Advanced radiotherapy techniques: Improving outcomes in sarcoma

By

Franel le Grange

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University College London

Faculty of Medical Sciences

Cancer Institute

Declaration

I, Franel le Grange, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Radiotherapy is an important modality in the management of the primary tumour in bone and soft tissue sarcomas. Traditionally radiotherapy for sarcomas has been delivered with a three-dimensional conformal technique (3DCRT). In extremity soft tissue sarcomas this frequently leads to high doses of radiation being given to normal soft tissues outside the target. In Ewing sarcoma arising in specific sites such as the pelvis, it is difficult to avoid significant dose from 3DCRT to sensitive normal tissue structures adjacent to the target (small bowel, rectum, bladder and reproductive organs), potentially limiting the dose that can safely be given to the target.

This body of work explores the burden of late effects of 3DCRT in patients with bone and soft tissue sarcoma and how advanced radiotherapy techniques including intensity modulated radiotherapy (IMRT) and proton beam therapy (PBT), that produce more conformal dose distributions around the target, might be used to reduce the risk of late side effects while optimising target coverage. The experimental work comprises three studies examining different aspects of the research topic, culminating in the development of a prospective phase II clinical trial. The first study is a survey of late effects and functional outcomes in patients with extremity bone and soft tissue sarcoma treated with 3DCRT. Risk factors for late toxicity in this cohort are identified. The second study is a comparative planning study of 3DCRT versus volumetric modulated arc therapy (VMAT), a rotational IMRT technique, in upper and lower extremity sarcomas. The third study is a comparative double planning study of VMAT and PBT in patients with pelvic Ewing sarcoma. How this work has directly fed into the development and opening of IMRiS, a currently recruiting prospective national phase II clinical trial of IMRT in bone and soft tissue sarcoma, is discussed.

Impact Statement

The body of work set out in this thesis had a pivotal role in the development and set up of the IMRiS trial, a prospective national multi-centre trial of Intensity Modulated Radiotherapy (IMRT) in sarcoma. IMRiS made it possible for sarcoma radiotherapy centres across the UK to introduce IMRT into their practice in a standardised and quality-assured setting. This created the opportunity for national collaboration amongst participating centres to reach consensus on immobilisation techniques and target delineation through the pre-trial workshops held. The extremity sarcoma planning study enabled the UCLH radiotherapy physics department to introduce and refine Volumetric Modulated Arc Therapy (VMAT) for extremity sites with confidence. The results of IMRiS are awaited, and if the value of IMRT to reduce late effects in extremity sarcomas is confirmed, it will provide the evidence base to support IMRT as the new standard of care nationally and internationally.

Prior to this work there was little evidence on how IMRT and Proton Beam Therapy (PBT) compare for the treatment of pelvic Ewing sarcoma. The double planning study has generated objective data and established a new understanding of the dosimetric advantages and challenges of different advanced radiotherapy techniques to treat this group of patients. This has contributed to the development of the IMRiS trial, and in the implementation of PBT at UCLH. The results give reassurance that IMRT, which prior to this had been used more frequently for this patient group without a scientific evidence base, is in fact able to achieve an excellent dosimetric profile, validating IMRT as the appropriate modality for patients not eligible for PBT.

As a result of this research, we are able to have more informed discussions about the value of different radiotherapy techniques with patients in the clinic.

Contents

Abbreviations and symbols

3DCRT Three-dimensional conformal radiotherapy

CAN-NCIC-SR2 National Cancer Institute of Canada SR2 trial

CGE Cobalt Gray Equivalent

CI Confidence interval

CRUK Cancer research UK

CT Computed tomography

CTCAE Common Terminology Criteria for Adverse Events

CTV Clinical target volume

DVH Dose Volume Histogram

ECOG Eastern Cooperative Oncology Group

EORTC European organisation for research and treatment of cancer

EQD2 Total Equivalent Dose in 2 Gray fractions

GTV Gross tumour volume

Gy Gray - derived unit of ionizing radiation dose in the International System of Units (SI). It is defined as the absorption of one joule of radiation energy per kilogram of matter.

IGRT Image guided radiotherapy

IMPT Intensity Modulated Proton Therapy

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

IMRT Intensity modulated radiotherapy

LENT/SOMA Late Effects of Normal Tissues/ Subjective, Objective, Management, Analytic

LERTiSS Late effects of 3D conformal radiotherapy in extremity bone and soft tissue sarcomas (LERTiSS)

MSKCC Memorial Sloan Kettering Cancer Centre

MSTS Musculoskeletal Tumour Society Rating Score

MU Monitor units

N Number of

N/A Not applicable

NCI National Cancer Institute

NHS National Health Service

NIHR National Institute of Health Research

OAR Organ at risk

OR Odds ratio

PBT	Proton beam therapy
PTV	Planning target volume
QUANTEC	Quantitative Analysis of Normal Tissue Effects in the Clinic
RTTQA	Radiotherapy Trials Quality Assurance group
SRT	Stereotactic radiotherapy
STS	Soft tissue sarcoma
RBE	Relative Biological Effectiveness
RMH	Royal Marsden Hospital
RT	Radiotherapy
RTOG	Radiation therapy oncology group
SOM	Subjective, Objective, Management
TESS	Toronto extremity salvage score
UCL	University College London
UCL CTC	University College London Cancer Trials Centre
UCLH	University College London Hospitals NHS Foundation Trust
VMAT	Volumetric modulated arc therapy

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1. Chapter 1 Introduction

1.1 Sarcoma and the role of radiotherapy

Sarcomas are rare malignancies of mesenchymal origin representing 1% of cancers diagnosed in the UK. The incidence of primary bone sarcoma is 7.9 per million with 531 new bone sarcomas diagnosed in 2010 according to the National Cancer Intelligence Network. Primary soft tissue sarcoma incidence is higher at 45 per million with a total of 2980 new diagnoses in 2010. The 5 year survival rates for the 2006 to 2010 period were 56% for bone sarcoma and 55% for soft tissue sarcoma. (1)

Radiotherapy is an important modality in the management of the primary tumour in sarcoma. Data from The National Cancer Registration and Analysis Service (NCRAS) on annual number of radiotherapy courses (cases treated) and attendances (individual fractions of radiotherapy delivered) for patients with sarcoma in England is shown in Figure 1.1. More than 1500 courses of radiotherapy are delivered to patients with sarcoma each year.

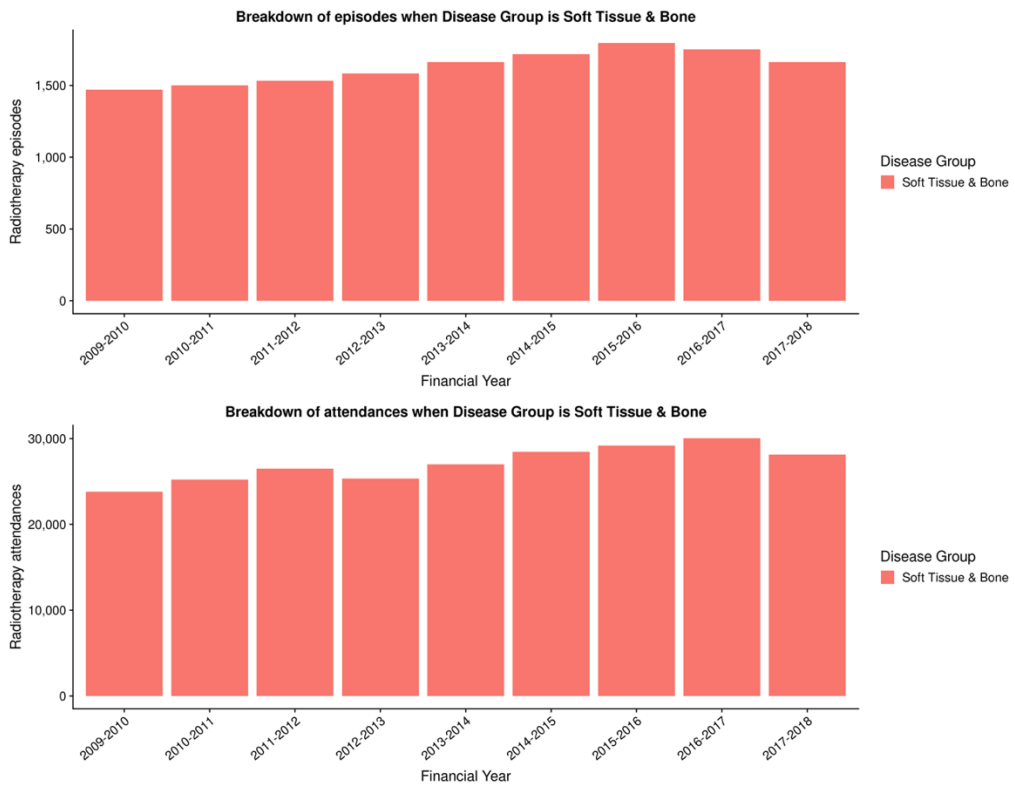
Radiotherapy is used in the pre-operative or post-operative setting to reduce the risk of local recurrence in soft tissue sarcomas. The majority of these tumours arise in the extremities and indications for radiotherapy include tumour size ≥5cm, histological high-grade tumours, inadequate surgical margins, tumours involving the anatomical deep compartment (deep to the fascia), and where initial surgery was incomplete and a second procedure was required to achieve complete resection.(2, 3) Local control rates with combined modality treatment are in excess of 80% in published series.(4-11) Radiation doses used are 50Gy in 25 fractions (preoperatively), and 60 to 66Gy in 30 to 33 fractions (post-operatively, delivered in 1 or 2 phases).(12) The side effects of neo-adjuvant and adjuvant radiotherapy include early wound healing complications, and late effects such as fibrosis, joint stiffness, oedema, pain and occasional bone fractures. The literature on radiotherapy and late effects in extremity sarcomas is reviewed in depth in Chapters 2 and 3.

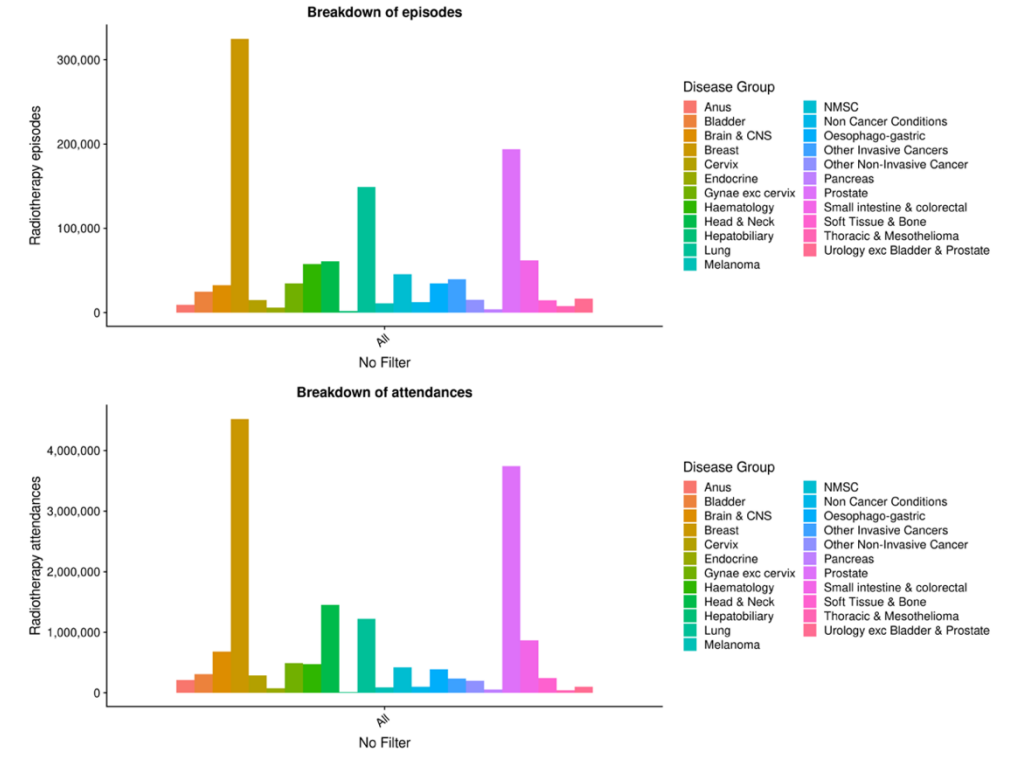
Radiotherapy is also an important modality in the treatment of the primary tumour in Ewing sarcoma. Ewing sarcoma is most common in children and teenagers. (1) In adult patients, the median age at presentation was 27 years (range 18 – 67) in a large series from Memorial Sloan Kettering Cancer Centre.(13) Pre-operative, post-operative or definitive radiotherapy are used in combination with chemotherapy at doses ranging

from 45 to 60Gy, and particularly at sites where complete surgical resection with adequate margins is not feasible, or where the response to chemotherapy is poor. Prognosis also depends on tumour size, and whether patients are treated on a trial protocol.(13-17) Ewing sarcoma is a radiosensitive tumour and radiotherapy as a sole modality can achieve long term local control. The therapeutic ratio and potential burden of late effects of any treatment modality needs to be taken into consideration in young patients who will live with potential long term side effects after treatment. Ewing sarcoma affect a variety of anatomical sites, and the data on late effects of radiotherapy are limited. The literature is reviewed in depth in Chapter 4.

Radiotherapy is also used in the treatment of high-grade non-Ewing bone sarcomas including osteosarcoma, chondrosarcoma, spindle cell sarcomas of bone and chordoma. These tumours are not as radiosensitive as Ewing sarcoma and high radiotherapy doses are needed to have an effect. Radiotherapy rarely achieves long term local control when used as sole modality. Photon or proton beam radiotherapy (PBT) are used alone or in combination with surgery, aiming for doses of 60Gy or higher, and ideally around 70Gy.(18-20) These high doses are challenging to deliver at anatomical sites such as the pelvis and spine due to the proximity of sensitive normal tissue including bowel and spinal cord. The literature on radiotherapy for high grade bone sarcomas and chordoma is reviewed in Chapter 5.

Figure 1.1 Radiotherapy for Sarcoma in England: 2009 - 2018





The National Cancer Registration and Analysis Service (NCRAS) data from the Radiotherapy Dataset (RTDS) on radiotherapy activity in hospitals in England, https://www.cancerdata.nhs.uk/radiotherapy

1.2 The therapeutic index

Oncological treatment, be it surgery, systemic therapy or radiotherapy, is aimed at eradicating or controlling the cancer. The ability of radiotherapy to damage cancer cells beyond the possibility of repair is linked to radiation dose. Higher doses cause more cell kill. There is however a cost in terms of side effects and damage to surrounding normal cells that need to be considered and weighed up for each patient and each situation. This fine balance between the tumour control probability (TCP) and the risk of normal tissue complications (NTCP) is the therapeutic index, and the clinical oncology community constantly strive to influence the balance in favour of safer and more effective radiotherapy treatment.(21, 22)

The damage to normal tissues depends on the inherent radio-sensitivity of the individual organ and its ability to repair damage, the volume irradiated, and the dose. Our understanding of the safe limits and organ specific tolerance doses have developed from radiobiological experiments with cell cultures, animal models, accidental exposures, and more recently from the very limited data from clinical research. The current understanding is still heavily dependent on modelling. Seminal papers by Emami in 1991 and updated in 2013 (23, 24), and the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) review in 2010 (25, 26) form the basis of our understanding of radiation normal tissue toxicity in clinical practice.

The therapeutic ratio could potentially be shifted by modulating the radiobiology to sensitise tumours and to protect normal tissues, or by reducing the volume of normal tissue that receives damaging doses while increasing the volume of the tumour that receives an effect dose. The most common radiobiological strategy is the use of different fractionation schedules to deliver the total dose. Hypoxia modulators and radiosensitisers have also been explored. Chemoradiation uses concurrent cytotoxic chemotherapy to increase radiation sensitivity of tumours and improve tumour control outcomes, but may carry a cost of significant increased toxicity.(21)

Strategies to reduce the volume of normal tissue receiving radiation include brachytherapy, where a radioactive source is placed directly in or near the target. This is used most frequently in cervical and prostate cancer treatment. More recently, advances in radiotherapy planning and delivery have made it possible to reduce the uncertainty margin around the target, and consequently reducing the ratio of the total irradiated volume including normal tissues, and the target volume. Improved quality of diagnostic imaging, the use of functional imaging, and image fusion have made it possible to define the target more accurately at the time of planning, but also during

treatment with the use of image guided radiotherapy (IGRT). Other techniques include stereotactic radiotherapy (SRT) delivered in high doses per fraction to small volumes using limited margins. Motion management techniques such as deep inspiration breath hold (DIBH) in breast cancer, allows more accurate positioning of the target and enables the use of smaller planning target volume (PTV) margins.(21, 22)

Developments in radiotherapy technology have allowed us to create more conformal dose distributions to effectively reduce the volume of normal tissue that receive damaging doses of radiation.

1.3 Advanced radiotherapy techniques

Two-dimensional photon radiotherapy planning is limited to the use of very simple shielding to reduce the dose to normal tissue at the edges of the beam. It is impossible to limit dose to normal tissue structures in front of or behind the target in the direction of the beam. With the introduction of 3-dimensional Computer Tomography based planning (3D-conformal radiotherapy, 3DCRT), it became possible to create more sophisticated treatment plans taking the anatomy and different tissue densities into account, and using two or more beams from different angles to deliver the radiation dose to the target while avoiding entry or exit dose through critical normal tissue structures. A significant percentage of the dose is however still deposited in the pathway of the beam in order to deliver adequate dose to the target.(27)

1.3.1 Intensity modulated radiotherapy (IMRT)

Advances in computer software led to the development of photon intensity modulated radiotherapy (IMRT) techniques that result in highly conformal dose distributions around the target, with significant reduction in the volume of normal tissue receiving moderate to high doses. IMRT fields are made up of multiple small beamlets within each radiotherapy beam of which the individual intensity is modulated during treatment to deliver non-homogenous beams. Multiple such beams from either fixed angles or through a moving arc technique are combined by sophisticated computer software to create a highly conformal cumulative treatment plan. Different volumes within the target can be treated to different dose levels in the same plan, making it possible to shape the high dose around sensitive structures.(28) The increased conformality seen in the dose distribution with IMRT, has been shown to lead to clinical benefit with a reduction in early and late side effects of radiotherapy in several tumour sites including head and neck cancer, breast cancer and prostate cancer. (29, 30) However, IMRT results in a larger volume of normal tissue receiving low radiation doses, which raises concerns

about an estimated 0.75% increased risk of developing secondary radiation-induced malignancies compared to 3DCRT. This is particularly relevant when children are treated with radiotherapy.(31)

The literature on IMRT, with particular reference to sarcoma, is reviewed in more detail in Chapter 3.

