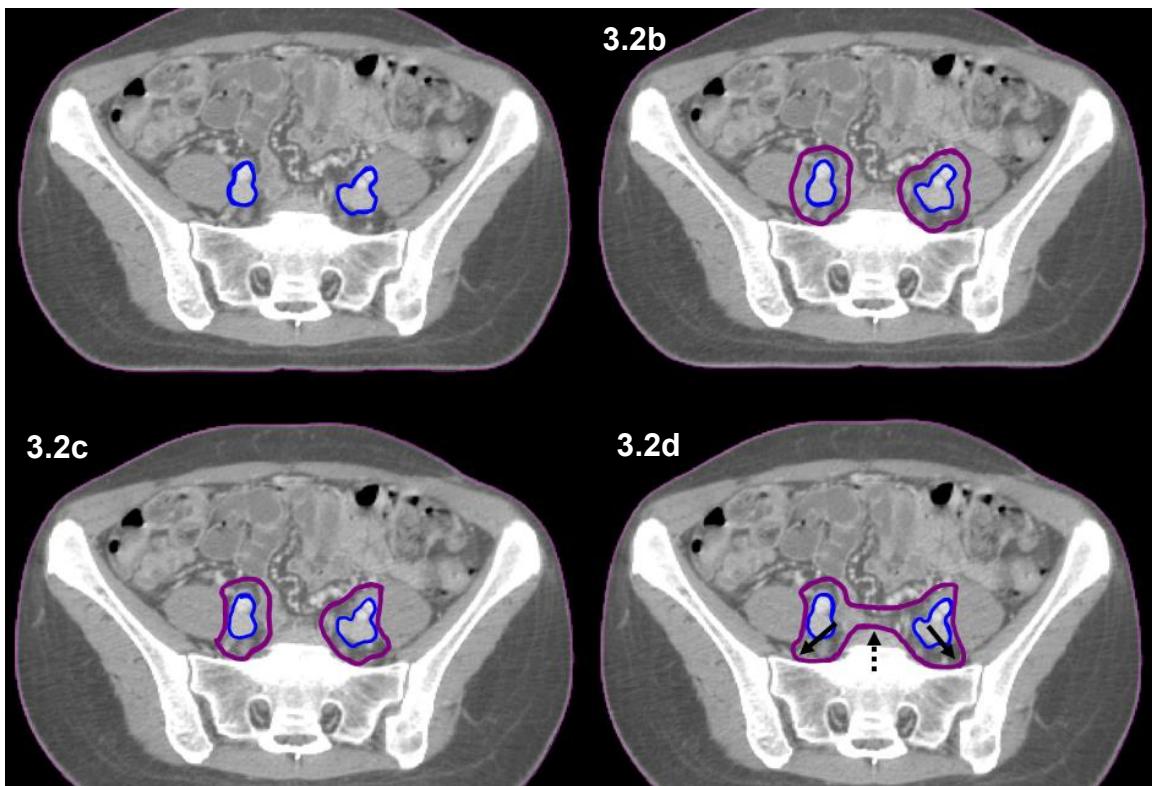


Figure 3.2: (a) Axial CT image at the level of iliac bifurcation with vessels (blue). (b) 7mm margin added (purple). (c) edited to exclude muscle and bone (d) extended posterolaterally to include area between psoas muscle and vertebral body (solid arrow) and addition of a presacral strip (dashed arrow d)

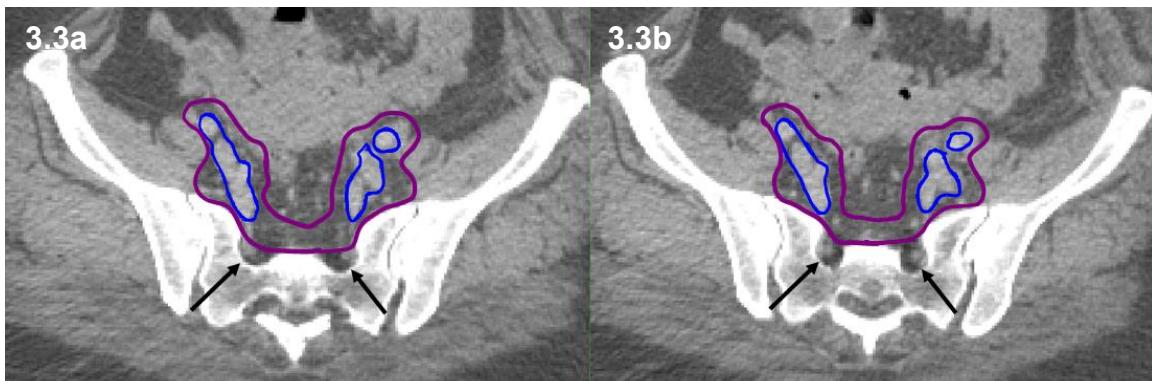


Figure 3.3: Axial CT of CTV2, not including the sacral foramina (arrowed)

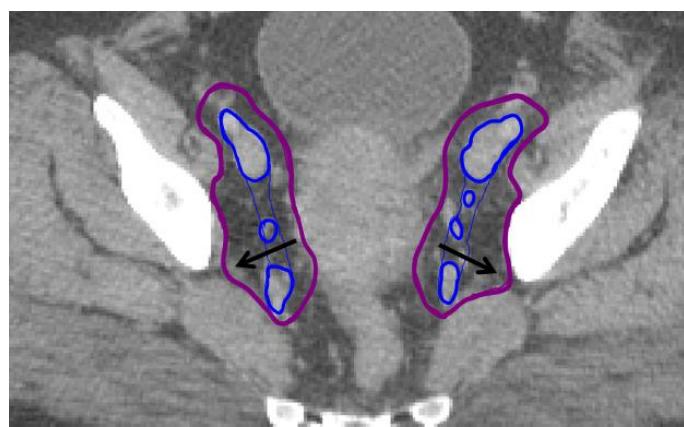


Figure 3.4: Axial CT of CTV2 extended laterally (in direction of arrows) to pelvic sidewall

Step 6: Edit the outline using the rollerball or drawing tools to ensure no space is present laterally between the outline and pelvic side wall ie the outline extends to pelvic bones and muscles (fig 3.4).

Step 7 only if external iliac nodal involvement (Figure 3.5): Edit the outline to extend 10mm anteriolaterally along the iliopsoas muscle in the region of the external iliac vessels (arrowed fig 3.5a and 3.5b) (to include lateral external iliac nodes).

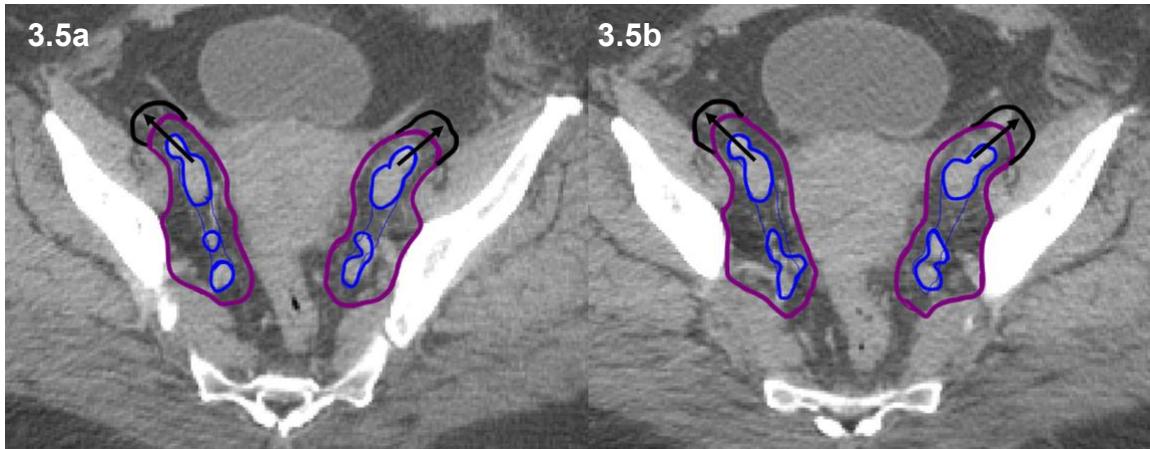


Figure 3.5: Axial CT in the region of the internal and external iliac vessels (blue) showing anteriolateral extent (arrowed) along the iliopsoas muscle to include lateral external iliac nodes

Step 8: Using the rollerball or drawing tools, join the outlines around the internal and external iliac vessels together with an 18mm strip parallel/medial to the pelvic sidewall (arrowed in fig 3.6d). This ensures the obturator and infra-iliac nodes are included.

TIP: Stop outlining the external iliac vessels when the femoral heads are visible or when the vessels are anterior to the pelvic bone. This ensures you do not include the inguino-femoral region.

TIP: When outlining the internal iliac vessels only outline the main vessels and not the smaller branching vessels as this leads unnecessary inclusion of areas such as pudendal and gluteal vessels.

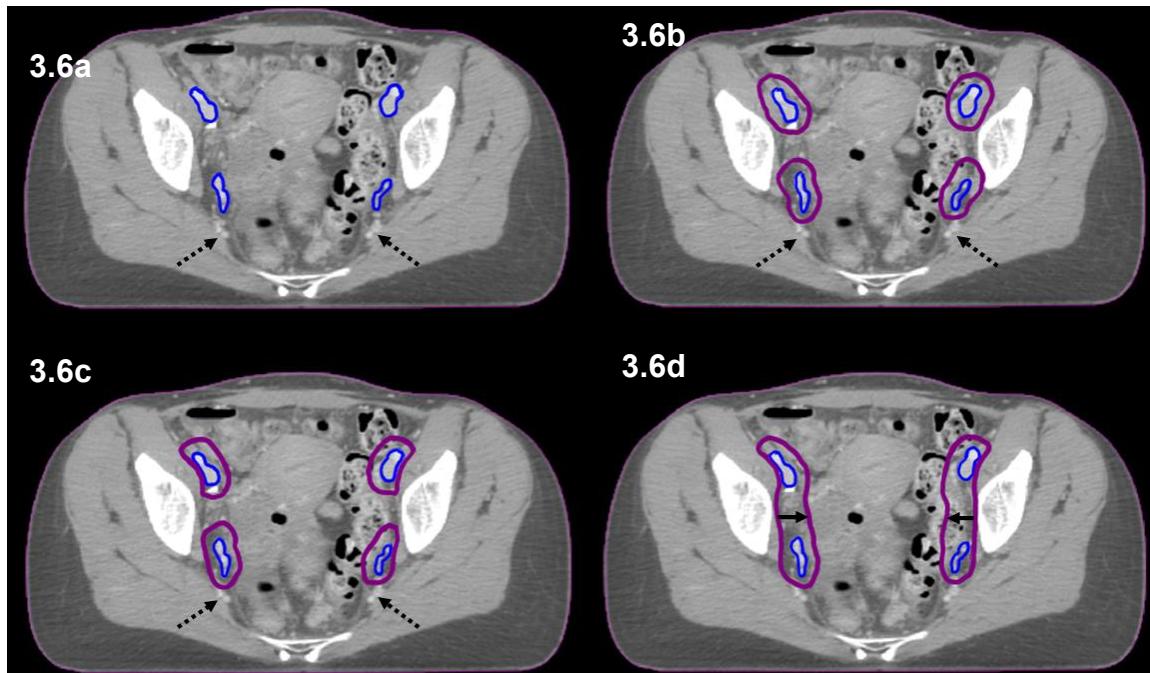


Figure 3.6: (a) Axial CT at distal level of internal and external iliac vessels (blue). (b) 7mm margin added (purple). (c) edited to exclude muscle and bone. (d) 18mm strip added (solid arrows) to cover obturator/infra-iliac nodal region. Gluteal vessels (dashed arrows) not to be included

