INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
www.redjournal.org

CLINICAL INVESTIGATION

The IMRiS Trial: A Phase 2 Study of Intensity Modulated Radiation Therapy in Extremity Soft Tissue Sarcoma

Beatrice Seddon, MD, PhD,[*] Franel Le Grange, MD,[*] Rita Simões, MSc,[†] Chris Stacey, BSc, MSc,[‡] Shumona Shelly, BSc, MSc,[§] Sharon Forsyth, BSc,[§] Laura White, BSc,[§] Charles Candish, MD,[‖] Peter Dickinson, MD,[¶] Aisha Miah, MD,[#,**] Syed Ali Moinuddin, MSc,[‡] James Wylie, MD,[††] and Andre Lopes, BSc, MSc[§]

[*]*London Sarcoma Service, Department of Oncology, University College Hospital, London, United Kingdom;* [†]*National Radiotherapy Trials Quality Assurance Group, Mount Vernon Hospital, London, United Kingdom;* [‡]*Radiotherapy Physics Department, University College Hospital, London, United Kingdom;* [§]*Cancer Research UK & University College London Cancer Trials Centre, London, United Kingdom;* [‖]*Gloucestershire Oncology Centre, Cheltenham General Hospital, Cheltenham, United Kingdom;* [¶]*Leeds Cancer Centre, Leeds Teaching Hospitals, Leeds, United Kingdom;* [#]*Sarcoma Unit, Royal Marsden Hospital, London, United Kingdom;* [**]*The Institute of Cancer Research, London, United Kingdom; and* [††]*Greater Manchester and Oswestry Sarcoma Service, The Christie Hospital, Manchester, United Kingdom*

Received Dec 20, 2023; Accepted for publication May 24, 2024

Purpose: Primary soft tissue sarcoma (STS) is rare, with many tumors occurring in extremities. Local management is limb-sparing surgery and preoperative/postoperative radiation therapy (RT) for patients at high risk of local recurrence. We prospectively investigated late normal tissue toxicity and limb function observed after intensity modulated RT (IMRT) in extremity STS.
Methods and Materials: Patients with extremity STS, age ≥16 years. Two treatment cohorts: IMRT 50 Gy in 25 × 2 Gy fractions (preoperative) or 60/66 Gy in 30/33 × 2 Gy fractions (postoperative). The primary endpoint was the rate of grade ≥2 late soft tissue fibrosis (subcutaneous tissue) at 24 months after IMRT (Radiation Therapy Oncology Group late radiation morbidity scoring).
Results: One hundred sixty-eight patients were registered between March 2016 and July 2017. Of those, 159 (95%) received IMRT (106, 67% preoperative RT; and 53, 33% postoperative RT) with a median follow-up of 35.2 months (IQR, 32.9-36.6); 62% men, median age 58 years. Of 111 patients assessable for the primary endpoint at 24 months, 12 (10.8%; 95% CI, 5.7%-

Corresponding author: Beatrice Seddon, MD, PhD; E-mail: ctc.imris@ucl.ac.uk

Author Responsible for Statistical Analysis: Andre Lopes, Cancer Research UK & Univeristy College London Cancer Trials Centre, London W1T 4TJ, United Kingdom; Email: andre.lopes@ucl.ac.uk

Disclosures: B.S. reports consulting fees from Proton International for job as Medical Director for Proton International London, working 3 days per week, and support from Proton International to attend Partical Therapy Co-operative Group annual conference 2022 and 2023 (flights, hotel, and registration fee). R.S. reports clinical doctoral research fellowship (number CDR-2018-04-ST2-004), funded by Health Education England/National Institute for Health and Care Research, and is committee member (unpaid) of the European Society for Radiotherapy and Oncology Radiation Therapists Alliance and the European Particle Therapy Work Package 3. A.M. was supported by the National Institute for Health and Care Research Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London; reports financial reimbursement for European Society of Medical Oncology (ESMO) lectures (invited); is trustee for Sarcoma UK; and is on the Sarcoma Group Scientific Committee for ESMO. S.A.M. reports leadership or fiduciary role in the SARON trial managment group and the HIT MESO trial management group. The trial was funded by Cancer Research UK (C2921/A17558) with Clinicaltrials.gov registration NCT02520128. The funding source had no role in the design of this study and did not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Data Sharing Statement: B.S. and A.L. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All other authors had access to the primary clinical trial data. Deidentified individual patient data that underlie the reported results may be shared with other researchers after a data sharing agreement is in place. Proposals for access should be sent to ctc.imris@ucl.ac.uk.

Supplementary material associated with this article can be found in Appendix E1 in the online version at doi:10.1016/j.ijrobp.2024.05.024.

https://doi.org/10.1016/j.ijrobp.2024.05.024

18.1%) had grade ≥2 subcutaneous fibrosis. The overall rate at 24 months of Radiation Therapy Oncology Group late skin, bone, and joint toxicity was 7 of 112 (6.3%), 3 of 112 (2.7%), and 10 of 113 (8.8%), respectively, and for Stern's scale edema was 6 of 113 (5.3%). More wound complications were observed with preoperative than postoperative RT (29.2% vs 3.8%). Overall survival at 24 months was 84.6%, and the local recurrence event rate at 24 months was 10%.

Conclusions: The rate of grade ≥2 subcutaneous fibrosis at 24 months after IMRT was 10.8%, consistent with other recent trials of IMRT and lower than historically reported rates in patients treated with 3-dimensional conformal RT. This trial provides further evidence for the benefits of IMRT in this patient population.

Introduction

Primary soft tissue sarcomas (STSs) are rare tumors that can occur at any site in the body. The annual incidence in the United Kingdom is 3943 cases per year (2013-2017),[1] and 25% of these are limb sarcomas.[2] The preferred local management of localized nonmetastatic limb sarcomas is limb-sparing surgery, often in combination with preoperative or postoperative radiation therapy (RT) for patients at higher risk of local tumor recurrence. Intensity modulated RT (IMRT) is an advanced RT technique that can deliver a highly conformal dose to a target with improved sparing of the surrounding normal tissues from moderate and high radiation doses, and it can potentially reduce acute and late RT toxicities.

The current evidence supporting the use of IMRT in STS consists of RT planning studies,[3-5] retrospective series,[6-10] and 2 phase 2 clinical trials.[11,12] When designing this trial, 3-dimensional conformal RT (3DCRT) was the standard RT technique for extremity STS in the United Kingdom. We conducted a retrospective study of late toxicity observed in 247 patients treated with RT (simple simulated RT fields in 46 patients, planned 3DCRT in 200 patients, IMRT in 1 patient) for extremity STS between 1991 and 2012, reporting a rate of grade ≥2 subcutaneous fibrosis of 28%.[13]

The purpose of the trial was to prospectively investigate late normal tissue toxicity and limb function observed after IMRT in extremity STS and whether this was reduced compared with the historical use of non-IMRT techniques. In addition, the trial investigated whether the implementation of IMRT in extremity STS was feasible in a large number of treatment centers.

Methods and Materials

Patients

Eligible patients were 16 years or older, with histopathologic confirmation of STS of the upper or lower limb/limb-girdle, requiring preoperative or postoperative RT, fit to undergo RT treatment, and World Health Organization (WHO) performance status (PS) 0 to 2. Patients were excluded from trial entry if they had had previous RT to the same site, were receiving concurrent chemotherapy with RT (neoadjuvant chemotherapy prior to RT was permitted), were diagnosed with pediatric type alveolar/embryonal rhabdomyosarcomas, were pregnant, or had a concurrent or previous malignancy that could compromise the assessment of the primary/secondary endpoints of the trial.

Trial design and procedures

IMRiS was a multicenter, prospective, phase 2 trial evaluating RT modality delivered with fixed beam IMRT, rotational/arc IMRT techniques, or tomotherapy before or after surgery as follows: preoperative RT: 50 Gy in 25 daily fractions over 5 weeks, postoperative RT with clear resection margins (R0): 60 Gy in 30 daily fractions to the high dose planning target volume (PTV) (PTV_6000) and 52.2 Gy in 30 daily fractions to the low dose PTV (PTV_5220) treated concurrently as a simultaneous integrated boost (SIB) over 6 weeks, postoperative RT with positive resection margins (R1): 66 Gy in 33 daily fractions to the high dose PTV (PTV_6600), and 53.46 Gy in 33 fractions to the low dose PTV (PTV_5346) treated concurrently as a SIB over 6.5 weeks. The doses to the lower dose PTV volumes used in the SIB technique (52.2 Gy for patients receiving 60 Gy to SIB volume; 53.5 Gy for patients receiving 66 Gy to SIB volume) were calculated on the basis of delivering an equivalent dose in 2 Gy fractions (EQD2) of approximately 50 Gy, with an alpha:beta ratio of 3. The rationale for this was to replicate the 3DCRT 2-phase technique used in the United Kingdom at the time of trial design, which delivered 50 Gy in 25 fractions to a larger PTV, followed sequentially by 10 Gy (after R0 resection) or 16 Gy (after R1 resection) to a smaller PTV.

Postoperative RT was aimed to start within 4 weeks of registration and no longer than 12 weeks after surgery. For patients receiving postoperative RT, delays in starting RT due to wound healing were permissible. For preoperative RT, surgery was planned to be carried out approximately 6 weeks after completion of RT.

Daily image guided RT was required for all patients. A minimum of 2-dimensional orthogonal kilovoltage (kV) or megavoltage (MV) imaging was mandated, and cone beam computed tomography (CT) was recommended.

Supportive management and treatment for RT-related toxicity were according to treatment protocols at individual sites. Patients were seen weekly while on treatment, 28 to 35 days after their last fraction of RT, then followed up 3 monthly for up to 3 years after the date of registration.

RT target volume definition

All patients underwent immobilization of the limb using rigid immobilization devices fixed to a baseboard indexed to the treatment couch. The contralateral limb was also immobilized to allow accurate measurement of the dose to the contralateral limb. A planning CT scan was performed with a slice thickness of 2 to 3 mm and intravenous contrast for preoperative RT patients. Target volume definition was guided by pretreatment diagnostic magnetic resonance imaging (MRI) scans, which were fused with planning CT scans if feasible. For preoperative RT, gross tumour volume (GTV) was delineated using the contrast-enhanced T1-weighted MRI images. A clinical target volume (CTV) CTV_5000 was created by adding to GTV a 2 to 3 cm radial margin and 3 to 4 cm proximally and distally, editing at bone, skin, and fascial barriers where required. For postoperative RT, the preoperative GTV was reconstructed on the planning CT scan using information from the preoperative diagnostic MRI scan, operation report, and histopathology report, taking into account any altered anatomy after surgery and the growth of GTV between MRI scanning and surgery. The principle of treatment was to treat a larger lower dose volume CTV_5220/CTV_5346 (reconstructed GTV with margins of 2-3 cm radially and 5 cm proximally and distally, editing at bone, skin, and fascial barriers where required) and a smaller higher dose volume CTV_6000/CTV_6600 (GTV with a margin of 2-3 cm radially and proximally and distally), using a SIB technique, for R0/R1 resection margins, respectively. The lower and higher dose volumes for postoperative RT were CTV_5346 and CTV_6600, respectively. Based on local protocols and set-up audits, a margin of 5 to 10 mm was added for PTV. PTV was cropped back by up to 5 mm from the skin to create a planPTV to avoid optimization errors where excess fluence is generated in an attempt to top up these areas. Organs at risk (OARs) were delineated as radiation avoidance structures as follows, with optimal dose constraints: normal tissue limb corridor, a longitudinal strip of skin and subcutaneous tissue (volume receiving 20 Gy [V_{20Gy}], <50%), weight-bearing bone − bone in treatment field (volume receiving 50 Gy [V_{50Gy}], <50%), and weight-bearing bone − whole bone (mean dose, ≤40 Gy; volume receiving 40 Gy [V_{40Gy}], ≤64%). These were nonmandatory, and PTV coverage was not compromised to meet them.

The normal tissue corridor was delineated as follows: a longitudinal cylindrical strip of skin and subcutaneous soft tissue was contoured (by the clinician or the planner) as an OAR according to the clinical judgment of the treating radiation oncologist to allow sparing of lymphatic drainage. The near-minimum and near-maximum doses within the PTV were required to be within a range of 90% to 107% of the prescription dose.

Quality assurance of target volume definition and RT planning

An RT quality assurance program was conducted by the National Radiotherapy Trials Quality Assurance Group and included preaccrual and during-accrual components. Prior to trial opening, centers were required to complete a facility questionnaire, a dosimetry audit, and outlining and planning benchmark cases. An immobilization workshop was organized to facilitate discussions around setup accuracy, PTV margins, and image guided RT.[14]

During trial accrual, prospective outlining and planning case reviews were conducted for the first preoperative and postoperative cases, followed by retrospective review of all cases.

Endpoints and assessments

The primary endpoint was the rate of grade ≥2 late soft tissue fibrosis (subcutaneous tissue) at 24 months (any assessment between 21 and 27 months) after completion of IMRT as assessed by Radiation Therapy Oncology Group (RTOG) late radiation morbidity scoring system.[15] Secondary endpoints were incidence and pattern of acute and late RT-related toxicity; rate and severity of surgical adverse reactions and wound complications (within 120 days of surgery); physician-assessed and patient-reported limb function and quality of life; time to local recurrence; disease-free survival (DFS); and overall survival (OS).

Assessment of acute radiation morbidity used the RTOG Acute Radiation Morbidity Scoring Criteria[16] for up to 90 days after the start of treatment. Late radiation morbidity was assessed using the RTOG Late Radiation Morbidity Scoring Criteria (skin, subcutaneous tissue fibrosis, joint stiffness, and bone) and Stern's scale for edema[17] from day 91, on a 3-month basis for up to 3 years after registration. Time to first late RTOG grade ≥2 event was defined as the time from the end of RT to the first time the patient experienced an event of interest with a grade 2 or higher. Patients who did not have an event of interest with a grade 2 or higher were censored at the date they were last assessed.

Adverse reactions were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03[18] during RT and between 28 and 35 days after the last fraction of RT. Serious adverse reactions were reported from the start of RT until the end of the trial. Wound complications were assessed during assessment visits occurring up to 120 days after surgery. Postsurgery wound assessment wound complications were defined as a second operation under general or regional anesthesia for wound repair (debridement, operative drainage, unplanned secondary wound closure using free muscle flaps or skin grafts) and wound management without a second operation (invasive procedure without general or regional anesthesia, eg, aspiration of seroma, readmission for wound care such as intravenous antibiotics, persistent deep wound packing for ≥120 days).

Quality of life and function were assessed at baseline and 12 and 24 months after registration, using the WHO PS, Toronto

Extremity Salvage Score (TESS),[19,20] European Organisation for Research and Treatment of Cancer quality of life questionnaire C30 (EORTC-QLQ-C30),[21] and Musculoskeletal Tumor Society Rating Scale (MSTS)[22,23] questionnaires.

Disease was assessed by MRI or CT scan at preregistration, and chest imaging (CT/chest x-ray) was required within 3 months of registration. Patients were reviewed 3 monthly with clinical assessment of local tumor control at the primary tumor site and chest x-ray, as per standard of care in the United Kingdom at that time. Further investigations were carried out only if clinically indicated. Time to local recurrence was measured from the date of registration until local tumor recurrence within the primary tumor site. Patients without local recurrence were censored at death or the date last seen. DFS events included local relapse, locoregional lymph node relapse, distant disease progression, new malignancy, or death. DFS was measured from the date of registration to the first time a DFS event was reported. Patients were censored at the date they were last seen alive if they did not have a reported DFS event. OS was measured as the date of registration to the date of death from any cause. Patients were censored at the date they were last seen alive if they did not have a reported death.

Data analysis

With an 85% power, 1-sided 5% significance level, and accounting for a 17% dropout rate, this A'Hern's single-stage phase 2 trial aimed to recruit 167 patients, sufficient to detect a 10% reduction in the grade ≥2 soft tissue fibrosis at 24 months from a 28% rate assumed based on historical control data.[13]

The percentage of patients who received trial treatment with a reported grade ≥2 late soft tissue fibrosis at 24 months was determined among patients assessable at 24 months, along with exact binomial 90% and 95% CI. Other adverse events were reported in a descriptive manner using frequencies and percentages.

Time-to-event endpoints were analyzed using standard survival techniques and depicted using Kaplan-Meier plots. As an exploratory analysis, OS and DFS were compared between RT modalities using Cox regression.

TESS, EORTC-QLQ-C30, and MSTS measures were reported as means and 95% CIs at specified time points derived from random intercept and slope model (mixed model) with time from registration included as a fixed and random effect. A multilevel ordinal logistic regression with a random intercept was used to analyze WHO PS changes across time.

Results

Recruitment and follow-up

One hundred sixty-eight eligible patients were recruited from 18 UK/Irish sites from March 2016 to July 2017. Of those, 159 (95%) received IMRT (106, 67% preoperative RT; and 53, 33% postoperative RT) with a median follow-up of 35.2 months (IQR, 32.9-36.6). These patients form the basis of this report (Fig. 1).

Baseline characteristics

Baseline patient and tumor characteristics are shown in Table 1. The median age was 58 years (range, 17-89). More patients in the preoperative RT cohort were PS 0 compared with the postoperative RT cohort (79, 74.5% vs 26, 49.1%). The most common histologies were myxofibrosarcoma (41, 25.8%), pleomorphic sarcoma (30, 18.9%), myxoid liposarcoma (28, 17.6%), and sarcoma not otherwise specified (NOS) (19, 11.9%).

Tumor location was lower extremity in 130 (81.8%) and upper extremity in 29 (18.2%). Twenty-seven of 28 patients with myxoid liposarcoma were treated with preoperative RT and 1 with postoperative RT. Most tumors were located deep to the fascia (120, 75.5%), with a median maximum tumor diameter at the surgery of 80 mm (range, 20-220). Most patients had localized nonmetastatic disease (155, 98%).

Treatment delivery

In the preoperative RT cohort, the median time from the end of RT to definitive surgery was 6.9 weeks (range, 3.6-15.4), with 102 (96%) of patients undergoing an R0 resection. In the postoperative RT cohort, the median time from definitive surgery to the start of RT was 10.4 weeks (range 5.2-21.3), with 43 (81%), 9 (17%), and 1 (2%) achieving R0, R1, and R2 resections, respectively.

RT was completed as planned in 158 of 159 patients. One patient stopped their IMRT plan after a single 2 Gy fraction and was replanned with 3DCRT because their arm position did not allow the acquisition of adequate imaging for on-treatment verification. The median RT dose delivered was 50 Gy (range, 2-50) for 106 patients who received preoperative RT and 60 Gy (range, 60-66) for 53 patients who received postoperative RT. Bolus was used to increase RT dose at the skin surface in 15 (9.4%) patients, 12 (11.3%) in the preoperative RT cohort, and 3 (5.7%) in the postoperative RT cohort. Twenty-six patients (16%) had at least 1 delay during RT, 11 (10%) in the preoperative RT cohort, and 15 (28%) in the postoperative RT group. Reasons for delays were acute skin reaction, acute skin infection, muscle spasm, diabetes-related event, wound healing issues, patient choice, machine breakdown, transport issues, and scheduled bank holiday. Replanning was required for 13 of 159 patients, 1 in the postoperative RT cohort (improving GTV coverage/change in outline) and 12 in the preoperative RT cohort (growth of tumor, 6; improving GTV coverage/change in outline, 5; not reported, 1). The mean PTV for the whole cohort was 1391.2 cm^3 (range, 76.6-9918.6), with a mean PTV of 1537.4 cm^3 (range, 76.6-9918.6) for the preoperative cohort and 1081.2 cm^3 (range, 99.4-3368.0) for the postoperative cohort, respectively.

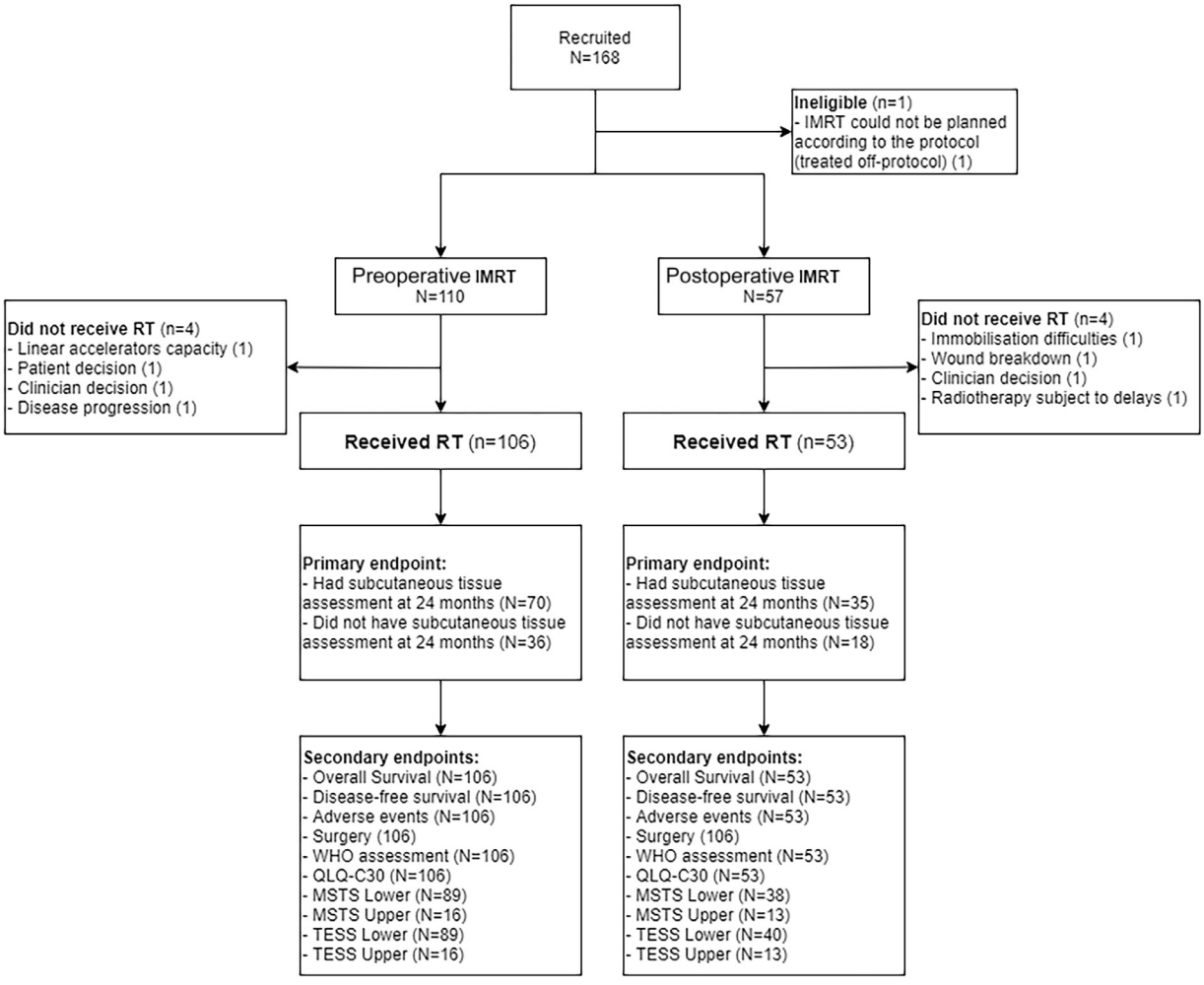

Fig. 1. Consort diagram.

Primary endpoint

Rate of grade ≥2 soft tissue fibrosis (subcutaneous tissue) at 24 months

Of the 159 patients who received IMRT, 111 (69.8%) were assessable for RTOG late toxicity for soft tissue fibrosis (subcutaneous tissue) at 24 months. RTOG soft tissue fibrosis at 24 months could not be assessed in 48 (30.2%) patients for the following reasons: 29 (60.4%) had died, 9 (18.8%) failed to have an assessment within the required timeframe of 21 to 27 months post-RT, 8 (17%) were lost to follow-up, and for 2 (4%) patients the toxicity site was not within radiation treatment volume (eg, subcutaneous tissue for a deeply located tumor). Of 111 patients assessable for the primary endpoint, 12 (10.8%; 90% CI, 6.4%-16.9%; 95% CI, 5.7%-18.1%) had grade ≥2 soft tissue fibrosis at 24 months (Table 2), indicating with a 1-sided 5% and 2.5% significance level that the RTOG soft tissue event rate grade ≥2 at 24 months is below a 28% rate seen in historical control data.[13] Furthermore, of patients who received preoperative and postoperative RT, grade ≥2 soft tissue fibrosis at 24 months was seen in 8 of 73 (11.0%) and 4 of 38 (10.5%) patients, respectively.