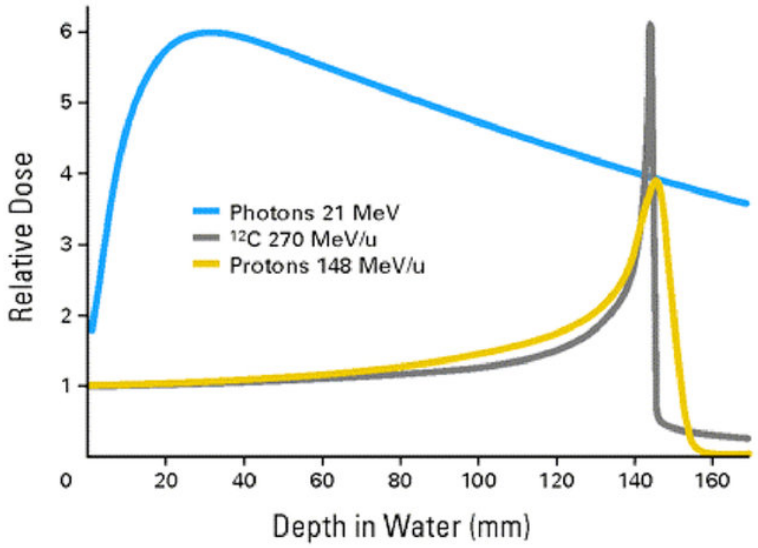
1.3.2 Proton beam therapy

Proton beam therapy can reduce both low and high doses to normal tissues. This effect is because of the physical properties of protons. These subatomic particles were discovered by Ernest Rutherford in 1918. At ambient temperatures protons are present as hydrogen gas. They are very small, extremely dense, and carry a positive charge.(32) Protons were only explored for therapeutic use in the 1940s, with the advent of high energy accelerators.(33) The majority of energy from a proton beam is delivered over a short distance. This sharp peak in deposition of energy is referred to as the Bragg peak, and beyond this there is no radiation dose to the normal tissues. The depth at which this happens in the patient (the range of the proton beam) is related to the accelerating energy. The comparative depth-dose curves of proton, photon and carbon ion beams are shown in Figure 1.2. In practice, to treat a tumour several centimetres thick, multiple proton beams of different energies are used creating a so-called spread out Bragg-peak. Originally this was achieved through passively scattered beams to the required field width. More recently the technology has developed to deliver individual small pencil beams each targeting a small area in the target.(34) This also allows for an intensity modulated approach to using proton beams.(35)

As a result of the physical characteristics of PBT, significantly less whole-body dose is delivered, and the volume of normal tissues receiving low as well as high doses is reduced. This may reduce late effects of radiation outside the target as well as the risk of radiation-induced malignancies. However, the production of secondary neutrons during PBT has been cited as a concern for increased risk of radiation induced malignancy. The current understanding of the impact of the various factors influencing second malignancy risk and how PBT may compare with photon radiotherapy is mostly model-based, and therefore limited. (36, 37) A retrospective review concluded that the risk was no higher with PBT than with photons.(38) The dosimetric benefit has been sufficient to introduce PBT as the preferential radiation modality in the treatment of many paediatric cancers.(39)

The literature on proton beam therapy for Ewing sarcoma and other high-grade bone sarcomas is reviewed in Chapters 4 and 5.

Figure 1.2 Depth-dose curves



Depth-dose distributions from 10 MV x-rays, proton beams, and carbon ion beams superimposed with each other for comparison.
Dilmanian et al, 2015. (40)

1.3.3 Other charged particles: Carbon ions

Carbon ions are 12 times as heavy as protons. They produce a similar peak of energy distribution in tissue (Figure 1.2). There is slightly more radiation effect distal to this peak, but sharper lateral penumbras are achieved. The radiobiological equivalent effect of carbon ions is about 2.5 times greater than PBT.(41) Clinical facilities are most located in Japan where there is the greatest long-term clinical experience, but with newer facilities being built in recent year, in China, USA and Europe. Results are promising for dose escalation in chondrosarcomas and chordomas, and a comparative trial with PBT and carbon ion therapy is underway.(42-44)

1.4 Improving outcomes in sarcoma

The standard technique for sarcoma radiotherapy in the UK at the time of this experimental work in 2013 and 2014, was three-dimensional conformal radiotherapy (3DCRT). A small proportion of patient at selected centres were being considered for IMRT on an individual case basis where this was readily available. Paediatric cancer patients, and adult patients with spinal and paraspinal bone and soft tissue sarcomas, were considered for treatment with PBT abroad.

The challenge in clinical practice when treating patients with extremity soft tissue sarcomas with radiotherapy, was the limited conformality of the high dose around the target with 3DCRT plans. This frequently led to high doses of radiation being given to normal soft tissues and bone outside the target. Patients developed uncomfortable skin reactions towards the end of the radiotherapy course, and frequently struggled with stiffness, fibrosis of soft tissues and reduced range of motion around joints in the longer term.

In Ewing sarcoma, the most challenging cases were those in the pelvis or along the spine where it was difficult to avoid significant dose from 3DCRT to sensitive normal tissue structures including the spinal cord, small bowel, and reproductive organs. The tolerance of these normal tissues was frequently the dose limiting factor, with typical prescriptions of no more than 50.4Gy in 28 fractions of 1.8Gy at these sites. It was often not possible to deliver the required 54Gy for post-operative or definitive indications. Patients with Ewing sarcoma are young and when treated with curative intent, long term survival issues and fertility preservation needed to be considered.

This challenge was even more pronounced in other high-grade primary bone sarcomas and chordomas because of the significantly higher doses of at least 60 to 70Gy or more required for tumour control. Delivering the necessary dose without an unacceptable risk of toxicity was very difficult. This meant that 3DCRT was an inadequate treatment for many patients with tumours arising in the pelvis and spine, due to its inability to deliver therapeutic radiotherapy doses.

1.5 Scope and aims of this thesis

The principal aim of the experimental work embodied in this thesis is to suggest ways in which the therapeutic index of the radiotherapy treatment for these different groups of patients with sarcoma might be improved through the use of advanced radiotherapy techniques.

In Chapter 2 the late effects and functional outcomes following the current standard treatment (3DCRT) in extremity sarcomas are explored.

In Chapter 3 the application of volumetric modulated arc therapy (VMAT), a rotational IMRT technique, to treat extremity soft tissue sarcoma is examined.

The planning study described in Chapter 4 compares IMRT and PBT in the treatment of pelvic Ewing sarcoma and specifically with regards to normally tissue sparing of small bowel, rectum, bladder and of the female reproductive organs.

The development of a phase 2 trial of IMRT in three cohorts of patients with sarcoma is discussed in Chapter 5.

The implications for clinical practice of the data obtained in the experimental studies outlined above are discussed in Chapter 6, and the questions which should be addressed in future studies are also considered.

2. Chapter 2 Late effects of 3D conformal radiotherapy in extremity bone and soft tissue sarcomas (LERTiSS)

2.1 Introduction and literature review

2.1.1 Background

Limb-sparing surgery is the current standard treatment for patients with adult extremity Soft Tissue Sarcomas (STS). Adjuvant radiotherapy is given to patients at high risk of local disease recurrence.(2, 3) Radiotherapy may be given pre-operatively or post-operatively, using external beam radiotherapy or brachytherapy, alone or in combination. Local control rates for this combined modality approach are in excess of 80% in published series.(4-11) Radiation doses used are 50Gy in 25 fractions (preoperatively), and 60 to 66Gy in 30 to 33 fractions (post-operatively, delivered in one or two phases).(12)

Adjuvant or definitive radiotherapy form part of the management of Ewing sarcoma with a dose range of 45 to 60Gy.(14-17) In extremity primary Ewing sarcoma of bone, the surgery necessarily involves resection of the involved segment of bone and an internal stabilisation procedure frequently involving a metal implant.

Radiotherapy has also been used in the treatment of high grade non-Ewing bone sarcomas including osteosarcoma, chondrosarcoma, and spindle cell sarcomas of bone, using radiotherapy alone or in combination with surgery, aiming for doses of 60Gy or higher.(18-20) There are no guidelines on the indications for adjuvant radiotherapy in this setting but poor prognostic factors taken into account include pathological fracture through the tumour, poor response to induction chemotherapy, and involved resection margins. There is significant variation in dose, fractionation and timing of radiotherapy in which best practice may be hidden.

2.1.2 Conformal Radiotherapy

Since the early 1990's, the standard practice for delivering extremity radiotherapy in the UK, has been with three-dimensional conformal computed tomography (CT) based external beam radiotherapy (3DCRT).(45) This was also the technique used in the UK randomised trial of post-operative radiotherapy given to adult patients with extremity

soft tissue sarcoma (VORTEX), recruiting patients between 2007 and 2013.(46) Typical 3DCRT beam arrangements use two or three opposed and/or angled fields optimised to spare a longitudinal corridor of normal soft tissue. Ideally dose to the weight-bearing bones, joint spaces and remaining normal tissues is reduced as far as possible but there are limitations to achieving this with 3DCRT which are further explored in Chapter 3. There is inevitably a significant volume of normal tissue that receives radiation doses close to the prescription dose or even higher due to dose hot spots created by the opposed fields.

2.1.3 Late effects of conformal extremity radiotherapy

Most of the literature on late effects of 3DCRT was published before 2006, reporting mainly on the incidence of bone fracture, ranging from 4% - 8.6% at 5 years. Potential risk factors for fracture vary across studies, and include anterior thigh tumour site, periosteal stripping, marginal or intralesional resection, female gender, age greater than 50 years and additional treatment with chemotherapy.(5, 47-50) Radiation specific risk factors were retrospectively reported in 2009 and include prescription doses of 60Gy or above, volume of bone receiving more than 40Gy, and higher maximum and mean dose to bone. (51)

In reality, though not as dramatic as bone fracture, patients are far more frequently affected by soft tissue effects. Soft tissue late effects (and incidence) reported in published series include:

- Soft tissue induration (57%) (47)
- fibrosis (31- 48%) (52)
- joint stiffness/joint contracture/decrease in range of motion (8 – 32%) (5, 47, 52)
- oedema (8 -23%) (5, 47, 52)
- decrease in muscle strength (20%) (47)
- long term pain (7%) (47)
- peripheral neuropathy (4%) (5)

Bone growth defects and secondary malignancies have been described in addition in the paediatric population.(53)

Risk factors for significant late soft tissue and joint toxicity in the 3DCRT era seem to be primarily associated with two factors: volume of tissue irradiated, and total dose delivered. A study published in 1992 demonstrated increased risk with larger field size, the volume of tissue irradiated to more than 55Gy, more than 50% of the joint space in

the radiation portal, the volume of and dose to hot spots, and higher total radiation prescription dose.(9) The incidence of fibrosis, joint stiffness and oedema were significantly lower after pre-operative radiotherapy (using smaller field sizes and lower doses) compared to post-operative radiotherapy in the CAN-NCIC-SR2 trial, a randomised controlled trial comparing pre-operative and post-operative radiotherapy.(52) The incidence of early wound complications was higher (35% after pre-operative radiotherapy compared to 17% for post-operative radiotherapy).(6) Grade 2 or greater late effects seen in that trial were: fibrosis in 48.2% and 31.5% for pre-operative and post-operative radiotherapy respectively, oedema in 23.2% and 15.1%, and joint stiffness in 23.2% and 17.8%. Fibrosis, joint stiffness and oedema correlated with functional outcomes, particularly at six weeks and three months.(54)

There is a lack of data on late effects and functional outcomes for patients treated with limb sparing surgery and 3DCRT in the last 10 years since the publication of these studies. In this period surgical techniques and radiotherapy strategy have evolved, and recommended target volume margins and subsequent radiation field sizes were reduced.(55) This may have had an impact on late effects of treatment.

2.2 Aim of this study

The aim of this project was to understand the pattern of late normal tissue effects and patient reported outcomes after radical radiotherapy in patients with extremity bone and soft tissue sarcoma treated at UCLH. Potential risk factors for late treatment related toxicity were explored. The data was to be utilised in the development of a clinical trial of intensity modulated radiotherapy (IMRT) in this patient cohort and will serve as a historical reference when evaluating this new radiotherapy technique. The development of IMRiS: A phase II study of intensity modulated radiotherapy (IMRT) in primary bone and soft tissue sarcoma,(56) is discussed further in chapter 5.

2.2.1 Study objectives

2.2.1.1 Primary objective:

- To evaluate late radiotherapy toxicities, limb functionality and overall level of disability

2.2.1.2 Secondary objectives:

- To correlate the incidence of late radiotherapy toxicities with radiotherapy plan parameters and dosimetric data
- To correlate late toxicity scores with limb functionality and overall disability
- To identify any subgroups at greater risk of developing late treatment related toxicity
- To establish a benchmark of outcomes of current treatment practice

2.3 Materials and methods

This project was developed in Spring 2012. It was discussed with the UCLH Research and Development Department and classed as a service development project which did not require an ethics application. A protocol was developed and titled 'Late Effects of Radiotherapy in Sarcoma Survey (LERTiSS)'. Patients seen in sarcoma clinics were given an information sheet and they consented to the use of their data. (LERTiSS protocol and study documentation is attached in Appendix 1)

2.3.1 Review of literature on late effects scoring systems

A review of available and validated systems for scoring late effects of radiotherapy was undertaken to select the most appropriate system. These scores are completed by the clinician as an objective measure of late effects. Data collection tools were developed accordingly. (Appendix 1)

2.3.1.1 RTOG/EORTC score

This system has been in use across RTOG/EORTC studies by international agreement since 1981 for documenting late effects of radiotherapy, and in 1985 additional acute toxicity scores were agreed. The current version was published in 1995.(57) The effects of radiotherapy are evaluated on a scale of 0 to 5. There are four scores applicable to extremities: Skin, Subcutaneous Tissue, Bone and Joint. (Table 2.1)

Important recent trials of radiotherapy in soft tissue sarcoma have used the RTOG score including CAN-NCIC-SR2 trial(52), VORTEX(46), and RTOG-0630 (Phase II Trial of Image Guided Preoperative Radiotherapy for Primary Soft Tissue Sarcomas of the Extremity)(58). Due to its established use across clinical and research practice, the RTOG system was included for this survey.

Table 2.1 RTOG/ EORTC Late Radiation Morbidity Scoring Schema

GRADE	0	1	2	3	4
SKIN	None	Slight atrophy Pigmentation change; Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic Slight field contracture <10% linear reduction	Severe induration and loss of subcutaneous tissue Field contracture >10% linear measurement	Necrosis
BONE	None	Asymptomatic No growth retardation Reduced bone density	Moderate pain or tenderness Growth retardation Irregular bone sclerosis	Severe pain or tenderness Complete arrest of bone growth Dense bone sclerosis	Necrosis/ Spontaneous fracture
JOINT	None	Mild joint stiffness Slight limitation of movement	Moderate stiffness Intermittent or moderate joint pain Moderate limitation of movement	Severe joint stiffness Pain with severe limitation of movement	Necrosis/

2.3.1.2 LENT/SOMA scales

The LENT/SOMA scales (Late Effects of Normal Tissues/ Subjective, Objective, Management, Analytic) were proposed by the EORTC late effects working group in 1995.(59) The 'Analytic' section refers to useful investigations such as imaging but no numerical score is assigned to these. The SOM scores (Subjective, Objective, Management) evaluate up to 15 different symptoms in each score set on a scale of one to four. Score sets for extremities include Muscle/ Soft Tissue (13 symptoms), Peripheral Nerves (13 symptoms), Mature Bone (14 symptoms) and Skin/ Subcutaneous tissue (15 symptoms). The LENT score for each set is a summed score divided by the number of elements in the score.(60, 61). SOM scores relevant to extremities are represented in Tables 2.2, 2.3, 2.4 and 2.5.

There are four small studies published between 2000 and 2008 using the LENT/SOMA score for extremity radiotherapy: A feasibility study of 32 adult patients comparing the LENT/SOMA and MSTS (Musculoskeletal Tumour Society Rating Score)(62) found it useful (63); A survey of 15 children treated for extremity sarcoma reported individual SOM scores only (53); A study of 32 patients treated with isolated limb perfusion and external beam radiotherapy used adapted SOM scores(64); a retrospective review of 195 patient treated with intraoperative electron radiotherapy (including 70 sarcomas at unspecified sites) reported modified LENT/SOMA results.(65)

An advantage to the SOM scores is their detailed nature and the fact that specific symptoms such as pain and oedema are included which are absent from the RTOG sores.

However, when the data from LERTiSS were analysed, it became apparent that it was very difficult to interpret the combined LENT scores. A further literature search revealed an addendum published by the authors of the original LENT/SOMA scale in 1996, that highlighted this problem and pointed out the uncertainty about how to devise total scores for each category.(66)

The data on selected individual symptoms in each SOMA category is presented in the results section with particular reference to scores of fibrosis, oedema and pain. The combined LENT scores were not analysed due to the concerns described above.