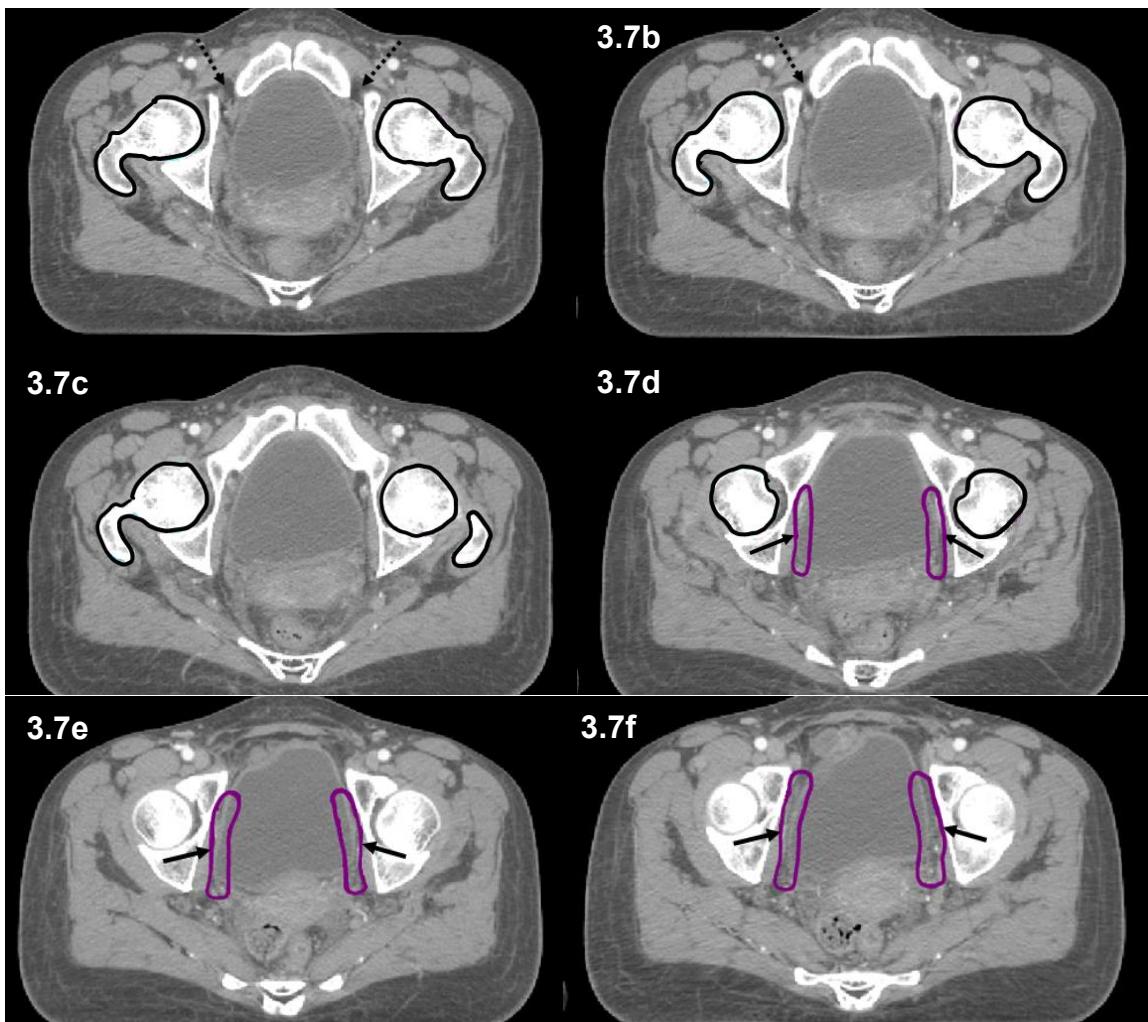


Figure 3.7: Axial CT of inferior extent of CTV2 (purple) ~ mid-axial slice of femoral heads (black) and ~1cm superior from the top of obturator foramen (dashed arrows)

Step 9 (Figure 3.7): Continue with a 10-18mm diameter strip inferiorly to cover the obturator nodes (fig 3.6d-f). The most inferior axial slice to include should be at the level of mid femoral heads or approximately 1cm superior to the obturator foramen (demonstrated in fig 3.6a-d). This outline should not include muscle or bone. Do not edit to exclude bladder or bowel.

(iii) CTV3: Para-aortic nodal volume

Where there is common iliac involvement, the whole para-aortic strip should be outlined, usually to the level of the renal hilum at T12/L1 (or at least L1/2). Delineation of the PA nodes is described below:

Step 1 (Figure 4.1a): With the aid of intravenous contrast outline the aorta (fig 4.1a solid arrow) and medial half of the inferior vena cava ((IVC; fig 4.1a dashed arrow). Involved nodes lateral to the IVC (paracaval) are uncommon and extension in this direction may increase kidney doses. The aortocaval space (between aorta and IVC) is a common location for nodal disease and must be included.

Step 2 (Figure 4.1b): Using your treatment planning software add a margin of 7mm in all directions to the blood vessels.

Step 3 (Figure 4.1c): Edit to exclude muscle and bone.

Step 4 (Figure 4.1d): Extend the outline posterior-laterally along the vertebral body (arrowed in fig 4.1d) to cover the left para-aortic area. Also edit to include any lymphoceles if applicable.

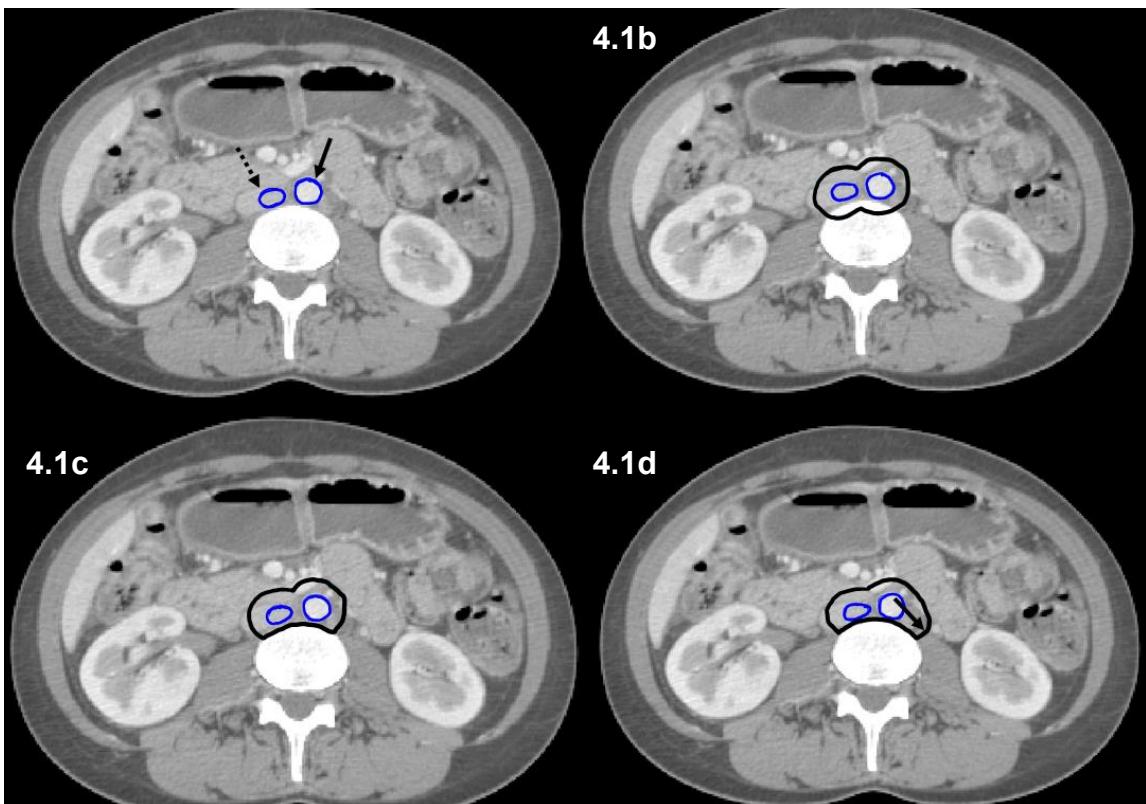


Figure 4.1: (a) Axial CT of vessels (blue: aorta solid arrow; IVC dashed arrow). (b) 7mm margin added (black). (c) edited off bone and muscle. (d) extended along vertebrae to psoas muscle (arrowed) to create CTV3

The CTV may be edited further where the kidney tolerances are exceeded despite efforts to minimise kidney dose e.g. using oblique/angled beams. It is important when treating the para-aortic region that renal function has been formally assessed as well as the differential function of each kidney.

(iv) Clinical target volume Boost (CTV_Boost)

This should include any area of macroscopic or microscopic disease to receive an elective boost dose and **must be outlined**.

(v) PTVs and Margins

Details of the planning target volumes (PTV) including typical margins are detailed below and should be applied taking account of any known local limitations.

PTV1:

- For **3D conformal planning** add 15 to 20mm to CTV1 anteriorly, posteriorly, superiorly and inferiorly. Add 7 to 10mm in the lateral extension.
- If using **IMRT/rotational arc therapy** we suggest adding 20-30mm to CTV1 anteriorly, posteriorly and superiorly (to allow for organ motion), keeping the rest as for 3D conformal.

PTV2: Add 7 to 8mm to CTV2.

PTV3: Add 5mm to CTV3.

PTV Boost: Add 5mm to CTV_Boost.

2. EBRT PLANNING GUIDELINES

It is important to document and deliver radiotherapy as described within a clinical trial setting (ICRU 83) [10]. This will allow for treatment compliance to be assessed across all treatment centres. Peters *et al* having recently reported on the critical impact of radiotherapy protocol compliance and the quality in the treatment of advanced head and neck cancers using the TROG 02.02 study [11]. This phase III

study of radical radiotherapy with cisplatin +/- tirapazamine demonstrated no difference in survival outcome between the two arms of the study. However, major deficiencies to the quality of the radiotherapy treatment plan were related to adverse clinical outcomes: disease free survival and overall survival. It was a large trial designed with 90% power to detect a 10% improvement in overall survival at 2 years attributable to tirapazamine but poor radiotherapy gave a 20% decrement in overall survival, regardless of randomisation arm.

INTERLACE patients will be treated using 3D conformal or IMRT/rotational arc therapy. 3D conformal radiotherapy will be performed using the local treatment planning system. IMRT and rotational arc therapies are now permitted (Rapid Arc™, VMAT™ and Tomotherapy™). The methods of treatment planning and delivery must be specified in each centre's process document. Centres introducing IMRT or rotational techniques are recommended to read the Jadon et al paper [12].

The application of IMRT in cervical cancer treatment is fraught with difficulties, the principle of which is organ motion, especially the uterus. Movement of both the uterus and the cervix are influenced by both bladder and rectal filling and hence the need for centres to review their bladder and bowel preparation protocols.

Successful implementation of IMRT involves accurate delineation of the structures which we hope the pictorial guideline will aid and selection of an appropriate CTV to PTV margin taking account of organ motion. However, a larger margin size is required to ensure adequate CTV coverage which may negate any theoretical improvement in the dose to OARs.