Secondary endpoints

Late RT toxicity

Of the 159 patients who received IMRT, 112 (70%), 112 (70%), 113 (71%), and 113 (71%) were assessable for RTOG late toxicity for skin, bone, and joint, and Stern's scale for edema at 24 months, respectively. The overall rate at 24 months of RTOG late skin, bone, and joint toxicity was 7 of 112 (6.3%), 3 of 112 (2.7%), and 10 of 113 (8.8%), respectively, and for Stern's scale edema was 6 of 113 (5.3%) (Table 2). At the 24-month time point, there were no reported pathologic fractures. However, 1 pathologic fracture was reported that occurred prior to the 24-month time point in a patient who had received postoperative RT. At 24 months, RTOG late toxicity grade ≥2 was similar between preoperative and postoperative RT for bone (2/74, 2.7%; 1/38, 2.6%), joint (7/75, 9.3%; 3/38, 7.9%), and Stern's scale for edema (4/76, 5.3%; 2/37, 5.4%), respectively. However,

Table 1 Patient, tumor, and treatment characteristics

Baseline characteristics	Overall N = 159	Preoperative RT n = 106	Postoperative RT n = 53
Sex, n (%)			
Male	99 (62.3)	69 (65.1)	30 (56.6)
Female	60 (37.7)	37 (34.9)	23 (43.4)
Age (y)			
Median (range)	57.8 (17.2-88.7)	56.5 (17.2-88.7)	62.4 (25.2-87.5)
WHO performance status, n (%)			
0 (asymptomatic)	105 (66.0)	79 (74.5)	26 (49.1)
1 (symptomatic but completely ambulatory)	50 (31.4)	26 (24.5)	24 (45.3)
2 (symptomatic, <50% in bed during the day)	4 (2.5)	1 (0.9)	3 (5.7)
Receiving neoadjuvant/adjuvant chemotherapy, n (%)			
Yes	2 (1.3)	1 (0.9)	1 (1.9)
Histological subtype, n (%)			
Myxofibrosarcoma	41 (25.8)	26 (24.5)	15 (28.3)
Pleomorphic sarcoma	30 (18.9)	15 (14.2)	15 (28.3)
Myxoid liposarcoma	28 (17.6)	27 (25.5)	1 (1.9)
Sarcoma NOS	19 (11.9)	13 (12.3)	6 (11.3)
Synovial sarcoma	12 (7.5)	8 (7.5)	4 (7.5)
Leiomyosarcoma	9 (5.7)	4 (3.8)	5 (9.4)
Liposarcoma	9 (5.7)	7 (6.6)	2 (3.8)
Malignant peripheral nerve sheath tumor	5 (3.1)	4 (3.8)	1 (1.9)
Clear cell sarcoma	2 (1.3)	-	2 (3.8)
Extraskeletal myxoid chondrosarcoma	2 (1.3)	1 (0.9)	1 (1.9)
Alveolar soft part sarcoma	1 (0.6)	1 (0.9)	-
Fibrosarcoma	1 (0.6)	-	1 (1.9)
Limb subsite, n (%)			
Lower extremity	130 (81.8)	90 (84.9)	40 (75.5)
Buttock	7 (4.4)	4 (3.8)	3 (5.7)
Upper leg	85 (53.5)	63 (59.4)	22 (41.5)
Knee	9 (5.7)	7 (6.6)	2 (3.8)
Lower leg	27 (17.0)	14 (13.2)	13 (24.5)
Foot	2 (1.3)	2 (1.9)	-
Upper extremity	29 (18.2)	16 (15.1)	13 (25.5)
Shoulder	8 (5.0)	4 (3.8)	4 (7.5)
Upper arm	6 (3.8)	4 (3.8)	2 (3.8)
Elbow	3 (1.9)	1 (0.9)	2 (3.8)
Forearm	11 (6.9)	7 (6.6)	4 (7.5)
Hand	1 (0.6)		1 (1.9)
M stage at registration, n (%)			
M0	156 (98.1)	103 (97.2)	53 (100.0)
M1	3 (1.9)	3 (2.8)	-

(*Continued*)

Table 1 (*Continued*)

Baseline characteristics	Overall N = 159	Preoperative RT n = 106	Postoperative RT n = 53
Tumor location, n (%)			
Deep	120 (75.5)	82 (77.4)	38 (71.7)
Superficial	39 (24.5)	24 (22.6)	15 (28.3)
Tumor diameter (mm), median (range)			
Baseline (at registration)*	75 (15-191)	83.5 (20-191)	70 (15-180)
At surgery†	80 (20-220)	81 (20-210)	75 (24-220)
Surgical resection margins, n (%)			
R0	145 (91.2)	102 (96.2)	43 (81.1)
R1	12 (7.5)	3 (2.8)	9 (17.0)
R2	2 (1.3)	1 (0.9)	1 (1.9)
RT dose delivered, n			
2 Gy in 1 fraction‡	-	1	-
50 Gy in 25 fractions	-	105	-
60 Gy in 30 fractions (R0)	-	-	49
66 Gy in 33 fractions (R1/2)	-	-	4

Abbreviations: NOS = not otherwise specified; RT = radiation therapy; WHO = World Health Organization.
* Based on tumor measurements on magnetic resonance imaging scan at diagnosis.
† Based on tumor measurements on histopathology report.
‡ One patient stopped their intensity modulated radiation therapy plan after a single 2 Gy fraction and was replanned with 3-dimensional conformal radiation therapy because their arm position did not allow acquisition of adequate imaging for on-treatment verification.

RTOG late skin toxicity was higher for postoperative than preoperative RT (4/38, 10.5%, vs 3/74, 4.1%, respectively).

Acute RT skin toxicity

RTOG acute skin toxicity grade ≥2 up to 90 days after the start of RT occurred in 23 of 106 (21.7%) and 22 of 53 (41.5%) patients receiving preoperative and postoperative RT, respectively.

Surgical morbidity events

Preoperative RT was associated with more surgical complications than postoperative RT, with any surgical adverse reactions (grade 1-4) occurring in 56 of 106 (53%, preoperative RT) and 20 of 53 (38%, postoperative RT). Of these, 16 of 56 (preoperative RT) and 3 of 20 (postoperative RT) were grade 3 or 4. Wound complications of all types also occurred more frequently in preoperative than postoperative RT patients (total complications in 31, 29.2% vs 2, 3.8%); secondary operation for wound repair (16, 15.1% vs 0, 0%), and wound management without second operation (15, 14.2% vs 2, 3.8%).

Quality of life

Figure 2 shows changes across time in EORTC-QLQ-C30 in the 30 months from registration. Physical functioning decreased significantly over time by 0.18 (95% CI, −0.32, −0.04; P = .012). However, global health status, social functioning, and emotional functioning all increased over time (estimated improvement per month increment was 0.17 [95% CI, 0.01, 0.33; P = .039] for global health status; 0.27 [95% CI, 0.08, 0.46; P = .004] for social functioning; and 0.28 [95% CI, 0.13, 0.43; P < .001] for emotional functioning). Dyspnea increased significantly over time by an estimated 0.37 (95% CI, 0.18, 0.56; P < .0001). There was no change over time for TESS and MSTS in up to 36 months from registration (P > .05), with mean TESS scores at 24 months of 77.7 and 78.02 for upper and lower limbs, respectively, and mean MSTS scores of 23.0 and 24.3 for upper and lower limbs respectively. There was no evidence of a time effect for WHO PS, for other EORTC-QLQ-C30 functional and symptom scales (P > .05).

Disease-related outcomes

There were 18 (11%) local recurrences reported, 12 (11%) in the preoperative RT cohort and 6 (11%) in the postoperative RT cohort. The local recurrence event rate at 24 months in the overall cohort was 10% (95% CI, 6%-16%), and the 2-year local recurrence−free survival in the overall cohort was 90% (95% CI, 84%-94%). The local recurrence event rate at 24 months was 10% (95% CI, 4%-21%) and 10% (95% CI, 6%-18%) in the preoperative and postoperative RT cohorts, respectively, and there was no evidence of a difference between preoperative and postoperative RT for time to local

Table 2 Late radiation therapy toxicity

Late RTOG toxicity	Overall, n (%) N = 159	Preoperative RT, n (%) n = 106	Postoperative RT, n (%) n = 53
Subcutaneous tissue			
<2	99 (62.3)	65 (61.3)	34 (64.2)
≥2	12 (7.5)	8 (7.5)	4 (7.5)
Not assessable*	48 (30.2)	33 (31.1)	15 (28.3)
Rate at 24 mo	12/111 (10.8)	8/73 (11.0)	4/38 (10.5)
Skin			
<2	105 (66.0)	71 (67.0)	34 (64.2)
≥2	7 (4.4)	3 (2.8)	4 (7.5)
Not assessable*	47 (30.0)	32 (30.0)	15 (28.3)
Rate at 24 mo	7/112 (6.3)	3/74 (4.0)	4/38 (10.5)
Bone			
<2	109 (68.6)	72 (67.9)	37 (69.8)
≥2	3 (1.9)	2 (1.9)	1 (1.9)
Not assessable*	47 (29.6)	32 (30.2)	15 (28.3)
Rate at 24 mo	3/112 (2.7)	2/74 (2.7)	1/38 (2.6)
Joint			
<2	103 (64.8)	68 (64.2)	35 (66.0)
≥2	10 (6.3)	7 (6.6)	3 (5.7)
Not assessable*	46 (28.9)	31 (29.2)	15 (28.3)
Rate at 24 mo	10/113 (8.8)	7/75 (9.3)	3/38 (7.9)
Edema (Stern's scale)			
<2	107 (67.3)	72 (67.9)	35 (66.0)
≥2	6 (3.8)	4 (3.8)	2 (3.8)
Not assessable*	46 (28.9)	30 (28.3)	16 (30.2)
Rate at 24 mo	6/113 (5.3)	4/76 (5.3)	2/37 (5.4)

Abbreviations: RT = radiation therapy; RTOG = Radiation Therapy Oncology Group.
* Not assessable: site not within radiation treatment volume, lost to follow-up, died, or no assessment due to other reasons.

recurrence (hazard ratio [HR], 1.02 [95% CI, 0.38, 2.73]; $P = .96$).

There were 41 (26%) deaths reported, 30 (28%) in the preoperative RT cohort and 11 (21%) in the postoperative RT cohort. Of these 41 deaths, 38 (93%) were due to disease progression and 3 (7%) due to other reasons (1 stroke, 1 sepsis, and 1 unknown). There were no treatment-related deaths. The OS rate at 24 months in the whole cohort was 84.6% (95% CI, 77.9%-89.4%), and was 83.6% (95% CI, 75.0%-89.5%) and 86.6% (95% CI, 73.9%-93.4%) in the preoperative and postoperative RT cohorts, respectively.

There were 66 (42%) DFS events reported, 46 (43%) in the preoperative RT cohort, and 20 (38%) in the postoperative RT cohort. The DFS rate at 24 months in the overall cohort was 63.4% (95% CI, 55.3%-70.3%), and was 62.9% (95% CI, 53.0%-71.4%) and 64.2% (95% CI, 49.7%-75.4%) in the preoperative and postoperative RT cohorts, respectively.

There was no evidence of a difference between preoperative versus postoperative RT for OS (HR, 1.44 [95% CI, 0.72, 2.88]; $P = .30$) or for DFS (HR, 1.20 [95% CI, 0.71, 2.03]; $P = .50$).

Discussion

This prospective phase 2 study aimed to investigate rates of late normal tissue toxicity and limb function observed after IMRT in extremity STS, with a primary end point of rate of grade ≥2 late soft tissue fibrosis (subcutaneous tissue) at 24 months after IMRT. In addition, we aimed to establish the incidence and pattern of other late normal tissue toxicity (skin, joint, bone, and edema) and acute RT toxicity, and to evaluate the effect of the use of IMRT on function and quality of life, and on the incidence and severity of wound complications related to surgery either before or after IMRT. We

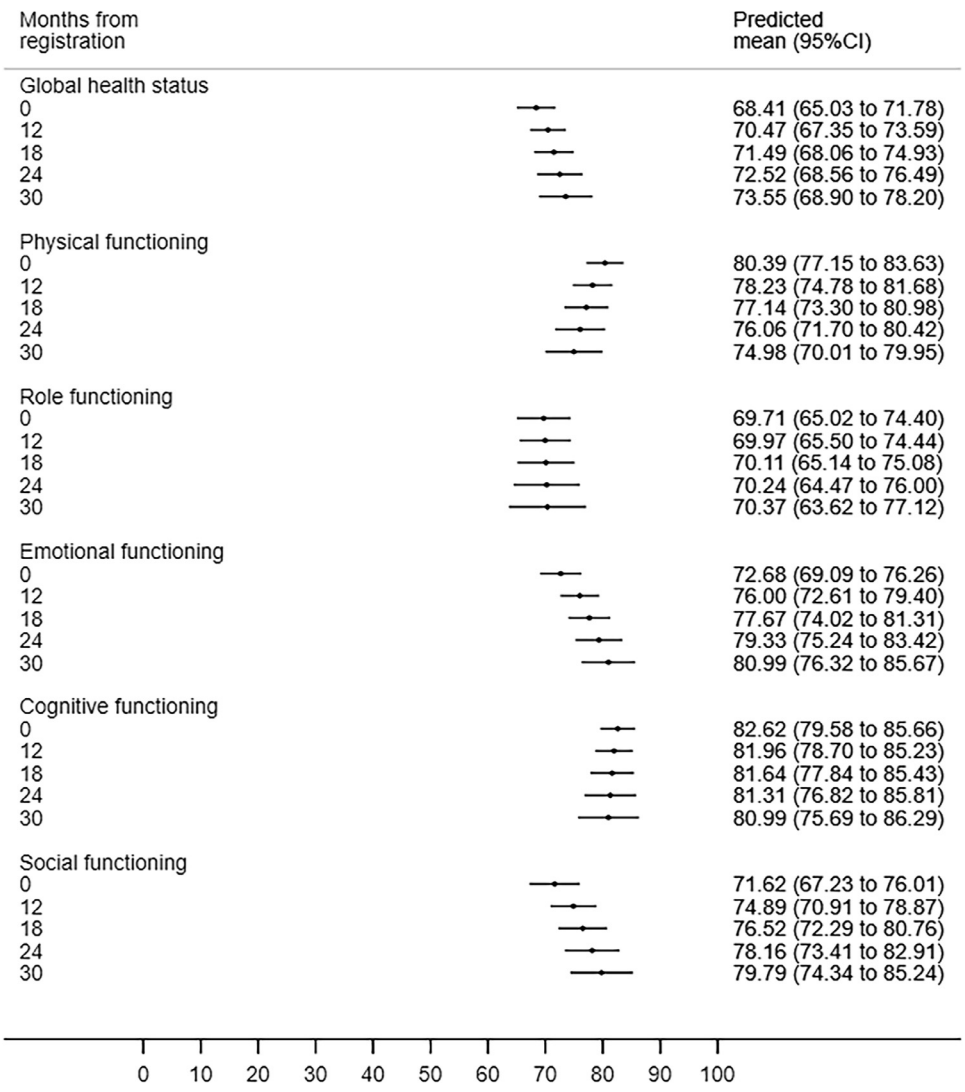

Fig. 2. Predicted means of global quality of life and functional scales (QLQ-C30) over time.

have shown a rate of grade ≥2 soft tissue fibrosis (subcutaneous tissue) at 24 months after IMRT of 10.8%, a clinically meaningful reduction from a 28% historical rate after non-IMRT techniques.[13] Rates of other late normal tissue toxicity were similarly low (skin, 6.3%; bone, 2.7%; joint, 8.8%; edema, 5.3%). These results are consistent with other recent studies of IMRT in limb sarcomas (Table 3).

Patients were treated either with preoperative (106 patients) or postoperative (53 patients) RT, although there was no planned intention in the study to formally compare any outcomes between the 2 cohorts. The rates of grade ≥2 - soft tissue fibrosis (subcutaneous tissue) were the same for the 2 cohorts. The rates of other grade ≥2 late toxicity (skin, joint, bone, and edema) were also very similar between the 2 cohorts; the only toxicity type showing any difference was grade ≥2 skin toxicity, which was greater in the postoperative group (11.4% vs 4.2%), which is likely due to the higher dose of postoperative RT (60-66 Gy vs 50 Gy), which is known to be associated with higher rates of late RT toxicity.[24] On this basis, it might have been expected to see higher rates of late toxicity for other toxicity types (joint, bone, and edema) in the postoperative RT cohort. Part of the explanation for the lack of an observed difference in toxicity rates between the 2 cohorts may be that the mean PTV volume was lower for the postoperative RT cohort (1081.2 cm^3) compared with the preoperative RT cohort (1537.4 cm^3), presumably reflecting that the median GTV size at the time of RT planning was smaller in the postoperative RT cohort (75 mm) compared with the preoperative cohort (83.5 mm), which may have resulted in lower late toxicity rates in the postoperative RT cohort. In addition, the preoperative cohort was treated in 2 Gy fraction sizes, whereas the postoperative RT cohorts were treated in 1.74 Gy fractions to the low dose PTV for those receiving 60 Gy in 30 fractions and 1.62 Gy to the low dose PTV for those receiving 66 Gy in 33 fractions, such that the smaller fraction sizes may have further reduced late toxicity rates in the postoperative cohort. A further explanation could be that the specified (nonmandatory) OAR dose constraints for the normal tissue limb corridor and bone were able to be met similarly

Table 3 Summary of clinical trials of radiation therapy in extremity soft tissue sarcoma

Study	N	Treatment	Technique	Wound complications	Late toxicity	Function (mean scores)	Local recurrence
NCIC SR.2 trial O'Sullivan et al[26] Davis et al[24]	182	Preop RT 50 Gy/25# (88) Postop RT 66 Gy/33# (94)	3DCRT	Preop RT 35% Postop RT 17%	Toxicity scored at 21-27 mo n = 129 (71% of the original cohort) Subcutaneous fibrosis ≥G2: Preop RT 31.5% Postop RT 48.2% Joint stiffness ≥G2: Preop RT 17.8% Postop RT 23.2% Edema ≥G2: Preop RT 15.1% Postop RT 23.2%	TESS at 24 mo: Preop RT 85.4 Postop RT 81.5 MSTS: Preop RT 30.0 Postop RT 28.2	Figures not reported
Phase 2 trial O'Sullivan et al[11]	70	Preop RT 50 Gy/25#	IMRT	Preop RT 30.5%	Toxicity scored at 2 years+ n = 54 (77% of the original cohort) Moderate* subcutaneous fibrosis 9.3% Moderate* skin toxicity 1.9% Moderate* joint stiffness 5.6% Moderate* edema 11.1%	TESS at 1 year+: Preop RT 83.1	5-year LRFS 88.2%
RTOG-0630 phase 2 trial Wang et al[12]	79	Preop RT 50 Gy/25#	IMRT 74.7% 3DCRT 25.3%	Preop RT 36.6%	Toxicity scored at 21-27 mo n = 57 (72% of the original cohort) Subcutaneous fibrosis ≥G2 5.3% Joint stiffness ≥G2 3.5% Edema ≥G2 5.3%	Not reported	2-year LRFS 94%
IMRiS study Seddon et al	159	Preop RT 50 Gy/25# (106) Postop RT 60-66 Gy/30-33# (53)	IMRT	Preop 29.2% Postop 3.8%	Toxicity scored at 21-27 mo n = 111-113 (70%-71% of the original cohort) Subcutaneous fibrosis ≥G2: All 10.8% Preop RT 11% Postop RT 10.5% Skin toxicity ≥G2: All 6.3% Preop RT 4% Postop RT 11% Joint stiffness ≥G2: All 8.8% Preop RT 9% Postop RT 8% Edema ≥G2: All 5.3% Preop RT 5% Postop RT 5%	TESS at 24 mo: Upper limb 77.7 Lower limb 78.0 MSTS: Upper limb 23.0 Lower limb 24.3	2-year LRFS 90%

Abbreviations: NCIC = National Cancer Institute of Cancer; 3DCRT = 3-dimensional conformal radiation therapy; G = grade; IMRT = intensity modulated radiation therapy; LRFS = local recurrence—free survival; MSTS = Musculoskeletal Tumor Society Rating Scale; Postop = postoperative; Preop = preoperative; RT = radiation therapy; RTOG = Radiation Therapy Oncology Group; TESS = Toronto Extremity Salvage Score.

* No definition given for moderate.

in both the preoperative and postoperative RT groups, resulting in a similar observed toxicity rate.

We have reported toxicity rates at a fixed time point at 24 months after completion of RT, which was chosen to be consistent with toxicity reporting in previous studies (Table 3).[11,12,24-26] However, reporting in this way means that only patients available for assessment at that time point can contribute to the primary endpoint. For our study, 66%

of patients were assessable, consistent with 72% of patients in the study of Wang et al,[12] with the remaining patients having died, been lost to follow-up, or missing the assessment at the 24-month time point. The implication is that these missing patients may have experienced toxicity at an earlier point, such that the 24-month toxicity rates may underestimate the true rates of toxicity.

The OS rate at 24 months for the whole cohort was 84.6%, and there was no survival difference between the preoperative and postoperative cohorts (83.6% and 86.6%, respectively). The local recurrence rate at 24 months was 9% for the whole cohort and 10% and 9% for the preoperative and postoperative RT cohorts, respectively. These results are consistent with results reported in other studies (Table 3).

Acute RT toxicity up to 90 days from the start of RT was shown to be greater in the postoperative than in the preoperative RT cohort (41.5% vs 21.7%), which would be as expected due to the higher postoperative dose (60-66 Gy vs 50 Gy).

Surgical wound complications occurred more frequently with preoperative than postoperative RT (29.2% vs 3.8%, respectively). The rate of wound complications after preoperative RT is similar to the 35% rate reported in the National Cancer Institue of Canada SR.2 (NCIC SR.2) study of preoperative versus postoperative 3DCRT.[26] However, we recorded fewer postoperative wound complications than the reported 17% for the postoperative RT patients in the NCIC SR.2 study. The similar rates associated with preoperative RT for 3DCRT (NCIC SR.2 trial) and IMRT (Intensity Modulated Radiotherapy in Sarcoma, IMRiS trial) are consistent with the results of 2 subsequent phase 2 studies using IMRT, which did not show a lower complication rate with IMRT.[11,12] The lower rate of wound complications in the group who received postoperative RT in the IMRiS study may reflect changes in surgical technique in the 20-year interval between when the 2 trials were run.

The EORTC-QLQ-C30 global quality of life assessments improved over time after completing surgery and RT for global health status, emotional functioning, and social functioning. Physical functioning decreased over time, but there was no significant change over time for the TESS and MSTS assessments of upper and lower limb function. This is consistent with previous studies that have shown generally high scores prior to treatment, a dip in scores at 6 weeks after surgery, particularly for preoperative RT patients, followed by good recovery of function by 6 months.[25,27] We studied time points at baseline and at 12 and 24 months, as we were interested in long-term function relating to RT rather than the impact of surgery, so it is not surprising that we did not see changes over time.

This is the largest trial of IMRT in limb sarcomas and gives important information on the feasibility of implementing a consistent IMRT technique in multiple centers across the United Kingdom and Ireland. As part of the preparation for launching the trial, interactive workshops were held on protocol development to maximize participating clinician engagement in the trial and on limb immobilization techniques, which were variable across the United Kingdom.[14] In addition, a robust quality assurance program was run prior to and during the trial, which involved a benchmark training case of a limb sarcoma in which all centers were required to submit planning volumes and an RT treatment plan. Feedback was provided to individual centers, and modifications were requested where required before centers were approved for trial participation. In addition, there was a real-time prospective review of the first preoperative and postoperative RT cases for all centers during the trial. In this way, we ensured that centers were volumizing and planning consistently according to the trial protocol. This has shown that IMRT for limb sarcomas can be delivered in a consistent way across a whole country (the trial was run at all designated sarcoma centers and many smaller centers linked to sarcoma centers), which is an important achievement in a rare tumor type. As such, the trial results are representative of an unselected population of limb sarcoma patients being treated at a range of different sized hospitals. As a result of the trial, the use of IMRT is now part of the standard of care for extremity STS in the United Kingdom. A further benefit of the trial was that with the gaining of experience of IMRT for this patient group, it was also apparent that not all patients require IMRT, in that for some tumor locations (such as lower leg and forearm), a 3DCRT might be superior in effective sparing of normal tissues and maintaining an untreated normal tissue limb corridor.

There are a number of limitations of the trial. Firstly, as discussed above, the primary endpoint of the rate of grade ≥2 soft tissue fibrosis (subcutaneous tissue) at 24 months only captured patients at this time point (in a time window of 21-27 months), which means that toxicity occurring prior to this time point would not necessarily be captured, particularly in patients who had died or been lost to follow-up. Thus, this primary endpoint may underestimate the actual rate of toxicity occurring in patients. However, we chose to use this endpoint in order for our results to be comparable to previous studies that had also used this endpoint, and indeed, our results for this endpoint were comparable to these previous studies.

A further point is that the primary endpoint of the trial includes patients who received preoperative and postoperative RT. It might be argued that the postoperative RT patients would experience higher rates of grade ≥2 toxicity than preoperative RT patients due to the higher RT dose of 60 Gy, making the whole patient cohort more heterogeneous than one receiving only preoperative or postoperative RT. However, the observed toxicity rates were very similar for the preoperative and postoperative RT cohorts, suggesting that it may not be possible to detect small differences in rates of late toxicity observed at dose levels of 50 Gy and 60 Gy, respectively.

Conclusions

In conclusion, we have demonstrated that IMRT for limb sarcomas results in a low rate of grade ≥2 soft tissue fibrosis (subcutaneous tissue) at 24 months after RT, which is

indeed lower compared with historical controls treated with non-IMRT techniques. In addition, we have shown the feasibility of implementing IMRT for limb sarcomas in multiple centers across a whole country, delivered with consistency in technique and quality, such that IMRT for extremity STS is now the standard of care in the United Kingdom. The trial provides further evidence of the benefits of an IMRT technique for patients with extremity STS requiring preoperative or postoperative RT.