Table 2.2 SOM scores for Muscle/ Soft tissue

Muscle / Soft tissue					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Subjective Pain	None	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating
Function	None	Interferes with athletic recreation	Interferes with work	Interferes with daily activity	Complete lack of function
Objective Oedema	None	Present/ asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction
Mobility & extremity function	None	Present/ asymptomatic	Symptomatic	Secondary dysfunction	No mobility, frozen
Fibrosis	None	Detectable	≤20% of muscle	>20% - 50% of muscle	>50% of muscle
Atrophy	None	≤10%	>10% - 20%	>20% - 50%	>50%
Contraction	None		≤10% linear field	>10% - 30% linear field	>30% linear field
Management Pain	None	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Oedema	None		Compression	Medical intervention	Surgical intervention
Mobility & extremity function	None	Occasional physiotherapy	Intermittent physiotherapy	Persistent physiotherapy / medical intervention	Surgical intervention
Fibrosis	None	Occasional physiotherapy	Intermittent physiotherapy		Surgical intervention
Atrophy	None		Intermittent physiotherapy		Surgical intervention

Table 2.3 SOM scores for Skin/ Subcutaneous tissue

Skin / Subcutaneous tissue					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Subjective Scaliness/ Roughness	None	Present/ asymptomatic	Symptomatic	Requires constant attention	
Sensation	None	Hypersensitive or pruritus	Intermittent pain	Persistent pain	Debilitating dysfunction
Objective Oedema	None	Present/ asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction
Alopecia (scalp)	None	Thinning	Patchy, permanent	Complete, permanent	
Pigmentation change	None	Transitory, slight	Permanent, marked		
Ulcer/ necrosis	None	Epidermal only	Dermal	Subcutaneous	Bone exposed
Telangiecta-sia	None	Minor	Moderate <50%	Gross ≥50%	
Fibrosis/ scar	None	Present/ asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction
Atrophy/ Contraction (depression)	None	Present/ asymptomatic	Symptomatic / <10%	Secondary dysfunction/ 10% - 30%	Total dysfunction/ >30%
Management Dryness	None		Intermittent medical intervention	Medical intervention	
Sensation	None		Intermittent medical intervention	Continuous medical intervention	
Ulcer	None		Intermittent medical intervention	Medical intervention	Surgical intervention/ amputation
Oedema	None		Intermittent medical intervention	Medical intervention	Surgical intervention/ amputation
Fibrosis/ scar	None		Intermittent medical intervention	Medical intervention	Surgical intervention/ amputation

Table 2.4 SOM scores for Peripheral Nerves

Peripheral Nerves					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Subjective Pain	None	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating
Strength	None		Detectable weakness	Persistent weakness	Paralysis, transverse myelitis
Sensory	None	Occasional paraesthesia, hyperesthesia	Intermittent paraesthesia	Persistent paraesthesia	Paralysis
Motor paresis	None	Occasional	<50% decrease from base line capabilities	≥50% decrease from base line capabilities	Paralysis
Objective Motor dysfunction	None	<20% loss	20% – 30% loss	>30% - 50% loss	>50% loss
Sensory dysfunction	None	Paraesthesia	Vibration decrease	Decrease to pin prick	Complete anaesthesia
Reflex	None	Decrease deep tendon reflex	Absent deep tendon reflex		
Management Pain	None	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Motor dysfunction	None			Physical or medical intervention	Surgical intervention
Sensory dysfunction	None			Physical or medical intervention	Surgical intervention
Sensory	None				Neurosurgical intervention

Table 2.5 SOM scores for Mature Bone

Mature bone (excluding mandible)					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Subjective Pain	None	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating
Function	None	Interferes with athletic recreation	Interferes with work	Interferes with daily activity	Complete lack of function
Joint movement	None	Stiffness interfering with athletic recreation	Stiffness interfering with work	Stiffness interfering with daily activity	Complete fixation. Necrosis
Objective Fracture	None			Partial thickness	Full thickness
Mucosa soft tissue	None			Sequestration	
Skin over bone	None	Erythema	Ulcer	Sinus	Fistula
Joint movement	None	<10% decrease	>10% - 30% decrease	>30% – 80% decrease	>80% decrease
Management Pain	None	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Function	None	Occasional physiotherapy	Intermittent physiotherapy	Persistent physiotherapy or medical intervention	Surgical intervention
Joint movement	None	Occasional physiotherapy	Intensive physiotherapy	Corrective Surgery	

2.3.1.3 CTCAE - Common Terminology Criteria for Adverse Events

These criteria were developed by the NCI in 2003 for adverse event reporting in clinical trials. V4.03, June 2010, was in use at the time of this research.(67) A large number of side effects can be evaluated on a scale of one to five. It is noted that these are not specific to radiotherapy effect. The only trial in soft tissue sarcoma radiotherapy using the CTCAE is the RTOG 0630 trial.(58) It was decided not to use the CTCAE score as it was the least specific for late effects of extremity radiotherapy.

2.3.2 Review of literature on limb functionality and quality of life scoring systems

Patient reported functional scores were reviewed for inclusion in this study.

2.3.2.1 TESS – Toronto Extremity Salvage Score

The TESS was developed by Dr Aileen Davis in 1996 for patients undergoing limb-sparing surgery.(68) It evaluates a patient's physical disability in performing routine daily activities.

It is in the format of a questionnaire and patients score their ability on a scale of one to five for activities specific to upper limb (30 questions) or lower limb (29 questions). There is the option to score 'not applicable' for activities that don't apply to the individual. There are also two general ability/disability questions. The final score (ranging from 0 to 100) is calculated according to a formula:

$$\frac{\text{sum of the item scores - \# items}}{\text{possible score range}} \times 100\%$$

where,

sum of the item scores = sum of difficulty responses

 # items = items completed excluding the 'not applicable' response items

possible score range = (5 x # items) - (1 x # items)

Poor function is reflected by a lower score, and good function by higher scores.

The TESS was validated against four other scores in 97 patients with lower extremity sarcomas and found to be reliable in this setting.(69) The questionnaire takes less than 15 minutes to complete. Recent trials of radiotherapy in sarcoma have all used the TESS including CAN-NCIC-SR2(52), VORTEX(46), and RTOG-0630.(58)

The mean TESS score two years after treatment in the CAN-NCIC-SR2 trial was 85.4 in the pre-operative radiotherapy cohort, compared to 81.5 in the post-operative radiotherapy cohort.(54) Median TESS scores at baseline were 92 and 97 in the control arm and research arm of the VORTEX trial respectively, and dropped by a mean value of -5.0 and -4.9 in the 2 arms at 2 years after treatment.(46)

Dr Davis was contacted via email for permission to use the TESS, which was granted, and it was included in the LERTiSS study.

2.3.2.2 MSTS – Musculoskeletal Tumour Society Rating Score

The MSTS was developed in 1993 to assess surgical outcomes after limb sparing surgery and a modified score was field tested and accepted by the MSTS.(62)
Seven items are rated from 0 to 5 by the patient: Pain, Function, Emotional acceptance of functional result, Need of supports (lower limb) / hand positioning (upper limb), Walking (lower limb) / lifting ability (upper limb), Gait (lower limb) / dexterity (upper limb) and Overall Satisfaction with results of treatment. A total score is then calculated. It takes 5 minutes to complete.

The only relevant trial using MSTS at the time of the review was the CAN-NCIC-SR2 trial.(52, 54) They referenced an earlier 1981 version published in a book chapter in 1987 that assessed seven clinical measures rated by clinician: pain, joint range of motion, strength, joint stability, joint deformity, overall function, general acceptance of treatment. The MSTS was not included in LERTiSS due to its limited use in sarcoma radiotherapy research at the time.

2.3.3 Study design

LERTiSS was designed as a prospective cross-sectional survey of patients attending sarcoma outpatient clinics for routine follow-up appointments.

2.3.4 Primary endpoints and outcome measures:

- Incidence of grade 2 or greater radiotherapy toxicity, as measured by the RTOG/EORTC late effects scoring system and the LENT/SOMA score
- Limb functionality measured by the Toronto Extremity Salvage Score (TESS)
  Overall disability measured through the general questions on the Toronto Extremity Salvage Score (TESS)

2.3.5 Secondary endpoints and outcome measures:

- Correlation between tumour, patient and treatment details and grade 2 or greater late toxicity (RTOG and individual SOM scores)
- Correlation between grade 2 or greater late toxicity (RTOG and individual SOM scores) and TESS score

2.3.6 Patient selection

Patients were identified when they attended for routine follow-up appointments in the sarcoma clinics at UCLH.

2.3.6.1 Inclusion criteria

- Histological confirmed soft tissue sarcoma or bone sarcoma
- Tumours of upper and lower limbs/limb girdles
- Previous treatment with radical radiotherapy (dose ≥45Gy EQD2), preoperatively, post-operatively or given as definitive treatment
- Minimum of 12 months interval since completion of radiotherapy
- Age 18 years or older

2.3.6.2 Exclusion criteria

- Patients with active locally recurrent disease
- Patients who could not be assessed for late effects such as those who have had amputation of the affected limb
- Inability to give informed consent to the survey
- Inability to understand and complete the TESS questionnaire

2.3.7 Data collection

Patients were identified from sarcoma clinics and approached by the clinician. They were given an information sheet about the study and gave informed consent.
Data were collected at one clinic visit for each patient during the survey period.

2.3.7.1 Late toxicity data

These data were collected through objective assessment by a clinician (consultant or specialist trainee) and documented according to the RTOG and selected LENT/SOMA scores discussed in 2.2.1.

2.3.7.2 Limb functionality

Patients completed the TESS questionnaire, specific to either upper or lower limb function as described in 2.2.2.1. Gait (normal or abnormal) and use of walking aids were documented. (Appendix 1)

2.3.7.3 Additional patient reported outcomes

Data were collected on work status, analgesia use, perceived impact treatments had had on lifestyle and quality of life, and patient satisfaction.

2.3.7.4 Disease and treatment specifics

Data were collected retrospectively from patient notes and radiotherapy treatment plans and included:

2.3.7.4.1 Patient details:

Demographic information, performance status at presentation, co-morbidities, current disease status, current systemic therapy

2.3.7.4.2 Tumour details:

Tumour anatomical site (buttock / medial thigh / other thigh site / popliteal fossa / calf / shin / ankle or foot / shoulder girdle / upper arm / elbow / forearm / wrist or hand); laterality; histological type; grade; size; depth; surgical margins; staging at diagnosis

2.3.7.4.3 Treatment details

Surgical details: Number and type of surgical procedures including complex procedures that may impact on long-term functional outcomes (skin graft / muscle flap / bone prosthesis / periosteal stripping / motor nerve damage / resection of a deep vein); incidence of significant wound complications within 3 months of surgery: The same criteria were used as in the CAN-NCIC-SR2 (6) trial (complications requiring readmission to hospital within 120 days of surgery for either intravenous antibiotics or secondary surgical procedure).

Radiotherapy plan parameters and dosimetric information: technique; field size; whether PTV crossed a joint; treatment dose; fractionation; timing of radiotherapy (pre-operative, post-operative or definitive)

2.3.7.4.4 Relapse free survival

Data on local and distant recurrence were collected.

2.3.8 Statistical considerations

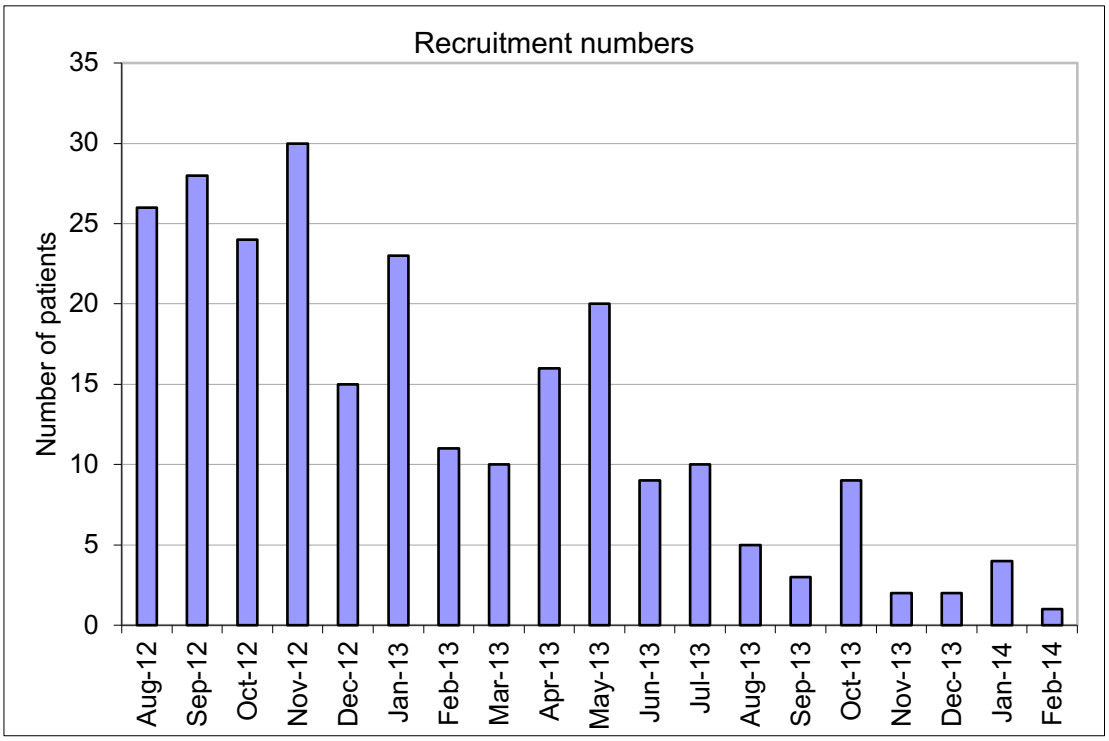
Data were entered into an Excel spreadsheet. Statistical analysis was performed in collaboration with statisticians from the CRUK and UCL Cancer Trials Centre using STATA/SE v 15.1 software. The incidence and severity of late toxicities observed were calculated. The incidence of toxicities was correlated with potential prognostic factors. Odds Ratio (OR) was calculated with 95% confidence interval (CI) for each potential predictive factor in univariate and multivariate analysis. The relationship between late toxicity and functional outcomes was explored through regression analysis. Statistical significance was defined as a p-value <0.05 and borderline significance as p-value >0.5 and <0.1. Kaplan-Meyer survival curves were produced for relapse free survival.

2.4 Results

2.4.1 Data collection

Between August 2012 to February 2014, data were collected on 249 extremity radiotherapy courses in 246 patients attending appointments in the UCLH Sarcoma clinics. Three patients received radiotherapy to two different extremity sites. There was no overlap of radiation fields and each site was separately included for assessment of late effects, function and time to recurrence.

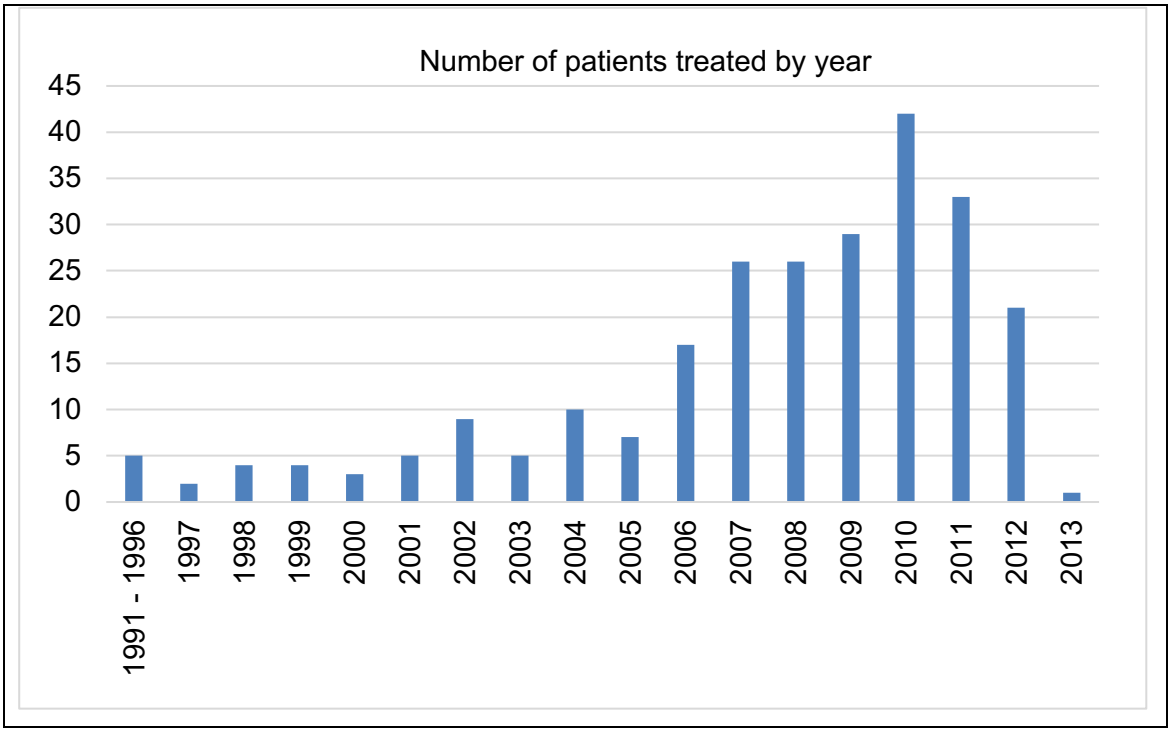
Figure 2.1 Recruitment



2.4.2 Radiotherapy delivery

Radiotherapy treatment took place between January 1991 and March 2013 and the distribution across the period of treatment is illustrated in Figure 2.2.

Figure 2.2 Year of radiotherapy delivery



2.4.3 Follow up

Median follow up time from radiotherapy was 46 months (range 1 to 21 years).

23 patients were treated more than 10 years before the survey (9%) and were included to increase the total numbers and the statistical power of the correlation analysis.

2.4.4 Patient Characteristics

Patient characteristics are summarised in Table 2.6.

Table 2.6 Patient characteristics

Patient Characteristics (N=249)		Years
Age at radiotherapy	median (range)	50 (13 - 88)
Age at time of survey	median (range)	55 (19 - 92)
		N (%)
Gender	Female	132 (53.0)
	Male	117 (47.0)
ECOG* Performance Status at time of Survey	0	176 (70.7)
	1	48 (19.2)
	2	7 (2.8)
	3	4 (1.6)
	Missing data	14 (5.6)
ECOG* Performance Status at time of radiotherapy	0	162 (65.0)
	1	43 (17.3)
	2	8 (3.2)
	Missing data	36 (14.5)
Time elapsed since radiotherapy	<2 years	61 (24.5)
	2-5 years	95 (38.2)
	>5 years	93 (37.4)
Disease status at time of survey	Disease Free	227 (91.2)
	Distant relapse	19 (7.6)
	Missing data	3 (1.2)
Receiving systemic therapy at time of survey	Yes	7 (2.8)
	No	241 (96.8)
	Missing data	1 (0.4)
Significant Co-morbidities that may affect limb function (including but not limited to diabetes, vascular insufficiency, cardiac failure, joint replacement surgery)	Yes	47 (18.9)
	No	202 (81.1)

**ECOG (Eastern Cooperative Oncology Group) Performance status score:*
0 - Fully active, able to carry on all pre-disease performance without restriction
1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3 - Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4 - Completely disabled; cannot carry on any selfcare; totally confined to bed or chair

2.4.5 Disease Characteristics

Disease characteristics are shown in Table 2.7. The majority of patients had soft tissue sarcoma. There were 17 cases of bone sarcoma including Ewing sarcoma (7), osteosarcoma (7), leiomyosarcoma (1), malignant fibrous histiocytoma (1) and giant cell tumour (1).