Currently, internationally, a number of strategies are being used to address these issues, including adaptive radiotherapy and increased PTV margins. Daily CBCT is strongly recommended for INTERLACE and is mandatory for all patients according to NRIG [13]. Radiographers on set must also be adequately trained to assess the daily scans and make appropriate decisions on the patient's treatment each time. Centres participating in INTERLACE should ideally adopt one of the following:

- An adaptive RT protocol based on generating a number of plans on multiple CTs, each with different bladder filling and then adopting the "plan of the day" approach for each fraction. This will have a significant impact on the workload of both the clinician and dosimetrist, as well as on the treatment unit.
- Alternatively centres can generate both an IMRT and a 3D-conformal plan for each patient (one CT, one set of outlines, except for CTV to PTV margins and switch to the conformal plan as and when the CTV falls outside the PTV).
- Centres with other solutions should discuss them with the RTTQA team and the Chief Investigator.

The margins from CTV1 to PTV1 will be increased for IMRT/rotational techniques compared to 3D conformal plans. We also suggest that that IMRT is reserved for those patients with small volume ($\leq 4\text{cm}$) stage IIb tumours and those where the uterus is uninvolving.

Centres treating cervix patients with IMRT/rotational arc therapy not currently using adaptive RT ("plan-of-the-day") are strongly recommended to have a 3D-CRT back-up plan.

(a) PTVs and Margins

The margins for the planning target volumes (PTV) are detailed in [Section 1c](#) and should be applied bearing in mind the individual centre's accuracy achievable with the local immobilisation system.

(b) Nomenclature

<i>Body</i>	<i>Body outline</i>
<i>CTV1</i>	<i>CTV to receive a radical dose</i>
<i>PTV1</i>	<i>Unedited PTV to receive a radical dose</i>
<i>CTV2</i>	<i>Tissue and Nodal CTV to receive a radical dose</i>
<i>PTV2</i>	<i>Unedited PTV to receive a radical dose</i>
<i>CTV3</i>	<i>Tissue and Nodal CTV to receive an elective dose</i>
<i>PTV3</i>	<i>Unedited PTV to receive an elective dose</i>
<i>CTV_Boost</i>	<i>Tissue CTV to receive an elective boost dose i.e. pelvic side wall</i>
<i>PTV_Boost</i>	<i>Unedited PTV to receive an elective boost dose</i>

<i>PTV1+2</i>	<i>For PTV dose reporting on the PAF</i>
<i>PTV1+2+3</i>	<i>For PTV dose reporting on the PAF</i>
<i>Bladder</i>	<i>Bladder outline</i>
<i>Rectum</i>	<i>Rectum outline (including the anal canal, up to the level of the rectosigmoid junction)</i>
<i>Bowel</i>	<i>Bowel outline (including sigmoid, small bowel and colon from 3cm above the superior extent of the PTV)</i>
<i>Femur_R</i>	<i>Right femur outline (including femoral head and proximal femur to the lowest level of the ischial tuberosities)</i>
<i>Femur_L</i>	<i>Left femur outline (including femoral head and proximal femur to the lowest level of the ischial tuberosities)</i>
<i>Kidney_R</i>	<i>Right kidney outline</i>
<i>Kidney_L</i>	<i>Left kidney outline</i>
<i>Cord</i>	<i>Spinal canal outline (from L2/3 intervertebral space to 2cm superior of the PTV)</i>

(c) Dose Prescription

The dose to the radical PTV and any elective PTV is prescribed to the isocentre (ICRU 83) [22] . Treatment is delivered 5 days per week and the overall treatment time (EBRT & Brachytherapy) should not exceed 50 days. An overall treatment time up to 56 days may be acceptable providing there is prior agreement with the TMG. Every effort should be made to avoid breaks in treatment and hyperfractionation (maximum once per week with a 6 hour gap) may be considered to ensure overall treatment time is not exceeded. Centres will be required to submit dose and fractionation schedules prior to site initiation and changes will only be permitted in exceptional circumstances.

A summary of the commonest EBRT dose schedules for the trial are given in Table 2 below.

Dose Per Fraction (Gy)	Number of Fractions	Total Dose (Gy)
2	20	40
1.8	25	45
2	25	50
1.8	28	50.4

Table 1: A summary of the commonest INTERLACE EBRT dose/fractionation schedules

Centres approved to use 50.4Gy EBRT can treat PA nodes+pelvis using 2 phases, where the PA nodes get 45Gy and pelvis 50.4Gy.

(d) 3D-CRT

(i) Field Arrangement

A four-field box technique is recommended (3 fields may be acceptable in some cases) with individual shielding in all fields. Energies \geq 10MV are recommended. The dose is specified at the ICRU reference point and **ICRU-50/62 recommendations on dose homogeneity should be followed [14, 15]**. Dose constraints to be followed can be seen in Table 3, below and recorded on the EBRT PAF. A four field technique should ideally be used when treating nodes beyond the aortic bifurcation (i.e. extended field) although treatment with an anterior/posterior field will be permitted if a 4-field technique is not possible due to the field length or dose to the kidneys.

Centres can make use of field-in-field techniques, extending field lengths and, if no other option, moving the normalisation point in order to improve the plan and achieve the dose constraints and guidelines set by the trial. SUP-INF wedges may also be used if necessary, although increasing ANT and POST beam weightings and opening up the MLCs may have the same desired effect.

Volume	Objective	Constraint
PTV D98%		$\geq 95\%$
PTV D95%	$\geq 97\%$	$\geq 95\%$
D2%		$\leq 107\%$

Table 3: PTV 3D-CRT dose-volume constraints

(ii) Dose Constraints for Organs at Risk

Organ at Risk	Dose-Volume Constraint
Bladder	$D_{2cc} \leq 107\%$. Please record V100% and V103%
Rectum	$D_{2cc} \leq 107\%$. Please record V100% and V103%
Kidneys	$V_{15Gy} \leq 25\%$, Mean Dose $\leq 18Gy$ [16]
Cord	$D_{max} \leq 48Gy$

Table 4: OAR dose-volume constraints

(iii) Calculations

Dose distributions should be calculated and corrected for inhomogeneities.

(iv) Plan Evaluation

A DVH should be produced to show as a minimum: radical PTV, elective PTVs, rectum, bladder, kidneys (if present) and cord (from L2/3 junction). Ideally centres should produce DVH data for each phase of EBRT treatment and also a summed DVH which includes all phases of treatment. The plan evaluation form (EBRT PAF) to be submitted with the treatment plans is available for download on the INTERLACE webpage found on the RTTQA website (www.rttqa.org.uk); it should be filled in electronically and sent.

2-phase treatments:

- (i) Phase 1 to PTV1+2+3, Phase 2 to PTV1+2 only: PTV1+2+3 and PTV3 should be reported for Phase 1 only, relative to the lower dose level; PTV1+2 reported for the composite plan, relative to the higher dose level. All OAR dose constraints must be reported for the composite plan.
- (ii) Phase 1 to Pelvis, Phase 2 to PAN (matched): PTV3 should be reported for Phase 2 only, relative to the lower dose level; PTV1+2+3 and PTV1+2 should be reported for the composite plan, relative to the lower and higher dose levels, respectively. All OAR dose constraints must be reported for the composite plan.

Plans should be inspected on each and every slice to ensure that the PTVs are **adequately covered by the 95% isodose**. Even if the DVH criteria are met, plans with inadequate coverage should be rejected. There should be no avoidable low dose regions inside the PTVs and no avoidable high dose regions in normal tissue in accordance with ICRU reports 50 and 62 [14, 15].

(e) IMRT / Rotational Arc Therapy

(i) Field Arrangement

5 to 7 co-planar fields are recommended for IMRT using 6MV photons. Beams should not be directly opposing. Rotational arc therapy is also accepted. **Patients should be planned according to ICRU-83 recommendations** [10]. Dose-volume constraints to be followed can be seen in Table 5, below and recorded on the EBRT PAF. Simultaneous integrated boosts are allowed.

(ii) Calculations

Dose distributions should be calculated and corrected for inhomogeneities.

(iii) Plan Evaluation

A DVH should be produced to show as a minimum: radical PTV, elective PTVs, rectum, bladder, bowel, femur, kidneys (if present) and cord (from L2/3 junction). The plan evaluation form (EBRT PAF) to be submitted with the treatment plans is available for download on the INTERLACE webpage found on the RTTQA website (www.rttqa.org.uk); it should be filled in electronically and sent.

(iv) Dose Constraints

In addition to dose constraints in Table 4, please record the following (see Table 5 below).

Volume	Dose-Volume Constraint	
PTV1	D99%	95-105%
	D1%	≤ 105%
Bladder	V51Gy	40%
	V55Gy	15%
	V60Gy	5%
Rectum	V51Gy	30%
	V55Gy	15%
	V60Gy	5%
Bowel	V45Gy	≤ 195cc [16]
	V52Gy	≤ 20cc
	V55Gy	≤ 5cc
Femur	V51 Gy	≤ 50%

Table 5: Additional IMRT/rotational dose-volume constraints

(f) Treatment Plan QA

(i) Monitor Unit Checking

Monitor units should be checked by measurement for a minimum of one dose point in an appropriate homogeneous region of the high dose volume. Independent calculation programs may be used in place of measurements, provided the centre has a previous high level of experience in measurement QA and has a system in place for verifying errors found by the independent calculation.

(ii) Patient QA for IMRT / Rotational Arc Therapy

Individual patient QA must be carried out for all patients initially until the centre develops enough experience and understanding of the new technique and is satisfied that all treatments are safe for delivery. In this case patient QA may be reduced to a minimum.

(g) Treatment Verification

Orthogonal isocentre check fields should be incorporated into each patient's plan, using either the treatment fields or by addition of supplementary isocheck fields. Supplementary Mega-Voltage (MV) fields should avoid irradiating outside the treatment volume and the monitor units used to produce an image should be minimised. For dose verification, centres are requested to perform in-vivo dosimetry on their patients.

Minimum requirements for imaging are as follows:

1. Orthogonal kiloVoltage (kV) or MegaVoltage (MV) isocentre images, or Cone Beam CT (CBCT) images, are to be taken on fractions 1 to 3 and assessed off line on day 3.
2. If patient set up changes are made, then 2 consecutive in-tolerance images must be achieved afterwards.
3. Weekly images should be taken thereafter.
4. **For IMRT and rotational techniques daily CBCT imaging is strongly recommended (and mandatory in the NRIG IGRT Report 2012, [13]).**

Please ensure staff training is adequate for those involved in the daily CBCT assessment and decision-making process for IMRT/rotational treatments.

3. BRACHYTHERAPY GUIDELINES

A brachytherapy boost will be delivered to all INTERLACE trial patients where technically possible using the local hospital's brachytherapy protocol. Within the trial the total EQD2 dose (EBRT & brachytherapy & PSW boosts) to Point A / HR-CTV D90 should be 78–86Gy and overall treatment time (EBRT & brachytherapy) should not exceed 50 days. An overall treatment time up to 56 days may be acceptable providing there is prior agreement with the TMG. The treatment will be intra-cavitary but the use of additional interstitial needles will be permitted to boost the pelvic sidewall.

The plan evaluation form (Brachytherapy PAF) to be submitted with the treatment plans is available for download on the INTERLACE webpage found on the RTTQA website (www.rttqa.org.uk); it should be filled in electronically and sent.

(a) Image-guided (3D) Planning

For 3D brachytherapy planning it is recommended that centres follow the GEC-ESTRO guidelines for voluming [17] and dose limits to the organs at risk [18]. Centres can use ovoids or ring applicators, as well as interstitial needles.