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IMRiS

A phase II study of intensity modulated radiotherapy (IMRT) in primary bone and soft tissue sarcoma

Trial Sponsor:	University College London
Trial Sponsor reference:	UCL/13/0376
Trial funder:	Cancer Research UK
Funder reference:	C2921/A17558
Clinicaltrials.gov id:	NCT02520128
Protocol version no:	4
Protocol version date:	01/07/2020

Protocol version 4, 01/07/2020

Authorisation signatures

Name & Role:	Signature:	Date authorised:
Chief Investigator: Dr Beatrice Seddon Consultant Clinical Oncologist	DocuSigned by: Beatrice Seddon 4F00217037C44A5...	13 August 2020
For the Sponsor: Professor Jonathan Ledermann Director, UCL CTC	DocuSigned by: Jonathan Ledermann C5BE7428BBDB4F4...	13 August 2020
Miss Laura White Clinical Trials Group Manager, UCL CTC	DocuSigned by: Laura White 294B70A718B443D...	13 August 2020

Please note: This trial protocol must not be applied to patients treated outside the IMRiS trial. Cancer Research UK & UCL Cancer Trials Centre (UCL CTC) can only ensure that approved trial investigators are provided with amendments to the protocol.

We would like to acknowledge the members of the National Cancer Research Institute Consumer Liaison Group, UCLH sarcoma user group and CTRAD consumers who contributed to reviewing the trial.

COORDINATING CENTRE:

For general queries, supply of trial documentation and central data management please contact:

IMRiS Trial Coordinator
Cancer Research UK & UCL Cancer Trials Centre
90 Tottenham Court Road
London W1T 4TJ

Tel: +44 (0) 20 7679 9518
Fax: +44 (0) 20 7679 9871
09:00 to 17:00 Monday to Friday, excluding Bank Holidays

Email: ctc.imris@ucl.ac.uk

Other trial contacts:

Chief Investigator:	Dr Beatrice Seddon
Address:	Department of Oncology, University College Hospital 1st Floor Central, 250 Euston Road London NW1 2PG

Trial Management Group (TMG):

Dr Beatrice Seddon	Consultant Clinical Oncologist	University College Hospital, London
Dr Franel Le Grange	Consultant Clinical Oncologist	University College Hospital, London
Dr Aisha Miah	Consultant Clinical Oncologist	Royal Marsden Hospital
Dr Charles Candish	Consultant Clinical Oncologist	Cheltenham General Hospital
Dr Peter Dickinson	Consultant Clinical Oncologist	St. James's University Hospital, Leeds
Dr James Wylie	Consultant Clinical Oncologist	Christie NHS Foundation Trust
Mr Syed Ali Moinuddin	Research Radiographer	University College Hospital, London
Andrew Gosling	Proton Therapy Physicist	University College Hospital, London
Narinder Lalli	Radiotherapy Physicist	University College Hospital, London
Ms Rita Simões	Trials Radiographer	National Radiotherapy Trials Quality Assurance Group
Miss Laura White	Trials Group Lead	CR UK & UCL Cancer Trials Centre
Mrs Sharon Forsyth	Senior Trial Coordinator	CR UK & UCL Cancer Trials Centre
Mrs Shumona Shelly	Trial Coordinator	CR UK & UCL Cancer Trials Centre
Mr Andre Lopes	Trial Statistician	CR UK & UCL Cancer Trials Centre

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

1.1 SUMMARY OF TRIAL DESIGN

Title:	A phase II study of intensity modulated radiotherapy (IMRT) in primary bone and soft tissue sarcoma
Short Title/acronym:	IMRiS
Sponsor name & reference:	University College London (UCL/13/0376)
Funder name & reference:	Cancer Research UK (C2921/A17558)
Clinicaltrials.gov id:	NCT02520128
Design:	**A prospective multicentre phase II trial with three separately analysed cohorts:** Cohort 1: Limb/limb girdle soft tissue sarcoma (STS) receiving (neo)-adjuvant radiotherapy (RT) Cohort 2: Patients with Ewing's sarcoma of the spine/pelvis receiving definitive radical or (neo)-adjuvant RT Cohort 3: Patients with non-Ewing's primary bone sarcomas of the spine/pelvis receiving definitive radical or adjuvant RT
Overall aim:	To assess the feasibility, efficacy and toxicity of IMRT in three different cohorts of patients with bone and soft tissue sarcoma and to demonstrate whether IMRT can improve on current clinical outcomes.
Primary endpoint:	Cohort 1: The rate of grade 2 or more late soft tissue fibrosis at 2 years following RT as assessed by RTOG late radiation morbidity criteria. Cohort 2: (Ewing's sarcoma of the spine/pelvis): The proportion of patients in whom 90% of the plan PTV receives 95% of the optimal prescription dose Cohort 3: (non-Ewing's primary bone sarcomas of the spine/pelvis): The proportion of patients in whom 80% of the plan PTV receives 95% of the optimal prescription dose
Secondary endpoints:	Cohort 1: Acute and late RT toxicity; patient reported limb function and quality of life; rate and severity of wound complications within 120 days of surgery; time to local tumour recurrence; disease free and overall survival. Cohorts 2 and 3: Acute and late RT toxicity; response by RECIST 1.1 (for definitive radical RT/evaluable residual disease post-surgery); time to local recurrence (for adjuvant RT); time to local disease progression (for definitive radical RT); disease-free survival; overall survival; dosimetric

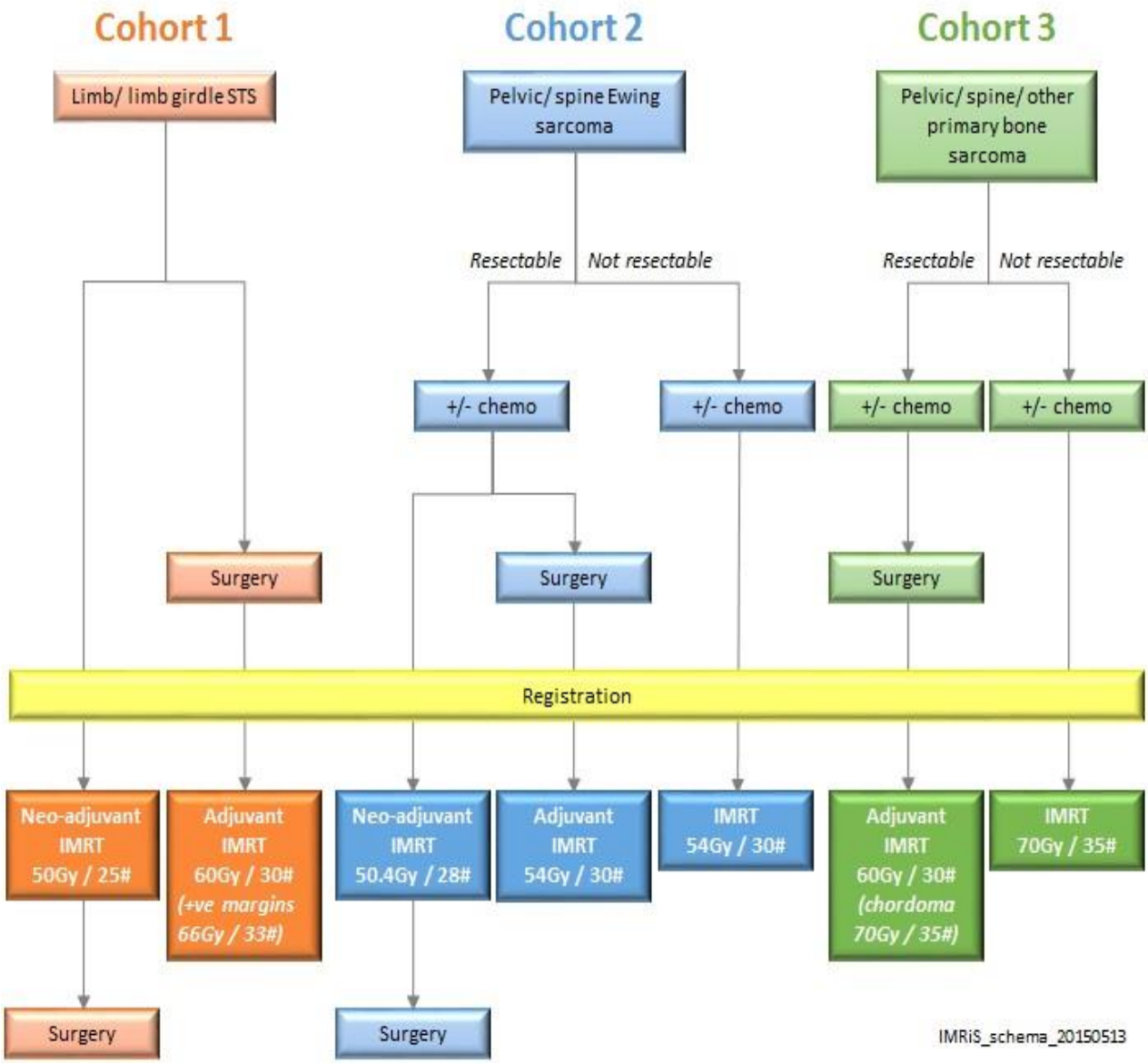
	analysis from double planning of patients using IMRT and proton beam radiotherapy (PBRT).
Target accrual:	188 patients over 2 ½ years: Cohort 1: 167 patients; Cohort 2: 9 patients; Cohort 3: 12 patients

Inclusion & exclusion criteria:	Inclusion criteria:
	• Histopathological diagnosis of:
	  o soft tissue sarcoma of the upper or lower limb or limb girdle, *or*
	  o Ewing's sarcoma of bone arising in the pelvis or spine, *or*
	  o High grade primary bone sarcoma (non-Ewing's) or chordoma arising in the pelvis or spine
	• Patients requiring (neo)adjuvant or definitive radical radiotherapy
	• WHO performance status 0-2
	• Patients aged ≥ 16 years
	Exclusion criteria:
	• Previous radiotherapy to the same site
	• Patient receiving *concurrent* chemotherapy with radiotherapy (neo-adjuvant chemotherapy *prior* to radiotherapy is permissible) (applies to cohort 1 only)
	• Patient with bone sarcomas eligible for proton beam radiotherapy via the UK Proton Panel
	• Paediatric type alveolar or embryonal rhabdomyosarcomas
	• Pregnancy
	• Patients with concurrent or previous malignancy that could compromise assessment of primary and secondary endpoints of the trial

Number of sites:	Approximately 30
Treatment summary:	Radiotherapy will be delivered with fixed beam IMRT, arc IMRT techniques, or tomotherapy. Dose schedules: ***Cohort 1*** • Pre-operative RT – 50 Gy in 25 daily fractions over 5 weeks • Post-operative RT – 60 Gy in 30 daily fractions to the high dose planning target volume (PTV) and 52.2 Gy in 30 daily fractions to the low dose PTV treated concurrently over 6 weeks • Post-operative RT (positive resection margins) – 66 Gy in 33 daily fractions to the high dose PTV, and 53.46Gy in 33 fractions to the low dose PTV treated concurrently over 6 ½ weeks ***Cohort 2*** • Pre-operative RT – 50.4 Gy in 28 daily fractions over 5½ weeks • Post-operative RT - 54 Gy in 30 daily fractions over 6 weeks

	• Primary RT - 54 Gy in 30 daily fractions over 6 weeks ***Cohort 3*** • Primary RT – 70 Gy in 35 daily fractions over 7 weeks • Post-operative RT (non-chordoma) – primary bone sarcoma 60 Gy in 30 daily fractions over 6 weeks • Post-operative RT (chordoma) – 70 Gy in 35 daily fractions over 7 weeks
Duration of recruitment:	2 ½ years
Duration of follow up:	Until death or a maximum of three years after registration
Definition of end of trial:	3 years after registration of the final patient or death of all patients, whichever is sooner

1.2 TRIAL SCHEMA



2 INTRODUCTION

2.1 BACKGROUND

Study population

Primary bone and Soft Tissue Sarcomas (STS) are rare tumours, collectively accounting for 1% of all malignancies diagnosed in the UK. In 2010 there were 531 new bone sarcoma and 3,298 new STS diagnosed. The incidence of bone sarcoma remained constant at around 7.9 per million, and the STS incidence increased slightly to 45 per million between 1996 and 2010. The 5-year relative survival rates in 2006-2010 were 55% for STS and 56% for bone sarcoma [1].

Radiotherapy (RT) plays an important role in the local management of the primary tumour in bone and STS. The IMRiS study is aiming to evaluate the role of intensity modulated radiotherapy (IMRT) in soft tissue and bone sarcomas. Three separate sarcoma cohorts will be studied: limb soft tissue sarcomas, pelvic and spinal Ewing's sarcomas, and pelvic and spinal non-Ewing's primary bone sarcomas. The role and rationale for radiotherapy in the management of each cohort is described below.

Intensity Modulated Radiotherapy

IMRT is an advanced radiotherapy technique that is able to deliver a highly conformal dose to a target with improved sparing of the surrounding normal tissues from moderate to high radiation doses. IMRT is likely to be of particular benefit for tumours that have complex shapes, or those in close proximity to sensitive normal tissues and critical organs. Reducing the dose to normal tissues may in turn reduce the acute and late side effects of treatment.

Known and potential risk/benefit of IMRT

Review of the clinical evidence supporting the use of IMRT confirms that it reduces acute and late treatment toxicity [2]. This has been investigated most extensively in head and neck cancers where IMRT has been shown to effectively reduce acute and late xerostomia. Late rectal toxicity is reduced in prostate cancer where IMRT has made safe dose escalation possible. IMRT has also been shown to improve cosmesis following RT for breast cancer. Several non-randomised studies showed consistent reduction of radiation toxicity across a variety of other tumour sites that include gynaecological cancers, central nervous system cancers, anal canal cancer and lung cancer [2].

Evidence and rationale for using IMRT in sarcoma

Evidence to support the use of IMRT in sarcoma is scant and consists of radiotherapy planning studies, retrospective case series' and a two small phase 2 studies. There has been a move towards using IMRT in Europe and the USA, but its use across the UK is sporadic and dependent upon the availability of facilities and funding rather than robust clinical evidence.

The IMRiS study will address this gap in evidence and examine the role of IMRT in three subsets of sarcoma patients which are anticipated to benefit from IMRT in slightly different ways, to evaluate whether IMRT can improve on current clinical outcomes in these disease settings. The available evidence and rationale for IMRT in each cohort are outlined below.

Delivering IMRT

IMRT can be delivered from multiple fixed beam angles or through rotational arc applications such as volumetric modulated arc therapy (VMAT) and tomotherapy. The radiotherapy is delivered using multiple small beams (beamlets) of non-uniform intensity. The IMRT treatment planning process uses a complex iterative computer-based algorithm [3]. Both fixed field and rotational IMRT techniques are allowed in the IMRiS study.

2.1.1 IMRiS Cohort 1: Primary STS of the extremities

Radiotherapy in the management of primary STS of the extremities

The majority of primary STS occur in the extremities. The standard approach to local management of these tumours is limb-sparing surgery with the addition of neo-adjuvant or adjuvant RT for patients deemed at high risk of local recurrence [4, 5]. Until recently RT has routinely been delivered using 3-dimensional conformal RT (3DCRT). 5 year local recurrence free survival rates ranging from 80% to 90% are reported with this approach [6-11].

Side effects of combined modality treatment using 3DCRT

In order to deliver the required dose to the tumour with 3DCRT (typically to a dose of 50 Gy pre-operatively and 60 to 66 Gy post-operatively), large volumes of adjacent normal soft tissue and bone can potentially receive high RT doses. The most important acute toxicity in this setting is early wound complications. In a Canadian randomised controlled trial (SR2) of 190 patients comparing pre-operative and post-operative RT, the incidence of significant wound complications (requiring a secondary operation, other invasive procedure or readmission for wound care within 120 days of surgery) was 35% and 17% respectively [12].

Late toxicity data for 3DCRT are available from retrospective series' and the SR2 trial. Side effects commonly reported include spontaneous fracture, soft tissue fibrosis, joint stiffness and oedema. The incidence of spontaneous fracture of the femur in patients treated for STS of the thigh varies from 1.2% to 8.6% [13-16]. In a database review of 691 patients, risk factors for fracture were analysed [16]. Fracture rates were reduced for the following radiotherapy dose-volume parameters: <64% of the femur receiving 40 Gy; mean dose to the femur, <37 Gy; maximum dose to the femur <59 Gy [16]. In the SR2 trial, the incidence of ≥ grade 2 late effects at 2 years after treatment in the pre-operative (50Gy) and post-operative (66Gy) cohorts respectively were fibrosis 31.5% and 48.2%; oedema 15.1% and 23.2%; joint stiffness 17.8% and 23.2% [17]. Patients who had ≥ grade 2 fibrosis, joint stiffness or oedema had significantly reduced limb functional scores [17] (Toronto Extremity Salvage Score (TESS) [18]). Retrospective series' report rates of oedema of 10% - 22% [19-21] and joint stiffness of 8% [20]. A trend is seen between radiotherapy field size and volume treated, and incidence of late soft tissue toxicity [17, 19, 22].

Intensity Modulated Radiotherapy (IMRT) for extremity STS

The current evidence supporting the use of IMRT in STS consists of RT planning studies, retrospective series', and two phase II studies.

Planning studies comparing 3DCRT with IMRT have been carried out almost exclusively in lower limb sarcomas, and have shown that IMRT increases conformality of dose to the planning target volume (PTV), reduces dose and hot spots to surrounding soft tissues and skin outside PTV, and reduces dose to the femur [23-25]. On this basis, one would expect that IMRT should reduce late radiotherapy toxicity as compared with 3DCRT.

Retrospective reviews from Memorial Sloan Kettering Cancer Centre indicate that combined modality treatment with surgery and IMRT has acceptable local control results: the 5 year local control rate was 94% in a cohort of 41 patients treated between 2002 and 2005 [26], and the 5 year incidence of local recurrence was lower following IMRT (7.6%) compared to routine 3DCRT (15.1%) in a retrospective comparison of 319 patients treated between 1996 and 2010 [27]. Both series' also reported acceptable toxicity profiles. The earlier series of 41 patients treated with pre-operative (7) or post-operative (34) IMRT and surgery, at a median follow-up of 35 months, reported rates of wound complications (19.5%), bone fracture (4.8%), ≥ grade 2 joint stiffness (17.1%) and oedema (12.2%) [26]. The later series showed reduction in toxicity compared with 3DCRT, with rates of ≥ grade 2 radiation dermatitis of 31.5% and 48.7% (p=0.002), and ≥ grade 2 oedema of 7.9% and 14.9% (p=0.05) for IMRT and 3DCRT, respectively [27].

A phase II study of 59 patients with lower limb STS treated with pre-operative IMRT aimed to reduce the dose to future surgical flaps in an attempt to reduce the incidence of wound complications. The rate of significant wound complications was 30.5%, which was not significantly lower than that seen in the pre-operative arm (35%, p=0.2) of the team's previous SR2 trial (see above) comparing pre-operative and post-operative 3DCRT [12]. There was however improved primary wound closure following IMRT, with fewer patients requiring surgical management for wound complications [12, 28].

The RTOG0630 phase II study used pre-operative image guided RT to reduce clinical target volume margins (3D CRT and IMRT) in extremity STS, aiming to reduce late radiation toxicity [29]. At a median follow-up of 3.6 years, 79 patients were enrolled, with 57 evaluable for the primary end point of ≥ grade 2 radiation toxicity at 2 years. The rates seen were lower than that in the SR2 study, with all ≥ grade 2 toxicities (subcutaneous tissue fibrosis, joint stiffness, or oedema) in 10.5% versus 37% (p<0.001). However, rates of wound complications were similar, at 36.6% and 35%, respectively.

Rationale and need for a clinical trial

IMRT is being used increasingly in Europe and the USA to treat extremity STS, but there have been no randomised controlled trials directly comparing IMRT with 3DCRT. These are unlikely to take place due to the rarity of STS. In the UK uptake of IMRT has been slower. IMRT represents a relatively recent technological advance in the delivery of radiotherapy. As such, it is costly, and access to IMRT has been prioritised for sites such as head and neck cancer, where it has been shown to be the new standard of care. In the absence of sufficient evidence, 3DCRT remains the standard approach for extremity STS in the UK. Prospective studies are required to address this lack of evidence in order to establish the use of IMRT as routine treatment for this rare disease.

The theoretical advantage to IMRT is the potential reduction in late toxicity and subsequent potential for functional improvement. There have been no prospective studies to date powered to address this, particularly where IMRT is used post-operatively. IMRiS cohort 1 will address this question.

2.1.2 IMRiS Cohort 2: Ewing's sarcoma of the pelvis and spine

Radiotherapy in the management of Ewing's sarcoma

Ewing's sarcoma is the third most common primary bone sarcoma in the UK and occurs most commonly in children and adolescents, although it can occur in adults [1]. The most common site

affected by bone sarcomas are the extremities (more than 40% of cases) followed by the pelvic bones (25%), ribs (12%) and spine (8%) [30]. Ewing's Sarcoma is treated with multimodality treatment, with chemotherapy, surgery and RT. Complete surgical excision is usually the local treatment of choice [31], and adjuvant RT may be added to reduce the risk of local recurrence. In cases where complete surgical excision is not feasible, radiotherapy alone is used to treat the primary tumour [32]. RT doses ranging from 45 to 65 Gy are recommended, depending on whether RT is used as definitive treatment or in the neo-adjuvant or adjuvant setting, although a median radical dose is usually around 55 Gy [32-34].

Until recently 3DCRT has been the standard approach to RT for Ewing's sarcoma. Treating tumours arising in the pelvis and spine with 3DCRT is challenging due to the proximity of radiosensitive normal structures such as the spinal cord and small bowel, which can limit the radiation dose that can safely be given to the tumour. A retrospective review of 24 cases treated with 3DCRT at University College London Hospital, showed that the optimal recommended RT dose could be safely given in only 70% of cases (unpublished data). The inability to deliver the optimal RT dose means that local tumour control may not be achieved.

IMRT for Ewing's sarcoma of the pelvis and spine

More conformal RT techniques including IMRT and proton beam radiotherapy (PBRT) are now used on an individual patient basis, when available, to treat these challenging tumours [35-37]. There is however very little published evidence, and a lack of robust data on the feasibility and toxicity of these techniques. PBRT has clear advantages in the dose distributions achieved, making this an attractive technique when treating children and/or tumours close to critical structures. A retrospective review of 30 children with Ewing's sarcoma at a variety of sites reported that PBRT was well tolerated with few adverse effects. Three year event free survival was 60%, the local control rate was 86% and overall survival 89% [37]. UK patients with Ewing's sarcoma who are being treated with curative intent are considered for PBRT through the UK Proton Panel. PBRT may not be feasible for all patients, and the alternative is to use IMRT. IMRT has been shown to be dosimetrically superior to 3DCRT in a planning study of three paediatric pelvic sarcomas [38], and in a study of two paediatric pelvic Ewing's sarcomas [35]. IMRT was used in 43% of cases in a series that included in total 33 spinal/pelvic tumours [36].

Rationale and need for a clinical trial

There have been no clinical trials of IMRT in Ewing's sarcoma. It is important to establish the feasibility of IMRT to achieve the required radiation doses to the tumour, and to prospectively document the side effects of treatment in this setting. IMRiS cohort 2 will address this, in Ewing's sarcoma of the spine and pelvis.

2.1.3 IMRiS Cohort 3: Other primary high grade bone sarcomas and chordoma of the spine and pelvis

Radiotherapy in the management of other high grade bone sarcomas and chordoma

IMRiS cohort 3 includes osteosarcoma, chondrosarcoma, and other less frequently diagnosed primary sarcomas of bone. Osteosarcoma commonly affects an adolescent population, chondrosarcoma occur more frequently in older patients, and chordomas are rare tumours, arising from the notochord remnants in the skull base, sacrum and spine and account for around 5% of bone sarcomas diagnosed in the UK [1]. Current standard multi-modality treatment of

osteosarcoma is with chemotherapy and surgery, aiming for wide resection margins while retaining function [39, 40]. Radiotherapy is sometimes used in the adjuvant setting [41]. Chondrosarcomas and chordomas are resistant to conventional chemotherapy, and complete surgical resection is the optimal treatment option [42, 43].

Radiotherapy may be used to treat the primary tumour when surgery is not possible. These tumours are much less radiosensitive than Ewing's sarcoma, and significantly higher radiation doses are required. This is often not feasible with 3DCRT, and local control is often difficult to achieve. A retrospective review of a series of 22 radio-resistant pelvic and spinal bone sarcomas treated at UCH with 3DCRT revealed that the intended dose (60-66Gy) was achieved in only 14% of cases with this technique (unpublished data).

High grade bone sarcomas of the pelvis and spine

Currently IMRT is used for individual patients, where available, although published evidence is very limited. Radiotherapy is used adjuvantly for resectable high grade bone sarcomas at high risk of local recurrence, or as sole modality for local treatment of inoperable tumours. In the latter setting the aim is palliation and prolonged local tumour control, aiming to deliver a dose of at least 70 Gy [41, 44]. IMRT resulted in similar dose conformality as protons in a planning study of 5 paraspinal sarcomas [45] and stereotactic IMRT with a non-invasive body frame in a series of 35 paraspinal malignancies (14 sarcomas) achieved excellent precision, allowing target doses of up to 70 Gy [46]. Reports on combined photon RT/PBRT for spinal and pelvic sarcomas are encouraging [47] with 5 year local control rates of >70%, and doses of up to 77 Gy have been used safely in a phase II study of high dose photon RT/PBRT in spinal sarcomas [48].