Table 2.7 Disease characteristics

Disease Characteristics (N=249)		N (%)
Limb affected	Upper	59 (23.7)
	Lower	190 (76.3)
Dominant hand affected	Yes	27 (10.8)
	No	216 (86.8)
	Missing data	6 (2.4)
Tumour site	Shoulder girdle	9 (3.6)
	Upper arm	20 (8.0)
	Elbow	4 (1.6)
	Forearm	19 (7.6)
	Wrist/hand	7 (2.8)
	Buttock	15 (6.0)
	Thigh	115 (46.2)
	Popliteal fossa	12 (4.8)
	Shin	9 (3.6)
	Calf	19 (7.6)
	Ankle/foot	20 (8.0)
Tumour site in relation to deep fascia	Deep	166 (66.7)
	Superficial	56 (22.5)
	N/A (bone tumours)	17 (6.8)
	Missing data	10 (4.0)
Tumour type	Soft tissue	232 (93.2)
	Bone	17 (6.8)
Tumour size (median 8cm; range 1-26cm)	<5cm	47 (18.9)
	5-10cm	111 (44.6)
	>10cm	75 (30.1)
	Missing data	16 (6.4)
Stage at presentation	M0 (no metastases)	238 (95.6)
	M1 (metastatic disease)	11 (4.4)

2.4.6 Treatment Characteristics

The details of surgery are shown in Table 2.8. Four patients did not have surgery: three patients with Ewing sarcoma, and one with embryonal rhabdomyosarcoma.

Table 2.8 Surgical Treatment

Surgical Treatment Characteristics (N=249)		N (%)
Number of surgical procedures to the radiotherapy site (including surgery for wound complications)	0	4 (1.6)
	1	150 (60.2)
	2	66 (26.5)
	3	24 (9.6)
	4	4 (1.6)
	5	1 (0.4)
	1 operation or no surgery	154 (61.9)
	More than 1 operation	95 (38.2)
Complex surgery* (The different procedures classified as complex are outlined below)	Yes	68 (27.3)
	No	177 (71.1)
	No surgery (3 Ewing sarcoma, 1 embryonal rhabdomyosarcoma)	4 (1.6)
Type of complex surgery* (13 patients had >1 complex procedure)	Bone prosthesis or fixation	24 (9.6)
	Bone resection without prosthesis	6 (2.4)
	Periosteal stripping	1 (0.4)
	Muscle flap	17 (6.8)
	Skin graft	16 (6.4)
	Motor nerve resection/ trauma	10 (4.0)
	Tendon resection/ transfer	5 (2.0)
	Deep vessel resection/ vascular graft	2 (0.8)
	Joint fusion	1 (0.4)
Wound complications (within 120 days of surgery and requiring admission)	Yes	14 (5.6)
	No	231 (92.8)
	N/A (no surgery)	3 (1.6)
**At the time of primary surgery or subsequent procedure*		

Radiotherapy and chemotherapy details are presented in Table 2.9.

The standard technique for post-operative radiotherapy was with two dose levels treated in two phases: 50Gy was delivered to a larger volume with a 5cm craniocaudal expansion from GTV to CTV, and a smaller volume with 2cm expansion to CTV was boosted to 60Gy (clear resection margins) or 66Gy (involved resection margins). Pre-operative radiotherapy was delivered to 50Gy in a single phase with a 2cm axial and 3cm craniocaudal expansion to CTV. Twenty-six patient had been treated within the VORTEX trial. As per protocol these patients received post-operative radiotherapy to a higher dose of 66Gy irrespective of surgical margin status. Target definition in the control arm of the trial was done as for patients treated outside the trial. Patients in the experimental arm were treated to a single dose volume to a 2cm CTV expansion.(46)

Beside the standard prescription, multiple other fractionation schedules were used which varied slightly. For the purpose of reporting and analysing the results these were converted to the equivalent dose in 2Gy per fraction and divided in three groups.

Table 2.9 Radiotherapy and chemotherapy details

Radiotherapy and other Treatment Characteristics		N (%)
Neoadjuvant or adjuvant chemotherapy	Yes	33 (13.3)
	No	216 (86.8)
Timing of radiotherapy	Post-operative	211 (84.7)
	Pre-operative	34 (13.7)
	Sole modality/definitive	4 (1.6)
Post-operative radiotherapy technique	Standard target volumes	185 (74.3)
	VORTEX experimental arm	13 (5.2)
	VORTEX control arm	13 (5.2)
Radiotherapy dose (Equivalent dose in 2Gy fractions; α/β=3)	< 60Gy	60 (24.1)
	60Gy	155 (62.3)
	>60Gy	33 (13.3)
	Missing data	1 (0.4)
Radiotherapy field length (Median 22.35cm; range 8 – 40cm)	<20 cm	83 (33.3)
	20 - 30 cm	100 (40.2)
	30 - 40 cm	49 (19.7)
	Missing	17 (6.8)
Radiotherapy field crossed a joint	Yes	120 (48.2)
	No	111 (44.6)
	Missing data	18 (7.2)

2.4.7 Late effects of treatment

2.4.7.1 RTOG scores

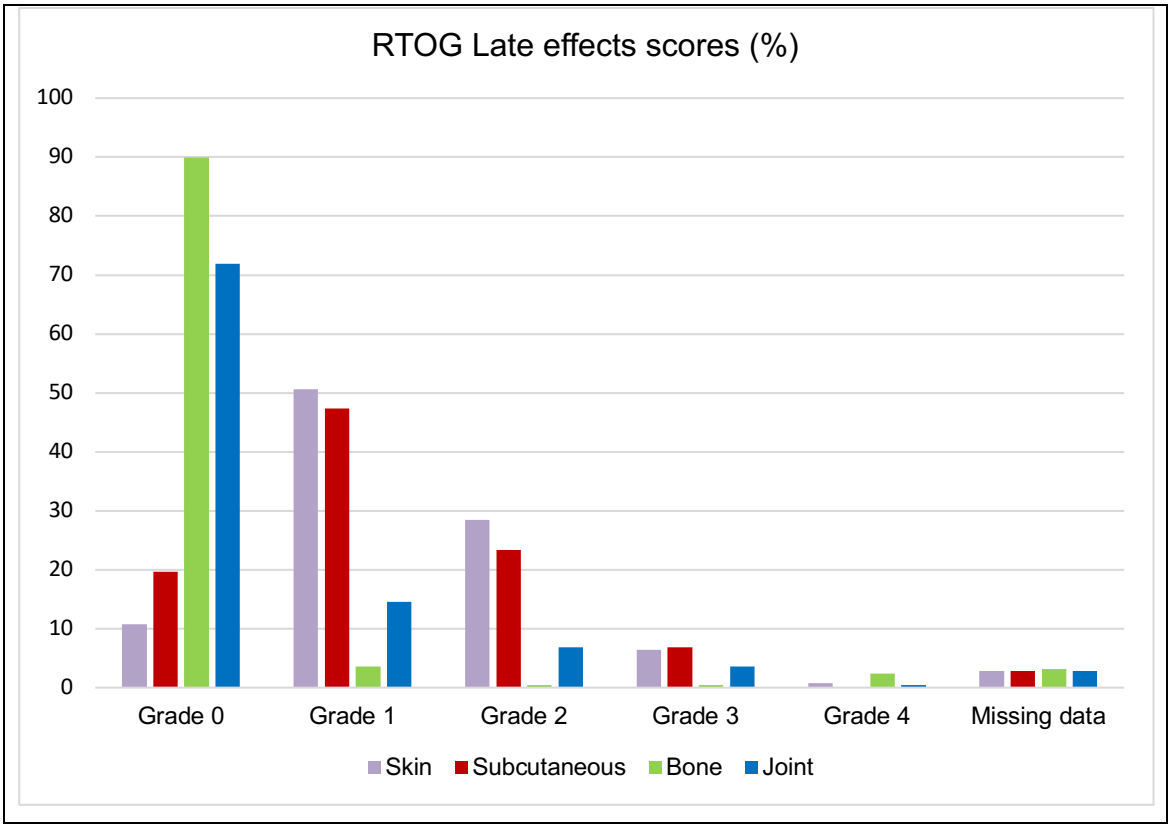
The RTOG late effects scores are shown in Table 2.10 and Figure 2.3.

Grade 2 or greater late effects across scores were observed in 48.9% of patients. Subcutaneous fibrosis ≥ grade 2 (moderate) was seen in 30.1%; Joint late effects ≥ grade 2 (moderate stiffness) was seen in 10.8% and ≥ grade 3 (severe stiffness/limitation) in 4.0%. Grade 3 or greater late effects were observed in 14.9% of patients. The fracture rate was 2.4% (6 cases). Of these, five patients received radiotherapy to the thigh, and one to the forearm.

Table 2.10 RTOG late effect scores

RTOG Late effects scores Results shown as number (percentage of total N=249)						
RTOG score	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing data
Highest score overall	16 (6.4)	104 (41.8)	85 (34.1)	28 (11.2)	9 (3.6)	7 (2.8)
Individual scores:						
Skin	27 (10.8)	126 (50.6)	71 (28.5)	16 (6.4)	2 (0.8)	7 (2.8)
Subcuta-neous	49 (19.7)	118 (47.4)	58 (23.3)	17 (6.8)	0 (0.0)	7 (2.8)
Bone	224 (89.9)	9 (3.6)	1 (0.4)	1 (0.4)	6 (2.4)	8 (3.2)
Joint	179 (71.9)	36 (14.5)	17 (6.8)	9 (3.6)	1 (0.4)	7 (2.8)

Figure 2.3 RTOG late effects scores



2.4.7.2 SOM scores

SOM oedema and pain scores were graded according to the highest score across the system (objective, subjective or management) for each symptom (see extract from the sheets for oedema and pain in Table 2.11 for illustration). Results are presented in Table 2.12 and Figure 2.4.

Table 2.11 SOM oedema and pain scores

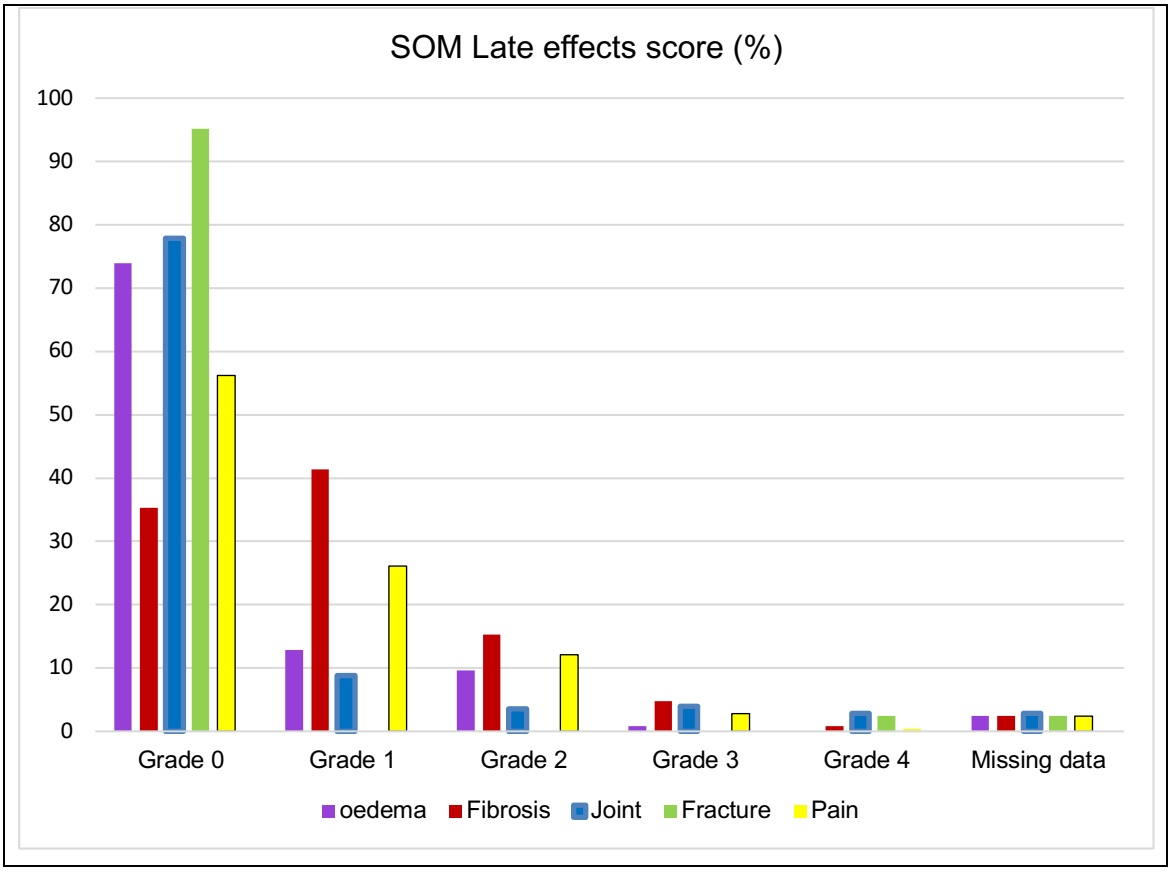
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Oedema (objective)	None	Present/ asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction
Oedema (management)	None		Compression	Medical intervention	Surgical intervention
Pain (subjective)	None	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating
Pain (management)	None	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention

Oedema was present in 58 (23.9%) patients (≥ grade 1). Symptomatic oedema/requiring compression treatment (≥ grade 2) was present in 26 (12.9%). Long-term pain was experienced by 103 patients (41.4%) of which 65 (26.1%) were grade 1, and 38 (15.3%) were ≥ grade 2.

Table 2.12 Selected SOM late effect scores

Individual SOM late effect scores Results shown as number (percentage of total N=249)						
SOM score	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Missing data
Highest overall	44 (17.7)	103 (41.4)	59 (23.7)	21 (8.4)	15 (6.0)	6 (2.4)
Individual scores:						
oedema	184 (73.9)	32 (12.9)	24 (9.6)	2 (0.8)	0 (0.0)	6 (2.4)
Fibrosis	88 (35.3)	103 (41.4)	38 (15.3)	12 (4.8)	2 (0.8)	6 (2.4)
Joint	194 (77.9)	22 (8.8)	9 (3.6)	10 (4.0)	7 (2.8)	7 (2.8)
Fracture	237 (95.2)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.4)	6 (2.4)
Pain	140 (56.2)	65 (26.1)	30 (12.1)	7 (2.8)	1 (0.4)	6 (2.4)

Figure 2.4 SOM late effects scores



2.4.8 Univariate Analysis of potential predictive factors of RTOG late effects

2.4.8.1 Variables included in unilateral analysis:

2.4.8.1.1 Continuous variables:

- Age at start of radiotherapy (for an increase in 10 years)
- Time from end of radiotherapy (for an increase of 5 years)
- Tumour size (for an increase of 5cm)

2.4.8.1.2 Categorical variables:

- Gender
- ECOG performance status at baseline
- Comorbidities that may affect limb function
- Site (upper vs lower limb)
- Location relative to the deep fascia (deep vs superficial)
- Number of surgical procedures
- Wound complications
- Complex surgery
- (Neo)adjuvant chemotherapy
- Timing of radiotherapy
- Post-operative radiotherapy technique
- Radiotherapy field crossing a joint
- Radiotherapy dose groups

All the variables were analysed for correlation with any RTOG late effects score ≥ grade 2 and ≥ grade 3; subcutaneous late effects ≥ grade 2 and ≥ grade 3, skin late effects ≥ grade 3, bone late effects ≥ grade 4 (fracture) and joint late effects ≥ grade 3 (severe stiffness and limitation).

Significant and borderline significant results are presented below. The full, very large dataset is appended (Appendix 2). Statistical significance was defined as a p-value <0.05 and borderline significance as p-value >0.5 and <0.1.

2.4.8.2 Any RTOG late effects score ≥ Grade 2

Larger tumour size, wound complications, complex surgery and bone prosthesis or fixation, correlated significantly with any RTOG late effect score ≥ grade 2. (Table 2.13)

Older age at the time of radiotherapy, poor ECOG performance status at the time of radiotherapy, lower limb site, post-operative radiotherapy, and muscle flap surgery were borderline statistically significant with 95% confidence intervals crossing 1.00.

Gender was not significant (OR 0.79; 95%CI 0.48 – 1.32; p=0.3711) and neither was radiotherapy dose (OR 2.03;95% CI 0.81 – 5.06; p=0.1054).

Table 2.13 Univariate analysis: Any RTOG late effects score ≥ Grade 2

Factor	OR	95% CI Lower Limit	95% CI Upper Limit	p-value
Age at start of radiotherapy (for an increase in 10 years)	1.14	0.99	1.31	0.0690
Tumour size (for an increase of 5cm)	1.55	1.16	2.05	0.0017
ECOG performance status at the time of radiotherapy				0.0845
PS 0	1.00			
PS 1	1.84	0.92	3.68	
PS 2	3.27	0.64	16.70	
Site (upper vs lower limb)				0.0815
Upper	1.00			
Lower	1.70	0.93	3.11	
Wound complications within 3 months of surgery				0.0078
No	1.00			
Yes	5.85	1.27	27.01	
Timing of radiotherapy				0.0802
Post-operative	1.00			
Pre-operative	0.51	0.24	1.10	
Muscle Flap				0.0799
No	1.00			
Yes	2.51	0.86	7.37	
Bone Prosthesis or Fixation				0.0022
No	1.00			
Yes	4.25	1.53	11.80	
Complex surgery				0.0050
No	1.00			
Yes	2.27	1.27	4.06	

2.4.8.3 RTOG subcutaneous late effects score ≥ Grade 2

Larger tumour size, lower limb site, female gender, older age at the time of radiotherapy, wound complications, and muscle flap surgery correlated significantly with a score ≥ grade 2. ECOG performance status at the time of treatment was borderline statistically significant. (Table 2.14)

Timing of radiotherapy (OR 0.83; 95%CI 0.36 – 1.88; p=0.65), radiotherapy dose (OR 1.94; 95%CI 0.78-4.8; p=0.21) and Bone Prosthesis or Fixation (OR 1.71; 95%CI 0.72 – 4.06; p=0.23) were not statistically significant.

Table 2.14 Univariate analysis: RTOG subcutaneous late effects score ≥ Grade 2

Factor	OR	95% CI Lower Limit	95% CI Upper Limit	p-value
Age at start of radiotherapy (for an increase in 10 years)	1.19	1.02	1.39	0.0219
Tumour size (for an increase of 5cm)	1.58	1.19	2.10	0.0012
ECOG performance status at the time of radiotherapy				0.0767
PS 0	1.00			
PS 1	2.04	1.02	4.08	
PS 2	2.58	0.62	10.75	
Site (upper vs lower limb)				0.0090
Upper	1.00			
Lower	2.55	1.21	5.37	
Wound complications within 3 months of surgery				0.0032
No	1.00			
Yes	5.66	1.68	19.04	
Muscle Flap				0.0473
No	1.00			
Yes	2.76	1.02	7.47	
Gender				0.0402
Female	1			
Male	0.56	0.32	0.98	

2.4.8.4 RTOG bone score of Grade 4 (fracture)

The variables showing significant correlation with bone fracture are shown in Table 2.15. There were no borderline statistically significant variables.