Centres doing CT/MR-based planning must use the correct nomenclature for all structures:

<i>Body</i>	<i>Body outline</i>
<i>GTV</i>	<i>Gross tumour volume</i>
<i>IR-CTV</i>	<i>Intermediate-Risk CTV outlined following GEC-ESTRO guidelines [17]</i>
<i>HR-CTV</i>	<i>High-Risk CTV outlined following GEC-ESTRO guidelines [18]</i>
<i>Bladder</i>	<i>Bladder outline</i>
<i>Rectum</i>	<i>Rectum outline (including the anal canal, up to the level of the rectosigmoid junction)</i>
<i>Bowel</i>	<i>Bowel outline proximal to the high dose region and must include the sigmoid</i>

Centres should plan to the OAR dose constraints below (as recommended by the RCR):

1. Bladder D2cc: 90–95Gy EQD2 for EBRT+BT
2. Rectum D2cc: 75Gy EQD2 for EBRT+BT
3. Bowel D2cc: 75Gy EQD2 for EBRT+BT

(b) 2D Planning

Non-UK centres may use 2D brachytherapy planning techniques for intracavitary treatments. Use of interstitial needles will not be permitted with this technique.

4. QUALITY ASSURANCE OVERVIEW

Radiotherapy Quality Assurance Programme

Prior to site activation, centres must have completed the quality assurance programme. This section gives an overview of the process and should be used in conjunction with the RTTQA trials website where all the necessary documents and datasets can be found (www.rttqa.org.uk). The QA programme consists of the following modules:

- A. Pre-trial (facility) questionnaire: containing questions on a range of aspects relevant to the trial including details of the equipment to be used to plan and treat INTERLACE patients and the staff involved in the QA process.
- B. Process document: to be submitted by the centre detailing all aspects of the tasks required for complete external beam and brachytherapy treatments. This should include all steps from immobilisation, scanning, through planning and verification to treatment. Please note that centres will already have such a document for peer review and this can be submitted without alteration.
- C. EBRT Outlining (benchmark) cases: clinicians will participate in the pre trial QA process through the submission of test outlining cases. These will be available for download from the RTTQA

- website. In some circumstances sample cases of previously treated patients may be reviewed instead but they must be protocol-compliant.
- D. **EBRT Planning (benchmark) cases:** QA of 3D conformal, IMRT and rotational planning will be monitored using a similar technique. Pre-outlined 3D test cases will be available for download from the RTTQA website and each participating centre will be expected to submit them for assessment of adherence to trial protocol and plan quality. In some circumstances sample plans from previously treated patients may be submitted for review instead but both outlines and plan must be protocol-compliant.
 - E. **Brachytherapy example case (dummy run):** each centre will be asked to submit an anonymised example case they have already treated to complete their brachytherapy outlining and planning QA.
 - F. **Brachytherapy TPS check:** centres will need to create a line source on their brachytherapy TPS and note the doses at various points from the sources and submit these to the RTQA team to assess their planning system algorithms.
 - G. **Brachytherapy dosimetry audit:** all UK centres taking part in INTERLACE will be required to take part in the INTERLACE phantom audit, the IPEM film phantom audit and the IPEM HDR well chamber audit. These can be completed at any time and is NOT required PRE-recruitment.
 - H. **Plan data collection:** On-going QA will be carried out as required (including prospective review of first few patients) and data will be collected for all patients treated in the INTERLACE trial. This will include:
 - a. 3D EBRT and brachytherapy: patient history, CT and MR datasets, registration objects, structure, plan and dose-cube files.
 - b. 2D brachytherapy: printouts from the TPS and imaging.
 - I. **Verification of electronic data transfer:** to ensure data can be transferred to the QA centre and analysed using their software, as well as to verify data is suitably anonymised. Data transfer will be verified through submission of the outlining and planning exercises. Anonymisation will be checked through plan collection.
 - J. **Patient in-vivo dosimetry:** All centres are strongly recommended to routinely carry out in-vivo dosimetry for dose verification in all patients [19].
 - K. **IMRT/Rotational techniques:** Centres planning on using either of these techniques to plan and treat INTERLACE trial patients must have completed the **NCRI IMRT credentialing programme**. This includes an external dosimetry audit. It is also recommended centres read through the Jadon et al paper [12] before implementing IMRT/rotational techniques in their clinic. *Centres already approved for 3D-CRT will need to replan case 2 with IMRT/VMAT and edit and resubmit the process document to achieve approval for use of IMRT/Rotational techniques within INTERLACE.*

SECTION A: Pre-trial (Facility) Questionnaire

The INTERLACE questionnaire is designed to provide guidance to the QA team on the main aspects of the Radiotherapy and Brachytherapy parts of the trial, as well as contact details of staff involved. The questionnaire needs to be completed in the first instance and can be downloaded from www.rttqa.org.uk.

SECTION B: Process Document

The purpose of the process document is to create a detailed workflow for the tasks required for the patients entered into the trial. The written form of the document allows each centre to describe their processes in the most appropriate way for them.

The process documents should include information on all aspects of the patient pathway and QA processes for the treating centre. Detail should be such that each step is clearly described, **however short bullet point type sentences are encouraged**. Numbering sections and subsections helps us for discussion of specific points in the future. **The document can refer to local protocols and work instructions instead of describing them in full**. These will need to be submitted together with the Process Document for review.

If using IMRT/rotational techniques please also include your bladder and bowel preparation protocols and describe your planning and verification procedures (in particular to address uterine flip). Also include staff training to assess daily CBCTs and the decision-making process.

The process document forms an important part of the quality assurance of a multi-centre trial. The Process Document Template and a completed example are available for download from the RTTQA website.

SECTION C: EBRT Outlining QA Benchmark Cases

All UK centres and those International centres that plan to deliver 3D conformal radiotherapy or IMRT/rotational arc therapy are required to complete the following two contouring exercises. The DICOM CT data sets and diagnostic MR data sets can be downloaded from the INTERLACE trial page on the RTQA website (www.rtrialsqa.org.uk).

(a) Outlining Case 1: FIGO Stage IIIB

History: A 64 year old lady presenting with post-menopausal bleeding who on routine examination was found to have a cervical mass.

Biopsy: Poorly Differentiated squamous cell carcinoma.

Staging Scan: There is a bulky barrel shaped cervical mass lesion which measures 43mm x35mm x 34.6mm. There is full thickness stromal involvement with spread into the parametrium bilaterally, more marked on the right where it reaches the pelvic side wall and obstructs the lower right ureter, with resulting more proximal hydronephrosis. Posteriorly the tumour mass contacts the anterior rectum but no definite local invasion has been demonstrated. There is small volume tumour spread anteriorly which contacts the posterior bladder wall. The fat planes with the posterior bladder wall are however maintained with no bladder invasion.

There is a necrotic tumour mass within the endocervical canal which is expanded. Tumour protrudes through the external os. Superiorly the tumour mass obstructs the endometrial cavity which is mildly dilated to 7.20 mm and contains fluid. The lower third myometrium is heterogeneous suggestive of local tumour infiltration.

There is a 5.7 mm subserosal anterior wall fibroid. The retroperitoneum is normal. There are no enlarged abdominal nodes. There is a 20mm x 17mm left adnexal structure, which looks intraperitoneal, probably ovary rather than an enlarged pelvic node. Right ovary not identified. No enlarged pelvic or groin nodes. No free fluid. No other significant findings.

Instructions

1. Please import patient **INTERLACEOutliningQA1** into your TPS.
2. Please outline the following volumes as per the trial protocol:
 - a) CTV1
 - b) CTV2
 - c) Bladder
 - d) Rectum
 - e) Bowel (for IMRT/rotational techniques only)
 - f) Femur_R (for IMRT/rotational techniques only)
 - g) Femur_L (for IMRT/rotational techniques only)
3. Please create the following volumes as per trial protocol using EBRT margins (NOT IMRT margins):
 - a) PTV1
 - b) PTV2
 - c) PTV1+2
4. Submit to the RTTQA group for assessment following instructions in Section I.

(b) Outlining Case 2: FIGO Stage IIB

History: A 64 year old lady presenting with post-menopausal bleeding who on routine examination was found to have a cervical mass.

Biopsy: Moderately differentiated squamous cell carcinoma.

Staging Scan: There is an extensive abnormality of the proximal half of the cervix. This shows full-thickness stromal tumour infiltration. More distally, there is tumour extending into the periphery of the posterior lip and the right lateral margin of the cervix. There is minor signal abnormality related to the ectocervix.

Proximally, the tumour in the cervix is contiguous with full-thickness myometrial involvement of the uterus. This is involving both the anterior and posterior wall and extends about to 2 cm proximal to the internal os. The fundus of the uterus is normal. There is no uterine obstruction.

There is abnormality of the parametrium at its both lateral margins of the cervix but this does not extend to the pelvic side walls. There is further posterior parametrial involvement but this does not extend to involve the rectum. There is anterior breach of the anterior wall of the uterus but no involvement of the bladder.

The ureters are not distended. Only the lower poles of the kidneys are shown and on the images available, there is no evidence of hydronephrosis. There is no significant pelvic or inguinal lymphadenopathy. Both ovaries are normal but relatively atrophic without any residual follicles. There are no retroperitoneal nodes seen below the level of the renal veins. No further significant findings.

Instructions

1. Please import patient **INTERLACEOutliningQA2** into your TPS.
2. Please outline the following volumes as per the trial protocol:
 - a) CTV1
 - b) CTV2
 - c) Bladder
 - d) Rectum
 - e) Bowel (for IMRT/rotational techniques only)
 - f) Femur_R (for IMRT/rotational techniques only)
 - g) Femur_L (for IMRT/rotational techniques only)
3. Please create the following volumes as per trial protocol using EBRT margins (NOT IMRT margins):
 - a) PTV1
 - b) PTV2
 - c) PTV1+2
4. Submit to the RTTQA group for assessment following instructions in Section I.

SECTION D: EBRT Planning QA Benchmark Cases

All UK centres and those International centres that plan to deliver 3D conformal radiotherapy or IMRT/rotational arc therapy are required to complete the following two contouring exercises. *Centres already approved for 3D-CRT will need to replan case 2 with IMRT/VMAT.*

(a) Planning Case 1 (standard field)

History: A 49 year old lady presenting with post-menopausal bleeding who on routine examination was found to have a cervical mass.

Biopsy: Moderately differentiated squamous cell carcinoma.

Initial Staging Scan: There is a bulky barrel shaped cervical mass with no enlarged pelvic or abdominal nodes. No free fluid or other significant findings seen.

Treatment: The patient was consented for the INTERLACE trial and randomised to the experimental arm. They received neo-adjuvant chemotherapy and are now due to receive radical chemoradiotherapy.

Radiotherapy Planning Exercise: Please import the CT and structure sets of patient **InterlacePlanningQA1** into your own TPS.

Structures: The CT has been delineated by a trial clinician (see table 6). Please **DO NOT** edit any of these structures. The names and number of slices on which the structures appear on have been given so that you can check that the structures have been imported properly.

Doses: A single plan should be submitted using a beam configuration and dose fractionation compatible with the trial protocol (please refer to [Section 2c](#) for acceptable dose/fraction schedules). For dose reporting purposes on the PAF please use PTV1+2.

Structure	Volume (cc)	No. contours	No. slices
Body	27343.3	162	137
CTV1	213.38	46	46
CTV2	390.23	92	50
PTV1	828.49	58	58
PTV2	1072.31	81	56
PTV1+2	1525.37	69	69
Bladder	355.65	40	40
Rectum	115.72	51	51
Bowel*	1192.45	70	52
FemHead_R*	143.20	44	43
FemHead_L*	141.30	42	41

Table 6: Planning case 1 structures. *For IMRT/rotational arc therapy centres only

Please export the dose files as the summation of all beams and NOT all fields separately.
 Centres who have treatment machines that use MLCs instead of the X-jaw, please can you send the field size in this direction? Thank you.