Chordoma of the sacrum and spine

IMRT has been used in the treatment of chordoma, both adjuvantly and as definitive treatment [49], with one study reporting using IMRT in 34 patients with sacral chordoma to a median dose of 66Gy with a 5 year local control rate of 27%. There is evidence that superior and prolonged local control and survival can be achieved in sacral chordoma with PBRT and carbon ion radiation at doses above 70 Gy [50-54]. Combined photon/proton radiotherapy has also been used to doses >73 Gy [55].

Rationale and need for a clinical trial

There is very little published on the use of IMRT in high grade bone sarcomas and chordomas. It is important to establish the feasibility of IMRT to achieve the required radiation doses to adequately treat these tumours, and to prospectively document the side effects of treatment in this setting. IMRiS cohort 3 will address this, in high grade bone sarcomas and chordomas of the pelvis and spine.

3 TRIAL DESIGN

This is a prospective multicentre phase II trial of IMRT in patients with bone or soft tissue sarcoma. Patients will be enrolled in one of three cohorts depending on the type of sarcoma they have. Each cohort will be analysed separately. Radiotherapy will be delivered with fixed beam IMRT, arc IMRT techniques, or tomotherapy.

Cohort 1: Patients with limb/limb girdle soft tissue sarcoma receiving (neo)-adjuvant radiotherapy. Pre-operative RT will be delivered at a dose of 50 Gy in 25 daily fractions over 5 weeks. Post-operative RT will be delivered at a dose of 60 Gy in 30 daily fractions to the high dose planning target volume (PTV), and 52.2 Gy in 30 daily fractions to the low dose PTV treated concurrently over 6 weeks. For patients with positive resection margins (for whom further surgery is not possible), dose is 66 Gy in 33 daily fractions to the high dose PTV, and 53.46 Gy in 33 daily fractions to the low dose PTV treated concurrently over 6 weeks.

Cohort 2: Patients with Ewing's sarcoma of the spine/pelvis receiving definitive radical or (neo)-adjuvant radiotherapy. Pre-operative RT will be delivered at a dose of 50.4 Gy in 28 daily fractions over 5 ½ weeks. Post-operative RT will be delivered at a dose of 54 Gy in 30 daily fractions over 6 weeks. Primary RT will be delivered at a dose of 54 Gy in 30 daily fractions over 6 weeks.

Cohort 3: Patients with non-Ewing's primary bone sarcomas of the spine/pelvis receiving definitive radical or adjuvant radiotherapy. Primary RT will be delivered at a dose of 70 Gy in 35 daily fractions over 7 weeks. Adjuvant RT for primary bone sarcoma will be delivered at a dose of 60 Gy in 30 daily fractions over 6 weeks. Adjuvant RT for chordoma will be delivered at a dose of 70 Gy in 35 daily fractions over 7 weeks.

3.1 TRIAL OBJECTIVES

3.1.1 Primary objectives

Cohort 1 (limb soft tissue sarcomas):

- To establish if the use of IMRT will reduce late normal tissue toxicity (fibrosis)

Cohort 2 and 3 (pelvis and spine bone sarcomas):

- To establish if the use of IMRT will enable the achievement of a radiotherapy treatment plan that delivers the optimal dose while keeping within normal tissue tolerances

3.1.2 Secondary objectives

All cohorts:

- To explore the incidence and pattern of radiotherapy-related acute toxicity from IMRT
- To explore the incidence and pattern of all radiotherapy-related late normal tissue toxicities (including oedema and joint stiffness)
- To describe clinical outcomes (survival, local control, disease progression) following IMRT in these patient populations

Cohort 1 (limb soft tissue sarcomas) only:

- To establish the incidence and severity of wound complications in patients who have definitive surgery before or after IMRT
- To establish the effect of IMRT on function and quality of life
- To identify specific dose-volume constraints for anatomical regions of interest within the normal limb tissues lying outside the target volume, predicting for the frequency and intensity of side-effects induced by radiotherapy
- To identify the anatomical regions of interest within normal limb tissues where delivery of high dose radiotherapy may result in specific toxicities such as fibrosis, joint arthrosis and lymphoedema

Cohorts 2 and 3 only:

- To perform dosimetric analyses using data from patients double planned using IMRT and PBRT.

3.2 TRIAL ENDPOINTS

3.2.1 Primary endpoints

Cohort 1 (limb soft tissue sarcomas):

- The rate of ≥ grade 2 late soft tissue fibrosis at 2 years following radiotherapy as assessed by RTOG late radiation morbidity criteria.

Cohort 2 (Ewing's sarcoma of the spine/pelvis):

- The proportion of patients in whom 90% of the planPTV receives 95% of the optimal prescription dose

Cohort 3 (non-Ewing's primary bone sarcomas of the spine/pelvis):

- The proportion of patients in whom 80% of the planPTV receives 95% of the optimal prescription dose

For further details on how the endpoints were derived for cohorts 2 & 3 please refer to section 17.5 (Notes on primary endpoints for cohorts 2 and 3).

3.2.2 Secondary endpoints

Cohort 1 (limb soft tissue sarcomas):

- Acute RT toxicity
- Late RT toxicity
- Patient reported limb function and quality of life
- Rate and severity of wound complications within 120 days of surgery
- Time to local tumour recurrence
- Disease free and overall survival
- Dose volume constraints for:
  - Lymphoedema
  - Fibrosis

- Fracture
- Joint stiffness

Cohorts 2 and 3 (pelvic and spinal bone sarcomas):

- Acute RT toxicity
- Late RT toxicity
- Response at RT treatment site by RECIST 1.1 (for definitive radical RT/patients with evaluable residual disease after surgery) at 6 months
- Time to local recurrence (for adjuvant RT, i.e. patients who had surgery)
- Time to local disease progression (for definitive radical RT i.e. patients who did not have surgery)
- Disease-free survival and overall survival
- Creation of additional proton beam radiotherapy plan for dosimetric comparison with IMRT plan

Cohort 2 (Ewing's sarcoma of the spine/pelvis):

For individual plans:

- Percentage volume of planPTV receiving 95% of the prescription dose (50.4Gy/54Gy)
- Dose delivered to 95%, 80%, 70%, 60% and 50% volume of planPTV

Cohort 3 (non-Ewing's primary bone sarcomas of the spine/pelvis) only:

For individual plans:

- Percentage volume of planPTV receiving 95% of prescription dose (60Gy/70Gy)
- Dose delivered to 95%, 80%, 70%, 60% and 50% volume of planPTV

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
- '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 a 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 Research Governance Framework
- Data collection requirements, including adherence to eCRF completion timelines as per section 10.4 (Timelines for Data Entry)
- Monitoring requirements, as outlined in protocol section 13 (Trial Monitoring and Oversight) and trial monitoring plan
- Radiotherapy treatment requirements

Sites must also meet the following trial-specific requirements:

- Successful completion of IMRT Quality Assurance (see section 4.2.2)

4.1.1 Selection of Principal Investigator and other investigators at sites

Sites must appoint an appropriate Principal Investigator (PI), i.e. a health care professional authorised by the site, to lead and coordinate the work of the trial on behalf of the site. Co-investigators at site wishing to participate in the trial must be trained and approved by the PI. All investigators must be medical doctors and have experience of treating bone and/or soft tissue sarcomas with radiotherapy and be a member (or an extended member) of a sarcoma MDT. 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 leaves/goes on a leave of absence, UCL CTC must be informed promptly and a new PI identified and appointed by the site.

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). A current, signed copy of the CV with evidence of GCP training (or copy of 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, 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, as per monitoring plan.

4.2.2 IMRT Quality Assurance

Sites are required to have completed the following before activation:

- the National Radiotherapy Clinical Trials Quality Assurance Group IMRT QA credentialing programme
- the IMRiS specific QA programme

Further details can be found in Appendix 3 and accompanying QA protocol document, and on the National Radiotherapy Clinical Trials Quality Assurance Group website (www.rttrialsqa.org.uk/).

4.2.3 Required documentation

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

- Trial specific UK **Site Registration Form** (identifying relevant local staff)
- Relevant **institutional approvals**
- A completed **Site Staff 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 signed and dated copy of the **PI's current CV** (with documented **up-to-date GCP training** or copy of GCP training certificate)
- Evidence of successful completion of the National Radiotherapy Clinical Trials Quality Assurance Group IMRT QA credentialing program
- Evidence of successful completion of the IMRiS QA programme
- A signed **Clinical Trial Site Agreement (CTSA)** between the Sponsor and the relevant institution (usually an NHS Trust) must also be in place before site activation.

4.2.4 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. **Sites may not start to approach patients until after the site activation letter has been issued.**

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 of eCRFs (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

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 for either soft tissue sarcoma (cohort 1) or bone sarcoma (cohorts 2 and 3), are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved consent form.

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.

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 trial patient information sheet for either soft tissue or bone sarcoma should be discussed with the patient. A **minimum of twenty four (24)** hours should be allowed for the patient to consider and discuss participation in the trial. However, in order to prevent unnecessary return visits patients may consent on the same day as being given the information sheet, provided the member of staff taking consent is satisfied that the patient understands the trial and implications. A member of the research team at the hospital must then phone the patient in the following days to confirm that they are still willing to participate in the trial. Written informed consent on the current approved version of the trial consent form must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient notes.

Site staff are responsible for:

- checking that the current approved version of the relevant patient information sheet and consent form are used
- checking that information on the consent form is complete and legible
- checking that the patient has initialled <u>all</u> relevant sections and signed and dated the form
- checking that an appropriate member of staff has countersigned and dated the consent form 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, follow up phone call if applicable etc.)
- following registration, adding the patient's trial number to all copies of the consent form, which should be filed in the patient's medical notes and investigator site file
- following registration, giving the patient a copy of their signed consent form, patient information sheet, and patient contact card
- The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time. Also refer to section 14 (Withdrawal of Patients).

6 SELECTION OF PATIENTS

6.1 SCREENING LOG

A screening log must be maintained and appropriately filed at site. Sites should record each patient considered for enrolment and/or discussed at an MDT meeting who is deemed potentially eligible, and the reasons why they were not registered in the trial if this is the case. The log must be sent to UCL CTC when requested.

6.2 PATIENT ELIGIBILITY

There will be no exception to the eligibility requirements at the time of registration. Queries in relation to the eligibility criteria must be addressed prior to registration. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

A patient's eligibility must be confirmed by an investigator who is suitably qualified and who has been allocated this duty, as documented on the site staff delegation log, prior to registering the patient. Confirmation of eligibility must be documented in the patient's notes and on the registration form on the eCRF.

Patients must give written informed consent before any trial specific screening investigations may be carried out. Refer to section 9.1.1 (Cohort 1 - Pre-registration Evaluation) and 9.2.1 (Cohorts 2 & 3 - Pre-registration Evaluation) for the list of assessments and procedures required to evaluate the suitability of patients prior to entry.

6.2.1 Inclusion criteria

1. Histopathological diagnosis of:
   - Soft tissue sarcoma of the upper or lower limb or limb girdle (cohort 1), ***or***
   - Ewing's sarcoma of bone arising in the pelvis or spine (cohort 2), ***or***
   - High grade non-Ewing's primary bone sarcoma or chordoma arising in the pelvis or spine (cohort 3)
2. Patient requires:
   - (neo)adjuvant RT (cohort 1)
   - (neo)adjuvant or primary radical RT (cohort 2)
   - adjuvant or primary radical RT (cohort 3)
3. WHO performance status 0-2 (see Appendix 2)
4. Aged ≥16 years
5. Patients fit enough to undergo radiotherapy treatment and willing to attend follow up visits as per protocol
6. Women of child-bearing potential must have a negative pregnancy test prior to trial entry. Female patients of child-bearing potential and male patients with partners of child-bearing

potential must agree to use adequate contraception methods, which must be continued for 3 months after completion of treatment (see section 6.2.3, Pregnancy and birth control)

7. Capable of giving written informed consent

N.B. Patients with metastatic disease who are receiving radical radiotherapy as part of their treatment are potentially eligible, as long as they are expected to be able to be assessed for the primary endpoints of the study. For cohort 1, the primary endpoint is defined as 'the rate of ≥ grade 2 late soft tissue fibrosis at 2 years following radiotherapy', which means that there must be a good expectation that the patient will be alive at 2 years following radiotherapy. For cohorts 2 and 3, the primary endpoints are planning endpoints, which will be reached once the radiotherapy plan has been completed, so inclusion of patients with metastatic disease will not impact this.

6.2.2 Exclusion criteria

1. Previous RT to the same site
2. Patients receiving *concurrent* chemotherapy with radiotherapy (neo-adjuvant chemotherapy *prior* to radiotherapy is permitted) (Cohort 1 only)
3. Patients with bone sarcomas eligible for proton beam radiotherapy (PBRT); **N.B.** if a patient is not to have PBRT for whatever reason, they may be considered for IMRiS
4. Diagnosis of paediatric type alveolar or embryonal rhabdomyosarcomas
5. Pregnancy
6. Patients with concurrent or previous malignancy that could compromise assessment of the primary and secondary endpoints of the trial (these cases must be discussed with UCL CTC prior to the patient being approached)

6.2.3 Pregnancy and birth control

In fertile men, RT can affect sperm count and function. It is difficult to predict the effect of radiation on a child fathered during RT treatment. The Investigator must discuss birth control measures with the patient, and where appropriate it must be used during RT until 3 months after treatment is completed. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

In women of childbearing potential, RT can affect the embryo/foetus. Adequate contraception is required during RT until 3 months after treatment is completed.

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
- been postmenopausal for 12 consecutive months (i.e. who has had menses at any time in the preceding 12 consecutive months without an alternative medical cause).

Pregnancy testing

All women of childbearing potential who are at risk of becoming pregnant must undergo a pregnancy test (blood or urine) prior to registration.

Pregnancy monitoring

If a female patient or the female partner of a male patient becomes pregnant from consent to 3 months after stopping RT, the site must inform UCL CTC immediately (See section 11 (Safety Reporting) for details on the reporting procedure).

6.2.4 Long term infertility

In fertile men, RT given to the pelvic or thigh area may cause infertility even at low doses to the testes. Fertility may be preserved by sperm banking prior to starting RT and may be offered.

In women of childbearing potential, RT given to the pelvic area may cause infertility, even at low doses to the ovaries. In addition, ovarian hormonal production is affected which may cause the onset of early menopause following RT. Ovarian transposition away from RT fields prior to RT may be offered to reduce this risk. Treatment for many patients with bone sarcomas will include systemic chemotherapy, which can similarly affect fertility, and this needs to be taken into account.

7 REGISTRATION PROCEDURES

7.1 REGISTRATION

Patient registration will be performed via a remote electronic data capture system hosted by UCL CTC. Please refer to the registration instructions provided in the IMRiS Database Manual. Patients must be confirmed to be eligible and have given consent prior to registration. Following pre-registration evaluations (as detailed in sections 9.1.1and 9.2.1), confirmation of eligibility and consent of a patient at a site, the registration should be completed on the remote data capture system. Registration must take place prior to commencement of trial treatment.

Site staff responsible for patient registration must request access to the ECRF database by completing their contact details on the site contacts form and delegation log. Access to the database and instructions are provided by UCL CTC.

Note that patient initials and date of birth are required to register a patient. Upon registration a trial number will be assigned for the patient and these details appear on the registration confirmation screen. The trial number must be recorded in the patient notes. Confirmation of successful registration will be sent to the person registering the patient.

Sites should contact UCL CTC if there are any difficulties in accessing the registration database.

CONTACT DETAILS
IMRiS Trial Coordinator: 020 7679 9281

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

- A copy of their signed consent form and patient information sheet
- 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

8 TRIAL TREATMENT

8.1 TRIAL TREATMENT DETAILS

RT should aim to start within 4 weeks of registration, and no longer than 12 weeks after surgery. For adjuvant RT patients, if wound healing delays start of RT, this will be permissible and must be discussed with UCL CTC. RT will be given as follows:

Cohort 1 (limb/limb girdle soft tissue sarcoma):

- Pre-operative RT: 50 Gy in 25 daily fractions, delivered Monday to Friday over 5 weeks
- Post-operative RT: 60 Gy in 30 daily fractions to the high dose planning target volume (PTV) (PTV_6000) and 52.2 Gy in 30 daily fractions to the low dose PTV (PTV_5220) treated concurrently, delivered Monday to Friday over 6 weeks
- Post-operative RT with positive resection margins: 66 Gy in 33 daily fractions to the high dose PTV (PTV_6600), and 53.46Gy in 33 fractions to the low dose PTV (PTV_5346) treated concurrently, delivered Monday to Friday over 6 ½ weeks

Cohort 2 (Ewing's sarcoma of spine/pelvis):

- Pre-operative RT: 50.4 Gy in 28 daily fractions delivered Monday to Friday over 5 ½ weeks
- Post-operative RT: 54 Gy in 30 daily fractions delivered Monday to Friday over 6 weeks
- Primary radical RT: 54 Gy in 30 daily fractions delivered Monday to Friday over 6 weeks

RT may be given concurrently with or after completion of chemotherapy as indicated. The timing of RT and the chemotherapy schedule is to be decided by the treating clinician, or as per trial protocol for patients registered in the Euro-Ewing's 2012 trial. Delays in starting RT should be avoided.

Cohort 3 (primary non-Ewing's bone sarcoma of spine/pelvis):

- Primary radical RT: 70 Gy in 35 daily fractions, delivered Monday to Friday over 7 weeks
- Post-operative RT (non-chordoma): 60 Gy in 30 daily fractions, delivered Monday to Friday over 6 weeks
- Post-operative RT (chordoma): 70 Gy in 35 daily fractions, delivered Monday to Friday over 7 weeks

RT may be given following chemotherapy for patients with high grade primary bone sarcomas (spindle cell sarcoma of bone and osteosarcoma).

All patients must be treated using IMRT only (including fixed-beam or rotational arc therapy – VMAT or Tomotherapy) to obtain uniform coverage of the target volumes and fulfil the dose constraints detailed in the radiotherapy target definition outlining and planning guidelines (Appendix 3).

For full details of RT planning and delivery, please refer to Appendix 3.

8.2 SUPPORTIVE CARE

Supportive management and treatment for RT related toxicity will be according to treatment protocols at individual sites.

8.3 CLINICAL MANAGEMENT AFTER TREATMENT DISCONTINUATION

Subsequent treatment will be at the discretion of the treating investigator. Also refer to sections 9 (Assessments) and 14 (Withdrawal of Patients) for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.

9 ASSESSMENTS

For a summary of scheduled assessments, please see the Schedule of Assessments (Appendix 4).

9.1 COHORT 1 ASSESSMENTS

9.1.1 Pre-registration Evaluation

Patients must give written informed consent **before** any trial specific screening investigations may be carried out. The following assessments or procedures are required to evaluate the suitability of patients prior to entry into the trial:

- Histological confirmation of disease
- Diagnostic MRI and/or CT (if there is a contraindication to MRI) of the primary tumour site as per routine practice
    - For patients receiving adjuvant radiotherapy the MRI/CT should ideally have been performed within 1 month prior to surgery
    - For patients receiving neo-adjuvant radiotherapy, the MRI/CT should ideally be performed within 1 month of starting radiotherapy, although decisions on repeating scans older than 1 month will be made at the treating clinician's discretion
- Chest imaging (CT or chest x-ray) within 3 months of registration, as per routine practice

Within 14 days prior to registration:

- Clinical review
- Relevant medical history
- Assessment of adverse events (AEs) using CTCAE v4.03
- Assessment of WHO performance status
- Pregnancy test (urine or blood) in females of child bearing potential
- Measurement of height & weight, assessment of smoking status, diabetic status and limb function or mobility

9.1.2 Pre-treatment Assessments

Within 28 days prior to starting treatment.

- Assessment of wound related clinical findings up to 120 days after surgery (if applicable)
- EORTC QLQ-C30 quality of life questionnaire
- Toronto Extremity Salvage Score (TESS) questionnaire
- Musculoskeletal Tumor Society Rating Scale (Appendix 5)

The following pre-registration assessments do not need to be repeated if done within 28 days prior to starting treatment:

- Clinical review
- Assessment of AEs using CTCAE v4.03
- Assessment of WHO performance status

9.1.3 Post-surgery Assessment of Wound Complications up to 120 Days after Surgery

Patients should be assessed for wound complications during assessment visits occurring from surgery and up to 120 days after surgery. Post-Surgery Wound Assessment wound complications are defined as:

- 2nd operation under general or regional anaesthesia for wound repair (debridement, operative drainage, unplanned secondary wound closure using free muscle flaps or skin grafts)
- Wound management without 2nd operation (invasive procedure without general or regional anaesthesia, e.g. aspiration of seroma, readmission for wound care such as intravenous antibiotics, persistent deep wound packing for ≥120 days)

9.1.4 Assessments during Treatment

During treatment patients should be seen weekly (in an appropriate on-treatment review clinic, which may be run by a doctor, radiotherapy nurse or radiographer) and the following assessments performed:

- Clinical review
- Assessment of adverse reactions (ARs) using CTCAE v4.03
- Assessment of acute radiation morbidity using the RTOG Acute Radiation Morbidity Scoring Criteria
- WHO performance status
- Assessment of wound related clinical findings up to 120 days after surgery (if applicable)

9.1.5 Assessments on Completion of Trial Treatment

The following should be carried out at least **28 days (and up to 35 days)** after the last fraction of radiotherapy:

- Clinical review
- Assessment of ARs using CTCAE v4.03
- Assessment of acute radiation morbidity using the RTOG Acute Radiation Morbidity Scoring Criteria
- WHO performance status
- Assessment of wound related clinical findings up to 120 days after surgery (if applicable)

9.1.6 Follow-up Assessments after Completion of Treatment

Patients will be followed monthly for the first 3 months after completion of radiotherapy, then 3-monthly for up to 3 years after date of registration. All visits should be carried out at the specified time +/- 2 weeks.

N.B. For pre-operative RT patients, following their last fraction of RT, it may be necessary to omit a follow up visit immediately after surgery, as it may be difficult for the patient to attend clinic.

Patients should have the following assessments at each visit unless stated otherwise:

- Clinical review

- WHO performance status
- Assessment of radiation morbidity:
  - using the RTOG Acute Radiation Morbidity Scoring Criteria up to day 90 after start of treatment
  - using the RTOG/EORTC Late Radiation Morbidity Scoring Criteria [56] (skin, subcutaneous tissue fibrosis, joint stiffness, bone) from day 91 after start of treatment
  - using Stern's scale [29, 57] for oedema from day 91 after start of treatment (Appendix 6)
- Clinical assessment of local tumour control at primary site at each 3-monthly visit
- Assessment of wound related clinical findings up to 120 days after surgery (if applicable)
- Chest x-ray at each 3-monthly follow up visit
- TESS questionnaire [18, 58] at 1 year and 2 years after registration
- Musculoskeletal Tumor Society Rating Scale [59, 60] at 1 year and 2 years after registration (Appendix 5)
- EORTC QLQ-C30 quality of life questionnaire at 1 year and 2 years after registration
- Assessment at 2 years after registration of any further surgeries or use of antibiotics for wound management in the last 24 months

9.1.7 Assessments after Disease Progression

If a patient progresses within 2 years from the date of registration, they should continue to be followed up if possible, fitting in with their routine oncological care. Investigators should use their judgement on a case-by-case basis to perform follow up on patients according to their circumstances and what is clinically reasonable.

Where possible the following assessments should be performed:

- Clinical review
- WHO performance status
- Assessment of radiation morbidity:
  - using the RTOG Acute Radiation Morbidity Scoring Criteria up to day 90 after start of treatment
  - using the RTOG/EORTC Late Radiation Morbidity Scoring Criteria [56] (skin, subcutaneous tissue fibrosis, joint stiffness, bone) from day 91 after start of treatment
  - using Stern's scale [29, 57] for oedema from day 91 after start of treatment (Appendix 6)
- Clinical assessment of local tumour control at primary site
- TESS questionnaire [18, 58] at 1 year and 2 years after registration
- Musculoskeletal Tumor Society Rating Scale [59, 60] at 1 year and 2 years after registration (Appendix 5)
- EORTC QLQ-C30 quality of life questionnaire at 1 year and 2 years after registration

After the 2 year follow up visit patients should continue to be followed up on a regular basis as per standard oncological care.

9.2 COHORT 2 & 3 ASSESSMENTS

9.2.1 Pre-registration Evaluation

Patients must give written informed consent **before** any trial specific screening investigations may be carried out. The following are required to evaluate the suitability of patients prior to entry into the trial:

- Histological confirmation of disease
- Diagnostic MRI and/or CT (if there is a contraindication to MRI) of the primary tumour site as per routine practice
    - For cohort 2 patients, radiotherapy should be planned with reference to the baseline pre-chemotherapy MRI when the tumour was at its greatest extent
    - For cohort 3 patients receiving adjuvant radiotherapy after surgery alone (i.e. no neo-adjuvant chemotherapy) the MRI/CT should ideally have been performed within 1 month prior to surgery
    - For cohort 3 patients receiving adjuvant radiotherapy who have also received neo-adjuvant chemotherapy prior to surgery, radiotherapy should be planned with reference to the baseline pre-chemotherapy MRI when the tumour was at its greatest extent
    - Patients receiving radical radiotherapy, or those who have evaluable residual disease after surgery, should have their disease measured according to RECIST v1.1
- Chest imaging (CT or chest x-ray) as per routine practice

Within 14 days prior to registration:

- Clinical review
- Relevant medical history
- Assessment of adverse events (AEs) using CTCAE v4.03
- Assessment of WHO performance status
- Pregnancy test (urine or blood) in females of child bearing potential

9.2.2 Pre-treatment Assessments

Within 28 days prior to starting treatment.