Table 2.15 Univariate analysis: Fracture/RTOG bone score Grade 4

Factor	OR	95% CI Lower Limit	95% CI Upper Limit	p-value
Comorbidities that may affect limb function				
No	1.00			0.0088
Yes	9.46	1.68	53.41	
Number of surgical procedures				0.0188
≤ 1 operation	1.00			
≥ 2 operations	8.82	1.01	76.78	
Bone Prosthesis or Fixation				0.0006
No	1.00			
Yes	21.10	3.64	122.43	
Complex surgery				0.0047
No	1.00			
Yes	13.33	1.53	116.37	

The treatment for bone fracture involves a further surgical procedure to stabilise the fracture. This would account for the correlation with these variables and the relationships seen is therefore unlikely to indicate a causative effect but rather the result of suffering a fracture.

There was no correlation with the following variables and the confidence interval crossed 1

- Gender (OR 0.55; 95%CI 0.09 – 3.06; p=0.4825)
- Age at time of radiotherapy (OR 1.03; 95%CI 0.66 – 1.60; p=0.9105)
- Adjuvant chemotherapy (OR 1.27; 95%CI 0.14 – 11.21; p=0.8346)
- Lower limb site (OR 1.56; 95%CI 0.18 – 13.67; p=0.6718)
- Dose 60Gy (OR 1.90; 95%CI 0.22 – 16.67; p=0.5341)

2.4.8.5 RTOG joint score ≥ Grade 3

Grade 3 or greater joint stiffness (severe) was elected as the most clinically relevant late joint effects. Larger tumour size, upper limb site, complex surgery, and bone prosthesis or fixation and (neo)adjuvant chemotherapy correlated significantly with a score ≥ grade 3. (Table 2.16)

Longer time interval since radiotherapy, adjuvant chemotherapy, and radiotherapy dose were borderline statistically significant.

There was no significant correlation with gender (OR 0.73; 95%CI 0.20 – 2.68; p=0.64) and age at the time of treatment (OR 0.78; 95%CI 0.54 – 1.12; p=0.16), factors that were significant for soft tissue late effects.

Table 2.16 Univariate analysis: RTOG joint score ≥ Grade 3

Factor	OR	95% CI Lower Limit	95% CI Upper Limit	p-value
Tumour size (for an increase of 5cm)	3.30	1.80	6.07	0.0000
Time from end of radiotherapy (for an increase of 5 years)	1.80	0.99	3.25	0.0718
Site (upper vs lower limb)				0.0116
Upper	1.00			
Lower	0.19	0.05	0.69	
(Neo)adjuvant chemotherapy				0.0000
No	1.00			
Yes	18.49	4.50	75.93	
Radiotherapy dose group				0.0815
<60Gy	1.00			
60Gy	0.26	0.06	1.22	
>60Gy	1.42	0.30	6.79	
Bone Prosthesis or Fixation				0.0000
No	1.00			
Yes	23.44	5.41	101.67	
Complex surgery				0.0017
No	1.00			
Yes	9.64	1.95	47.65	

2.4.8.6 RTOG skin late effects ≥ Grade 3

Grade 3 or greater skin late effects (necrosis) were analysed for potential predictive factors. ECOG performance status at the time of radiotherapy and (neo)adjuvant chemotherapy were the only statistically significant factors that correlated with this. Higher radiotherapy dose showed a strong trend with skin late effects and this was borderline statistically significant. The correlation with performance status was not linear and may be a random finding. (Table 2.17)

Table 2.17 Univariate analysis: RTOG skin score ≥ Grade 3

Factor	OR	95% CI Lower Limit	95% CI Upper Limit	p-value
ECOG performance status at the time of radiotherapy				0.0489
PS 0	1.00	.	.	
PS 1	2.94	1.05	8.24	
PS 2	1.00	.	.	
(Neo)adjuvant chemotherapy				0.0253
No	1.00			
Yes	3.65	1.26	10.52	
Radiotherapy dose group				0.0550
<60Gy	1.00			
60Gy	0.73	0.21	2.53	
>60Gy	3.18	0.82	12.29	

2.4.9 Multivariate analysis of potential predictive factors of RTOG late effects

Clinically relevant potential predictors from univariate analysis were included in multivariate regression analysis. Age at time of radiotherapy and Gender were included in all the models. Muscle flap and bone fixation/prosthesis were not included separately as events were already included within the complex surgery variable and numbers of individual complex procedures were small.

2.4.9.1 Multivariate analysis: Any RTOG late effects score ≥ Grade 2:

All the variables that were significant in the univariate analysis were either still significant or still showed a trend with an odds ratio >1 or <1 depending on the direction of association. These are shown in Table 2.18.

Larger tumour size, wound complications, complex surgery, lower limb tumour site, post-operative radiotherapy timing, and older age at the time of radiotherapy correlated statistically significantly with late effects ≥ grade 2.

Radiation dose was non-significant, but this may be a reflection of small numbers.

Table 2.18 Multivariate analysis: Any RTOG late effects score ≥ Grade 2

Factor	Odds Ratio	95% Conf. Interval		p-value
Tumour size (for an increase of 5cm)	1.92	1.35	2.72	0.000
Dose (for an increase of 5Gy)	1.26	0.84	1.90	0.262
Wound complications within 3 months of surgery	13.78	2.20	86.38	0.005
Complex surgery	3.44	1.67	7.10	0.001
Lower limb site	2.38	1.12	5.05	0.024
Pre-operative radiotherapy timing	0.25	0.07	0.89	0.032
Male Gender	0.87	0.48	1.58	0.651
Age at start of radiotherapy (for an increase in 10 years)	1.27	1.05	1.53	0.012

2.4.9.2 Multivariate analysis: RTOG subcutaneous late effects score ≥ Grade 2

The multivariate model is shown in Table 2.19.

Larger tumour size, lower limb site, older age at the time of radiotherapy, complex surgery and wound complications remained statistically significant for predicting ≥ grade 2 fibrosis.

Higher radiotherapy dose, timing of radiotherapy and gender were not statistically significant.

Table 2.19 Multivariate analysis: RTOG subcutaneous late effects score ≥ Grade 2

Factor	Odds Ratio	95% Conf. Interval		p-value
Tumour size (for an increase of 5cm)	1.94	1.37	2.74	0.000
Dose (for an increase of 5Gy)	1.45	0.92	2.29	0.112
Wound complications within 3 months of surgery	8.95	1.96	40.87	0.005
Complex surgery	2.65	1.26	5.58	0.010
Lower limb site	3.85	1.50	9.85	0.005
Pre-operative radiotherapy timing	0.57	0.15	2.13	0.405
Male Gender	0.78	0.41	1.49	0.450
Age at start of radiotherapy (for an increase in 10 years)	1.33	1.08	1.63	0.006

2.4.10 Univariate and Multivariate analysis of SOM late effect scores

Individual SOM scores did not show any additional relevant correlations to potential predictive factors in univariate analysis. As previously discussed, the analysis of total LENT scores was not done in view of lack of validation for these scores and low incidence of their use in clinical practice and research. Univariate analysis for selected individual SOM score is summarised in the tables below.

2.4.10.1 SOM fibrosis ≥ Grade 2

Significant correlation was found with larger tumour size and wound complications, similar to that seen with RTOG subcutaneous late effects score ≥2. Gender and age at time of radiotherapy did nor correlate and confidence intervals cross 1.00 for radiotherapy dose (Table 2.20)

Table 2.20 Univariate analysis: SOM fibrosis ≥ Grade 2

Factor	OR	95% CI Lower Limit	95% CI Upper Limit	p-value
Age at start of radiotherapy (for an increase in 10 years)	1.15	0.97	1.36	0.1085
Tumour size (for an increase in 5cm)	1.66	1.23	2.25	0.0009
Wound complications within 3 months of surgery				0.0070
No	1.00			
Yes	4.97	1.59	15.52	
Radiotherapy dose group				0.0192
<60Gy	1.00	.	.	
60Gy	0.56	0.27	1.16	
>60Gy	1.81	0.71	4.60	

2.4.10.2 SOM Oedema ≥ Grade 2

Tumour size and gender were clinically relevant statistically significant correlating factor for oedema. (Table 2.21) A random correlation was seen between fewer surgical procedures and increased oedema.

Lower limb tumour site, (neo)adjuvant chemotherapy and female gender were borderline significant with confidence intervals crossing 1.00.

Table 2.21 Univariate analysis: SOM Oedema ≥ Grade 2

Factor	OR	95% CI Lower Limit	95% CI Upper Limit	p-value
Tumour size (for an increase in 5cm)	1.64	1.14	2.35	0.0092
Site (upper vs lower limb)				0.0845
Upper	1.00			
Lower	2.67	0.77	9.21	
Number of surgical procedures				0.0061
≤ 1 operation	1.00			
≥ 2 operations	0.26	0.09	0.77	
(Neo)adjuvant chemo				0.0676
No	1.00			
Yes	2.56	0.99	6.64	
Gender				0.0472
Female	1.00			
Male	0.43	0.18	1.02	

2.4.10.3 SOM Pain ≥ Grade 2

Significant correlation with pain was seen for larger tumour size, and where patients had complex surgery (a skin graft or bone prosthesis). (Table 2.22.)

Table 2.22 Univariate analysis: SOM Pain ≥ Grade 2

Factor	OR	95% CI Lower Limit	95% CI Upper Limit	p-value
Tumour size (for an increase in 5cm)	1.49	1.06	2.09	0.0241
Bone Prosthesis or Fixation				0.0012
No	1.00			
Yes	4.77	1.93	11.77	
Complex surgery				0.0001
No	1.00			
Yes	4.05	1.97	8.3	
Skin graft				0.0289
No	1.00			
Yes	3.58	1.22	10.54	

Multivariate analysis was done for potential factors correlating with pain. Tumour size and complex surgery remained significant. (Table 2.23)

Table 2.23 Multivariate analysis: SOM Pain ≥ Grade 2

Factor	OR	95% CI Lower Limit	95% CI Upper Limit	p-value
Tumour size (for an increase in 5cm)	1.47	1.02	2.13	0.039
Complex surgery	5.19	2.27	11.86	0.000
Lower limb site	2.47	0.76	7.99	0.131
Male Gender	0.65	0.28	1.47	0.298
Age at start of radiotherapy (for an increase in 10 years)	1.10	0.86	1.39	0.444

2.4.11 TESS scores

TESS scores were available for 237 patients and 232 patients responded to the two general quality of life questions at the end of the questionnaire. Results are presented in table 2.24, table 2.25 and figure 2.5.

The median TESS score was 89.2 (out of a potential of 100) for the whole cohort. A minority of 46 patients (18.5%) had a normal functional score of 100 with no functional deficit following treatment. A further 69 patients (27.7%) had TESS scores between 90 and 99.3. More than a third, 86 patients (34.5%), had a low TESS score below 80, an indication of less than average function.

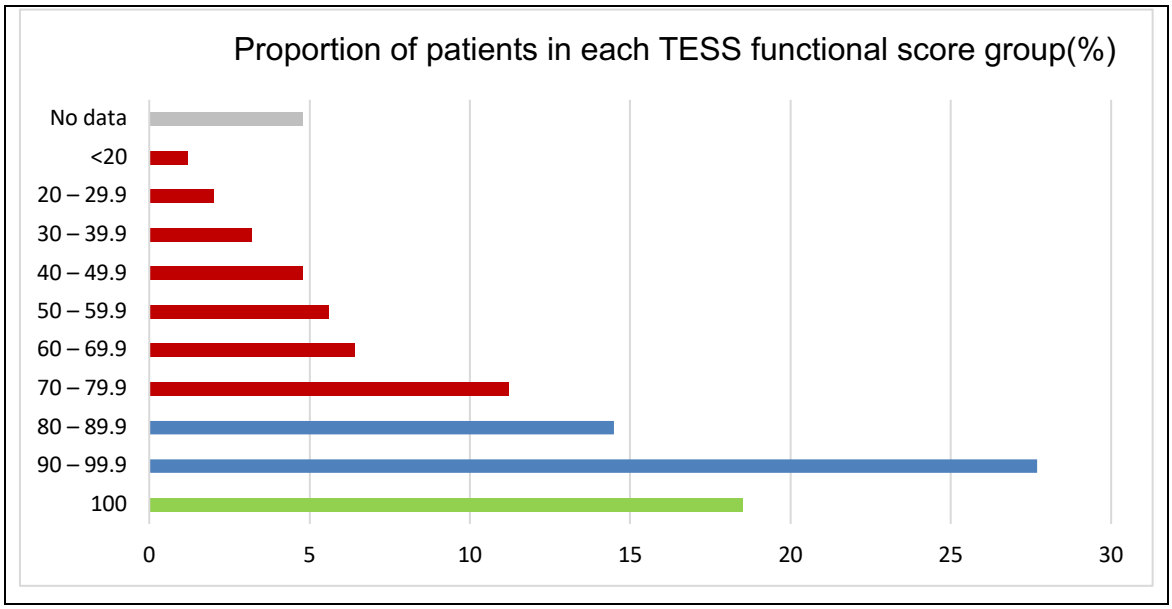
Table 2.24 TESS score results

	N	Mean TESS score	Median TESS score	TESS range
Overall TESS score (out of 100)	237	81.1	89.2	10-100
TESS quality of life questions (out of 10)	232	8.44	9.0	3-10

Table 2.25 TESS score distribution

TESS score group	N (%)
100	46 (18.5)
90 – 99.9	69 (27.7)
80 – 89.9	36 (14.5)
70 – 79.9	28 (11.2)
60 – 69.9	16 (6.4)
50 – 59.9	14 (5.6)
40 – 49.9	12 (4.8)
30 – 39.9	8 (3.2)
20 – 29.9	5 (2.0)
<20	3 (1.2)
No data	12 (4.8)

Figure 2.5 TESS score distribution



2.4.12 TESS score correlation with RTOG and SOM late effects scores

Linear regression was performed. Significance was set at a p-value < 0.05

Higher RTOG scores were associated with a lower TESS score. The same trend was seen across all scores and was statistically significant for all except a few of the higher-grade groups that had small numbers. Results are shown in Table 2.26.

Subcutaneous fibrosis ≥Grade 2 was associated with a mean TESS score of 70.9 (range 10 - 100) compared to a mean TESS score 85.7 (range14.7 – 100) for <Grade 2 toxicity (p=0.0000).

The lowest TESS scores were associated with RTOG joint late effects ≥ Grade 3 (mean TESS score 61.9; range 21.7-95.8) and RTOG bone late effects ≥ Grade 4/fracture (mean TESS score 67.3; range 28.7-98.1)

A similar correlation was seen between the individual SOM scores (including oedema) and TESS score, and this was statistically significant.

SOM pain scores correlated significantly with the lowest mean TESS values. Pain ≥ Grade 2 correlated with mean TESS score 57.1 (range 14.7-95) and Pain ≥ Grade 3 with mean Tess score 48.9 (range 14.7-88)

Table 2.26 TESS score correlation with RTOG and SOM late effects scores

Grade	Num-ber	TESS mean score	TESS range	Correlation estimate/ Beta coefficient	Beta coefficient 95% CI		p-value
					Lower limit	Upper limit	
Highest RTOG late effects score overall (data available for N= 242)							
< Grade 2	120	86.2	14.7-100				
≥ Grade 2	122	76.2	10-100	-10.1	-15.4	-4.7	0.0002
≥ Grade 3	37	70.6	21.7-100	-12.5	-19.8	-5.1	0.0010
RTOG Subcutaneous late effects score (soft tissue fibrosis)							
< Grade 2	167	85.7	14.7-100				
≥ Grade 2	75	70.9	10-100	-14.9	-20.5	-9.3	0.0000
≥ Grade 3	17	76.1	28.7-93.1	-5.4	-15.9	5.0	0.3063
Other clinically relevant RTOG late effects score							
Skin ≥ Grade 3	18	76.1	28.7-93.1	-12.4	-22.4	-2.3	0.0163
Bone ≥ Grade 4 (fracture)	6	67.3	28.7-98.1	-14.2	-31.3	2.9	0.1023
Joint ≥ Grade 3	10	61.9	21.7-95.8	-20.0	-33.9	-6.1	0.0049
SOM clinically relevant late effects scores							
Fibrosis < Grade 2	191	84.6	14.7-100				
Fibrosis ≥ Grade 2	52	69.2	10-100	-15.4	-21.7	-9.2	0.0000
Oedema ≥ Grade 2	27	68.5	27.6-100	-14.3	-22.7	-5.8	0.0010
Pain ≥ Grade 2	38	57.1	14.7-95	-28.9	-35.2	-22.6	0.0000
Pain ≥ Grade 3	8	48.9	14.7-88	-33.5	-47.8	-19.2	0.0000
Joint ≥ Grade 2	26	60.5	18.3-100	-23.0	-31.5	-14.6	0.0000

2.4.13 Additional patient reported outcomes

Patients were asked to comment on their work status, analgesia use, gait and the general impact they felt treatment had had on their lifestyle. The results are shown in Table 2.27.

Table 2.27 Patient reported outcomes

Patient reported outcome		N (%)
Lower limb site N=190		
Gait	Abnormal	60 (31.6)
	Normal	119 (62.6)
	Missing data	11 (5.8)
Walking aid required	Yes	45 (23.7)
	No	145 (76.3)
All Sites N=249		
Work status	Employed (full time)	91 (36.6)
	Employed (part time)	36 (14.5)
	Student	2 (0.8)
	Retired	75 (30.1)
	Unemployed	22 (8.8)
	Disabled	11 (4.4)
	Missing data	12 (4.8)
Regular analgesia required	Yes	96 (38.6)
	No	139 (55.8)
	Missing data	14 (5.6)
Type of analgesia used	Mild (paracetamol, codeine)	55 (22.1)
	Non-steroidal anti-inflammatory	29 (11.7)
	Opioid	12 (4.8)
	No analgesia use reported	153 (61.5)
Impact of treatment on lifestyle	Negative impact	88 (35.3)
	No impact	130 (52.2)
	Improvement	14 (5.6)
	Missing data	17 (6.8)
Negative impact on lifestyle acceptable or not (N=88)	Acceptable	70 (79.6)
	Not acceptable	17 (19.3)
	Missing data	1 (1.1)

2.4.14 Relapse free survival results

At the time of the survey, there had been 6 local recurrences and 37 distant relapses since radiotherapy in this cohort. One patient experienced both local and distant relapse.