(b) Planning Case 2 (extended field)

History: A 51 year old lady presenting with post-menopausal bleeding who on routine examination was found to have a cervical mass.

Biopsy: Poorly differentiated squamous cell carcinoma.

Initial Staging Scan: There is a cervical mass with enlarged para-aortic lymph nodes seen on the staging scan. No free fluid or other significant findings noted.

Treatment: The patient was consented for the INTERLACE trial and randomised to the experimental arm. They received neo-adjuvant chemotherapy and are now due to receive radical chemoradiotherapy.

Radiotherapy Planning Exercise: Please import the CT and structure sets of patient *InterlacePlanningQA2* into your own TPS.

NB: the patient has been scanned with arms down by the side for cannulation and contrast delivery. They have been outlined as a separate contour. This should be dealt with as per departmental protocol. If TPS (e.g. Eclipse or Oncentra) ignores the presence of the arms if not included in the "Body" contour please delete the "Arms" contour. Otherwise (e.g. Pinnacle) do one of the following:

- i. To treat patient with arms crossed over the chest, override the "Arms" contour with block density zero.
- ii. To treat patient in planned position with arms to the sides, use anterior obliques instead of direct laterals to avoid treating through the arms.

Structures: The CT has been delineated by a trial clinician (see Table 7). Please **DO NOT** edit any structures, other than deleting or overriding the "Arms" contour, if required, as mentioned above. Names, volumes and number of contours and slices on which the structures appear on have been provided to check that the structures have been imported properly.

Doses: A single plan should be submitted using a beam configuration and dose fractionation compatible with the trial protocol (please refer to **Error! Reference source not found.** for acceptable dose/fraction schedules). For dose reporting purposes on the PAF please use PTV1+2, PTV1+2+3 and PTV3.

When 2 phases are prescribed PTV1+2+3 and PTV3 should be reported for Phase 1 only, relative to the lower dose level; PTV1+2 reported for the composite plan, relative to the higher dose level. All OAR dose constraints must be reported for the composite plan.

Export the CT images, structure, plan and dose files in DICOM format and send to the RTTQA team for review together with the completed EBRT Plan Assessment Form (downloadable from RTTQA website) following instructions in Section I.

Please export the dose files as the summation of all beams and NOT all fields separately.
 Centres who have treatment machines that use MLCs instead of the X-jaw, please can you send the field size in this direction? Thank you.

Structure	Volume (cc)	No. contours	No. slices
Body	31226.6	220	202
Arms	1419.21	442	202
CTV1	258.01	45	45
CTV2	519.49	107	71
CTV3	120.16	35	35
PTV1	857.64	57	57
PTV2	1319.02	114	78
PTV3	240.70	35	35
PTV1+2	1966.70	109	99
PTV1+2+3	2178.47	143	133
Bladder	198.97	33	33
Rectum	154.08	47	47
Bowel*	2669.65	133	102
Femur_R*	175.01	44	42
Femur_L*	177.61	45	42
Kidney_R	160.68	42	42
Kidney_L	169.23	43	43
Cord	34.71	43	43

Table 7: Planning case 2 structures. *For IMRT/rotational arc therapy centres only

SECTION E: Brachytherapy Pre-trial Example Case (Dummy run)

This section will detail the INTERLACE QA requirements for sites using 2D, non-adaptive 3D or 3D adaptive brachytherapy.

No formal outlining or planning brachytherapy exercises will be set due to widely varying techniques and equipment used. Centres will be required to electronically submit one planned patient case study (**including all fractions**) for trial QA approval before patient recruitment can begin. The example chosen should represent a typical patient and should be imaged and planned using local protocol. If the centre uses interstitial needles, these need to have been used in the submitted case.

Please ensure all structures are fully outlined and not just interpolated, as the interpolation may be lost in the data transfer. *Also (in particular for Nucletron users), please ensure you run a full 3D dose calculation and not just a quick 2D, otherwise the RTTQA team will not be able to import the dose file.*

(a) Imaging-based (3D) Planning

Information submitted should include:

- Patient history and histology.
- Completed Interlace brachytherapy plan assessment form (downloadable from the RTTQA website) for each fraction.
- TPS dose cube (including RS, RP and RD files).
- All imaging used during brachytherapy planning, including contoured imaging data sets (CT and/or MRI) where applicable. Please note that if CT and MR are registered then the registration object, RE, should also be exported and sent. It may also help to copy any volumes that have been outlined on the MR to the CT.

Please follow instructions for data transfer from Section I.

(b) 2D Planning

Centres using 2D brachytherapy planning should send electronic images of the anterior and lateral films used in the planning process. They should also complete and send the Brachytherapy PAF. If there is

any TPS visualisation please send a screen shot of it.
Please follow instructions for data transfer from Section I.

SECTION F: Brachytherapy TPS Check

As a basic check of planning system dose calculation, both UK and international centres planning in 3D will be required to create a single 5.5cm 'line source' plan (see Figure 5) in their treatment planning system, TPS, and to determine the resulting dose distribution. This will be checked against gold standard Monte Carlo data.

The plan should comprise of 11 dwells with 5mm spacing running cranio-caudally and will be displayed in the coronal plane. 10 Gy will be prescribed and normalised to point 2 (2 cm from the centre of the central dwell), with all dwells being delivered for equal times. The 100% isodose should run through this point.

Dose in water to the 7 specified points in Figure 6 should be reported for a nominal 10 Ci source (or the local decayed source strength if the TPS displays this instead, but please make a note of this).

A screenshot displaying the 20, 30, 50, 80 and 100% isodoses and the 7 dose point positions in the plane of the diagram above should be electronically submitted to the trials QA team for approval, along with the point dose results and source strength used in calculation.

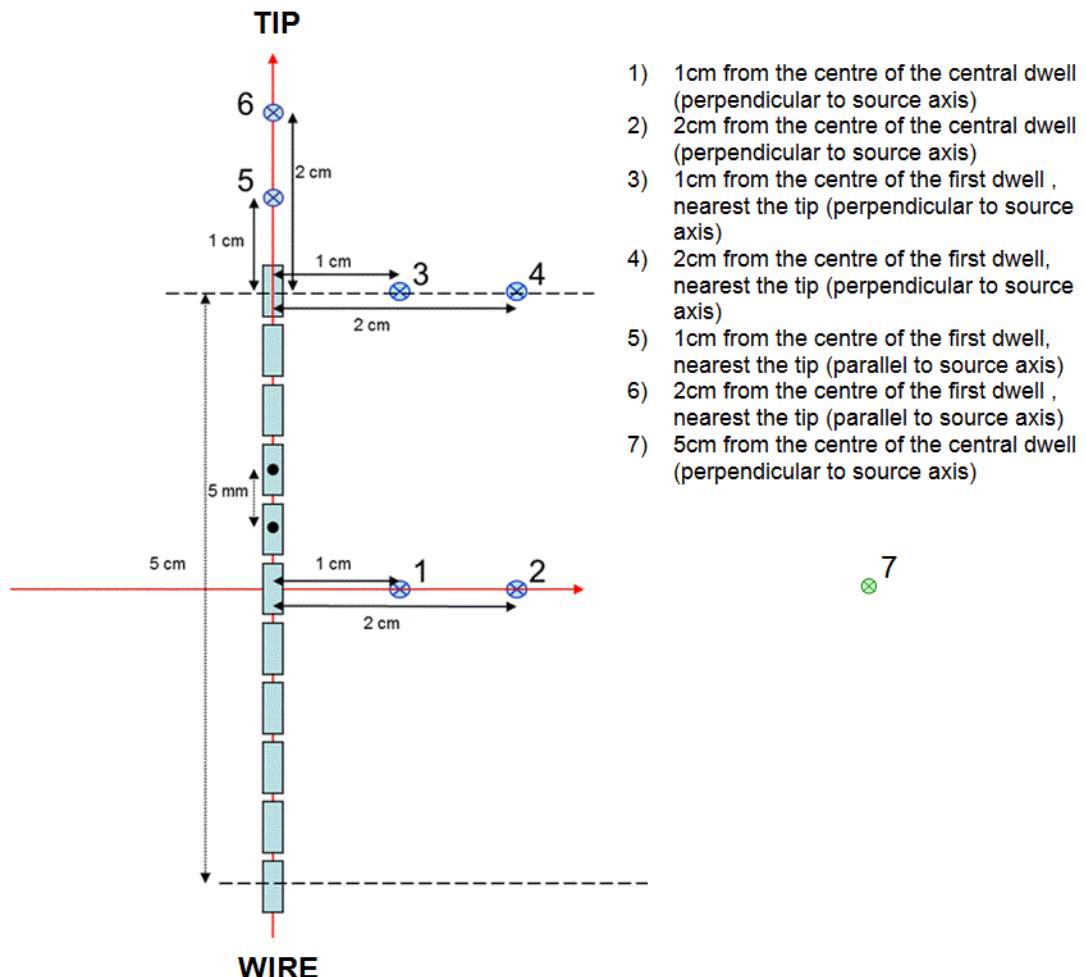


Figure 5: Line source for TPS check and points for dose reporting

SECTION G: Brachytherapy Dosimetry Audit

(a) UK Centres

(i) Source Calibration Measurement

UK centres will be required to take part in the national IPEM HDR audit. Centres will be visited by a regional audit group lead who will measure the source strength of the local source using a calibrated well-type ionisation chamber. Participation will be required within a year from the start of patient recruitment into the trial. Results from the audit will be made available to the Interlace QA team.

(ii) In-Phantom Dose Measurement

The RTTQA Team (INTERLACE Trial) and an IPEM RT-SIG Working Party, in collaboration with the NPL, have undertaken between October 2013 and June 2016 a coordinated dosimetry audit of HDR/PDR brachytherapy in the UK. Two phantoms were used, which were constructed at Clatterbridge Cancer Centre and tested at 3 pilot sites.

The audit measurements aimed to check:

- TPS set-up; basic data and operation (source strength, TG-43 data set [20])
- HDR unit performance; mechanical/physical delivery accuracy
- Measurement of dose in pseudo-clinical situations; within a phantom

The RTTQA phantom used alanine and a Farmer chamber to make an accurate measurement of the point dose at 2 cm from a 5 cm line source. The alanine was processed at the NPL [21] The RT-SIG phantom was CT-scanned, planned, and used film to sample the dose distribution around a cervix applicator compared to the TPS dose distribution, with film readout at Portsmouth [22].

INTERLACE Centres were asked to participate in this national HDR/PDR dosimetry audit. The alanine phantom audit was mandatory for QA compliance, however it was strongly recommend that the film phantom audit was also undertaken. Results from the film phantom audit will be made available to the Interlace QA team.

Audit visits with both phantoms have now been completed at all UK HDR/PDR brachytherapy centres and the results published [21, 22].

(b) International Centres

International centres are required to provide a positive independent evaluation of brachytherapy dosimetry (e.g. EQUAL dosimetry test, IAEA or equivalent) within the first year of participation in the trial.

SECTION H: Plan Data Collection

(a) Real-Time (Prospective) Case Reviews

Prospective, EBRT real-time case reviews are no longer mandatory for the trial, centres must, however, submit each case once the patient has gone for treatment so the outlines and plan can be reviewed in good time to enable feedback to be provided BEFORE the next recruited patient requires planning. This will be the case for the first 2 patients recruited as long as no major protocol deviations are noted. In the event that outlining or planning for the patient is not protocol-compliant, the next patient will undergo prospective, real-time review following the guidelines below.