- Post-surgery assessment of wound healing (if recent surgery)

The following pre-registration assessments do not need to be repeated if done within 28 days prior to starting treatment:

- Clinical review
- Assessment of AEs using CTCAE v4.03
- Assessment of WHO performance status

9.2.3 Assessments during Treatment

During treatment patients should be seen weekly (in an appropriate on-treatment review clinic, which may be run by a doctor, radiotherapy nurse or radiographer) and the following assessments performed:

- Clinical review
- Assessment of adverse reactions (ARs) using CTCAE v4.03
- Assessment of acute radiation morbidity using the RTOG Acute Radiation Morbidity Scoring Criteria
- WHO performance status

9.2.4 Assessments on Completion of Trial Treatment

The following should be carried out at least **28 days (and up to 35 days)** after the last fraction of radiotherapy:

- Clinical review
- Assessment of ARs using CTCAE v4.03
- Assessment of acute radiation morbidity using the RTOG Acute Radiation Morbidity Scoring Criteria
- WHO performance status

9.2.5 Follow-up Assessments after Completion of Treatment

Patients will be followed up for up to 3 years after the date of registration or until June 2020, whichever is sooner, approximately 3-monthly for the first 2 years and then as per local practise for the 3rd year of follow up.

Patients should have the following assessments at each visit unless stated otherwise:

- Clinical review
- WHO performance status
- Assessment of radiation morbidity:
  - using the RTOG Acute Radiation Morbidity Scoring Criteria up to day 90 after start of treatment
  - using the RTOG/EORTC Late Radiation Morbidity Scoring Criteria (skin, subcutaneous tissue fibrosis, bone, joint stiffness) from day 91 after start of treatment
- Post-radiotherapy MRI of the treated site 6 months after completion of radiotherapy to assess response at RT treatment site by RECIST 1.1 for definitive radical RT/patients with evaluable residual disease after surgery
- Clinical assessment of local tumour control at primary site
- Post-surgery assessment of wound healing (if recent surgery)

9.2.6 Assessments after Disease Progression

After documentation of progressive disease, patients will continue to be followed up on a regular basis as per standard oncological care but will not need specific trial assessments. Assessment

for information on local control at the primary tumour site and survival will be requested to be submitted every 6 months.

10 DATA MANAGEMENT AND DATA HANDLING GUIDELINES

Data will be collected from sites using an eCRF (electronic case report form) created and maintained by UCL CTC. Data entered onto the eCRF must be verifiable from source data at site.

10.1 ENTERING DATA INTO THE ECRF

The eCRF must be completed by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. Each authorised staff member will have their own unique login details for the eCRF. They must never be shared among staff as the eCRF audit trail will record all entries/changes made by each user. The PI is responsible for the accuracy of all data reported in the eCRF.

The use of abbreviations and acronyms should be avoided.

10.2 CORRECTIONS TO ECRF FORMS

Corrections can be made to data on the eCRF where necessary, the eCRF audit trail will record the original data, the change made, the user making the change and the date and time.

10.3 MISSING DATA

To avoid the need for unnecessary data queries, fields should not be left blank on the eCRF. If data is unavailable, please refer to the eCRF user guide for information on how to indicate that data is “Not Done”, Not Applicable”, “Not Available” or “Not Known” (only use if every effort has been made to obtain the data).

10.4 TIMELINES FOR DATA ENTRY

The relevant eCRF forms must be completed as soon as possible after a patient’s visit. Eligibility and registration forms must be completed for a patient to be registered onto the study. All other forms must be completed within 7 days of the patient being seen.

Sites who persistently do not enter 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 13.2 (’For Cause’ On-Site Monitoring) for details.

10.5 DATA QUERIES

Data entered onto the eCRF will be subject to some basic checks at the time of entry, and any discrepancies will be flagged to the user in the form of a warning. The data can be corrected immediately, or where this is not possible, the warning can be saved and the data amended at a later stage.

Further data review will be carried out at UCL CTC and queries raised where necessary. Further guidance on the process for handling data queries can be found in the eCRF user guide.

11 SAFETY REPORTING

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 radiotherapy 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 radiotherapy, whether or not related. See section 11.2.1 for AE reporting procedures.

Adverse Reaction (AR)

All untoward and unintended responses to radiotherapy treatment related to any dose administered. A causal relationship between radiotherapy 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)

Related and Unexpected Serious Adverse Reaction

An adverse reaction meeting the following criteria:

- Serious – meets one or more of the serious criteria above
- Related – assessed by the local investigator 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 (RSI)

11.2 Reporting Procedures

11.2.1 All Adverse Events (AEs)

All adverse events that occur between informed consent and start of radiotherapy must be recorded in the patient notes and the trial eCRF.

All adverse reactions that occur between the start of radiotherapy and 30 days after last radiotherapy administration must be recorded in the patient notes and the trial eCRF. In addition, all SARs (i.e. a SAE considered related to radiotherapy) that occur between the start of radiotherapy and end of trial (see section 15.1 (End of Trial) for end of trial definition) must be reported to UCL CTC using the trial specific SAR Report. Also refer to section 11.2.6 (Serious Adverse Reactions (SARs)).

Pre-existing conditions do not qualify as adverse events unless they worsen.

11.2.2 Overdoses

All accidental or intentional overdoses, whether or not they result in adverse events, must be recorded in the patient notes and eCRF. Overdoses resulting in an adverse reaction are classified as SARs and must also be reported to UCL CTC according to SAR reporting procedures. The fact that an overdose has occurred must be clearly stated on the SAR Report. Also refer to section 11.2.6 (Serious Adverse Reactions (SARs)).

Sites must inform UCL CTC immediately when an overdose has been identified. Also refer to section 12 (Incident Reporting).

11.2.3 Adverse Event Term

An adverse event term must be provided for each adverse event. Wherever possible a valid term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v4.03, should be used. This is available online at:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

11.2.4 Severity

Severity grade of each adverse event must be determined by using CTCAE v4.03

11.2.5 Causality

The relationship between the treatment and an adverse event will be assessed. For ARs, the local PI or designee will assess whether the event is causally related to trial treatment. For SARs, a review will also be carried out by the Sponsor's delegate.

Causal relationship to radiotherapy must be evaluated as either:

- 'Related' (reasonable possibility), or
- 'Not related' (no reasonable possibility)

11.2.6 Serious Adverse Reactions (SARs)

SARs must be submitted to UCL CTC by fax within **24 hours** of observing or learning of the event, using the trial specific SAR Report. All sections on the SAR 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 SAR Report to avoid unnecessary queries.

11.2.7 Exemptions from SAR Report submission

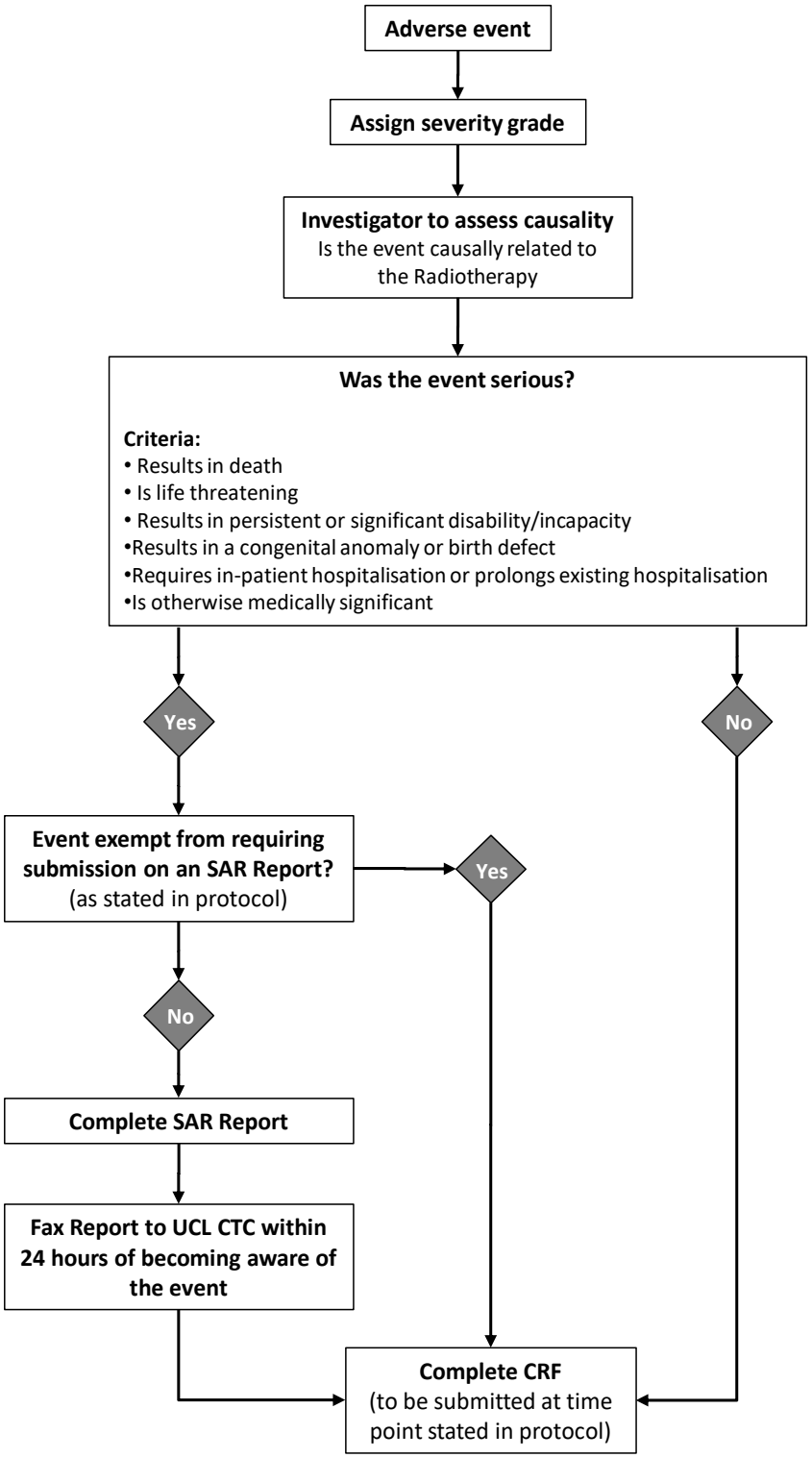
For this trial, the following events are exempt from requiring submission on a SAR Report, but must be recorded on the relevant forms of the trial eCRF:

- hospitalisation for elective treatment or palliative care
- disease progression (including disease related deaths)
- any event occurring in patients that is not considered to be causally related to radiotherapy (e.g. related to chemotherapy or surgery)
    - n.b. any serious events related to chemotherapy should be reported by sites to the MHRA using the yellow card system

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

Fax: +44 (0)20 7679 9871

Adverse Event Reporting Flowchart



11.2.8 SAR Follow-Up Reports

All SARs must be followed-up until resolution and until there are no further queries. The PI, or other delegated site investigator, must provide follow-up SAR Reports if the SAR had not resolved at the time the initial report was submitted. Sites must ensure any new and relevant information is provided promptly. If the 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 within 24 hours to UCL CTC, the circumstances that led to this must be detailed in the SAR Report to avoid unnecessary queries.

11.2.9 SAR Processing at UCL CTC

On receipt of the SAR 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 list of expected adverse events in protocol Appendix 7.

The CI, or their delegate (e.g. a clinical member of the TMG), may be contacted to review the SAR and to perform an evaluation of causality on behalf of UCL CTC.

11.3 Related and Unexpected Serious Adverse Reactions

If the event is evaluated as a Related and Unexpected SAR, UCL CTC will submit a report to the REC within 15 calendar days. Where there are conflicting evaluations of causal relationship by the site and UCL CTC/CI, both opinions will be reported.

11.3.1 Informing Sites of Related and Unexpected SARs

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

11.4 Safety Monitoring

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

Trial safety data will be monitored to identify:

- new adverse reactions to the radiotherapy
- trial related events that are not considered related to radiotherapy

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

11.5 Pregnancy

Reporting Period

If a female patient or the female partner of a male patient becomes pregnant at any point from consent to 3 months after stopping radiotherapy, a completed trial specific Pregnancy Report must be submitted to UCL CTC by fax within **24 hours** of learning of its occurrence.

Consent must be requested from the pregnant patient/partner to collect information on the pregnancy. The trial-specific pregnancy monitoring information sheets and informed consent

form for trial patients/partners must be used for this purpose. If Consent is not given by the patient/partner, 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 a completed Pregnancy Report within 24 hours of becoming aware of the pregnancy to UCL CTC

Fax: +44 (0)20 7679 9871

Pregnancy Follow-Up Reports

For pregnant patients/partners who consent, their pregnancy must be followed-up until an outcome is determined and may also be followed for up to 6-8 weeks following delivery of the child to collect information on any ante- or post-natal problems. Follow-up Pregnancy Reports must be submitted to UCL CTC by fax within **24 hours** of learning of the outcome. Reports must include an evaluation of the possible relationship of each trial treatment to the pregnancy outcome.

SARs during pregnancy

Any SAR occurring in a pregnant patient/partner must be reported using the trial specific SAR Report, according to SAR reporting procedures. Refer to section 11.2.6 (Serious Adverse Reactions (SARs)) for details.

Pregnancy Report processing at UCL CTC

UCL CTC will submit a report to the REC should the pregnancy outcome be evaluated as a related and unexpected SAR. Refer to section 11.3 (Related and Unexpected Serious Adverse Reactions) for details.

12 INCIDENT REPORTING AND SERIOUS BREACHES

12.1 INCIDENT REPORTING

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. An incident report may be requested and will be provided but an equivalent document (e.g. Trust Incident Form) is acceptable where already completed.

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.

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.

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 (or equivalent standards for conduct of non-CTIMPs) 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 the principles of GCP and/or the protocol, including failure to report SARs occurring on study within the specified timeframe, may be deemed a serious breach.

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

13 TRIAL MONITORING AND OVERSIGHT

Participating 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.

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 will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

13.1 CENTRAL MONITORING

Sites will be requested to submit screening logs and staff delegation logs to UCL CTC at the frequency detailed in the trial monitoring plan, or on request and these will be checked for consistency and completeness. Also refer to sections 4.2.2 (IMRT Quality Assurance) and 6.1 (Screening Log).

Sites will be required to complete information about the patient's informed consent process on the eCRF when registering the patient. Details of the versions of informed consent form/patient information sheet used, patient completion of the consent form, the name of the person taking consent etc., will be recorded and are subject to review by UCL CTC as part of patient eligibility. Also refer to section 5 (Informed consent).

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File at the frequency detailed in the trial monitoring plan. 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 10.5 (Data Queries).

Where central monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk (e.g. evidence of an overdose having been administered), the matter will be raised urgently with site staff and escalated as appropriate (refer to section 12 (Incident Reporting) and 13.2 ('For Cause' On-Site Monitoring) for further details).

13.2 'FOR CAUSE' ON-SITE MONITORING

On-site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements. Sites will be sent a letter in advance outlining the reason(s) for the visit and confirming when it will take place. The letter will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities and who will be performing the visit.

Following a monitoring visit, 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.

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) for details.

13.3 Oversight Committees

13.3.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialities and IMRiS trial staff from UCL CTC (see page 1). 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 Sarcoma Clinical Studies Group.

The TMG will review substantial amendments to the protocol prior to submission to the REC. All PIs will be kept informed of substantial amendments through their nominated responsible individual and are responsible for their prompt implementation.

A TMG charter, which outlines the responsibilities for the IMRiS trial, must be signed by all members of the committee before the first meeting is held.

13.3.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder and the Sponsor.

The IMRiS trial is reviewed by an established UCL CTC TSC that has oversight of a number of trials. All members have signed a TSC charter.

13.3.3 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 safety reporting which are conducted in accordance with section 11 (Safety Reporting).

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

14.2 DISCONTINUATION OF TRIAL TREATMENT

A patient may be withdrawn from trial treatment whenever such treatment 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 during radiotherapy
- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- Patient decision not to continue with trial treatment
- Any alterations in the patient's condition which justifies the discontinuation of radiotherapy in the site investigator's opinion
- Non-compliance with radiotherapy treatment and trial procedures
- If a female patient becomes pregnant or fails to use adequate birth control (for patients of childbearing potential)

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

Patient withdrawal from trial treatment

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.

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 essential safety data, and recorded on the relevant eCRF form. In this event, data due up to the date of withdrawal must be completed but no further data other than essential safety data sent to UCL CTC.

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 data.

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.

15 TRIAL CLOSURE

15.1 END OF TRIAL

For regulatory purposes the end of the trial will be 3 years after registration of the final patient in cohort 1, which will be in June 2020, or death of all patients, whichever is sooner, at which point the 'declaration of end of trial' form will be submitted to the ethics 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 securely for a minimum of 5 years after the end of the trial, and in accordance with national legislation and for the maximum period of time permitted by the site.

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 (see section 13.3.2). 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 any patients recruited into the trial at that site and other responsibilities continue as per the CTSA.

16 QUALITY ASSURANCE

16.1 QA FOR RADIOTHERAPY

Quality Assurance for Radiotherapy

The radiotherapy quality assurance (RT QA) programme for the trial will be co-ordinated by the National Radiotherapy Trials Quality Assurance (RTTQA) group. Details on the QA programme and all required documentation can be found via the IMRiS link at www.rttrialsqa.org.uk. A separate document (Radiotherapy QA guidelines) will be provided to sites and should be adhered to for all IMRiS trial patients.

The RT QA programme developed for the IMRiS trial will include the following:

Pre-trial:

- Facility questionnaire
- Process document
- Outlining benchmark cases
    - Soft tissue – 1 thigh case (all participating sites)
    - Bone – 1 Ewing's case, 1 non-Ewing's case (selected participating sites only)
- Planning benchmark case
    - Soft tissue – 1 thigh case (all participating sites)
    - Bone – 1 non-Ewing's case, treated to 70Gy (selected participating sites only)
- Dosimetry audit visit

Outlining benchmark cases completion is per investigator, rather than per principal investigator of a site. Therefore all investigators at a site wishing to recruit patients in the trial must successfully complete the outlining benchmark cases.

On trial:

- Data collection for all registered patients
- Prospective and retrospective case reviews
    - Soft tissue – prospective review for 2 cases (first pre-operative and first post-operative cases) per named site investigator, retrospective review for subsequent patients
    - Bone – prospective review of all cases (due to the variation across cases and the small numbers to be recruited)

Full planning data (clinical history, diagnostic MRI, planning CT, structures, plan, dose and plan assessment form) for all IMRiS trial patients will also be collected. Sites and clinicians who have already participated in other trials involving RT QA may be eligible for QA streamlining; please contact the RTTQA group to discuss. Please refer to the Radiotherapy QA Guidelines document for full details on the trial specific QA process.

Full details of the radiotherapy QA programme can be found at www.rttrialsqa.org.uk.

17 STATISTICS

17.1 SAMPLE SIZE CALCULATION

COHORT 1:

Based on a retrospective review of late RT toxicity in UCH limb sarcoma patients, we believe the rate of grade 2+ subcutaneous fibrosis at 2 years to be approximately 30% [61]. We aim to show that this can be reduced to 20% using IMRT. A sample size of 138 has been calculated (using the increase in patients not experiencing grade 2+ fibrosis from 70% to 80%) with a 5% significance level and an 85% power. IMRT will be deemed effective in this cohort if the lower bound of the two-sided 90% confidence interval for the proportion exceeds 70%. As this is to be measured at 2 years, we must take into account deaths and loss to follow-up. It is expected that 83% of patients will be assessable at 2 years (data from UCH sarcoma radiotherapy database), so the total number needed to be recruited will be 167.

COHORT 2: Using current 3DCRT techniques, the proportion of patients in whom 90% of the planPTV receives 95% of the optimal prescription dose is only 70% (data from UCH sarcoma RT database). We aim to increase this proportion to 95% (see section 17.5 for further details). Using a 20% significance level and 80% power, we require 9 patients. IMRT will be deemed to be effective in this cohort if the lower bound of the one-sided 80% confidence interval exceeds 70%.

COHORT 3: In a retrospective series of 22 patients treated with current 3DCRT techniques (data from UCH sarcoma RT database), there were no patients in whom 80% of the planPTV received 95% of the optimal prescription dose. We aim to show that the proportion of patients in whom 80% of the planPTV receives 95% of the optimal prescription dose could be 50% of patients by using IMRT (see section 17.5 for further details). Twelve patients will be required using these parameters, with a 10% significance level and 80% power. We will be aiming to show that the lower bound of the two-sided 80% confidence interval exceeds 20%.

The primary endpoints for cohorts 2 and 3 will be assessed before treatment, therefore all patients will be assessable.

All sample sizes were calculated using A'Hern's Single Stage Phase II design in the Sample Size Tables for Clinical Studies software [62].

17.2 POPULATION FOR ANALYSIS

Primary endpoint:

Cohort 1: All patients who receive trial treatment, for whom data on subcutaneous fibrosis is available at 2 years, will be included in the analysis of the primary endpoint.

Cohorts 2 and 3: All patients registered will be included in the analysis of the primary endpoint.

Secondary endpoints:

Toxicity and quality of life endpoints will be assessed in all patients treated with IMRT, except wound complications, which will be assessed in patients in Cohort 1 only.

Response will be assessed in all patients in cohorts 2 and 3 who are receiving definitive radical RT or patients with evaluable residual disease after surgery.

Time to event endpoints (time to local recurrence, disease-free and overall survival) will be assessed in all patients. In these endpoints the start date for analysis will be the date of registration.

17.3 Analysis of the Primary Endpoint

The primary endpoints for cohort 1 will be presented as proportions with 90% two-sided confidence intervals. The primary endpoints for cohorts 2 and 3 will be presented as proportions with 80% confidence intervals.

17.4 Analysis of Secondary Endpoints

- Kaplan Meier survival analysis will be used to assess overall and disease-free survival rates, though it is acknowledged that there will be limited statistical power to estimate survival rates accurately in cohorts 2 and 3.
- Survival times will be measured from the date of registration until death or date last seen.
- For patients who had surgery, disease-free survival will be measured from the date of registration until relapse, progression or death, patients alive and disease-free will be censored at the date last seen.
- For patients who did not have surgery, progression-free survival will be calculated as above.
- Time to local recurrence will be measured from registration until recurrence within the irradiated site. Patients without local recurrence will be censored at death or the date last seen.
- Receiving operator characteristic (ROC) analysis will be used to find optimal dose-volume constraints that best discriminate between patients with and without toxicity. Multivariate analysis will test associations between dose-volume variables, co-morbidities and radiation-induced side-effects.
- All other endpoints will be descriptive.

17.5 Notes on primary endpoints for cohorts 2 and 3

Cohort 2:

The aim of RT is to deliver a specified dose (54 Gy or 50.4 Gy) while keeping adjacent normal tissues within tolerance. For pelvic and spinal tumours this is often not possible with conformal RT and retrospective data from the UCH sarcoma RT database has shown that the indicated dose could only be prescribed in 70% of patients with 3DCRT plans. It is anticipated that with the use of IMRT it will be possible to prescribe the indicated dose in all cases, although areas within the PTV may receive a lower dose in order to spare critical normal structures. The extent of PTV compromise is likely to be dependent on site (spine more likely than pelvis), prescription dose and size of the PTV. Historical cases treated with IMRT from the UCH sarcoma RT database were

individually reviewed in an attempt to estimate the target coverage that might reasonably be expected for patients in Cohort 2.

- Case 1: Sacral Ewings, dose 54 Gy: *95.7%* of the planPTV received 95% of the dose
- Case 2: C-Spine Ewings, dose 50.4 Gy: *98.7%* of the planPTV received 95% of the dose
- Case 3: T-spine Ewings, dose 54 Gy: *81.5%* of the planPTV received 95% of the dose

The primary endpoint for Cohort 2 was derived taking these historical cases into account and in the context of what would be deemed a clinically relevant 95% PTV coverage.

Cohort 3:

The aim of RT is to deliver the recommended RT dose to as much of the PTV as possible, keeping normal tissues within tolerance. Retrospective data from the UCH sarcoma RT database of cases planned using 3DCRT showed that it was impossible to prescribe the indicated dose (70 Gy) to pelvic and spinal PTV. It is anticipated that with the use of IMRT it will be possible to prescribe the indicated dose in the majority of cases (at least 50%), although areas within the PTV will receive a lower dose in order to spare critical normal structures. The extent of PTV compromise is likely to be dependent on site (spine more likely than pelvis), prescription dose and size of the PTV. A case of sacral chordoma treated with IMRT at UCH was reviewed in an attempt to estimate the target coverage that might reasonably be expected for patients in Cohort 3.