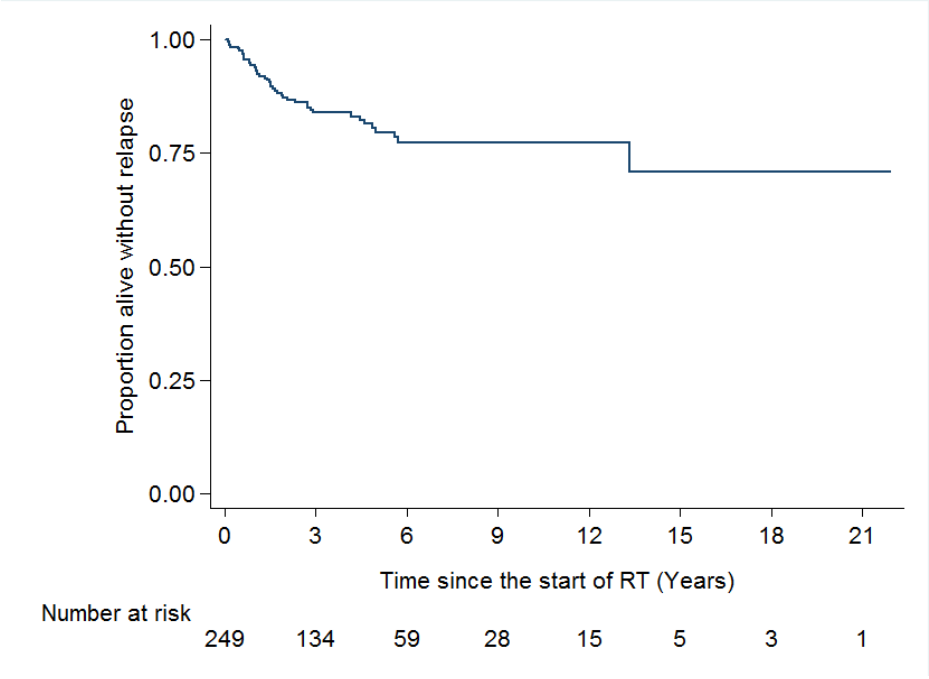
The median time to first relapse (local or distant) was 1.5 years (range 43 days to 13.3 years) (Figure 2.6)

The median time to distant relapse was 1.4 years (range 43 days – 13.3 years)

The median time to local relapse was 1.6 years (range 1.1 – 4.1 years)

The median time to relapse for the cohort had not been reached.

Figure 2.6 Relapse free survival



2.5 Discussion

2.5.1 Population

The data gathered in the LERTiSS study give an overview of the late effects of radiotherapy in extremity sarcomas in patients treated at UCLH in the decade leading up to 2012. Most patients (91%) were treated between 2002 and 2012. Only 23 (9%) patients were treated more than 10 years before the survey. The population is patients on long term follow up. Sixty-one patients (24%) had a minimum of one year but less than two years follow up since radiotherapy. The minimum follow up criterion of one year was decided pragmatically in order to increase the number of eligible patients. The literature reported late effects at various time points, and frequently at two years. It was felt that it would take at least a year for late effects to develop. It is possible that there may be an increase in the incidence of late effects with longer follow up that may not have been picked up in this survey, and the data may underreport the reality of the late effects burden in this group. There was however no correlation seen between time elapsed since radiotherapy and late effects scores suggesting that late toxicity is not evolving over longer time periods.

2.5.2 Quality of the data

Late effect scores and functional outcomes were current and collected in real time on the day patients attended outpatient clinics. Late effect score data were missing for only a small number (<3%) of cases. TESS questionnaires were not completed by 4.8% of patients. The remaining data were collected retrospectively, and this may have created unknown bias in the results. This could have reduced the statistical power of the study and underestimated the effect seen if events were under reported (not documented at the time). There may have been a component of recall bias where participants could not fully remember certain events such as wound complications that happened many years before. There were missing data for a few parameters, notably performance status at the time of radiotherapy (14%). Tumour characteristic data were missing for tumour size in 6% and tumour depth in 4%. Radiotherapy dose was unknown in only 1 case (0.4%).

2.5.3 Late effects of treatment

The RTOG scores indicate that 49% of patients attending follow up after treatment for extremity sarcomas live with a moderate burden of late effects of treatment (any late effect $\geq$ grade 2), and 15% of patients have significant long-term sequelae (any late effect $\geq$ grade 3).

2.5.3.1 Subcutaneous fibrosis

The incidence of subcutaneous fibrosis ≥ grade 2 was at the lower end of the range reported in the CAN-NCIC-SR2 trial(52), 30% in the current study compared to 31% in pre-operative radiotherapy arm and 48% in the post-operative radiotherapy arm of the SR2 trial. This is despite the majority of patients taking part in LERTiSS receiving post-operative radiotherapy (85%). The SR2 trial reported side effect at a minimum of 21 months from radiotherapy which is longer than our minimum follow up of 12 months from radiotherapy. The lower figure in the current study may be due to toxicity not manifested until after 12 months. It is noted that the radiotherapy dose in the post-operative arm of SR2 was 66Gy in 33 fractions. Doses higher than 60Gy was only given to 13% of patients we surveyed and LERTiSS data showed a trend towards increased toxicity with higher radiotherapy doses such that our lower rate of grade 2 or greater fibrosis may be due to lower radiotherapy doses used.

2.5.3.2 Skin late effects

There is no literature on late skin effects after extremity radiotherapy. The rate of grade 3 or greater late skin toxicity seen in the current study was 7.2%, with 16 patients (6.4%) developing grade 3 late effects (marked atrophy; gross telangiectasia) and two patients (0.8%) grade 4 late effects (necrosis). There was a statistically significant correlation between (neo)adjuvant chemotherapy and an increased risk of late skin effects. It is possible that chemotherapy may hinder wound healing and increase the risk of wound infections and in this way affect the development of late skin effects.

There was also a trend towards increase toxicity with higher radiotherapy doses that only just did not reach statistical significance (p=0.055). The correlation seen with ECOG performance status at the time of radiotherapy was not linear making it difficult to interpret. The risk increased as performance status deteriorated to one, and then decreased again with a worse performance status of two. This may be a random finding or because of small numbers as only 3% of patients had a performance status of two. The reason why performance status should be linked to skin toxicity is difficult to explain.

2.5.3.3 Joint stiffness

The Incidence of grade 2 or greater joint stiffness at 11% was at the lower end of the range compared to the literature, and incidence of severe stiffness (≥ grade 3) was 4%.

The CAN-NCIC-SR2 trial reported 17% joint stiffness ≥ grade 2 at two years in the pre-operative and 23% in the post-operative arm.(52) Alektiar et al reported low joint stiffness rates of 8% at 5 years in patients receiving post-operatives radiotherapy. The majority (63%) of patients in that study received brachytherapy to a mean dose of 45Gy which may explain the low rates.(5) Stinson reported the highest rate at 32%, at a minimum one year after radiotherapy, and this correlated with lower limb site and more than 50% of the joint space in the radiotherapy field. (47) Patients were treated between 1975 and 1986, and 3DCRT was only introduced after 1980. The CTV included the whole anatomical compartment. The lower rate of joint stiffness seen in the current study could be because patients were treated more recently than the published series and with 3DCRT.

In LERTiSS there was a strong correlation between significant joint stiffness ≥ grade 3 and tumour size, upper limb site, complex surgery, bone prosthesis surgery and (neo)adjuvant chemotherapy. The latter correlation could be because patients undergoing chemotherapy are generally less well and possible less active, and less likely to engage in physiotherapy or rehabilitation programs. They are also more likely to be patients with bone sarcomas who will have undergone complex surgery with bone prosthesis which is an additional risk factor.

2.5.3.4 Oedema

Any oedema was observed in 23% and symptomatic oedema (SOM ≥ grade 2) in 13% in the LERTiSS data. This is in line with published series. There was a significant correlation with larger tumour size presumably because bigger tumours require a larger proportion of the limb to be treated and a smaller potential normal tissue corridor spared. In the Stinson series, the incidence was 19% and this correlated with higher radiotherapy doses, radiotherapy field length and lower limb site.(47) Alektiar et al reported a 10% incidence of oedema at 5 years.(5) Friedman et al used Stern's scale (70) and reported a 28% incidence of any oedema (9% moderate or severe) at a minimum of 1 year after radiotherapy. (Stern's scale scores 4 levels of severity: 1 = mild swelling, 2 = moderate, 3 = severe and 4 = very severe). There was similarly a correlation with tumour size and depth in that series.(71) The CAN-NCIC-SR2 study also used Stern's scale and reported 23% oedema in the post-operative arm and 15% in the pre-operative arm. (70) Fewer surgical procedures (≤ one) correlated with an increased risk of SOM oedema in the current study. It is not clear why this would be and is likely a random correlation.

2.5.3.5 Bone fracture

The observed fracture rate of 2.4% was lower than published rates of 4 to 8.6%.(5, 47-50) There were no prognostic factors for risk of fracture identified which is likely due to the small number of events (6 cases). Risk factors identified in the literature (lower limb site, female gender, older age, periosteal stripping, additional treatment with chemotherapy and prescription doses of 60Gy or above (5, 47-51) were not significant in our analysis. The lower fracture rate seen in the LERTiSS data could be explained by the relatively infrequent use of chemotherapy (13%) and also the small proportion pf patients receiving more than 60Gy (13%). Data on periosteal stripping was not available from the oncology notes and we could not collect this.

2.5.3.6 Pain

Long-term pain of any severity (≥grade 1) was a feature in 103 patients (41%), in line with 38% of patients reporting regular use of analgesia. Grade 2 pain (intermittent and tolerable but requiring regular non-narcotic analgesia) was seen in 30 patients (12%) and grade 3 or greater pain (persistent/ intense/ requiring regular narcotics) was seen in 8 patients (3%). Twelve patients (5%) reported regular use of opioid analgesia, in line with 7% requiring narcotics reported by Stinson et al.(47) who also reported a correlation with radiotherapy dose.

On univariate analysis in the current study, grade 2 or greater pain was associated with larger tumour size, complex surgery and in particular skin grafts and bone prosthesis surgery. On multivariate analysis tumour size and complex surgery remained statistically significant. Pain was also inversely related to functional outcome and quality of life as reflected by the TESS score.

2.5.4 Wound complications within 120 days of surgery

The incidence of wound complications within 120 days of surgery was much lower than expected at 5%. This may be due to the retrospective data collection from oncology records without access to the surgical notes, and the long time interval from surgery. Patients may not have remembered some of these events accurately. In the CAN-NCIC-SR2 trial, the incidence was 17% in the post-operative arm and 35% in the pre-operative arm, and correlated with tumour size and lower extremity site (45% for upper leg/thigh tumours).(6) Cannon et al also reported this pattern of wound complications in a retrospective database review of lower extremity sarcomas, 34% after preoperative radiotherapy and 16% with post-operative radiotherapy. (72) Risk of wound complications correlated with tumour size in that series. Tseng et al reported a 32%

incidence after pre-operative radiotherapy, again more likely in lower limb tumours. (73) The RTOG-0630 study exploring image guided pre-operative radiotherapy to a smaller target volume reported equally high levels of 36.6%, all in lower extremity sites.(58) The incidence is lower in upper limbs, 10% in CAN-NCIC-SR2, and 11% in a series of upper extremity tumours treated with a non-conventional pre-operative chemo-radiotherapy schedule.(74)

2.5.5 Identifying patients at higher risk of late effects

There were several factors that correlated significantly with any RTOG late effects ≥ grade 2 and subcutaneous fibrosis ≥ grade 2, and except for timing of radiotherapy in the latter case, these retained significance in multivariate analysis.

2.5.5.1 Tumour size

Larger tumour size was the most consistent prognostic factor for any RTOG late effects in this survey, and was also statistically significant individually for subcutaneous fibrosis, joint stiffness, pain and oedema. Tumour size is a surrogate for the volume of tissue receiving radiotherapy. Field size also reflects the volume of tissue irradiated. As such this result is in line with the findings from the retrospective literature suggesting field size as an important prognostic factor for late effects (9). Field size was a risk factor for subcutaneous fibrosis and joint stiffness in the CAN-NCIC-SR2 trial (52) and there was an additional trend for correlation with oedema. This finding highlights the importance of limiting the volume of normal tissue that receives the prescription dose as this may be one way to improve the therapeutic ratio.

2.5.5.2 Wound complications

Wound complications in the LERTiSS data had a strong and statistically significant correlation with any RTOG late effects ≥ grade 2 (odds ratio 13.78) as well as subcutaneous fibrosis ≥ grade 2 (odds ratio 8.95). Delayed wound healing and multiple interventions including further surgery will have an impact on scar tissue formation and subsequently may affect the incidence of late fibrosis. One other series by Cannon et al reports a correlation between wound complications and late effects after post-operative radiotherapy specifically. (72) The CAN-NCIC-SR2 trial (52) reported fewer late effects despite a higher incidence of wound complications in patients treated with pre-operative radiotherapy compared to post-operative radiotherapy. In practice there are many potential advantages to giving radiotherapy pre-operatively and the increased

risk of wound complications needs to be considered when planning treatment for individual patients. A large retrospective review is underway at the Royal National Orthopaedic Hospital to look at all patients treated for extremity sarcomas with surgery with or without radiotherapy and includes wound complications as one of the outcomes. This may add to our understanding of other risk factors for wound complications that could be addressed in future.

2.5.5.3 Timing of Radiotherapy

Pre-operative radiotherapy correlated significantly with a lower risk of any RTOG late effects ≥ grade 2 in this survey (p=0.032). This is likely because pre-operative radiotherapy irradiates a smaller volume of tissue to a lower dose, with the potential to improve the therapeutic index.

The current results are in line with the literature that demonstrates a definite trend towards a risk reduction with pre-operative radiotherapy. Canon et al reported a trend towards a lower risk of late effects after pre-operative radiotherapy in a retrospective series of patients treated for lower extremity soft tissue sarcoma prior to 2003.(72) In the prospective CAN-NCIC-SR2 trial there was an increase in joint stiffness, oedema and soft tissue fibrosis with post-operative radiotherapy, although this was not statistically significant. The trial was not powered for late effects as the primary endpoint was early wound complications.(52) Only 13% of patients in the current study received pre-operative radiotherapy (prior to 2003). Since the publication of the late effects results from the SR2 trial in 2005, there has been a shift towards using more pre-operative radiotherapy in our practice at UCLH as well, initially in borderline resectable tumours (75), and then more generally.

2.5.5.4 Complex surgery

There was a significant correlation between complex surgery and any RTOG late effect ≥ grade 2, subcutaneous fibrosis ≥ grade 2, significant joint stiffness and long-term pain in this survey. This is a new finding and has not been demonstrated in any of the published series discussed.

Around a third of patients had a complex surgical procedure (27%). Complex surgery in this study included several different types of procedures which were analysed individually and also as a group for correlation with late effects. Most frequently noted complex procedures were bone prosthesis or fixation (10% of patients), muscle flap (7% of patients), and skin graft (6% of patients). In univariate analysis, bone prosthesis

correlated significantly with any late effect ≥ grade 2, with joint stiffness ≥ grade 3 and with SOM pain ≥ grade 2. Muscle flap surgery correlated with subcutaneous fibrosis ≥ grade 2. Skin graft correlated with SOM pain ≥ grade 2. All other procedures were carried out in less than 10 patients (<5%) and were as such not analysed individually but were included in the combined complex surgery factor.

Complex surgery may increase the risk of delayed wound healing and wound complications including infections. The review of surgical outcomes underway at the Royal National Orthopaedic Surgery mentioned above, will quantify the problem and may shed some light on aspects of surgery to explore that may be addressed to reduce late complications.

2.5.5.5 Lower limb site

Lower limb site carried a higher risk of any RTOG late effects and subcutaneous fibrosis ≥ grade 2 in this survey. This is most likely because of the increased risk of wound complications at this site (6) which correlates strongly with ≥ grade 2 late effects. Stinson et al and Cannon et al also found a correlation with late effects and lower extremity site.(47, 72) Alektiar et al did not find a correlation but did not include soft tissue fibrosis in their analysis.

2.5.5.6 Age at the time of radiotherapy

Older age at the time of radiotherapy correlated with an increased risk of any RTOG late effects ≥ grade 2 and subcutaneous fibrosis ≥ grade 2. The literature on bone fracture after extremity radiotherapy demonstrated a higher risk for patients older than 50 years but this has not been demonstrated for soft tissues fibrosis or other late effects. Cannon did not find a correlation with late effects retrospectively (72) and it is not commented on in the other series. The correlation seen in the current study could be explained by the possibility that older patients may have more wound healing problems or because they are less likely to be able to do intensive physiotherapy and rehabilitation after treatment. They may also be going into treatment with more co-morbidities that could affect joint stiffness such as osteoarthritis or previous joint replacement surgery.

2.5.5.7 Prescribed radiotherapy dose

The radiotherapy dose prescription did not correlate significantly with late effects in LERTiSS, but a trend was seen for radiotherapy dose as a continuous variable suggesting that higher doses may increase the risk of late effects. The lack of statistically significant correlation could be due to the small number of patients receiving more than 60Gy, only 33 patients (13%). Cannon et al found that radiotherapy dose ≥60Gy correlated with late effects (72) and Stinson et al demonstrated a correlation between radiotherapy dose ≥63Gy and pain, oedema, joint stiffness and decreased muscle strength.(47) There was no correlation in CAN-NCIC-SR2 trial.(52) in LERTiSS the majority of postoperative radiotherapy was given at a dose of 60Gy, which is a lower dose than that generally used in North America in the same era.(47, 52)

Data on the volume of normal soft tissue receiving the prescription dose was not included in the LERTiSS analysis. Karasek et al reported increase fibrosis with larger soft tissue volumes receiving more than 55Gy and the volume of the peak dose/hot spot.(9) This may be a more relevant dose measures in the era of modern radiotherapy techniques where isodose lines can be shaped more conformally around the target with IMRT or tomotherapy. We are no longer confined to two-dimensional measures of maximal tumour size and the subsequent field size when considering radiotherapy dose. These technical advances are explored in Chapter 3.

2.5.6 Functional outcomes and quality of life

2.5.6.1 TESS scores and other patient-reported outcomes

The majority of patients in LERTiSS had good functional outcomes. Two thirds (63%) had a TESS score above 80, with a median score of 89.2 for the whole cohort and 46(18%) had a score of 100 with no functional deficit following treatment. These results are similar to the CAN-NCIC-SR2 trial results where there was a mean TESS score of 85.4 and 81.5 at two years after treatment in the pre-operative and post-operative radiotherapy arms respectively.(54)

More than a third, 86 patients (34.5%), had low TESS scores below 80, an indication of less than average function. It is not possible to say to what degree function as measured by the TESS score was affected by treatment as no baseline TESS data was available for comparison but 88 patients (35%) subjectively reported a negative

impact on their quality of life. Of these patients, 20% felt this was not an acceptable outcome. Sixty patients (32% of those with lower extremity tumour site) had an abnormal gait and 24% of patients needed a walking aid. Only Stinson et al reported the use of walking aids, at 7% (of all patients including upper and lower limb sites) in their series.(47) Seventy percent of patients were not retired but only 51% were working, 37% full time and 14% part time. The survey did not capture data on the reasons this group was not working (for example due to functional limitation, or other reasons)

These subjective patient-reported outcomes indicate a substantial functional impact in a third of patients after combined modality treatment for extremity sarcoma and there is clearly room for improvement.