The RTTQA team aims to complete real time reviews of the patient's contours and plans within 48 hours. Please ensure that the EBRT outlining and planning data are submitted as soon as it is ready to help facilitate a rapid turnaround.

Please refer to the guide below for further details:

- Patient is randomised
- Trials unit to contact QA group with patient and centre details.

- Contact investigator site physicist/radiographer to contact QA physicist to discuss patient time line to treatment
- Agree dates with investigator site for export of outlines and plan
- Investigator site to export ANONYMISED outlines and send with patient history
- QA group to review outlines and feedback to investigator site
- Investigator site to plan and export case including PAF
- QA group to review plan and feedback to the investigator site
- Summary report of review to be sent to investigator site

If participating centres wish to undergo a real-time review of their outlines and/or planning please follow the guidelines above.

The QA team accepts that brachytherapy is not suitable for real time review. It is therefore expected that trial centres will submit their brachytherapy treatment data for QA team review within 48 hours of the patient receiving the brachytherapy treatment, and for each subsequent treatment thereafter.

(b) On-trial Data Collection

In addition to the first two cases, data for **all patients** treated in the trial should be submitted to the RTTQA team within 7 days of completing EBRT planning and brachytherapy treatment.

Data to be sent following instructions in Section I below.

SECTION I: Electronic Data Anonymisation and Transfer

(a) Data anonymisation

All data sent to the RTTQA centre must be anonymised prior to being sent; data that has not been anonymised will not be accepted. Any anonymising software may be used; DICOMpiler is available on the internet at <http://itc.wustl.edu/DICOMPILER/index.htm>. It is suggested that the trial number is used to identify the patient. It may be of use to keep your own list of names and IDs as well.

NB: Outlining and planning exercises are already anonymised.

(b) Data transfer

All plans should be exported in DICOM format to be sent to the RTTQA centre (see below). The export should include the CT data set, structure, dose and plan files from every plan used to treat the patient. **Please export the dose files as the summation of all beams and NOT all fields separately.** Centres who have treatment machines that use MLCs instead of the X-jaw, please can you send the field size in this direction? Thank you.

Patient history and PAFs also need submitting for every patient. For brachytherapy MR datasets may also be required.

To allow a quick turnaround of the case studies and to facilitate a secure method of data transfer, all data should be transferred to the RTTQA team via the **NHS secure server**. **International centres** may use the RTTQA drop box for data submission.

Questionnaires, Process Documents, patient histories, Plan Assessment Forms and TPS checks can be sent normally as an attachment in an email.

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6. APPENDIX

Example Bladder & Bowel Preparation Protocols

(a) Bladder Preparation

Bladder preparation aims to achieve a bladder which is comfortably full and reproducible, ideally with a volume of >150ml AND <300ml. To facilitate this, these steps should be followed:

- Ensure adequate hydration at all times, and emphasize this is very important for at least the 48 hours prior to planning scan and treatment commencing as well as throughout the radiotherapy course.
- The patient must drink 450ml water 30 minutes before planning CT and treatment
- If available, a bladder scan can be used before the planning CT to ensure bladder volume is adequate.
- If bladder volume < 150ml or > 300ml, the patient should be recalled for a rescan and if bladder is too small, ensure they are well pre-hydrated and drink 600ml 40 mins before CT, or 750ml 50 mins before.

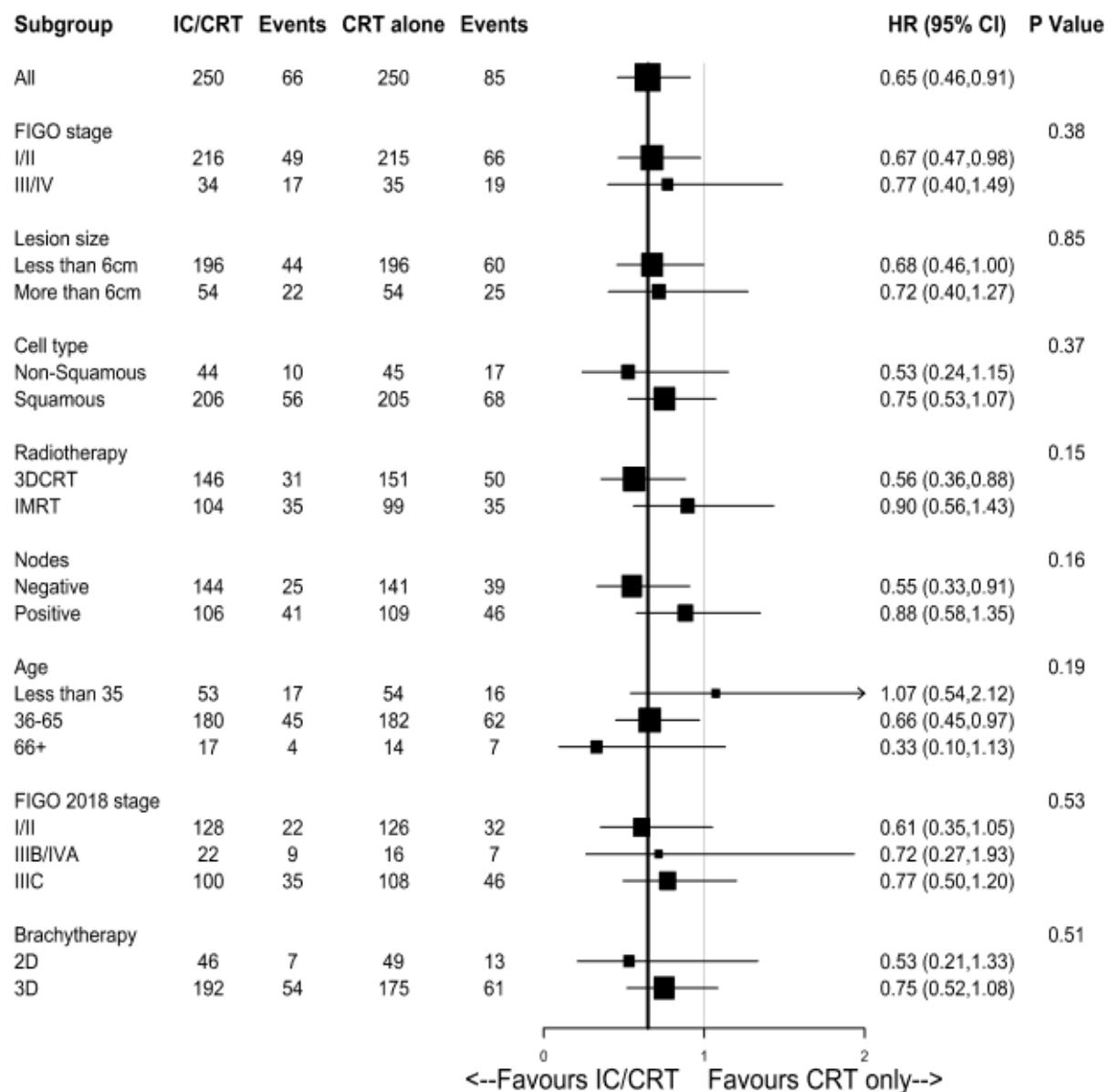
(b) Bowel Preparation

Bowel preparation aims to achieve a reproducible empty bowel and rectum, ideally with a rectal AP diameter of \leq 4cm. To facilitate this laxatives should ideally be used. The following is an example protocol which could be followed:

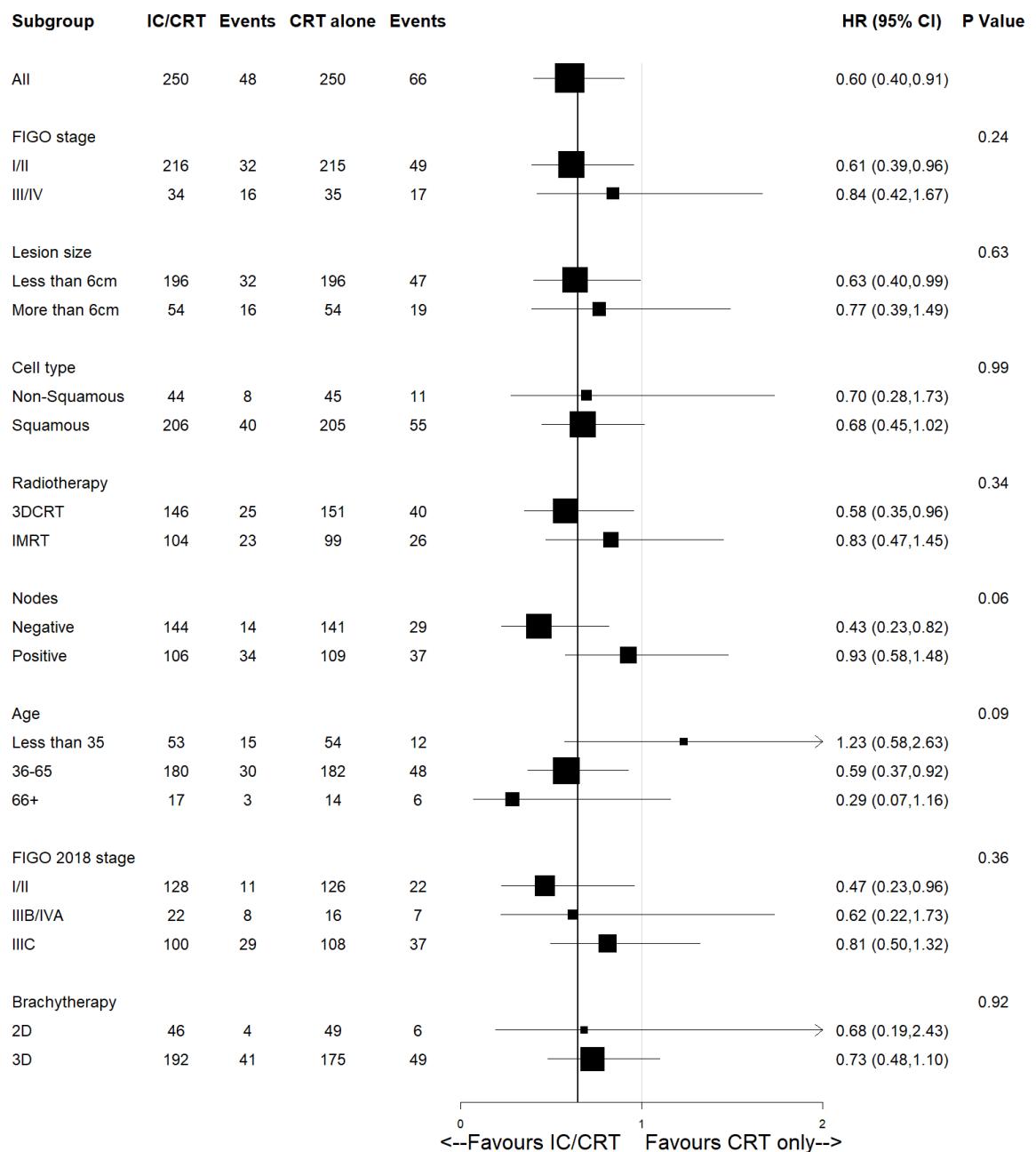
- All patients to receive dietary information sheet.
- All patients to receive sodium docusate prescription.
- Patients should complete stool chart (using Bristol Stool Chart type 1 to 7) documenting frequency and consistency of bowel motions from immediately after the first oncology clinic appointment.
- Dose sodium docusate according to stool type using Bristol stool chart:
 - None if type 6-7
 - Once daily if type 4 or 5
 - Twice daily if type 1-3.
 - Aim for type 4 or 5 stool consistency
- Administer sodium docusate daily for a minimum of 5 days before planning CT and treatments; therefore patients' possibly starting radiotherapy as part of primary treatment must start sodium docusate immediately after oncology clinic to ensure no delays in planning CT.
- Patients undergoing para-aortic nodal sampling should start taking sodium docusate the day after the procedure and have a planning CT at least 5 days afterwards.
- If rectal AP diameter >4cm at planning CT contact clinician regarding decision whether to rescan, increase/change laxatives or consider microlette enema.