- Case 4: Sacral chordoma, dose 70 Gy: *83.6%* of the planPTV received 95% of the dose

The primary endpoint for Cohort 3 was derived taking this historical case into account and in context of what would be deemed a clinically relevant 95% PTV coverage.

18 ETHICAL CONSIDERATIONS

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

- the principles of Good Clinical Practice
- Human Rights Act 1998
- Data Protection Act 1998
- Freedom of Information Act 2000
- Human Tissue Act 2004
- Mental Capacity Act 2005
- the Research Governance Framework for Health and Social Care, issued by the UK Department of Health (Second Edition 2005) or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006)

18.1 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 London – Bromley Research Ethics Committee and Health Research Authority (HRA) approval for conduct in the UK.

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

18.2 SITE APPROVALS

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

18.3 PROTOCOL AMENDMENTS

UCL CTC will be responsible for gaining ethical approval 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 promptly.

18.4 Patient Confidentiality & Data Protection

Patient identifiable data, including initials, gender and date of birth will be required for the registration 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 1998 with the Data Protection Officer at UCL.

19 SPONSORSHIP AND INDEMNITY

19.1 SPONSOR DETAILS

Sponsor Name:	University College London
Address:	Joint Research Office Gower Street London WC1E 6BT
Contact:	Director of Research Support
Tel:	020 3447 9995/2178 (unit admin)
Fax:	020 3447 9937

19.2 INDEMNITY

University College London holds insurance against claims from participants for injury caused by their participation in this clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if 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.

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.

20 FUNDING

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

Mrs Rita Simões is funded by High Education England and the National Institute of Health Research (HEE/NIHR ICA Programme Clinical Doctoral Research Fellowship reference ICA-CDRF-2018-04-ST2-004) to develop the dose-volume constraints predicting normal tissue toxicities as part of the project entitled 'Predicting radiotherapy response and Toxicities in soft tissue sarcoma of the extremities (PredicT)'.

21 PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the Trial Management Group. The TMG will form the basis of the writing committee and advise on the nature of the publications. Named authors should include the Chief Investigator and Statistician(s) involved in the trial. Other members of the TMG and Principal Investigators enrolling at least 5% of patients would normally be included as co-authors on the main publication. Other contributors to the trial will be acknowledged as appropriate.

Data from all sites will be analysed together and published as soon as possible after the primary endpoint for each cohort has been reached. 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 is owned by the TMG.

The ClinicalTrials.gov identifier and CR UK grant number allocated to this trial will be quoted in any publications resulting from this trial.

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APPENDIX 1: ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CR	Complete response
eCRF	Electronic Case Report Form
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTSA	Clinical Trial Site Agreement
CXR	Chest X-Ray
DFS	Disease Free Survival
HRA	Health Research Authority
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IMRT	Intensity Modulated Radiotherapy
MRI	Magnetic Resonance Image
NCRI	National Cancer Research Institute
OS	Overall Survival
PA	Posteroanterior
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PR	Partial Response
REC	Research Ethics Committee
RECIST	Response Evaluation Criteria in Solid Tumours
RTOG	Radiotherapy Oncology Group
RTTQA	Radiotherapy Trials Quality Assurance
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable Disease
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
WHO	World Health Organisation

APPENDIX 2: WHO PERFORMANCE STATUS

Grade	Description
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair

APPENDIX 3: RADIOTHERAPY TARGET DEFINITION OUTLINING AND PLANNING GUIDELINES

The following sections describe the outlining and planning for each cohort. All sites participating in the trial will be expected to plan and treat their patients using the guidelines set out below.

Radiotherapy treatment for all three cohorts will be delivered using IMRT. Fixed beam and rotational/arc IMRT techniques including Tomotherapy™ are allowed, and should be specified.

3.1. GENERAL GUIDANCE

Please refer to individual sections for cohort specific details.

Positioning and Immobilisation

Stable and reproducible patient positioning is essential and will be individualised for each patient depending on the anatomic localisation of the tumour. Immobilisation devices are to be used in all cases, according to local practice. Consideration will need to be given to likely beam arrangements, isocentre position and lateral patient offset so as to avoid collisions at treatment.

Outlining

Accurate target volume definition is an absolute requirement for radiotherapy planning. IMRT allows the delivery of very precise dose distributions, so that areas not specifically included in the target volume will not be treated to a therapeutic dose. Therefore, great care must be taken to ensure all the involved areas and those at risk are included in the planning volumes. Treatment will be CT planned after immobilisation. The use of intravenous contrast is recommended for pre-operative and definitive radiotherapy planning (unless contraindicated).

Target localisation

Target volumes are defined in accordance with ICRU reports 50, 62 and 83 [3, 63, 64].

IMRT Target Volume Definition

Volume definition will be guided by the pre-treatment diagnostic imaging (CT, MRI, PET-CT scan where available), operative findings and clinical information. Image fusion is strongly recommended, using MRI and/or PET-CT as available. Please note that the use of PET-CT (which will be for bone sarcomas), is suggested as an adjunct to MRI where it may identify areas of tumour extension not appreciated on MRI. However, it should not be used instead of MRI.

Planning guidelines

Radiotherapy will be delivered using IMRT. Fixed beam and rotational/arc IMRT techniques are allowed, and the chosen technique(s) should be specified by sites at trial entry.

For the purpose of IMRT planning and dose reporting, additional structures (PlanPTV) should be created if applicable, where the PTVs are cropped up to 5mm inside the patient surface (including the scar where this is part of the Clinical Target volume (CTV)) to avoid optimisation errors, where excess fluence is generated in an attempt to top up these areas. If a clinical decision is made to

include the skin, then use of physical bolus may be considered, as described below, although bolus should be used with caution because of the increased skin dose and reaction. For all cases where physical bolus is used, please inform the trial QA contact. To ensure field coverage when random motion moves the skin surface outwards, the original PTV volume should be retained for guidance. If options such as skin flash or virtual bolus are available in the planning system, they may be used to improve field coverage for IMRT plans. For example virtual bolus may be added for the plan optimisation but removed for final calculation.

Dosimetry/dose specifications

IMRT planning will be performed using the local planning system, comprising multiple beams/arcs to meet the PTV dose objectives and Organs at Risk (OAR) dose constraints. Rotational techniques are permitted (VMAT™, RapidArc™ and Tomotherapy™). Sites may determine optimum number and geometry of treatment fields.

Plans are to be optimised using inverse methods. Full 3D plan dose, corrected for tissue heterogeneity, must be calculated using an algorithm able to accurately handle IMRT fields (ideally Type B).

The near-minimum and near-maximum doses within the PTV should be within a range of 90% to 107% of the prescription dose. The planning process will be a balance between achieving optimal PTV dose/volume constraints and keeping OAR within specified limits, and final decisions will be at the treating clinician's discretion.

Plans should be prescribed and normalised to the median dose of the high dose volume. Sites unable to prescribe to the median dose due to their planning system capabilities can alternatively prescribe to the mean dose and should inform the QA team of this decision. The median and mean dose should both be reported on the plan assessment form and are expected to be within 1% of each other. Sites with any issues regarding the median/mean dose prescription should contact the QA team.

On treatment verification

Daily imaging is required for on treatment verification. Minimum mandatory imaging is daily kV or MV imaging using orthogonal fields with a daily shift to the isocentre, aiming to include part or all of joint to facilitate image matching. Cone beam CT (CBCT) imaging is recommended if practicable at least weekly to assess set-up and any change in PTV coverage and OAR avoidance. (In some cases, the tumour will be positioned too laterally for CBCT without collision, such that CBCT cannot be performed). For upper limb tumours it is frequently not possible to perform lateral kV imaging as the images are obscured by the patient's body, in which case it is accepted that only anterior-posterior kV imaging will be performed. Sites are advised to contact the RTTQA contact in cases where an orthogonal kV or MV imaging pair is not possible. The imaging action levels to be taken based on the assessment of daily imaging must be detailed in the process document and supported by local audits, if possible. For spinal sarcomas, it is suggested that CBCT is carried out daily.

On treatment quality assurance will be performed according to local protocols. Changes in patient contour or tumour may require re-planning. The decision to re-plan will be at the discretion of the treating clinician, aiming to complete the required re-plan within 5 working days.

Treatment delays

Treatment gaps should be avoided. All treatment interruptions should be accounted for according to local protocols. It is recommended to treat pre-operative radiotherapy patients as Royal College of Radiologists (RCR) category 1 and post-operative radiotherapy patients as category 2 [65].

3.2. COHORT 1: LIMB/LIMB GIRDLE SOFT TISSUE SARCOMAS

3.2.1. Positioning and Immobilisation

It is recommended that a rigid immobilisation device is used, such as an Orfit™ shell fixed to a baseboard and indexed to the couch top. VAC bags are not recommended if used alone, as the immobilisation accuracy may be less than with a system using an immobilisation shell. However, if local practice is to use VAC bags or a hybrid technique for immobilisation, the site should provide evidence to the QA team of the achievable accuracy of their system. It is recommended that the contralateral leg is also immobilised, in order to be sure of its exact location, and to enable accurate measurement of dose to the contralateral limb. In general, dose to the contralateral leg should be avoided, but it is acknowledged that this is not always possible.

3.2.2. Outlining

CT scan slice intervals should ideally be at 2-3 mm, and should include the whole bone adjacent to the tumour, the tumour bed and scar (for post-operative RT), which should be wired. If imaging shows that the tumour is/was located superficially very close to the skin, then consideration should be given to use of bolus in order to avoid the situation of PlanPTV being cropped back from the skin, with a resultant under-dosing of GTV, CTV and PTV.

Volume definition will be guided by the pre-treatment diagnostic MRI, and operative findings and histopathology reports (for post-operative radiotherapy). Image fusion is desirable, but frequently is not possible because of differences in external contour following surgery, and because of differences in limb positioning between diagnostic and planning scans even in the absence of surgery.

3.2.3. Target localisation

The principle is to deliver pre-operative radiotherapy as a single volume to include the tumour with an appropriate margin and to deliver post-operative radiotherapy to a large volume to include the tumour bed, scars and drain sites, with a simultaneous integrated boost to a smaller volume focussing on the tumour bed.

3.2.4. IMRT Target Volume Definition

a) Gross tumour volume (GTV)

- *Pre-operative radiotherapy:* the GTV is defined as the tumour as visualised on the diagnostic contrast-enhanced T1-weighted MRI scans.
- *Post-operative radiotherapy:* For patients who have undergone surgery, there is by definition no GTV. However, the pre-operative GTV should be reconstructed on the planning CT to enable the accurate delineation of the clinical target volume (CTV). Information from the pre-operative diagnostic MRI, operation report and pathology report is used to reconstruct the GTV, taking into account any altered anatomy after surgery, and growth of GTV between imaging and surgery. Careful localisation of the reconstructed GTV in the superior-inferior dimension is essential, and should be achieved by measuring GTV location against bony structures. It is useful to 'sense check' the GTV against the diagnostic imaging, particularly coronal and sagittal images. Post-operative

seroma should not be used as a surrogate for GTV as it will almost always be larger than GTV, and should in any case be part of CTV.

b) ***Clinical target volume (CTV)***

This comprises the GTV with a margin for suspected subclinical disease.

- *Pre-operative radiotherapy:* the CTV is created by adding a 2 - 3 cm margin to the GTV radially taking intact skin, bone and fascia barriers into account (a more generous 3 cm margin may be felt to be more appropriate for histologies known to be associated with high local recurrence rates, e.g. myxofibrosarcoma, malignant peripheral nerve sheath tumour). In the longitudinal direction, a margin of at least 3 - 4 cm proximally and distally is added to the GTV, although a shorter margin may be used if the muscle compartment containing the tumour ends before the 3 cm margin [66, 67]. The CTV usually includes any suspicious areas of oedema visualised on T2 MRI imaging, based on clinical judgement, which may require a larger margin than 3 cm. For tumours deep to the fascia, the CTV does not include the skin surface, but this may be included for subcutaneous tumours immediately superficial to the skin surface. Care should be taken when creating the CTV longitudinally so as not to taper the volume too much; ideally the CTV should be more of a cylinder rather than spindle shaped, by virtue of following the anatomical planes superiorly and inferiorly, rather than just the geometrical planes. This can be avoided by drawing the CTV freehand, rather than using isotropic growing algorithms, as these will automatically taper the grown volume.
- *Post-operative radiotherapy:* the principle of treatment is to simultaneously treat a larger lower dose volume CTV_5220 (GTV with margins of 2 - 3 cm radially and 5 cm superiorly and inferiorly) and a smaller higher dose volume CTV_6000 (GTV with a margin of 2 - 3 cm radially, and superiorly and inferiorly) (a more generous 3 cm margin may be felt to be more appropriate for histologies known to be associated with high local recurrence rates, e.g. myxofibrosarcoma, malignant peripheral nerve sheath tumour). In effect, there will be a cylinder shaped volume with a central high dose portion (CTV_6000), sandwiched between two lower dose portions on each end (CTV_5220a and CTV_5220b, figure 1). This is practically achieved by the creation initially of a larger composite volume (CTV_5220a+CTV_6000+CTV_5220b), and then reducing it to create the smaller CTV_6000, as follows:
    - Initially create a larger volume by adding a 2 - 3 cm margin radial to the reconstructed GTV, and a 5 cm margin superiorly and inferiorly or scar plus 1 cm, whichever is greater, taking intact skin, bone and fascial boundaries into account. If the GTV abuts bone, then the GTV to CTV margin should be 0 cm (i.e. CTV should also abut bone). CTV should include the scar, seroma, surgical clips, biopsy and drain sites, but remains within the skin surface unless a clinical decision is made to include the skin. In some cases it may not be feasible to include the full length of the scar if this extends the volume significantly, particularly if it includes treating two joints. Conversely, the longitudinal margin may need to be longer than 5cm in order to encompass the entire seroma, which should ideally always be fully included. Care should be taken when creating the CTV longitudinally not to taper the volume too much; ideally the CTV should be more of a cylinder rather than spindle shaped, by virtue of following the anatomical planes superiorly and

inferiorly, rather than just the geometrical planes. This can be avoided by drawing the CTV freehand, rather than using isotropic growing algorithms, as these will automatically taper the grown volume.

- Then create a smaller central volume (CTV_6000) by reducing the length of the larger volume to GTV with a 2 -3 cm margin superiorly and inferiorly, while keeping the radial extent unchanged. Seroma, scar, biopsy and drain sites will be included in CTV_6000 where these fall within the 2 - 3 cm radial, proximal and distal volume expansion. Specifically, the scar will be included in CTV_6000 as its coverage is inevitably in continuity with that in CTV_5220a & b. The CTV_6000 otherwise remains within the skin surface unless a clinical decision is made to include the skin in CTV_6000, in which case the use of skin bolus may be considered, and the planning CT scan should be performed with the bolus in place.
- The final result should be CTV_5220 with two separate components (CTV_5220a and CTV_5220b) located proximally and distally to the CTV_6000 (Figures 1 - 3).

For post-operative cases with flap reconstruction, the skin surface should not be included in both CTV_6000 and CTV_5220. How much of the flap to include within CTV should be carefully considered, as the flap is technically not part of CTV.

c) ***Planning target volume (PTV)***

This is a geometric margin for errors in set-up and patient/organ motion and is created by expanding the CTV isotropically in all directions. The margin usually ranges from 5 – 10 mm and will be site-specific, depending on the immobilisation and reproducibility of the set-up, and should be defined according to local protocols and local audits, if performed previously. It is strongly recommended that the same margin is used for similar anatomical sites, immobilised in the same circumstances. Any exceptions should be discussed with the RTTQA contact.

For post-operative radiotherapy the CTV_6000 and CTV_5220 should not overlap longitudinally but should end on adjacent CT slices. To create PTV_6000 and PTV_5220, CTV_5220 and CTV_6000 should be expanded isotropically by 5-10 mm. With this isotropic expansion, the PTV_6000 and the PTV_5220 will overlap longitudinally, so PlanPTV_5220 and PlanPTV_6000 must be created. Both PlanPTVs should be cropped back up to 5mm from skin and PlanPTV_5220 should be cropped back superiorly and inferiorly from PlanPTV_6000. Any cropping of the PlanPTVs to inside the skin should be done by the planner (not the oncologist).

Figures 1a - c: Cohort 1 – limb soft tissue sarcoma post-operative radiotherapy target volume delineation

Fig. 1a

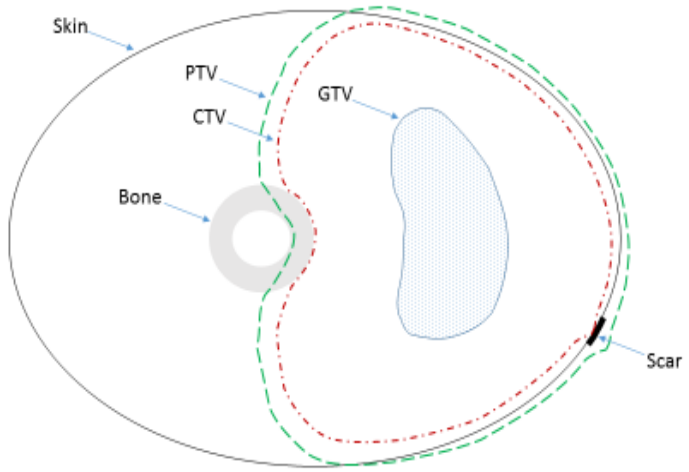


Fig. 1b

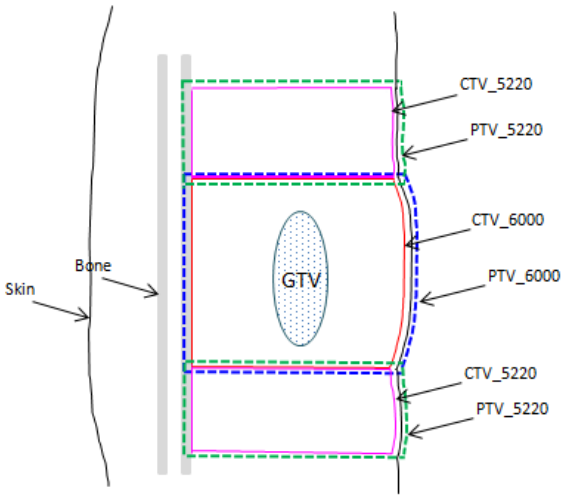
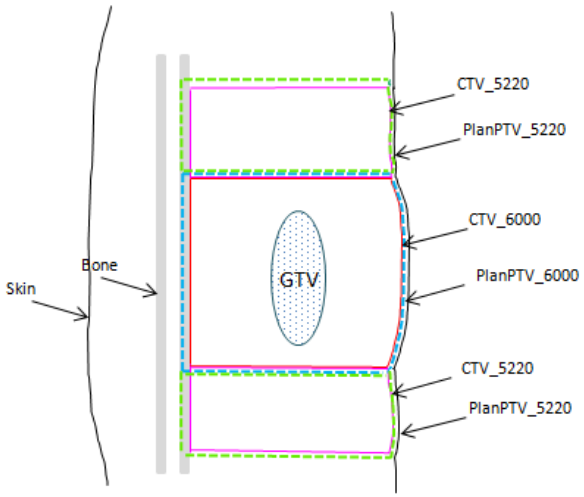


Fig. 1c



Figures 2a – c. Post-surgical axial planning CT slices of an extra-skeletal myxoid chondrosarcoma in right buttock completely excised with 1 mm of fascia. Green – GTV; Turquoise – CTV_6000. GTV was reconstructed on the planning CT based on pre-operative imaging, surgical and pathology reports. CTV_6000 was created from CTV_5220 with 2 cm radial, superior and inferior margins, edited to include scar, seroma and surgical clips, and taking into account natural barriers of spread (i.e. bone, skin, fascial boundaries).

Fig. 2a

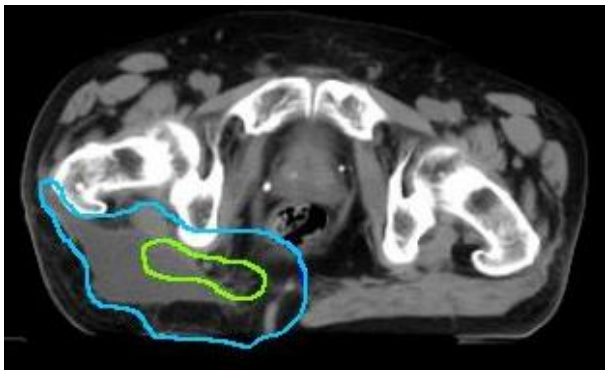


Fig. 2b

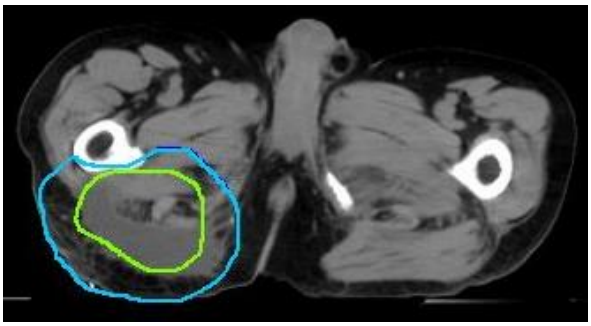
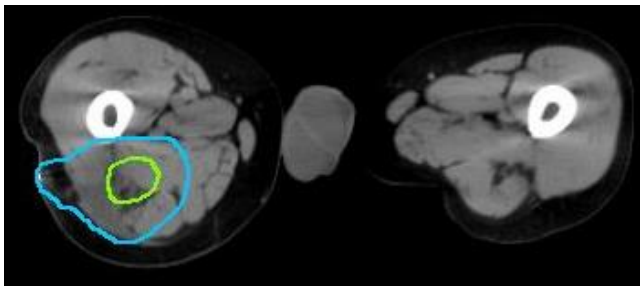


Fig. 2c



Figures 3a – b. Post-surgical planning CT slices of an extra-skeletal myxoid chondrosarcoma in right buttock completely excised with 1 mm of fascia, showing an example coronal slice (fig. 2a) and sagittal slice (fig. 2b). Green – GTV; Turquoise – CTV_6000; Dark Blue – CTV_5220. Note that CTV_5220 does not taper superiorly and inferiorly.

Fig. 3a

Fig. 3b

3.2.5. Organs at risk (OAR)

Volumes are defined in accordance to ICRU reports 50, 62 and 83 [3, 63, 64]. Radiation doses to normal tissues should be kept within accepted tolerances. The following suggested organs/structures should be outlined as appropriate, depending on anatomical location. Recommended dose constraints are detailed in table 1. OAR dose constraints are divided into mandatory and optimal. This is to reflect that dose constraints for some OAR will not be achievable without compromising PTV coverage. In this situation, the decision between PTV coverage and fulfilling OAR dose constraints will be a clinical one, on an individual patient basis. The normal tissue limb corridor and brachial plexus are mandatory dose constraints. However, other optimal (non-mandatory) dose constraints are provided *as a guide* for planning purposes (but may not be achievable due to PTV location, e.g. when PTV is abutting bone). The dose to the contralateral limb should be reported for all cases.

Table 1. Organs at risk dose constraints

OAR	Dose constraint
Mandatory	
Normal tissue limb corridor [68]	V_{20Gy} < 50%
BrachialPlexus [69]	Mean dose < 60 Gy Max dose (D0.1cc) < 65 Gy
Optimal	
Weight-bearing bone – bone in treatment field [68]	V_{50Gy} ≤ 50%
Weight-bearing bone – whole bone [16]	Mean dose ≤ 40Gy V_{40Gy} ≤ 64%
FemoralHeadNeck [70]	Mean dose <40Gy
Joint [68]	V_{50Gy} < 50%

- **Weight-bearing bone:** The whole bone(s) adjacent to the tumour should be included in the planning CT dataset and outlined as an OAR. Clinical discretion in individual cases is paramount and these constraints may need to be overridden in situations where adherence to the constraints would jeopardise adequate coverage of the PTV e.g. where the tumour invades bone, where part of the bone circumference is enclosed by the tumour or where the planned surgery will involve resection of that section of the bone. Bone in treatment field is defined as the whole cross-section of the bone (within the axial plane, that is encompassed within both PTVs in the longitudinal plane.
- **Femoral head/neck:** From top of femoral head to inferior aspect of lesser trochanter.
- **Soft tissue outside PTV:** This comprises the whole limb within the treatment area (proximal and distal limits defined as 2 cm longitudinally extending beyond the PTV), excluding the bony structures and the PTV itself. Aim to keep doses as low as possible.
- **Joint:** If possible the dose to any adjacent joint should be limited, although frequently this is not possible if the joint is in the PTV. It is appreciated that outlining of the joint will be very variable without a clear definition of what should be outlined. Therefore the purpose of including joint as an optimal dose constraint is to remind that dose to joints needs to be limited if possible, depending on PTV location.

  Normal tissue limb corridor: Ideally part of the circumference of the limb should be treated to a lower dose. A longitudinal strip of skin and subcutaneous soft tissue should be contoured (by the clinician or the planner) as an OAR according to the clinical judgement of the treating clinical oncologist, to allow sparing of lymphatic drainage. This will be used to optimise the IMRT plan. No more than 50% of the delineated limb corridor should receive 20 Gy (V_{20Gy} <50%) [68]. All slices should be assessed to ensure that dose on any individual slice is not excessive.