2.5.6.2 Factors correlating with lower TESS score

Poor functional outcomes correlated with late effects. Higher RTOG scores were significantly associated with lower TESS scores in this survey. The same trend was seen across all scores and was statistically significant for all except a few of the higher-grade groups that had small numbers. Subcutaneous fibrosis ≥Grade 2 was associated with a mean TESS score of 70.9. RTOG joint late effects ≥ Grade 3 was associated with a mean TESS score 61.9 and bone fracture with a mean TESS score 67.3.

A similar significant correlation was seen with the individual SOM scores. Oedema ≥ Grade 2 was associated with a mean TESS score of 68.5. SOM Pain scores correlated significantly with the lowest mean TESS values: Pain ≥ Grade 2 with mean TESS score 57.1 and Pain ≥ Grade 3 with mean Tess score 48.9.

TESS scores correlated with fibrosis, oedema and joint stiffness in CAN-NCIC-SR2 trial. Timing of radiotherapy had an impact on early functional outcomes, particularly at 6 weeks and 3 months after treatment.(54) Other predictors of lower TESS scores at 2 years in the SR2 trial included lower limb tumours and prior incomplete excision. Wound complications were associated with lower TESS scores in the first 6 months after treatment.

2.5.7 Conclusion

The LERTiSS study aimed to describe the late effects and functional outcomes after combined modality treatment in the modern era of 3DCRT at one of the largest sarcoma radiotherapy centres in the UK.

Nearly half of the patients in this study (49%) had moderate ≥grade 2 late effects and 15% experienced significant late effects (≥ grade 3). Functional outcomes as measured by the TESS scores were generally good, and in line with published data.

Nevertheless, a proportion of patients have significant late effects including long term pain. A third of patients had functional outcomes below average (TESS score <80) and 35% reported a negative impact on their quality of life after treatment which was felt not to be acceptable by 20% of these patients. Long-term pain was a feature in 41% of patients and was inversely related to functional outcomes and quality of life.

Patients at a higher risk of late effects included those with larger tumours, lower limb site, older age at the time of radiotherapy, complex surgery, post-operative radiotherapy and wound complications. Late effects correlated strongly with functional outcomes. The data demonstrated that the risk factors for late effects have remained largely similar to that demonstrated in earlier series. The impact of long-term pain on functional outcomes was demonstrated for the first time.

These data raise the question of what we can change in how we plan and deliver radiotherapy to improve the late effects profile. Tumour size cannot be changed but we can attempt to improve on the volume of normal tissue that is treated to the prescription dose. CAN-NCIC-SR2 reported the outcomes after pre-operative radiotherapy to a smaller volume and using a lower dose.(6, 52, 54) Reducing the size of the clinical target volume was the focus of the recent VORTEX trial (46) and the phase II RTOG-0630 (58) trial. The latter showed a reduction in late effects. An advanced radiotherapy technique, IMRT was used in 75% of patients in this trial.

Following LERTiSS, a trial protocol was developed to prospectively assess the late effects after IMRT (Chapter 5). To inform the protocol, a double planning study was done to explore volumetric modulated arc therapy (VMAT), a rotational IMRT technique used at UCLH, in order to understand how this could be used to improve radiotherapy dose distributions outside the target in extremity soft tissue sarcomas, compared to 3DCRT. This project is discussed in Chapter 3.

3 Chapter 3 Planning study comparing VMAT with 3DCRT for soft tissue sarcomas of the extremities

3.1 Introduction and literature review

3.1.1 Extremity radiotherapy

Chapter 2 described the LERTiSS project which demonstrated that 3DCRT carries a certain burden of late effects and subsequent functional deficit for a proportion of patients with extremity sarcomas managed by radical limb salvage surgery and adjuvant radiotherapy. There was a correlation between the late effects observed and the volume of tissue treated to the prescription dose, as reflected by the increased risk associated with increasing tumour size and consequent longer and wider radiotherapy fields.

The volume of soft tissue to be treated with radiotherapy is defined by the clinical target volume (CTV). This margin is added around the gross tumour volume (GTV) or tumour bed to incorporate areas deemed at risk of microscopic disease involvement. The standard CTV margin for extremity sarcoma post-operative radiotherapy is 1.5 to 2cm axially, and 2cm craniocaudally around the tumour bed. This high dose target is treated to 60 to 66Gy in 1.8 to 2Gy per fraction. A further minimum 2cm cranio-caudal extension is treated to a lower dose of 45 to 50Gy.(12) When using 3DCRT it is done through a sequential treatment with a larger volume incorporating both the low and high dose CTV treated to 45 – 50Gy, and then a smaller volume, the high dose CTV, boosted to a further 10 to 16Gy to a total of 60 – 66Gy (figure 3.1). For pre-operative radiotherapy the CTV is a 1.5 to 2cm axial expansion and a minimum of 2 to 3cm cranio-caudal expansion around the tumour, treated to 50Gy in 1-8 to 2Gy per fraction (figure 3.2). An additional expansion for movement and daily positioning error (planning target volume, PTV) is added around CTV. This margin varies per department, dependent on the immobilisation system used, and is usually between 5mm and 1cm. (12, 55)

When using a 3DCRT technique, high doses are frequently delivered to the normal soft tissues outside PTV. Multi-leaf collimators are used to conform the radiotherapy beam to the PTV, and so to minimise the normal tissue treated to high doses but is limited by the fact that conformation can only be done in two dimensions. Using multiple coplanar beams from multiple angles can improve this dose distribution, but also leads to more

exit dose through uninvolved tissue from multiple beams. This is often difficult in the extremities due to the small diameter of the extremity, and moreover, choice of beam angles is often limited when aiming to avoid entry or exit through the contralateral limb, pelvis and perineum, and to spare a longitudinal corridor of normal tissue to minimise the risk of lymphoedema.

Figure 3.1 Post-operative radiotherapy target volumes: axial and coronal views

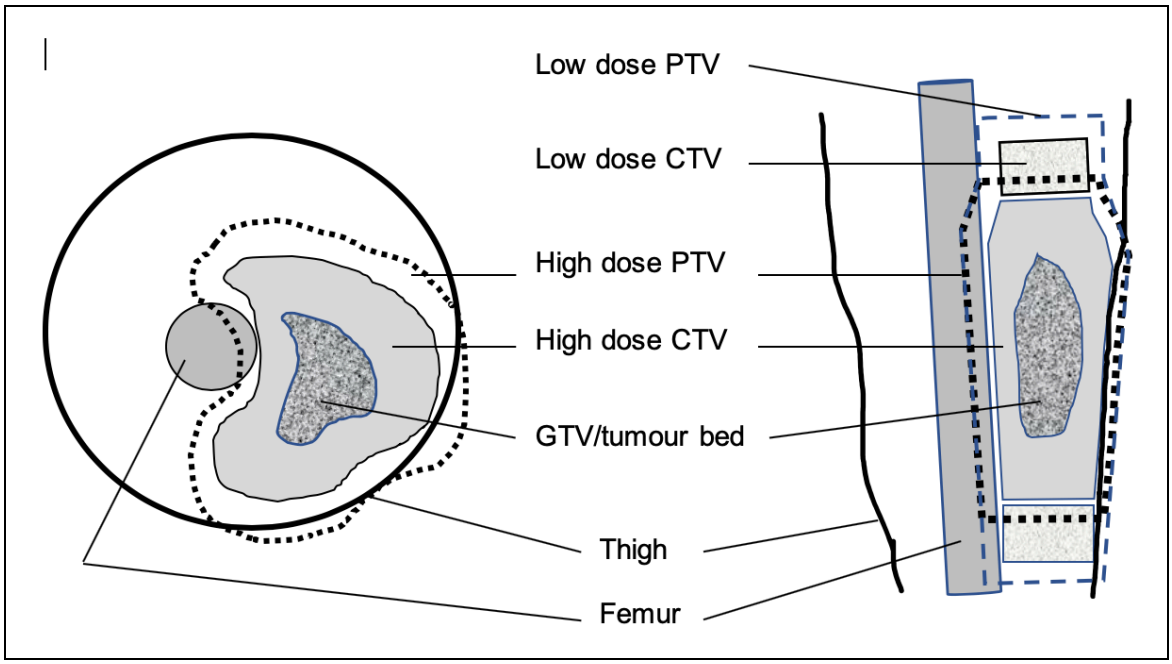
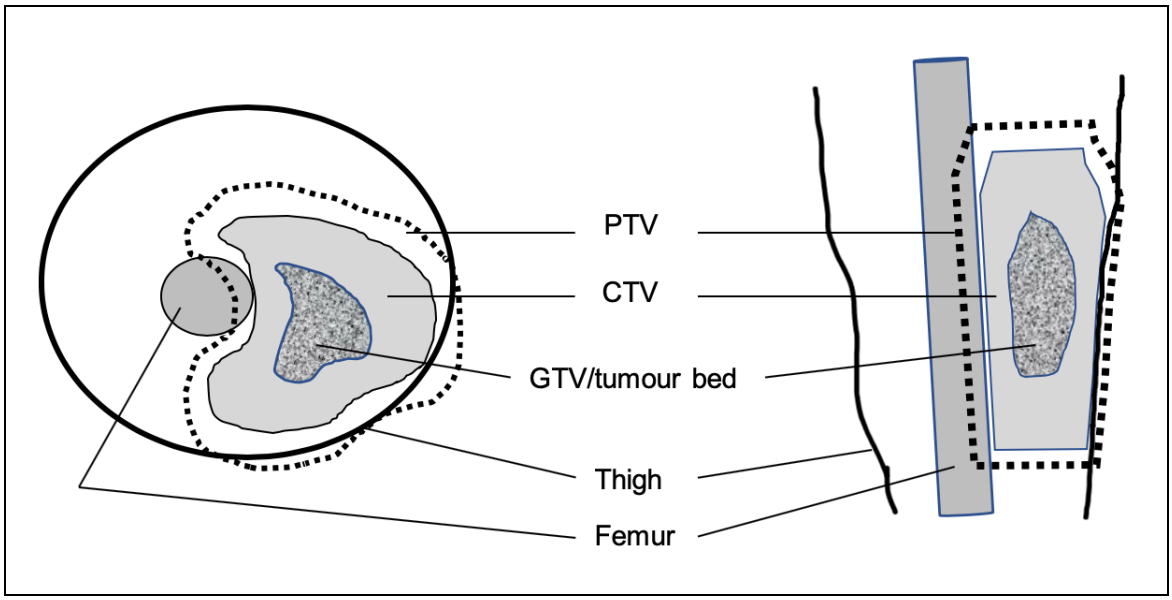


Figure 3.2 Pre-operative radiotherapy target volumes: axial and coronal views



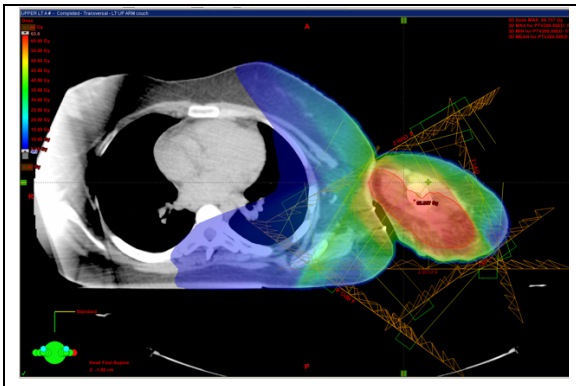
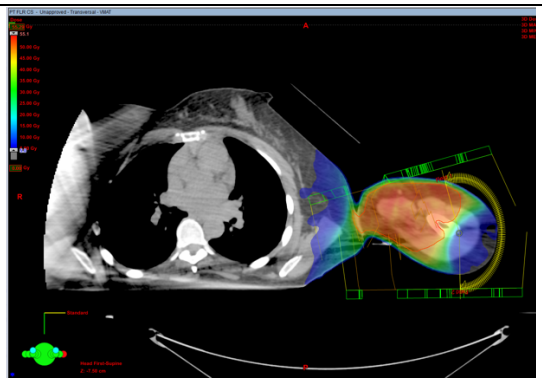
3.1.2 Intensity Modulated Radiotherapy

Intensity modulated radiotherapy (IMRT) is a modern radiotherapy technique that has the potential to achieve highly conformal radiotherapy dose distributions to the PTV by modulating dose across the PTV, as well as conforming dose around PTV. As a consequence it is possible to achieve a homogeneous dose distribution across the PTV, while reducing the high radiotherapy doses to the surrounding normal tissues. IMRT can also vary the dose delivered across the PTV if required. IMRT has been shown in randomised controlled trials and non-randomised studies to lead to a reduction in early and late side effects of RT in several tumour sites including head and neck cancer, breast cancer and prostate cancer. (29)

3.1.3 Different IMRT techniques

IMRT is comprised of multiple small beamlets within each RT beam of which the individual intensity is modulated during treatment to deliver non-homogenous beams. Multiple such beams from either fixed angles (fixed field IMRT) or through a moving arc (Volumetric modulated arc therapy or Tomotherapy) are combined by sophisticated computer software to create a cumulative treatment plan that is highly conformal and able to treat different dose levels within the target at the same time (figure 3.3). There are some inherent differences to 3DCRT. The PTV is typically cropped to 5mm within skin to avoid unrealistic attempts by the software to deliver 100% dose to the skin which is technically not possible. High, intermediate and low dose targets can be treated simultaneously with a gradient in fraction size across different dose levels. (28) Fixed field IMRT is more complex than 3DCRT, such that it takes longer to deliver, and the monitor units (radiation output from the linear accelerator) are higher with the potential consequence of increased low dose to the whole patient. Volumetric modulated arc therapy (VMAT) is more efficient than either 3DCRT or fixed field IMRT, in that it can be delivered faster with potentially fewer monitor units. (30)

Figure 3.3 examples of fixed field and continuous arc IMRT plans

	
Fixed field IMRT plan for upper arm sarcoma – post-operative radiotherapy. Dose colourwash set at 4.9Gy	Rotational arc IMRT plan for upper arm sarcoma – pre-operative radiotherapy. Dose colourwash set at 5.0Gy

3.1.4 Evidence for the use of IMRT in extremity soft tissue sarcoma

The literature on IMRT in extremity sarcomas consists of planning studies predominantly exploring fixed field IMRT for lower limb (mainly thigh) tumours (76-78), two retrospective clinical case series (79-81) and two small prospective phase 2 studies.(58, 82) These series showed acceptable local tumour control rates and a low incidence of late effects of treatment. The single planning study exploring VMAT in extremity soft tissue sarcoma focussed on thigh tumours treated in the post-operative setting and did not compare VMAT to 3DCRT.(83)

3.1.4.1 Planning studies of fixed field IMRT in extremity soft tissue sarcoma

Three planning studies have compared 3DCRT with fixed field IMRT in the lower limb, assessing predominantly thigh tumours.(76-78) Two of these were studies of post-operative radiotherapy, and the third explored specifically the value of IMRT to reduce the dose to the skin of anticipated surgical flaps for pre-operative radiotherapy. One further planning study compared VMAT with proton beam therapy (PBT) to treat thigh tumours in the post-operative setting and concluded that both techniques achieved good PTV coverage and normal tissue sparing. PBT had superior medium and low dose distributions. These techniques were not compared to 3DCRT in this study.(83) The planning studies are summarised in Table 3.1 below and demonstrate that fixed field IMRT increases conformality and dose homogeneity to the PTV, and reduces dose to the bone, skin and soft tissue outside the PTV.

Table 3.1 Planning studies of IMRT in lower limb extremity soft tissue sarcoma

Author/ institution	Aim	Cases/ Site	Timing/ Technique	Effect of IMRT
Stewart (76) Royal Marsden Hospital	Minimise dose to bone and skin corridor	N=10 Thigh	Post-operative Fixed field IMRT	Reduced Femur V45Gy Reduced Normal tissue V55Gy Reduced Normal tissue Dmax Improved conformality and homogeneity with at least 4 IMRT fields
Hong (77) Memorial Sloan Kettering Cancer Centre	Minimise dose to bone, skin and soft tissue	N=10 Thigh	Post-operative Fixed field IMRT	Reduced Femur V100% Reduced Femur hotspots Reduced Femur mean dose Increase Femur low dose Reduced Normal tissue dose Reduced Skin dose Improved conformality and homogeneity
Griffin (78) Princess Margaret Hospital, Toronto	Minimise superficial dose to planned surgical flaps	N=24 Lower Extremity	Pre-operative Fixed field IMRT vs 3DCRT vs 2DCRT	Reduced mean % flap >30Gy Reduced mean % bone >40Gy Reduced mean dose to flap Reduced mean dose to bone Improved conformality and homogeneity
Fogliata (83) Instituto Clinico Humanitas, Rozzano, Milan, Italy	Compare normal tissue dose and PTV coverage VMAT vs. Proton beam radiotherapy (PBT)	N=10 Thigh	Post-operative PBT vs VMAT	Both techniques resulted in good PTV coverage and normal tissue sparing PBT had superior medium and low dose distributions
V45Gy = Volume receiving 45Gy or more; V55Gy = Volume receiving 55Gy or more; Dmax = maximum dose; V100% = volume receiving full prescription dose				

3.1.4.2 Published retrospective cohort studies of IMRT in extremity soft tissue sarcoma

Retrospective data from Memorial Sloan Kettering Cancer Centre (MSKCC) show excellent local control rates after fixed field IMRT. A retrospective series published initially in 2007 (79) and updated in 2008 (80), reported on 41 patients treated with fixed field IMRT, with a median follow up of 35 months . Most patients (29) had lower limb tumours, and the majority received post-operative RT (34 patients). The five-year actuarial local control rate was 94%. The side effect profile was very good with grade 2 or greater wound complications in 17%; grade 2 joint stiffness in 17%, and grade 2 oedema in 12%. In 2014 the same authors published a retrospective comparison of 319 patients treated with 3DCRT and IMRT between 1996 and 2010. The local relapse rate at 5 years was significantly lower with IMRT (7.6%) than with 3DCRT (15.1%), which is reassuring in that IMRT conforms much more tightly to PTV than 3DCRT such that there could be concerns of potential under coverage. This series similarly reported low late complication rates with IMRT.(81)

3.1.4.3 Prospective studies of IMRT in extremity soft tissue sarcoma

There was only one published prospective study at the time that the work described in this thesis was carried out. The team from Princess Margaret Hospital, Toronto had followed up their planning study to reduce superficial dose to planned surgical flaps with a prospective phase 2 study to investigate whether use of fixed field IMRT would result in reduced wound complications.(82) The primary endpoint was the rate of acute wound complications. In 59 patients treated with pre-operative fixed field IMRT, the wound complication rate was 30.5%, which was not greatly different to the rate of 35% seen in the CAN-NCIC-SR2 trial which utilised 3DCRT (discussed in 2.1.2) (6). There was however a trend towards a reduction in the need for secondary surgery for wound complications (33% vs 43% for IMRT vs 3DCRT, respectively) and a higher rate of primary closure (93% vs 71% for IMRT vs 3DCRT, respectively). At a median follow-up of 49 months the late effects of radiotherapy were consistent with the retrospective data from the MSKCC series discussed in section 3.5.4.2, with rates of grade 2 or greater oedema of 11%, subcutaneous fibrosis of 9%, and joint toxicity of 5%.
The local relapse rate was 6.8%, which was comparable with the rate of 7.6% for the MSKCC series.