Laxative use must be clearly documented to ensure accurate treatment toxicity documentation and review of laxatives must occur weekly during treatment.

Supplementary tables and figures

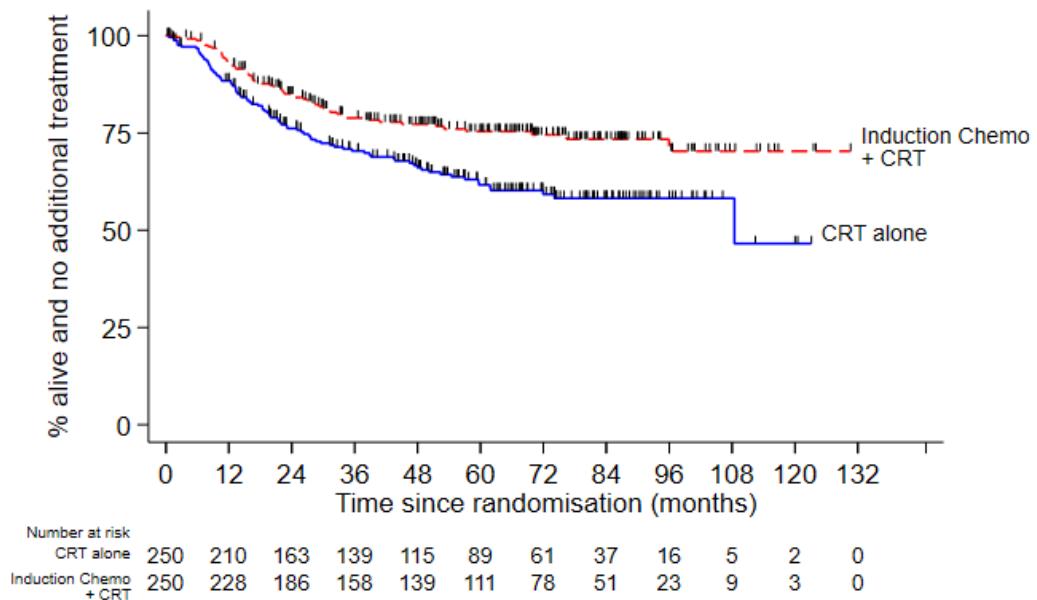


Supplementary Figure 1. Subgroup analyses for progression-free survival. All 95% confidence intervals include the overall HR of 0.65 and all interaction p-values are >0.05; hence, neither test provides evidence that the effect of IC/CRT materially differs between subgroups.¹¹

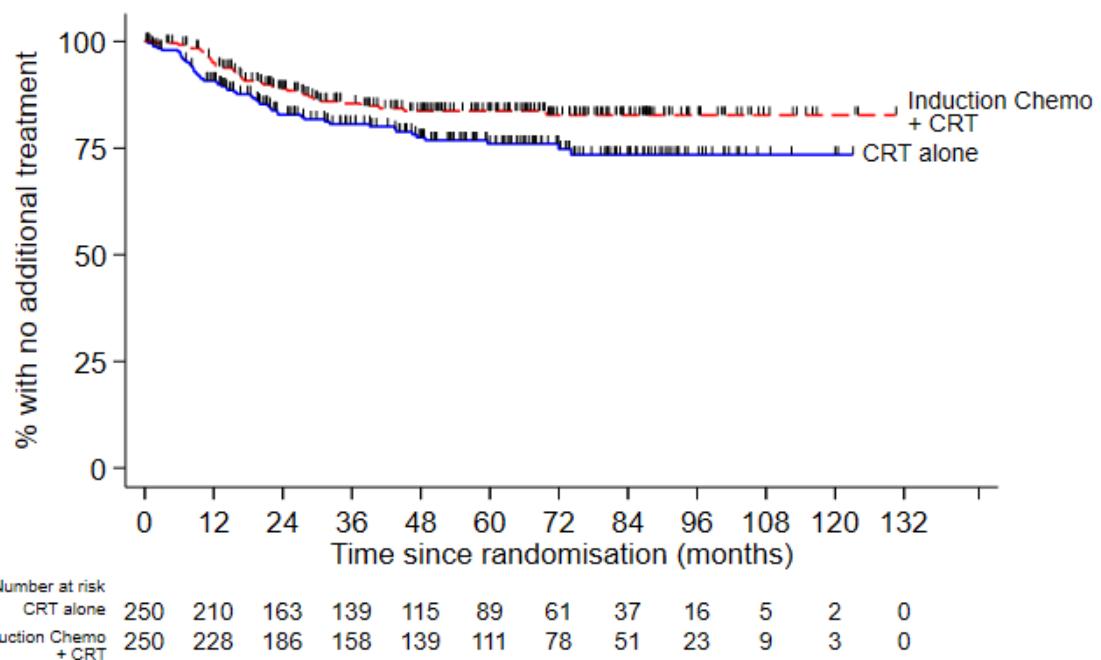


Supplementary Figure 2. Subgroup analyses for overall survival. All 95% confidence intervals include the overall HR of 0.60 and all interaction p-values are >0.05 ; hence, neither test provides evidence that the effect of IC/CRT materially differs between subgroups¹¹.

A



B



Supplementary Figure 3. Time to next anti-cancer therapy. In 4A, an event is next treatment or death, and all other patients are censored at date last seen (146 events, adjusted HR: 0.54 (0.38-0.77), p=0.0010). In 4B, an event is next treatment. Deaths are counted as a competing risk and all other patients are censored at date last seen (89 events, adjusted HR: 0.56 (0.34-0.91), p=0.019). HRs adjusted for the randomisation stratification factors.

Supplementary Table 1. Cause of death

	Induction chemo + CRT (N=250)	CRT alone (N=250)
	Number of patients (%)	
Disease / progression	42 (16.8)	52 (20.8)
Non-treatment related	6 (2.4)	12 (4.8)
Unknown	0	2 (0.8)

Supplementary Table 2. Patterns of relapse

	Induction chemo + CRT (N=250)	CRT alone (N=250)
Number of patients (%)		
Local / pelvic	27 (10.8)	22 (8.8)
Local / pelvic & distant	15 (6.0)	20 (8.0)
Distant*	17 (6.8)	30 (12.0)
Isolated para-aortic nodal recurrence – (% of distant relapses)	1 (5.9)	3 (10.0)

*2-sample proportion test, p=0.046

Supplementary Table 3A. Grade 3-4 adverse events seen during induction chemotherapy only.
The number of patients with each event type is shown

Grade 3-4 AE	Induction chemo + CRT (N=250)
	Number of patients (%)
Abdominal/Pelvic Pain	4
Abnormal lab	6 (2.4)
Allergic reaction	6 (2.4)
Alopecia	2
Anaemia	4
Atrial fibrillation	1
Constipation	1
Diarrhoea	1
Fatigue/muscle weakness/joint pain	3
Febrile neutropenia	1
Fever	1
Hand-foot syndrome	1
Headache	1
Hypertension	2
Infection	6 (2.4)
Insomnia	2
Kidney injury	1
Leucocytosis	1
Lymphatic disorder	1
Nausea	1
Neutropenia	18 (7.2)
Nose bleeds	1
Oral mucositis	2
Other pain	4
Peripheral Neuropathy	1
Rash/RT related	1
Sepsis	1
Thromboembolic event	4
Urinary tract infection / obstruction	7 (2.8)
Vaginal problems	2
Vomiting	2
Any event	54 (21.6)

Supplementary Table 3B. Grade 3-4 adverse events that occurred anytime during induction chemotherapy or chemoradiation. The number of patients with each event type is shown, and percentages only shown when there are at least 5 patients with the event

Grade 3-4 AEs at any time	Induction chemo + CRT (N=250)	CRT only (N=250)
	Number of patients(%)	
Abdominal/Pelvic Pain	13 (5.2)	18 (7.2)
Abnormal lab	14 (5.6)	8 (3.2)
Acidosis	1	0
Acute liver injury	0	1
Allergic reaction	6 (2.4)	1 (0.4)
Anaemia	13 (5.2)	9 (3.6)
Anxiety/depression	1	4
Appendicitis perforated	0	1
Atrial fibrillation	1	0
Bowel Obstruction	3	2
Breathing problems	2	0
Colitis	1	1
Constipation	3	2
Cystitis noninfective	0	2
Dehydration	1	1
Diarrhoea	20 (8.0)	31 (12.4)
Dyspepsia	0	1
Dyspnoea	1	0
Early menopause	2 (0.8)	5 (2.0)
Fatigue/muscle weakness/joint pain	28 (11.2)	14 (5.6)
Febrile neutropenia	7 (2.8)	5 (2.0)
Fever	2	2
Flatulence	1	0
Haematuria	2	0
Haemorrhoids	0	1
Hand-foot syndrome	1	0
Headache	1	1
Hernia	1	0
Hot flashes	1	1
Hyperglycaemia	1	0
Hypertension	4	3
Hypotension	1	0
Incontinence	3	1
Infection	14 (5.6)	13 (5.2)
Insomnia	3	3
Intercourse difficult	1	0
Kidney injury	5 (2.0)	2 (0.8)
Leucopenia	25 (10.0)	14 (5.6)

Leucocytosis	1	0
Lymphatic disorder	4	3
Lymphocytopenia	3	2
Lymphocytosis	2	0
Memory impairment	0	1
Menopause	1	1
Musculoskeletal issues	0	2
Myocardial infarction	1	0
Nausea	8 (3.2)	7 (2.8)
Neutropenia	48 (19.2)	13 (5.2)
Night sweats	0	1
Nose bleeds	1	0
Oedema (limbs)	0	1
Oral mucositis	3	0
Other GI	1	2
Other pain	9 (3.6)	7 (2.8)
Peripheral Neuropathy	4	2
Pleural effusion	0	1
Proctitis	1	1
Pruritus	0	1
Rash/RT related	2	2
Rectal fistula	1	0
Seizure	1	1
Sepsis	3 (1.2)	5 (2.0)
Skin infection	1	0
Syncope	1	2
Thrombocytopenia	13 (5.2)	5 (2.0)
Thromboembolic event	8 (3.2)	5 (2.0)
Typhlitis	0	1
Upper GI haemorrhage	0	1
Urinary tract infection / obstruction	17 (6.8)	6 (2.4)
Urinary tract problems (other)	4	3
Urostomy stenosis	0	1
Uterine perforation	0	1
Vaginal problems	9 (3.6)	14 (5.6)
Vomiting	6 (2.4)	7 (2.8)
Weight loss	6 (2.4)	4 (1.6)

145 people (58%) reported grade 1-2 alopecia in the induction chemo + CRT group and 24 people (10%) in the CRT alone group.