Contralateral limb: Limit exit beams angles through the contralateral limb if possible, in order to avoid high doses to the contralateral limb. Dose to the contralateral limb will be reported. Doses to the contralateral limb should be reported as follows:

- Dose to $1cm^3$, $2cm^3$, $5cm^3$
- Mean dose along the length of PTV +2cm superiorly and inferiorly

- **Brachial plexus:** It is recommended that the brachial plexus is outlined using the RTOG brachial plexus atlas for guidance [71]. Consensus recommendation suggests a 5% risk of radiation induced brachial plexopathy at 5 years from 62, 61, and 60 Gy to one-third, two-thirds, and the whole organ, respectively [72]. A maximum point dose of 65 Gy is associated with a 5% risk of developing symptomatic neuropathy [69].
- **Genitalia:** Genitalia should be avoided as much as possible. For males, the genitalia should be moved away from the treatment area, and sperm banking should be offered.

Other organs at risk

- Accepted normal tissue tolerance constraints should be taken into account at all times. Clinicians are referred to consensus guidelines as outlined by Emami et al [72] and the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) documents [73].

3.2.6. Planning guidelines

a) Prescribed dose and fractionation

The dose(s) should be prescribed to the PlanPTVs (as defined in section 3.1) rather than the unedited PTVs (if PlanPTVs are created). This is to avoid the low dose build-up unbalancing the overall dose and creating hotspots elsewhere. If bolus is used, dose can be prescribed to the unedited PTV if this is more appropriate.

- *Pre-operative radiotherapy:* 50 Gy to PlanPTV_5000 in 25 fractions of 2 Gy each delivered once daily over 5 weeks.
- *Post-operative radiotherapy:*
  - Adjuvant to surgery with clear surgical margins: 60 Gy to PlanPTV_6000 and 52.2 Gy to PlanPTV_5220 (EQD2 of 50 Gy) concurrently in 30 fractions treating once daily over 6 weeks.
  - Adjuvant to surgery with involved surgical margins: 66 Gy to PlanPTV_6600 and 53.5 Gy to PlanPTV_5350 (EQD2 of 50 Gy) concurrently in 33 fractions treating once daily over 6½ weeks.

b) PTV dose/volume constraints and reporting

The following dose-volume parameters should be reported, according to ICRU83 [3]. The near-minimum and near-maximum doses within the PTV should be within a range of 90% to 107% of the prescription dose. The planning process will be a balance between achieving optimal PTV dose/volume constraints and keeping mandatory OAR within specified limits, and final decisions will be at the treating clinician's discretion. PTV dose/volume constraints to be aimed for are detailed in table 2. These constraints should be met for the PlanPTVs as described above. Where possible, the constraints should be met for the unedited PTVs. The dose-volume values should be reported for both the PlanPTVs.

Plans should be prescribed and normalised to the median dose of the high dose volume. Sites unable to prescribe to the median dose due to their planning system capabilities can alternatively prescribe to the mean dose and should inform the QA team of this decision. The median and mean dose should both be reported on the plan assessment form and are expected to be within 1% of each other. Sites with any issues regarding the median/mean dose prescription should contact the QA team.

Table 2. Target dose constraints

PTV volume	**Pre-op Cases**	**Post-op Cases**	
	Dose to PlanPTV_5000	**Dose to PlanPTV_6000/PlanPTV_6600**	**Dose to PlanPTV_5220/PlanPTV_5350**
98%	>90%	>90%	>90%
95%	>95%	>95%	>95%
50% (median) or mean of volume	100%	100%	100% ± 1Gy
<5%	>105%	>105%	Avoid hotspots
<2%	>107%	>107%	Avoid hotspots

COHORT 2: EWING'S SARCOMA OF SPINE/PELVIS

Patients taking part in the Euro-Ewing's 2012 clinical trial are eligible to be enrolled in IMRiS for the radiotherapy component of their management if they meet all other eligibility criteria.

3.2.7. Positioning and Immobilisation

It is recommended that a formal immobilisation device is used, such as Combifix™ system or similar, to include knee supports and ankle stocks fixed to a baseboard and indexed to the couch top. Wherever possible patients should be treated supine as the most stable position.

For pelvic tumours and lumbar spine tumours, it is suggested that patients should be supine with hands on the chest, head in a headrest, with knee supports and ankle stocks. For thoracic spine tumours, arms should be above the head using a system such as a breast board. For cervical spine tumours an immobilisation shell of the head, neck and shoulders will be required.

3.2.8. Outlining

CT scan slice intervals should ideally be at 2-3 mm. The planning CT scan should include the whole tumour and involved bone, the tumour bed and scar (for post-operative radiotherapy), and entire lung volume for thoracic spine tumours. The use of a tissue spacer and/or bladder filling may be considered to minimise the volume of bowel in the treated area for pelvic tumours.

Volume definition will be guided by the pre-treatment diagnostic imaging (CT, MRI, bone scan, PET-CT scan where available), operative findings and clinical information. Image fusion is strongly recommended, using MRI and/or PET-CT as available.

3.2.9. Target Localisation

The principle of treatment is to treat all tissues involved by tumour at initial diagnosis and *prior* to chemotherapy (if given).

3.2.10. Target Volume Definition

a) *Gross tumour volume (GTV)*

- *Pre-operative or definitive radiotherapy:* The GTV includes all tissue originally involved by the tumour prior to chemotherapy and is defined by the tumour as visualised on the diagnostic imaging at its greatest extent prior to treatment. For patients with tumours with 'pushing' margins extending into body cavities (e.g. abdomen, thorax), GTV will require modification, because with regression of the tumour, normal tissues such as bowel and lung will have returned to their normal positions.
- *Post-operative radiotherapy:* For patients who have undergone surgery, there is by definition no GTV. However, reconstruction of the pre-operative gross tumour on the planning CT is necessary to aid the construction of the CTV. GTV is defined as the visible tumour on imaging at its maximum extent prior to any chemotherapy or surgery. Information from the pre-operative imaging, operation report and pathology report is used to reconstruct the GTV to include all tissues involved by tumour prior to chemotherapy as described above, taking altered anatomy after surgery into account.

b) *Clinical target volume (CTV)*

This comprises the GTV with a margin for suspected subclinical disease.

- *Pre-operative or definitive radiotherapy:* The CTV should encompass any sites of potential microscopic extension of GTV, and is generated by adding a margin of 1.5 to 2 cm (depending on exact anatomical location) to the GTV in all directions, taking patterns of spread and intact skin, bone and fascial barriers into account. The CTV does not include the skin surface unless involved or where the biopsy site will not be excised at the time of surgery.
- *Post-operative radiotherapy:* The post-operative CTV is generated by adding a margin of 1.5 to 2 cm to the reconstructed GTV in all directions, and extended further to include all areas of potential microscopic spread or contamination (including metallic prostheses, spinal rods and screws, drain sites and surgical scars, as long as inclusion of these does not increase the CTV to an unreasonably large size), taking patterns of spread and intact skin, bone and fascial barriers into account. CTV for spinal/paraspinal tumours should normally include one unaffected vertebra above and below the affected vertebra. The CTV may extend to the skin surface, in which case the use of skin bolus may be considered if clinically indicated, with the planning CT scan being performed with the bolus in place.
    - The CTV_5400 should encompass the GTV and surrounding sites of potential microscopic extension of tumour and should be no less than GTV with a 1 – 2 cm margin in all directions (depending on exact anatomical location). It should take into account anatomical barriers to tumour spread such as fascial barriers and bone.

c) *Planning target volume (PTV)*

The PTV includes a margin for errors in set-up and patient/organ motion and is defined by expanding the relevant CTV isotropically in all directions. The margin usually ranges from 5 – 10 mm. The margin used will be body site and hospital site specific depending on the immobilisation and reproducibility of the set-up and should be defined according to local protocols. As for the other cohorts, a PlanPTV must be created, by cropping the PTV up to 5mm from the skin. In cases where the full dose cannot be delivered to the PlanPTV without overdosing OARs, multiple PTV sub-volumes (OptimPTVs) can be created and two or more dose level distributions can be planned in order to fully optimise the dose to the target. The OptimPTVs should not overlap.

Figures 4a – b. Post-surgical axial planning CT slices following decompression of C7/T1 and chemotherapy for Ewing's sarcoma of the spine at C7/T1. Green – GTV; Turquoise – CTV_5400; Dark Blue – PTV_5400. GTV was reconstructed on the planning CT based on pre-operative imaging at its greatest extent prior to treatment. CTV_5400 was created using a 2 cm margin edited to include all areas of potential microscopic spread, and extended to include one unaffected vertebra above and below the disease. Natural barriers of spread (e.g. lungs) were also taken into account. PTV_5400 was created using a 5 mm isotropic expansion margin for set-up and patient/organ motion.

Fig. 4a

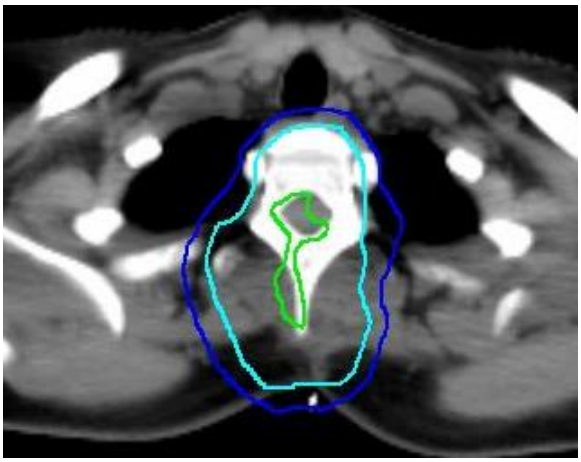


Fig. 4b

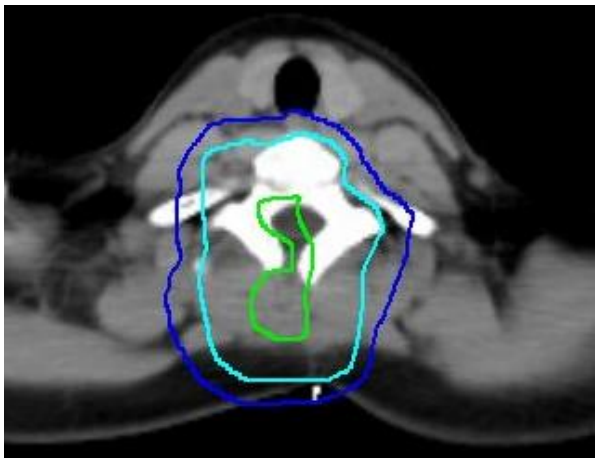
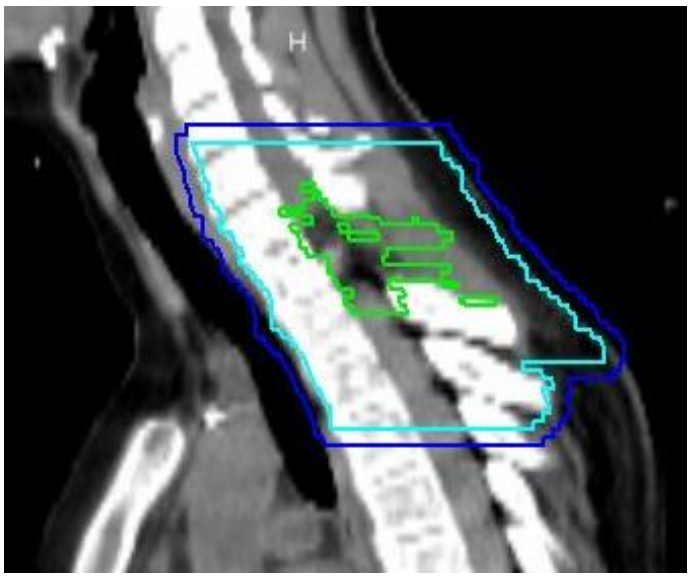


Figure 5. Post-surgical sagittal planning CT slices following decompression of C7/T1 and chemotherapy for Ewing's sarcoma of the spine at C7/T1. Green – GTV; Turquoise – CTV_5400; Dark Blue – PTV_5400.

Fig. 5



3.2.11. Organs at risk (OAR)

Volumes are defined in accordance to ICRU reports 50, 62 and 83 [3, 63, 64]. Organs/structures should be outlined as appropriate, depending on anatomical location. Radiation doses to normal tissues should be kept within accepted tolerances. Recommended dose constraints are detailed in table 3.

Optimal doses to be aimed for are given below. However, it is accepted that it may not be possible to deliver the optimal dose to the entire PTV and still stay within OAR dose constraints. If this is the case, then the clinician will need to make decisions as to the competing priorities of

achieving dose to PTV, and keeping specific OAR within dose constraints. This will need to be individualised for each patient, depending on the risk to individual OAR.

Table 3. Organs at risk dose constraints

<table>
<tr><th>OAR</th><th>Volume and dose constraint</th></tr>
<tr><td>BrachialPlexus [69]</td><td>Mean dose < 60 Gy
Max dose (D0.1cc) < 65 Gy</td></tr>
<tr><td>BrachialPlexus PRV (BrachialPlexus_05*)</td><td>Mean dose < 62Gy
Max dose (D0.1cc) <67 Gy</td></tr>
<tr><td>SpinalCord</td><td>Max (D0.1cc) ≤ 50Gy
1 cm^3 ≤ 48 Gy</td></tr>
<tr><td>Spinal cord PRV (SpinalCord_05*)</td><td>Max (D0.1cc) ≤ 52 Gy
1 cm^3 ≤ 50 Gy</td></tr>
<tr><td>CaudaEquina [72]
and LumbosacralPlexus</td><td>Mean dose <60Gy
Max (D0.1cc) < 65Gy</td></tr>
<tr><td>CaudaEquina PRV (CaudaEquina_05*)
and lumbosacralPlexus_PRV (lumbosacralPlexus_05)</td><td>Mean dose <62Gy
Max (D0.1cc) < 67Gy</td></tr>
<tr><td>BowelSpace [74]</td><td>Keep as low as possible. Volume outside PlanPTV receiving >45Gy should be <195cm^3 (grade 2 toxicity)
<table>
<tr><td></td><td>Gr 0</td><td>Gr 1</td></tr>
<tr><td>V_{45Gy}</td><td>78cc</td><td>158cc</td></tr>
<tr><td>V_{50Gy}</td><td>17cc</td><td>110cc</td></tr>
<tr><td>V_{55Gy}</td><td>14cc</td><td>28cc</td></tr>
<tr><td>V_{60Gy}</td><td>0.5cc</td><td>6cc</td></tr>
<tr><td>V_{65Gy}</td><td>0cc</td><td>0cc</td></tr>
</table></td></tr>
</table>

OAR	Volume and dose constraint
Rectum [75]	V_{30Gy}≤ 80% V_{40Gy}≤ 65% V_{50Gy} ≤ 55% V_{60Gy} ≤ 40% V_{65Gy} ≤ 30% V_{70Gy} ≤ 15% V_{75Gy} ≤ 3%
Kidneys (bilateral) [76]	V_{12Gy} ≤ 55% V_{20Gy} ≤ 32% V_{28Gy} ≤ 20% Mean dose ≤ 18 Gy
If mean dose to 1 kidney > 18 Gy	V_{6Gy} (remaining kidney) < 30%
Liver (partial irradiation) [77]	Mean dose ≤ 30Gy V_{30Gy} <50% V_{40Gy} <30% V_{50Gy} <15%
Bladder [78, 79]	V_{50Gy} ≤ 50% V_{60Gy} ≤ 25% V_{74Gy} ≤ 5%
Lung [80]	V_{20Gy} ≤30-35% Mean lung dose ≤20-23Gy
Heart [81]	V_{40Gy} ≤ 30% V_{25Gy} ≤ 50%

* PRVs for brachial plexus, spinal cord and cauda equina may also be labelled e.g. BrachialPlexus_05, but the '05' may vary depending on the exact PRV margin used (3 – 5mm, see below)

- **Brachial plexus:** It is recommended that the brachial plexus is outlined using the RTOG brachial plexus atlas for guidance [71]. A brachial plexus planning at risk volume (brachial plexus PRV) is created by adding a 3-5 mm margin to the brachial plexus volume (depending on local practice and accuracy of immobilisation). Consensus recommendation suggests a 5% risk of radiation induced brachial plexopathy at 5 years from 62, 61, and 60 Gy to one-third, two-thirds, and the whole organ, respectively [72]. A maximum point dose of 65 Gy is associated with a 5% risk of developing symptomatic neuropathy [69].
- **Spinal cord and spinal cord PRV:** The spinal cord is outlined on all CT levels. A spinal cord planning at risk volume (spinal cord PRV) is created by adding a 3-5 mm margin to the spinal cord volume (depending on local practice and accuracy of immobilisation). The risk

of myelopathy following conventional fractionation (1.8–2 Gy/fraction) radiation to the full-thickness cord is estimated to be 0.2% at 50 Gy, <1% at 54 Gy, 6% at 60 Gy and 50% at 69 Gy, with a strong dependence on dose/fraction (a/b = 0.87 Gy) [82].

- **Cauda equina and cauda equina PRV:** The cauda equina is outlined from L1/L2 to S2/S3. A cauda equina planning at risk volume (cauda equina PRV) is created by adding a 3-5 mm margin to the cauda equina volume (depending on local practice and accuracy of immobilisation).
- **Lumbosacral plexus:** The lumbosacral nerve roots from L4 to S2 should be contoured, in continuity with the lumbosacral plexus, from the level of L4/5 cranially to the level of the superior aspect of the femoral neck caudally (level of the sciatic nerve) [83]. A lumbosacral plexus planning at risk volume (lumbosacral plexus PRV) is created by adding a 3-5 mm margin to the lumbosacral plexus (depending on local practice and accuracy of immobilisation).
- **Small bowel:** It is recommended that the entire volume of the peritoneal space in which the small bowel can move is delineated. Efforts should be made to limit dose to the small bowel as much as possible. QUANTEC guidelines suggest that if the whole peritoneal cavity is outlined, the volume receiving >45 Gy should be <195 cm^3 when possible [74]. However, this may not be realistic for small bowel directly adjacent to tumour, when higher doses to small volumes may need to be accepted. When larger volumes of small bowel are directly adjacent to PTV, consideration should be given to using a PRV on BowelSpace to prevent delivery of unacceptably high doses to small bowel.
- **Rectum:** The rectum is outlined from the recto-sigmoid junction proximally to the ano-rectal junction distally. The circumference of the rectum should be outlined entirely.
- **Kidneys:** Both kidneys should be outlined as one structure. Nephrotoxic chemotherapy agents can enhance the renal injury from radiotherapy and this needs to be taken into account.
- **Liver:** The whole liver should be outlined [77].
- **Bladder:** Bladder size, shape and position varies on a daily basis and the dose distribution to the bladder volume as seen on the initial planning CT scan is unlikely to be representative of the radiation dose to the bladder during the course of treatment. Sites should use their own drinking protocol to ensure that bladder filling is as reproducible as possible.
- **Lung:** The dose constraints quoted will limit the risk of radiation pneumonitis to ≤ 20%. However, if there are co-morbidities such as chronic obstructive pulmonary disease, it may be prudent to be more conservative, to reduce the risk of radiation pneumonitis to lower levels, e.g. with V_{20Gy} ≤ 25 – 30 Gy, and mean lung dose to ≤ 15 – 18 Gy [80].
- **Genitalia:** Genitalia should be avoided as much as possible. For males, the genitalia should be moved away from the treatment area, and sperm banking should be offered.
- **Other organs at risk:** Other normal tissue structures are likely to require delineation, depending on the specific anatomical location. Accepted normal tissue tolerance constraints should be taken into account at all times. Clinicians are referred to consensus

guidelines as outlined by Emami et al [72] and the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) documents [73].

3.2.12. Planning guidelines

a) Prescribed dose and fractionation

Radiotherapy can be given either prior to or after surgery, or as definitive local therapy, and may be given concurrently with or after completion of chemotherapy. Delays in starting RT should be avoided.

- *Definitive radiotherapy:* 54 Gy to the PTV in 30 fractions of 1.8 Gy each delivered once daily over 6 weeks*
- *Pre-operative radiotherapy:* 50.4 Gy to the PTV in 28 fractions of 1.8 Gy each delivered once daily over 6 weeks. If there is concern regarding normal tissue tolerances, the dose may be reduced to 45 Gy in 25 fractions
- *Post-operative:* 54 Gy to PTV_5400 (EQD2 of 44.25 Gy assuming an α/β ratio of 10) concurrently in 30 fractions delivered once daily over 6 weeks

*There is some limited evidence that local tumour control is poorer for tumours ≥8cm [32, 86, 87], and those that have exhibited <50% regression on induction chemotherapy [86], and that dose escalation may improve local tumour control [86, 88]. Under such circumstances a boost of 5.4 Gy in 3 fractions may be considered.

Special Considerations

- The presence of metal stabilisation rods and cages may produce dosimetric uncertainties when using IMRT techniques, and ideally beams should not enter through the metalwork, as this may increase uncertainty in the dose to PTV, and that to OAR such as the spinal cord. This will need to be considered on an individual patient basis, depending on the proximity of the metalwork to the spinal cord, the accuracy of the planning software, and the anticipated degree of uncertainty in dosimetry in this area. It may be the case that the dosimetric uncertainty is such that an IMRT plan is not possible to deliver safely, and the patient will be better treated to a lower dose with conformal radiotherapy outside of the trial.
- Pelvic or sacral tumours may protrude significantly into the abdominal-pelvic cavity at presentation with subsequent regression after chemotherapy or surgery. The same may apply to some spinal/paraspinal tumours with extension into the thoracic cavity and displacement of the lung and pleura. Delineation of the GTV and CTV will need to take this into account to avoid treating large volumes of normal tissues unnecessarily. Surgical placement of spacer devices in the pelvis may be helpful, in order to displace bowel away from the involved bone.

b) PTV dose/volume constraints and reporting

If the PTV extends outside the skin, it should be cropped to 5 mm inside the skin, creating a PlanPTV, as described for cohort 1. In some cases it may be impossible to achieve the desired dose to the whole PTV, because of organs at risk within the volume (e.g. spinal cord PRV). In this case additional PTV sub-volumes, OptimPTVs may be required. These OptimPTVs will be created by cropping the OAR PRVs from the PlanPTV, and will aid the plan optimisation to different dose levels. Assessment of target dose constraints will be limited to the PlanPTV volume.

The following dose-volume parameters should be reported, according to ICRU83 [3]. The near-minimum and near-maximum doses within the PTV should be within a range of 90% to 107% of the prescription dose. The planning process will be a balance between achieving optimal PTV dose/volume constraints and keeping OAR within specified limits, and final decisions will be at the treating clinician's discretion. PTV dose/volume constraints to be aimed for are detailed in table 4.

Table 4. Target dose constraints

PTV volume	Dose to PlanPTV_5400	Dose to PlanPTV_5040
98%	>90%	>90%
95%	>95%	>95%
50% (median) or mean of volume	100%	100%
<5%	>105%	>105%
<2%	>107%	>107%

3.3. COHORT 3: PRIMARY NON-EWING'S BONE SARCOMAS OF SPINE/PELVIS

3.3.1. Positioning and Immobilisation

As for cohort 2.

3.3.2. Outlining

As for cohort 2.

3.3.3. Target Localisation

The principle is to deliver definitive radical radiotherapy as a single volume to include the tumour with an appropriate margin. Post-operative radiotherapy is delivered to a potentially larger volume to include the tumour bed, scars and drain sites, with the option for a simultaneous integrated boost to a smaller volume focussing on the tumour bed. If chemotherapy is given as initial treatment (for some primary bone sarcomas not including chordomas), then planning will be on the pre-chemotherapy imaging.

3.3.4. Target Volume Definition

a) ***Gross tumour volume (GTV)***

- *Definitive radiotherapy:* In unresected disease, the GTV is the visible extent of tumour on planning CT scan with reference to the diagnostic imaging, prior to chemotherapy if given.
- *Post-operative radiotherapy:* Reconstruction of the pre-operative gross tumour on the planning CT is necessary to aid the construction of the CTV. Information from the pre-operative imaging, operation report and pathology report is used to reconstruct the GTV to include all tissues involved by tumour prior to chemotherapy (if given) as described above, taking altered anatomy after surgery into account. For chordoma this is usually based on the T1-contrast enhancing tumour and abnormal bone on CT bony windows.

b) ***Clinical target volume (CTV):***

This comprises the GTV with a margin for suspected subclinical microscopic disease, taking patterns of spread into account. The CTV for both definitive and post-operative radiotherapy is generated by adding a margin of 2 - 3 cm on the GTV in all directions (for pelvic tumours), taking patterns of spread and intact skin, bone cortex and fascial barriers into account. For spinal tumours, margins will inevitably be smaller, and will be individualised. Where the cortex of the bone is not breached but the central part of the bone is involved, the CTV can be restricted to the intact cortex, for example including the whole vertebral body. If the cortex is breached with intraspinal or extraspinal disease, a CTV margin will need to be added.

c) Planning target volume (PTV)

The PTV includes a margin for errors in set-up and patient/organ motion and is defined by expanding the CTV isotropically in all directions. The margin usually ranges from 5 – 10 mm. The margin used will be body site and hospital site specific depending on the immobilisation and reproducibility of the set-up and should be defined according to local protocols. As for the other cohorts, a PlanPTV must be created, by cropping the PTV to 5mm inside the skin. In cases where the full dose cannot be delivered to the PlanPTV without overdosing OARs, multiple PTV sub-

volumes (OptimPTVs) can be created and two or more dose levels distribution can be planned in order to fully optimise the dose to the target. The OptimPTVs should not overlap.

Figures 6a – b. Axial planning CT slices of a high grade pleomorphic bone sarcoma in the left sacrum extending across midline following chemotherapy.

In view of the location of the disease in relation to the OARs, the treatment was delivered using 2 dose levels.

Dark Red – GTV, delineated based on visible extent of the disease prior to chemotherapy

Orange – CTV_7000, created using a 2 cm isotropic expansion margin around GTV edited for natural barriers of spread.

Red – plan PTV_7000, created using a 5mm isotropic expansion margin around CTV_7000. Dose coverage to this volume should be reported for the purpose of assessing the primary endpoint of the trial.

In view of the dose constraints to the bowel and cauda equina, OptimPTV_7000 and OptimPTV_6020 were created, editing from these OARs for treatment planning (Figure 6b).

Purple – bowel space

Cyan – cauda equina

Green – OptimPTV_7000 (PTV_7000 minus cauda equina PRV with additional margin to allow for dose fall-off at the edge, and minus bowel space with additional margin for dose fall-off)

Dark Blue – OptimPTV_6020 (the overlap of cauda equina PRV and PTV_7000)

Fig. 6a

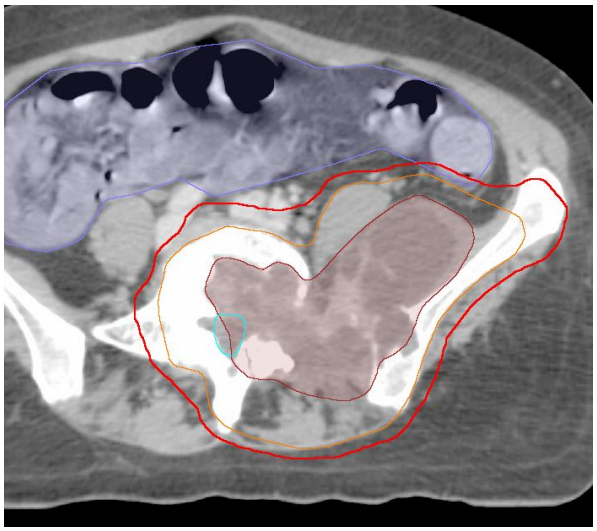
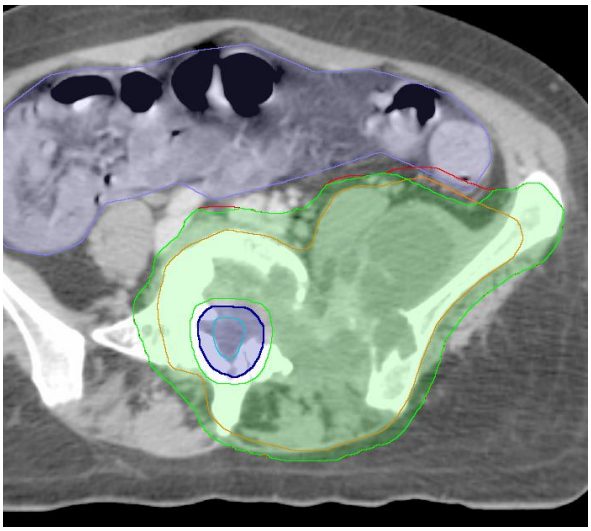


Fig. 6b



3.3.5. Organs at risk (OAR)

Volumes are defined in accordance to ICRU reports 50, 62 and 83 [3, 63, 64]. Organs/structures should be outlined as appropriate, depending on anatomical location. Radiation doses to normal tissues should be kept within accepted tolerances. Recommended dose constraints are detailed in table 5.

Table 5 Organs at risk dose constraints

<table>
<tr><th>OAR</th><th>Volume and dose constraint</th></tr>
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<tr><td>SpinalCord</td><td>Max (D0.1cc) ≤ 50Gy
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and LumbosacralPlexus PRV (LumbosacralPlexus_05*)</td><td>Mean dose <62Gy
Max (D0.1cc) < 67Gy</td></tr>
<tr><td>BowelSpace [74]</td><td>Keep as low as possible. Volume outside PlanPTV receiving >45Gy should be <195cm^3 (grade 2 toxicity) [89]
<table>
<tr><td></td><td>Gr 0</td><td>Gr 1</td></tr>
<tr><td>V_{45Gy}</td><td>78cc</td><td>158cc</td></tr>
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<tr><td>V_{65Gy}</td><td>0cc</td><td>0cc</td></tr>
</table></td></tr>
</table>

OAR	Volume and dose constraint
Rectum [75]	V_{30Gy}≤ 80% V_{40Gy}≤ 65% V_{50Gy} ≤ 55% V_{60Gy} ≤ 40% V_{65Gy} ≤ 30% V_{70Gy} ≤ 15% V_{75Gy} ≤ 3%
Kidneys (bilateral) [76]	V_{12Gy} ≤ 55% V_{20Gy} ≤ 32% V_{28Gy} ≤ 20% Mean dose ≤ 18 Gy
If mean dose to 1 kidney > 18 Gy	V_{6Gy} (remaining kidney) < 30%
Liver (partial irradiation) [77]	Mean dose ≤ 30Gy V_{30Gy} <50% V_{40Gy} <30% V_{50Gy} <15%
Bladder [78, 79]	V_{50Gy} ≤ 50% V_{60Gy} ≤ 25% V_{74Gy} ≤ 5%
Lung [80]	V_{20Gy} ≤30-35% Mean lung dose ≤20-23Gy
Heart [81]	V_{40Gy} ≤ 30% V_{25Gy} ≤ 50%

* PRVs for brachial plexus, spinal cord and cauda equina may also be labelled e.g. BrachialPlexus_05, but the '05' may vary depending on the exact PRV margin used (3 – 5mm, see below)

- **Brachial plexus:** It is recommended that the brachial plexus is outlined using the RTOG brachial plexus atlas for guidance [71]. A brachial plexus planning at risk volume (brachial plexus PRV) is created by adding a 3-5 mm margin to the brachial plexus volume (depending on local practice and accuracy of immobilisation). Consensus recommendation suggests a 5% risk of radiation induced brachial plexopathy at 5 years from 62, 61, and 60 Gy to one-third, two-thirds, and the whole organ, respectively [72]. A maximum point dose of 65Gy is associated with a 5% risk of developing symptomatic neuropathy [69].
- **Spinal cord and spinal cord PRV:** The spinal cord is outlined on all CT levels. A spinal cord planning at risk volume (spinal cord PRV) is created by adding a 3-5 mm margin to the spinal cord volume (depending on local practice and accuracy of immobilisation). The risk

of myelopathy following conventional fractionation (1.8–2 Gy/fraction) radiation to the full-thickness cord is estimated to be 0.2% at 50 Gy, <1% at 54 Gy, 6% at 60 Gy and 50% at 69 Gy, with a strong dependence on dose/fraction (a/b = 0.87 Gy) [82].

- **Cauda equina and cauda equina PRV:** The cauda equina is outlined from L1/L2 to S2/S3. A cauda equina planning at risk volume (cauda equina PRV) is created by adding a 3-5 mm margin to the cauda equina volume (depending on local practice and accuracy of immobilisation).
- **Lumbosacral plexus:** The lumbosacral nerve roots from L4 to S2 should be contoured, in continuity with the lumbosacral plexus, from the level of L4/5 cranially to the level of the superior aspect of the femoral neck caudally (level of the sciatic nerve) [83]. A lumbosacral plexus planning at risk volume (lumbosacral plexus PRV) is created by adding a 3-5 mm margin to the lumbosacral plexus (depending on local practice and accuracy of immobilisation).
- **Small bowel:** It is recommended that the entire volume of the peritoneal space in which the small bowel can move is delineated. Efforts should be made to limit dose to the small bowel as much as possible. QUANTEC guidelines suggest that if the whole peritoneal cavity is outlined, the volume receiving >45 Gy should be <195 cm^3 when possible [74]. However, this may not be realistic for small bowel directly adjacent to tumour, when higher doses to small volumes may need to be accepted. When larger volumes of small bowel are directly adjacent to PTV, consider using a PRV on BowelSpace to prevent delivery of unacceptably high doses to small bowel.
- **Rectum:** The rectum is outlined from the recto-sigmoid junction proximally to the ano-rectal junction distally. The circumference of the rectum should be outlined entirely.
- **Kidneys:** Both kidneys should be outlined as one structure. Nephrotoxic chemotherapy agents can enhance the renal injury from radiotherapy and this needs to be taken into account.
- **Liver:** The whole liver should be outlined [77].
- **Bladder:** Bladder size, shape and position varies on a daily basis and the dose distribution to the bladder volume as seen on the initial planning CT scan is unlikely to be representative of the radiation dose to the bladder during the course of treatment. Sites should use their own drinking protocol to ensure that bladder filling is as reproducible as possible.
- **Lung:** The dose constraints quoted will limit the risk of radiation pneumonitis to ≤ 20%. However, if there are co-morbidities such as chronic obstructive pulmonary disease, it may be prudent to be more conservative, to reduce the risk of radiation pneumonitis to lower levels, e.g. with V_{20Gy} ≤ 25 – 30 Gy, and mean lung dose to ≤ 15 – 18 Gy.
- **Genitalia:** Genitalia should be avoided as much as possible. For males, the genitalia should be moved away from the treatment area, and sperm banking should be offered.
- **Other organs at risk:** Other normal tissue structures are likely to require delineation, depending on the specific anatomical location. Accepted normal tissue tolerance constraints should be taken into account at all times. Clinicians are referred to consensus

guidelines as outlined by Emami et al [72] and the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) documents [73].

3.3.6. Planning guidelines

Optimal doses to be aimed for are given below. However, it is accepted that it may not be possible to deliver the optimal dose to the entire PlanPTV and still stay within OAR dose constraints. If this is the case, then the clinician will need to make decisions as to the competing priorities of achieving dose to PlanPTV, and keeping specific OAR within dose constraints. This will need to be individualised for each patient, depending on the risk to individual OAR. However, the original PlanPTV structure needs to be retained for reporting the primary endpoint even if it is subsequently modified in order to keep OARs within tolerance.

a) Prescribed dose and fractionation

Radiotherapy can be given as adjuvant treatment after surgery, or as definitive local therapy.

- *Definitive radiotherapy:* Aim for 70 Gy to the PTV in 35 to 38 fractions of 1.8 to 2 Gy each delivered once daily over 7 to 7½ weeks. A total dose of <70 Gy and fraction size <1.8 Gy is acceptable in cases where normal tissue tolerance would otherwise be exceeded. It may be possible to achieve doses or up to 74 Gy for pelvic tumours under certain circumstances. Please contact the RTTQA team if a higher dose is felt to be clinically warranted, and can be technically achieved.
- *Post-operative radiotherapy (high grade primary bone sarcomas, excluding chordoma):* 60 Gy to the PTV in 30 to 34 fractions of 1.8 to 2 Gy each delivered once daily over 6 to 7 weeks. A total dose of <60 Gy and fraction size <1.8 Gy is acceptable in cases where normal tissue tolerance would otherwise be exceeded.
- *Post-operative radiotherapy (chordoma):* Aim for 70 Gy to the PTV in 35 to 38 fractions of 1.8 to 2 Gy each delivered once daily over 7 to 7½ weeks. A total dose of <70 Gy and fraction size <1.8 Gy is acceptable in cases where normal tissue tolerance would otherwise be exceeded.

Special Considerations

- The presence of metal stabilisation rods and cages may produce dosimetric uncertainties when using IMRT/VMAT™/Tomotherapy™ techniques, and ideally beams should not enter through the metalwork, as this may increase uncertainty in the dose to PTV, and that to OAR such as the spinal cord. This will need to be considered on an individual patient basis, depending on the proximity of the metalwork to the spinal cord, the accuracy of the planning software, and the anticipated degree of uncertainty in dosimetry in this area. **It may be the case that the dosimetric uncertainty is such that an IMRT plan is not possible to deliver safely, and the patient will be better treated to a lower dose with conformal radiotherapy outside of the trial.**

b) PTV dose/volume constraints and reporting

As for cohort 2.

APPENDIX 4: SCHEDULE OF ASSESSMENTS

Cohort 1

SCHEDULE	Pre-registration	Pre-treatment Within 28 days prior to start of treatment	During Treatment Weekly during treatment (5 –6 ½ weeks)	Completion of Trial Treatment (28 days after last fraction of RT)	2 months (60 days) after last fraction of RT	3 months (90 days) after last fraction of RT	3 monthly follow up for up to 3 years after registration	Assessments after disease progression (where possible)[i]
Histological confirmation of disease	X							
MRI/CT	X[a]							
Chest x-ray	X[b]					X[b]	X[b]	
Informed consent	X							
Pregnancy test	X[c]							
Relevant Medical History	X[c]							
Clinical review	X[c, d]	X[e]	X	X	X	X	X	X
WHO performance status	X[c]	X[e]	X	X	X	X	X	X
RTOG Assessment		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]
Assessment of wound complications		X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	
Adverse events using CTCAEv4.03	X[c]	X[e]						
Adverse Reactions using CTCAEv4.03			X	X				
EORTC QLQ-C30 & TESS questionnaires		X					X[h]	X[h]
MSTS scale		X					X[h]	X[h]
Clinical assessment of local tumour control						X	X	

a For adjuvant radiotherapy, MRI/CT to be performed within 1 month prior to date of surgery; For neo-adjuvant radiotherapy, MRI/CT should ideally be performed within 1 month of starting radiotherapy

b Chest CT may be performed instead if routine local practice; chest x-rays should be carried out approximately 3 monthly after initial staging imaging for the first 2 years from diagnosis, and should be fitted in accordingly with follow-up visits

c Within 14 days prior to registration

d Includes measurement of height, weight, smoking status, diabetic status and limb function or mobility

e Does not need repeating if pre-registration assessment is within 28 days of start of treatment

f RTOG Acute Radiation Morbidity Scoring Criteria up to day 90 after start of treatment; RTOG Late Radiation Morbidity Scoring Criteria and Stern's scale for oedema from day 91 after start of treatment

g Assessment of wound related clinical findings if recent surgery

h TESS questionnaire, EORTC QLQ-C30 and MSTS scale completion at 1 and 2 years after registration

I If a patient progresses within 2 years from the date of registration, they should continue to be followed up if possible, fitting in with their routine oncological care. Investigators should use their judgement on a case-by-case basis to perform follow up on patients according to their circumstances and what is clinically reasonable

Cohorts 2 and 3

SCHEDULE	Pre-registration	Pre-treatment Within 28 days prior to start of treatment	During Treatment Weekly during treatment ($5^{1/2}$ – 7 weeks)	Completion of Trial Treatment (28 days after last fraction of RT)	Completion of Trial Treatment ~3 monthly follow up for up to 3 years after registration	Assessments after disease progression
Histological confirmation of disease	X					
MRI/CT	X[a]				X[g]	X[g]
RECIST v1.1 measurement	X[b]				X[g]	X
Chest x-ray/CT as per routine practice	X					
Informed consent	X					
Pregnancy test	X[c]					
Relevant Medical History	X[c]					
Clinical review	X[c]	X[d]	X	X	X	
WHO performance status	X[c]	X[d]	X	X	X	
RTOG Assessment			X[f]	X[f]	X[f]	
Post-surgery wound healing		X[e]			X[f]	
Adverse events using CTCAEv4.03	X[c]	X[d]				
Adverse Reactions using CTCAEv4.03			X	X		
Clinical assessment of local tumour control					X	X[i]
Assessment for survival						X[i]

a Refer to section 9.2.1 for Diagnostic MRI/CT schedule
b Only for patients receiving radical radiotherapy, or those who have evaluable residual disease after surgery
c Within 14 days prior to registration
d Does not need repeating if pre-registration assessment is within 28 days of start of treatment
e Assessment of wound healing only if recent surgery
f RTOG Acute Radiation Morbidity Scoring Criteria up to day 90 after start of treatment; RTOG Late Radiation Morbidity Scoring Criteria from day 91 after start of treatment
g Post radiotherapy MRI of the treated site 6 months after completion of RT for patients receiving radical radiotherapy or those who have evaluable residual disease after surgery
h To be submitted every 6 months

APPENDIX 5: MUSCULOSKELETAL TUMOR SOCIETY RATING SCALE

MSTS Lower Extremity

SCORE	PAIN	FUNCTION	EMOTIONAL	SUPPORTS	WALKING	GAIT
5	No pain	No restriction	Enthused	None	Unlimited	Normal
4	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate
3	Modest/Non-disabling	Recreational restriction	Satisfied	Brace	Limited	Minor cosmetic
2	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate
1	Moderate/Disabling	Partial restriction	Accepts	One cane or crutch	Inside only	Major cosmetic
0	Severe disabling	Total restriction	Dislikes	Two canes or crutches	Not independent	Major handicap
Patient score						

The MSTS is a subjective score about how the patient feels about each aspect on the scale, and should be completed by the patient. The recommendation is that, if possible, the patient is asked to complete this form prior to seeing the investigator. The investigator should then discuss this with the patient, calculate the score and sign it.

MSTS Upper Extremity

SCORE	PAIN	FUNCTION	EMOTIONAL	HAND POSITIONING	MANUAL DEXTERITY	LIFTING ABILITY
5	No pain	No restriction	Enthused	Unlimited	Unlimited	Normal load
4	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate
3	Modest/Non-disabling	Recreational restriction	Satisfied	Not above shoulder or no/Prosupination	Loss of fine movements	Limited
2	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate	Intermediate
1	Moderate/Disabling	Partial restriction	Accepts	Not above waist	Cannot pinch	Helping only
0	Severe disabling	Total restriction	Dislikes	None	Cannot grasp	Cannot help
Patient score						

The MSTS is a subjective score about how the patient feels about each aspect on the scale, and should be completed by the patient. The recommendation is that, if possible, the patient is asked to complete this form prior to seeing the investigator. The investigator should then discuss this with the patient, calculate the score and sign it.

APPENDIX 6: STERN'S SCALE FOR OEDEMA

Grade	Description
0	None
1	Mild (but definite swelling)
2	Moderate
3	Severe (considerable swelling)
4	Very severe (skin shiny and tight ± skin cracking)

APPENDIX 7: EXPECTED ADVERSE EVENTS

The following AEs are commonly associated with radiotherapy and will be considered expected for this treatment [29, 91-94]:

Adverse Events		
Incidence ≥50%	**Incidence ≥10%-<50%**	**Incidence <10%**
Skeletal muscle fibrosis	Moist desquamation	Anorexia
Erythema	Lymphoedema	Insufficiency Fracture
Epilation	Dry Skin	Osteoporosis
Pigmentation/depigmentation	Nausea	Radiation induced malignancy
Induration	Asthenia	Peripheral nerve fibrosis
Joint stiffness/immobility	Dysphagia/oesophagitis/discomfort swallowing from treatment to cervical and dorsal spine	Brachial/Sciatic nerve plexopathy
Dry desquamation	Radiation dermatitis	Diarrhoea
Lethargy	Wound infection	Tenesmus
Transient sore throat		Haematuria
		Bone necrosis
		Bone deformity
		Anaemia
		Reduced Bone marrow reserve
		Bowel ulceration/perforation/stenosis
		Rectal bleeding
		Frequency/Dysuria/Cystitis
		Abdominal pain
		Desquamating rash
		Wound dehiscence
		Skin infection

APPENDIX 8: PROTOCOL VERSION HISTORY

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
1.0	04/08/2015	N/A		
2.0	24/04/2017	2	General	Administrative changes correcting typographical and grammatical errors.
			Page 3, Trial Management Group	Dr Rob Turner & Stephen Nash removed. Hakim-Moulay Dehbi added.
			1.1 Summary of Trial Design	Wording changes made in line with updates throughout the protocol.
			3.2.1 Primary Endpoints	Clarification of cohort 2 & 3 primary endpoints
			3.2.2 Secondary Endpoints	Clarification of which patients require response to be measured by RECIST v1.1
			3.2.2 Secondary Endpoints	Secondary endpoints added to assess individual RT plans for cohorts 2 and 3.
			6.2.1 Inclusion Criteria	Clarification on eligibility of patients with metastatic disease.
			6.2.2 Exclusion Criteria	Addition of exclusion criteria clarifying use of concurrent chemotherapy and radiotherapy.
			6.2.3 Pregnancy and Birth Control	Change to definition of female of childbearing potential

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
			8.1 Trial Treatment Details	Clarification to allow RT to start more than 12 weeks after surgery if delays in wound healing.
			8.1 Trial Treatment Details	Clarification to include the high and low PTV doses.
			9 Assessments	Section split into assessments for cohort 1 (section 9.1) and cohorts 2&3 (section 9.2).
			9.1.1 Pre-registration Evaluation	Clarification to timelines for MRI/CT imaging. Addition of 3 month timeline for chest scans. Addition of physical assessments & function/mobility assessments.
			9.1.2 Pre-treatment Assessments	Timeframe for assessments increased to 28 days pre-treatment. RTOG assessment removed.
			9.1.4 Assessments During Treatment	Adverse Events changed to Adverse Reactions. Addition of wound related assessment.
			9.1.5 Assessments on Completion of Trial Treatment	Assessment window changed to 28-35 days. Adverse Events changed to Adverse Reactions. Addition of wound related assessment.
			9.1.6 Follow-up Assessments after Completion of Treatment	MRI/CT assessment removed Timeframe for assessment of local tumour control at primary site added.
			9.1.7 Assessments After Disease Progression	Section added

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
			9.2.1 Pre-registration Evaluation	Clarification to cohorts 2 & 3 as to which MRI should be considered the baseline scan.
			9.2.2 Pre-Treatment Assessments	Timeframe for assessments increased to 28 days pre-treatment. RTOG assessment removed.
			9.2.3 Assessments During Treatment	Adverse Events changed to Adverse Reactions.
			9.2.4 Assessments on Completion of Trial Treatment	Assessment window changed to 28-35 days. Adverse Events changed to Adverse Reactions.
			9.2.5 Follow-up Assessments After Completion of Treatment	Timeframe for follow ups clarified. Chest x-ray & plain x-ray assessments removed. Clarification of RECIST response requirements. Addition of clinical assessment of local tumour control at primary site.
			9.2.6 Assessments After Disease Progression	Section added
			11.2.1 All Adverse Events (AEs)	Clarification on collection of AEs from consent to start of RT, and on ARs from start of RT to 30 days post RT.
			11.2.7 Exemption from SAR Report Submission	Note regarding yellow card scheme for reporting chemotherapy related serious events added.

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
			11.5 Pregnancy	Clarification on process for obtaining consent from pregnant patient/partner to collect information relating to pregnancy
			12.2 Serious Breaches	Section added.
			14.1 Patients Who Do Not Start Trial Treatment	Section added.
			16.1 QA for Radiotherapy	Clarification added that completion of outlining benchmark case is per investigator at a site. Prospective case review requirements clarified. Addition of diagnostic MRI and clinical history requirements.
			17.1 Sample Size Calculation	Cohorts 1 sample size calculations updated in line with increased sample size. Cohort 2 & 3 sample size calculation amended following clarification of primary endpoints.
			17.2 Population for analysis	Clarification of text for cohorts 2 & 3.
			17.3 Analysis of the primary endpoint	Clarification on primary endpoint analysis for all cohorts.
			17.5 Notes on primary endpoints for IMRiS cohorts 2 & 3	Section added.
			21 Publication policy	Clarification of publication policy.

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
			Appendix 3: Radiotherapy Target Definition Outlining And Planning Guidelines	Updates and clarifications following review by UCLH and the RTTQA group.
			Appendix 4: Schedule of Assessments	Updated in line with updates made to Assessment section of protocol.
			Appendix 5: Musculoskeletal Tumor Society Rating Scale	New appendix - Musculoskeletal Tumor Society Rating Scale.
			Appendix 6: Stern's Scale For Oedema	New appendix - Stern's Scale for Oedema table.
			Appendix 7: Expected Adverse Events	Previously Appendix 5. Update of AE incidence rates. New expected AEs added.
3	14/01/2019	9	1.1 & 17.1,	Revision of Cohort 2 Sample size to 9 patients.
			3.2.2	Addition of secondary objectives – To perform dosimetric analyses using data from patients double planned using IMRT and PBRT.
			3.1.2 & 9.2.5	Removal of QoL assessment for cohorts 2 and 3.
			3.2.2	Addition of secondary assessment - Creation of additional proton beam radiotherapy plan for dosimetric comparison with IMRT plan.

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
			9.1.6	Assessment at 2 years after registration of any further surgeries or use of antibiotics for wound management in the last 24 months.
			9.2.5	Clarification that cohort 2 and 3 follow up will be until end of June 2020 or if patients reach 3 years of follow up, whichever is sooner.
4	01/07/2020	12	Page 3, Coordinating Centre	Trial coordinator contact telephone updated.
			Page 3, Trial Management Group	Chris Stacey & Hakim-Moulay Dehbi removed. Shumona Shelly, Andre Lopes, Andrew Gosling & Narinder Lalli added.
			3.1.2 (secondary objectives)	Additional secondary objectives added.
			3.2.2 (secondary endpoints)	Additional secondary endpoints added.
			17.4 (analysis of secondary endpoints)	Details of analysis of additional endpoints added.
			20 (funding)	Acknowledgement of Rita Simões' Clinical Doctoral Research Fellowship funding.

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