Supplementary Table 3C. Related grade 3-4 adverse events that occurred anytime during induction chemotherapy or chemoradiation. The number of patients with each event type is shown (percentages only shown if there are at least 5 patients with the event)

Related grade 3-4 AEs at any time	Induction chemo + CRT (N=250)	CRT only (N=250)
	Number of patients (%)	
Abdominal/Pelvic Pain	8 (3.2)	10 (4.0)
Abnormal lab	12 (4.8)	3 (1.2)
Acute liver injury	0	1
Allergic reaction	6 (2.4)	1 (0.4)
Anaemia	9 (3.6)	4 (1.6)
Anxiety/depression	0	2
Bowel Obstruction	2	1
Breathing problems	1	0
Colitis	1	1
Constipation	2	1
Cystitis noninfective	0	2
Dehydration	1	1
Diarrhoea	18 (7.2)	31 (12.4)
Dyspnoea	1	0
Early menopause	2 (0.8)	5 (2)
Fatigue/muscle weakness/joint pain	22 (8.8)	11 (4.4)
Febrile neutropenia	6 (2.4)	4 (1.6)
Fever	2	2
Flatulence	1	0
Haematuria	2	0
Haemorrhoids	0	1
Hand-foot syndrome	1	0
Hernia	1	0
Hot flashes	1	0
Hypertension	2	0
Hypotension	1	0
Incontinence	3	1
Infection	11 (4.4)	7 (2.8)
Insomnia	0	2
Intercourse difficult	1	0
Kidney injury	4	2
Leucopenia	25 (10.0)	12 (4.8)
Lymphatic disorder	0	2
Lymphocytopenia	3	2
Lymphocytosis	2	0
Memory impairment	0	1
Musculoskeletal issues	0	1
Nausea	7 (2.8)	6 (2.4)
Neutropenia	47 (18.8)	12 (4.8)
Night sweats	0	1

Oedema (limbs)	0	1
Oral mucositis	2	0
Other GI	1	1
Other pain	3	1
Peripheral Neuropathy	2	1
Pleural effusion	0	1
Proctitis	1	0
Pruritus	0	1
Rash/RT related	1	2
Rectal fistula	1	0
Seizure	0	1
Sepsis	2	4
Thrombocytopenia	13 (5.2)	3 (1.2)
Thromboembolic event	3	3
Typhlitis	0	1
Urinary tract infection / obstruction	7 (2.8)	1 (0.4)
Urinary tract problems (other)	3	2
Urostomy stenosis	0	1
Uterine perforation	0	1
Vaginal problems	8 (3.2)	8 (3.2)
Vomiting	5 (2)	7 (2.8)
Weight loss	3	2

Supplementary Table 3D. Grade 1-2 adverse events that occurred any time during induction chemotherapy or chemoradiation in at least 5 patients in either arm. The number of patients with each event type is shown. (% given if 5 or more events):

	Induction Chemo + CRT (n=250)	CRT alone (n=250)
	Number of patients (%)	
Abdominal/Pelvic Pain	182 (73)	176 (70)
Abnormal Lab	60 (24)	35 (14)
Alkaline Phosphatase Increased	7 (2.8)	6 (2.4)
Allergic Reaction	28 (11)	11 (4.4)
Alopecia	145 (58)	24 (9.6)
Anaemia	135 (54)	100 (40)
Anal Pain / Bleeding	9 (3.6)	3
Anxiety/Depression	39 (16)	36 (14)
Arthritis	12 (4.8)	5 (2.0)
Bloating	18 (7.2)	10 (4)
Blurred Vision	7 (2.8)	3
Bowel problems	13 (5.2)	5 (2.0)
Chest Pain / Infection	7 (2.8)	4
Chronic Kidney Disease	5 (2.0)	0
Constipation	149 (60)	110 (44)
Cough	17 (6.8)	13 (5.2)
Creatinine Increased	9 (3.6)	6 (2.4)
Cystitis	10 (4.0)	18 (7.2)
Diarrhoea	206 (82)	187 (75)
Dizziness	20 (8.0)	13 (5.2)
Dry Mouth	5 (2.0)	0
Dry Skin	14 (5.6)	2
Dysgeusia	42 (17)	18 (7.2)
Dyspepsia	35 (14)	17 (6.8)
Dyspnoea	32 (13)	13 (5.2)
Oedema	6 (2.4)	0
Eye Disorders	10 (4.0)	2
Fatigue/Muscle Weakness/Joint Pain	230 (92)	198 (79)
Fever	24 (9.6)	13 (5.2)
Flatulence	7 (2.8)	2
Flu Like Symptoms	5 (2.0)	2
Flushing	5 (2.0)	1
Gastroesophageal Reflux Disease	15 (6.0)	10 (4.0)
Haematuria	37 (15)	43 (17)
Headache	36 (14)	18 (7.2)
Hemorrhoids	6 (2.4)	5 (2.0)
Hot Flashes	46 (18)	40 (16)
Hyperglycemia	5 (2)	1
Hypertension	12 (4.8)	8 (3.2)
Hypoalbuminemia	13 (5.2)	10 (4.0)
Incontinence	65 (26)	65 (26)

Infection	75 (30)	57 (23)
Infusion Related Reaction	7 (2.8)	0
Insomnia	28 (11)	32 (13)
Intercourse Difficult	5 (2.0)	5 (2.0)
Kidney Injury/Pain	2	5 (2.0)
Leucopenia	100 (40)	59 (24)
Low Mood	5 (2)	1
Lymphatic Disorder	11 (4.4)	18 (7.2)
Lymphocytopenia	10 (4.0)	4
Metabolism And Nutrition Disorders	5 (2.0)	2
Mucosal Infection	5 (2.0)	2
Musculoskeletal Issues	26 (10)	20 (8.0)
Nausea	196 (78)	173 (69)
Nervous System Disorders	8 (3.2)	6 (2.4)
Neutropenia	97 (39)	30 (12)
Nose Bleeds	28 (11)	1
Oedema (Limbs)	13 (5.2)	14 (5.6)
Oral Mucositis	38 (15)	4
Oral Pain	9 (3.6)	3
Other GI	15 (6.0)	23 (9.2)
Other Pain	111 (44)	83 (33)
Palpitations	5 (2.0)	3
Paraesthesia	7 (2.8)	6 (2.4)
Peripheral Neuropathy	134 (54)	59 (24)
Proctitis	11 (4.4)	6 (2.4)
Pruritus	9 (3.6)	4
PV Bleeding	8 (3.2)	7 (2.8)
Rash/RT Related	73 (29)	27 (11)
Rectal Bleeding	71 (28)	65 (26)
Rectal Haemorrhage	8 (3.2)	5 (2.0)
Reproductive System and Breast Disorders	13 (5.2)	11 (4.4)
Skin And Subcutaneous Tissue Disorders	15 (6.0)	12 (4.8)
Skin Infection	2	5 (2)
Skin Soreness	45 (18)	24 (9.6)
Sore Throat	10 (4.0)	5 (2.0)
Tachycardia	6 (2.4)	1
Telangiectasia	8 (3.2)	12 (4.8)
Thrombocytopenia	79 (32)	40 (16)
Thromboembolic Event	7 (2.8)	5 (2.0)
Tinnitus	16 (6.4)	13 (5.2)
Tremor	6 (2.4)	2
Urgency (bowel or feacal)	5 (2.0)	1
Urinary Frequency	3	5 (2.0)
Urinary Incontinence	8 (3.2)	8 (3.2)
Urinary Tract Infection	89 (36)	85 (34)
Urinary Tract Problems	110 (44)	108 (43)
Vaginal Discharge	40 (16)	45 (18)

Vaginal Dryness / Haemorrhage / Vulvovaginal Abscess	95 (38)	104 (42)
Vaginal Fistula / Stricture	20 (8.0)	18 (7.2)
Vaginal Infection	13 (5.2)	4
Vaginal Inflammation	3	6 (2.4)
Vaginal Pain	11 (4.4)	6 (2.4)
Vaginal Stenosis	5 (2.0)	0
Vomiting	102 (41)	84 (34)
Weight Loss	89 (36)	81 (32)

Supplementary Table 4. EORTC-QLQC30 health-related quality of life for selected key items of interest

Domain	Mean score at baseline (SD)		Mean change in score from baseline to week 4 IC (SD)	Mean score at week 3 CRT (SD)		From a repeated measures analysis during trial treatment to 1 year of follow-up and allowing for baseline	P-value
	IC/CRT	CRT alone		IC/CRT arm only	IC/CRT	CRT alone	
Global health status	71 (21)	71 (22)	-5 (19)	55 (20)	62 (21)	-3.0 (-6.7 to 0.7)	0.035
Physical functioning	89 (17)	90 (17)	-4 (17)	76 (21)	82 (21)	-2.3 (-5.7 to 1.2)	0.087
Emotional functioning	73 (25)	69 (28)	10 (20)	77 (23)	29 (25)	1.5 (-2.7 to 5.6)	0.37
Cervical cancer specific:							
Symptom experience scale*	18 (15)	20 (16)	-5 (13)	14 (13)	17 (14)	-3.5 (-5.8 to -1.2)	<0.001
Peripheral Neuropathy	9 (21)	9 (22)	1 (26)	18 (26)	9 (21)	4.9 (1.0 to 8.9)	0.001
Lymphoedema	3 (13)	3 (13)	0.4 (16)	5 (15)	3 (11)	0.9 (-2.0 to 3.9)	0.41

SD: standard deviation

All scores are on a scale 0 to 100.

Global health status and physical functioning: 0 indicates poor health, 100 indicates good health

For the other items, 0 indicates good QoL (no/minimal symptoms), 100 indicates poor QoL/worse symptoms.

* Model includes an interaction between treatment group and timing (p-value for interaction is 0.001)

P-values are unadjusted for multiple comparisons and instead 99% CIs are provided

Supplementary Table 5. On-trial radiotherapy quality assurance: major protocol variations

	Induction chemo + CRT (N=250)	CRT alone (N=250)
	Number of patients (%)	
Received EBRT in trial	242 (96.8)	231 (92.4)
Total EQD2 (<70.2 Gy*)	33 (13.6)	29 (12.6)
OTT > 56 days	9 (3.7)	7 (3.0)
Total on-trial reviews	65 (26.9)	68 (29.4)
Prospective reviews completed**	46 (19.0)	49 (21.2)
Retrospective reviews completed***	19 (8.2)	19 (7.8)
EBRT contouring variations	7	8
EBRT planning variations	1	1
No major variations	11	10

*10% below min EQD2 for the trial

**prospective reviews were completed in real time by the CI, a designated research fellow and the RTQA physicist with any variation corrected prior to treatment start and therefore treatment was delivered as per protocol

***retrospective reviews were completed after treatment delivery by the CI and RTQA physicist in a randomly selected group of patients with at least 1 case per centre being reviewed, and therefore do represent true protocol variation

Major protocol variations included: total EQD2 70.2 Gy-77.9 Gy; OTT 51-56 days; EBRT contouring variation with failure to adequately contour the primary tumour, the parametria, a nodal region or an organ at risk or boost volume(s) not identified; EBRT planning variation with under-coverage of the primary PTV or whole nodal region rather than individual positive node boost. Minor protocol variations, not covered within this table, include all variations which are outside mandated parameters detailed within the RTQA document not fulfilling major criteria, including low EQD2, long OTT, EBRT contouring variation, and EBRT planning variation. The IDMC had oversight for safety of the trial and therefore reviewed toxicities, radiotherapy and chemotherapy compliance and efficacy but did not review all treatment protocol variations. Members of the TMG had oversight of the minor and major RTQA variations.

Supplementary Table 6. Reasons for overall treatment time > 56 days

	Induction chemo + CRT (N=250)	CRT alone (N=250)
Received EBRT	242 (96.8)	231 (92.4)
OTT > 56 days	9 (3.7)	7 (3.0)
Reasons for more than 56 days		
RT / BT scheduling	5	4
Adverse events	3	2
National holiday	1	0
Poor attendance	0	1