A subsequent prospective phase 2 study, RTOG-0630, published in 2015, investigated whether the use of image guided radiotherapy (IGRT) in pre-operative radiotherapy for

extremity soft tissue sarcoma could result in use of a reduced volume CTV, and consequently reduced late radiotherapy toxicity. The multicentre cohort was treated with two different techniques, IMRT (75%) or 3DCRT (25%), according to local practice. Most patients had lower extremity tumours (78%). The study demonstrated reduced grade 2 or greater late effects as compared with historical controls, with 10% of patients exhibiting at least one ≥ grade 2 late effect, and rates of fibrosis of 5%, joint stiffness of 3% and oedema of 5%, at a median follow up of 3.6 years. Early wound complications at 120 days were consistent with other series' at 36%. The local relapse rate was 6%.(58)

3.1.5 Normal tissue tolerance and dose constraints for IMRT planning

The optimisation software used for IMRT planning is guided by targets for PTV coverage and normal tissue sparing defined by the user and priorities for each are assigned a relative weighting. These are then adjusted in order to obtain the best plan in an iterative process. (28) The evidence for normal tissue toxicity thresholds are taken into account to inform the optimisation targets.

The literature on normal tissue tolerance in extremity radiotherapy is discussed fully in Chapter 2. Radiotherapy dose/volume parameters relevant to radiotherapy planning are highlighted here:

3.1.5.1 Bone fracture

Radiotherapy to bone is recognised to be associated with a risk of fracture of the irradiated bone. A large database review demonstrated reduced fracture risk with volume of bone receiving 40Gy or more (V40Gy) <64%, mean dose to the whole bone <37Gy, and a maximum dose to bone <59Gy.(51) Increased risk of fracture associated with doses >60Gy was observed by several authors.(47, 50, 72) The RTOG0630 trial protocol used a target of volume of weight bearing bone receiving 50Gy or more (V50Gy) <50%. However, this target is not achievable where the tumour wraps around more than 25% of the bone circumference or directly invades the bone.(58)

3.1.5.2 Soft tissue fibrosis

Retrospective data have shown increased fibrosis with increase in peak dose and the volume of the peak dose, as well as the volume receiving ≥55Gy.(9)

3.1.5.3 Limb lymphoedema and sparing of a normal tissue corridor of the limb

Conventionally, during radiotherapy planning for limb sarcomas, a corridor of untreated normal tissue is spared in order to preserve subcutaneous lymphatics and reduce the risk of lymphoedema of the distal limb. For 3DCRT, this involves a cylinder of tissue that is completely untreated. However, with IMRT, the entire area of the limb in cross-section will receive some dose to varying levels, and so the aim would be to define an area that would receive less dose in order to achieve the same as the untreated normal tissue corridor in 3DCRT. There is no consensus on how best to define the soft tissue corridor to be spared with IMRT, where low doses are spread through a substantial area outside the target, and the available evidence is from the 3DCRT era. The volume or percentage of limb spared (to <40Gy) did not correlate with incidence and severity of oedema in one retrospective series with very good long-term outcomes with very small corridors (9). There was an increased risk of ulceration and infection when >75% limb diameter was in the radiotherapy field in another series.(47) The RTOG0630 trial protocol, including the use of IMRT in limb soft tissue sarcoma, specified that the area within a user defined corridor receiving 20Gy should ideally be kept to <50%. The incidence of oedema at 2 years was 5.3% using this dose constraint.(58) However, there is not a clinically validated dose constraint, and there is also considerable variation in how a defined corridor might be contoured in terms of size and position.

3.1.5.4 Joint stiffness

Radiotherapy to a joint can result in stiffness of that joint. In one series dose to the joint did not correlate with joint stiffness (9), whereas in another series, there was an increased risk of joint stiffness with >50% joint in the treatment volume. (47) The RTOG0630 trial protocol aimed to keep the volume of joint receiving ≥50Gy (V50Gy) to < 50%.(58)

3.2 Purpose of this study

Cancer is a heterogenous disease and sarcoma even more so, affecting a variety of anatomical sites. It is important not to assume the value of any new technique without confirming it in specific sites and tumours. Experimental models such as radiotherapy planning studies are valuable to demonstrate the potential of new techniques. The published planning studies have demonstrated the dosimetric superiority of fixed field IMRT over 3DCRT in extremity sarcomas. Despite the subsequent change in practice in North America towards using IMRT to treat extremity sarcomas, the evidence base of these planning studies, in addition to two retrospective series and one negative prospective phase 2 study reporting no significant change in wound complications, the evidence was not strong enough to support a practice change within the NHS setting in the UK. It was the intention to develop a UK wide multicentre trial of IMRT in sarcoma to generate the necessary evidence, and to roll out IMRT in a quality assured setting across the country (Chapter 5). A more in-depth understanding of IMRT for all extremity sites, and in particular VMAT, the preferred IMRT technique in use at UCLH, was needed in order to do this.

This planning study set out to assess the utility of VMAT compared to 3DCRT in both upper and lower extremity sarcomas, in the pre-operative and post-operative setting. The aims were:

- To assess the feasibility of VMAT for extremity radiotherapy, and explore potential challenges in delivering this technique
- To compare VMAT dosimetrically with 3DCRT for extremity sarcomas
- To assess the value of VMAT to limit doses to adjacent normal structures while optimising target volume coverage.
- To develop VMAT class solutions for individual anatomical limb subsites, to potentially reduce the time required to produce individual IMRT plans
- To gain experience using this technique in preparation for introducing IMRT for extremity sarcomas at UCLH
- To inform the development of a prospective trial protocol (IMRiS)

3.3 Materials and methods

This planning study was developed in Spring 2012. It was discussed with the UCLH Research and Development Department and classed as a service development project which did not impact on individual patient care and did not require an ethics application. All patient data were anonymised.

3.3.1 Study aim

- To assess the feasibility of VMAT as treatment for extremity soft tissue sarcoma
- To compare dosimetry of VMAT and 3DCRT in the treatment of extremity soft tissue sarcoma
- To compare the ability of VMAT and 3DCRT to deliver the prescribed dose to PTV
- To compare the ability of VMAT and 3DCRT to reduce the dose to normal soft tissue outside the PTV as well as bone
- To compare the ability of VMAT and 3DCRT to reduce dose to other normal soft tissue structures and organs at risk

3.3.2 Study design

A double planning study using anonymised 3DCRT plan data from cases previously treated at UCLH compared to virtually generated VMAT plans.

3.3.3 Study endpoints

- PTV coverage (D100%, D98%, D95%, D2%)
- Homogeneity of dose
- Monitor units required for treatment delivery
- Normal soft tissue outside the PTV dose/volume parameters
    - Soft tissue $V_{60Gy,}$ $V_{50Gy,}$ $V_{40Gy,}$ $V_{30Gy,}$ V_{20Gy}
    - Maximum and mean dose to soft tissue
- Bone dose/volume parameters
    - Whole Bone V_{40Gy}
    - Bone in field V_{50Gy}
    - Whole bone maximum and mean dose
    - Femur head/ humerus head V60Gy
- Maximum dose to the contralateral limb
- Mean and maximum dose to other organs at risk
- Corridor $V_{5Gy,}$ $V_{10Gy,}$ $V_{20Gy,}$ V_{40Gy}

3.3.4 Case selection

Cases were identified retrospectively from the UCLH sarcoma radiotherapy database.

Inclusion and exclusion criteria

Three cases were selected from each of the following anatomical subsites:

- medial thigh
- anterior thigh
- posterior thigh
- calf
- shin
- upper arm
- forearm

Inclusion of more than one anatomically similar case was avoided where possible.
Pre-operative and postoperative radiotherapy cases were included.
Cases were excluded where the full 3DCRT plan data could not be retrieved from the archive and further cases were selected to replace these.

3.3.5 IMRT plan generation

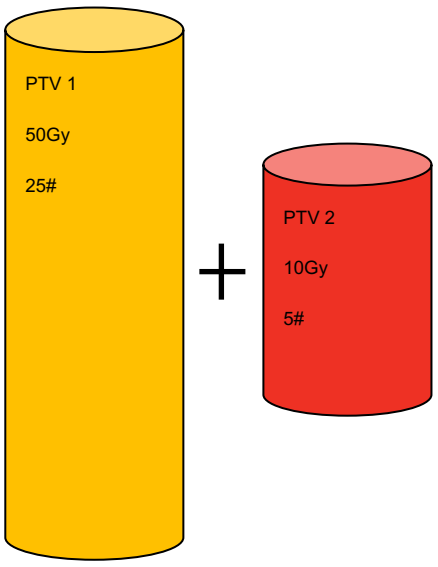
3D-CRT plans and structure sets were imported from *Oncentra Masterplan v4.1* to *Varian Eclipse v10.*
VMAT plans were generated by myself in collaboration with senior radiotherapy physicist Chris Stacey, using an iterative inverse planning approach.

3.3.5.1 Target volumes

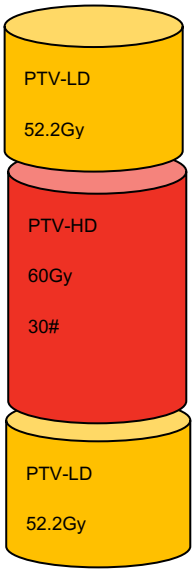
Pre-operative radiotherapy:
The original 3DCRT GTV and CTV were not changed. An edited PTV was created for VMAT planning, cropping the original PTV to 5mm within skin/body where indicated as per VMAT planning practice.

Post-operative radiotherapy:
The original 3DCRT volumes were adapted to allow for a simultaneous integrated boost technique with VMAT. GTV and boost/high dose CTV were not changed. The high dose PTV was cropped to 5mm within the skin/body contour. The original low dose CTV, which overlaps with the high dose CTV where 3DCRT is delivered in consecutive phases, was edited to create two separate low dose CTV volumes proximal and distal to the high dose CTV for the purpose of concurrent treatment with VMAT. Separate PTV volumes were created using the original margins form the 3DCRT volumes (7mm) (Figure 3.4)

Figure 3.4 Post-operative 3DCRT volumes adapted for VMAT



3DCRT: 2 phases



VMAT: 2 dose levels with integrated boost.
PTV-LD = low dose PTV
PTV-HD = high dose PTV

Planning target volume dose constraints (Table 3.2) were as per ICRU Report 83, 50 and 62. (27, 28, 84) VMAT plans were normalised to the median dose of the high dose PTV volume.

Table 3.2 Target volume planning dose constraints

Volume constraint	PTV dose target
98%	≥ 90%
95%	≥ 95%
100%	100%
2%	≤ 107%

3.3.5.2 Dose prescription

Pre-operative radiotherapy:
The 3DCRT prescription for pre-operative radiotherapy was 50Gy in 25 fractions. The same prescription was used for the VMAT plans.

Post-operative radiotherapy:
The 3DCRT prescription to the low dose PTV (PTV1 in Figure 3.4) was 50Gy in 25 fractions. The high dose PTV (PTV2 in Figure 3.4) received a further 10Gy in 2Gy per fraction boost to a cumulative dose of 60Gy in 30 fractions (11 cases) or 66Gy in 33 fractions (1 case). VMAT plans were created using a simultaneous integrated boost to the high dose PTV. The VMAT prescription to the high dose PTV was 60 to 66Gy in 30 to 33 fractions in standard 2Gy per fraction. The prescription to the low dose PTV was either 52.2Gy in 30 fractions of 1.74Gy per fraction, or 53.46Gy in 33 fractions of 1.62Gy using an alpha/beta ratio of around 4 (85) to deliver the equivalent of 50Gy in 2Gy per fraction (EQD2).

The formula used was: $EQD2 = dn \times (d + \alpha/\beta)/(2 + \alpha/\beta)$

Where: d = the dose per fraction; n = the number pf fractions; α/β = the alpha/beta ratio

3.3.5.3 Normal tissue structures

The original 3DCRT data sets mostly did not contain normal structure outlines as the main constraint for 3DCRT plan generation in limbs was to completely avoid a corridor of soft tissue representing around 25% of the limb circumference, usually 2cm deep. The following structures were outlined for VMAT planning and copied to the original 3DCRT structure set for 3DCRT dose calculation:

Long bones:

- Whole bone (if included in dataset)
- Bone in treatment field: bone within the radiotherapy portal (i.e. length of PTV + 1cm cranio-caudal to include dose fall-off at the edge of the field)

Soft tissue structures:

- Soft tissue outside PTV: external contour of the ipsilateral limb minus the PTV and bones, up to 1cm cranio-caudal to PTV
- Corridor: individually defined longitudinal structure within the ipsilateral limb, up to 1cm cranio-caudal to PTV. An example of a corridor structure is shown in Figure 3.5. The position of the corridor could be changed during the planning process if the original position made it impossible to meet the planning constraints.
- Contralateral limb/trunk: external contour of the other leg for lower limb sites, or the trunk for upper limb sites.
- Pelvic organs were outlined where the PTV was in proximity to the pelvis, including rectum, small bowel space, bladder, anal canal, genitalia. Lungs were outlined for upper limb sites.

3.3.5.4 Normal tissue dose constraints

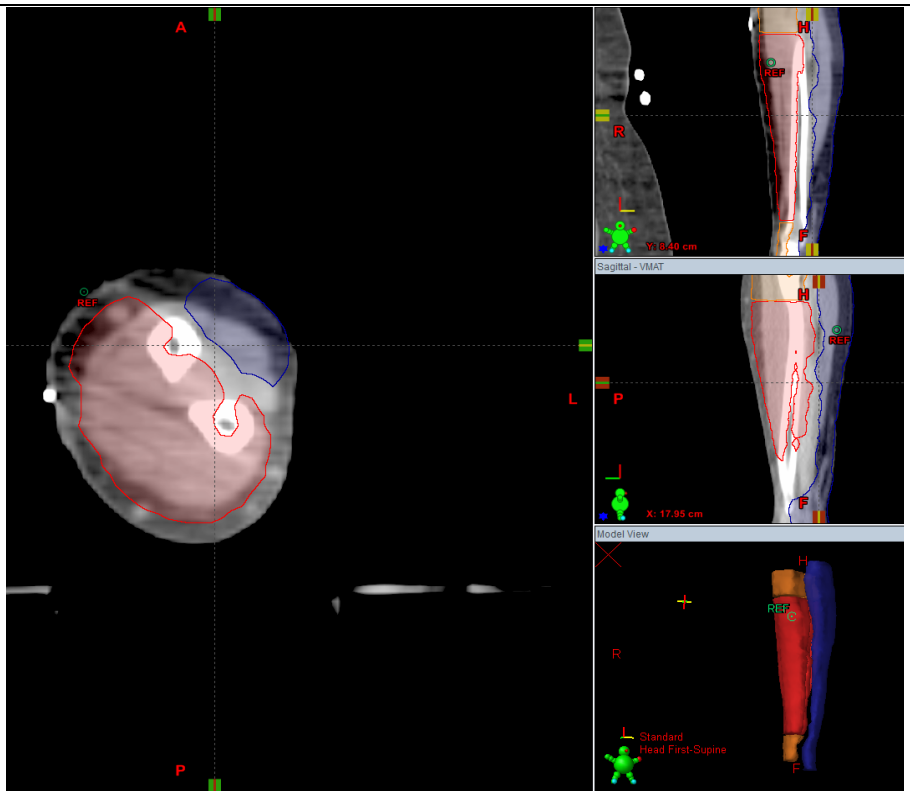
The planning objective was to limit dose to the bone and soft tissue outside the PTV. The following dose constraint from the retrospective literature (51) and the RTOG0630 trial (58) were aimed for, but not prioritised over PTV coverage:

- Whole bone V40Gy < 64%
- Whole bone Dmax < 59Gy
- Whole bone mean dose < 37Gy
- Bone in treatment field V50Gy < 50%
- Femoral head V60Gy < 5%
- Corridor V20Gy < 50%

Additional organ constrains were as per current practice and the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) review (25), including:

- Whole limb circumference <40Gy
- Contralateral limb: limit entry and exit of beam, aim to avoid completely
- Testis/vulva Dmax 6Gy and V3Gy < 50%

Figure 3.5 Example of soft tissue corridor (blue) and PTV (red/orange) in the arm.



3.3.6 Data collection

Dosimetric data:

- PTV coverage parameters as per the study endpoints (section 3.3.3)
- Homogeneity of dose according to the formula:

  Inhomogeneity coefficient = (D2% - D98%) / D50%

  Where D2% = the dose to 2% of the PTV (hotspot); D98%= the dose to 98% of the PTV (cold spot); D50% = the dose to 50% of the PTV
  A result of ≤0.17 indicates acceptable homogeneity

- Normal tissue dose/volume parameters as per the study endpoints (section 3.3.3)
- Monitor units required for treatment delivery

Qualitative data:

- Feasibility of VMAT for different anatomical subsites.
- Qualitative plan assessment done by myself with input from Chris Stacey and Dr Beatrice Seddon.

Statistical considerations

Data were entered into an Excel spreadsheet. Dose volume parameter results were evaluated using the Wilcoxon signed-rank non-parametric test for paired data. Statistical significance was defined as a p-value <0.05 and borderline significance as p-value >0.5 and <0.1.

3.4 Results

3.4.1 Case mix

There were 21 cases, representing three from each selected anatomical subsite. Nine were treated with pre-operative RT to 50Gy, and the remaining 12 in the post-operative setting to either 60Gy to the high dose volume (in 11) or 66Gy (in 1).

3.4.2 PTV dose parameters and homogeneity

The summative results are presented in Table 3.3. Both 3DCRT and VMAT IMRT techniques resulted in acceptable PTV coverage for all cases.

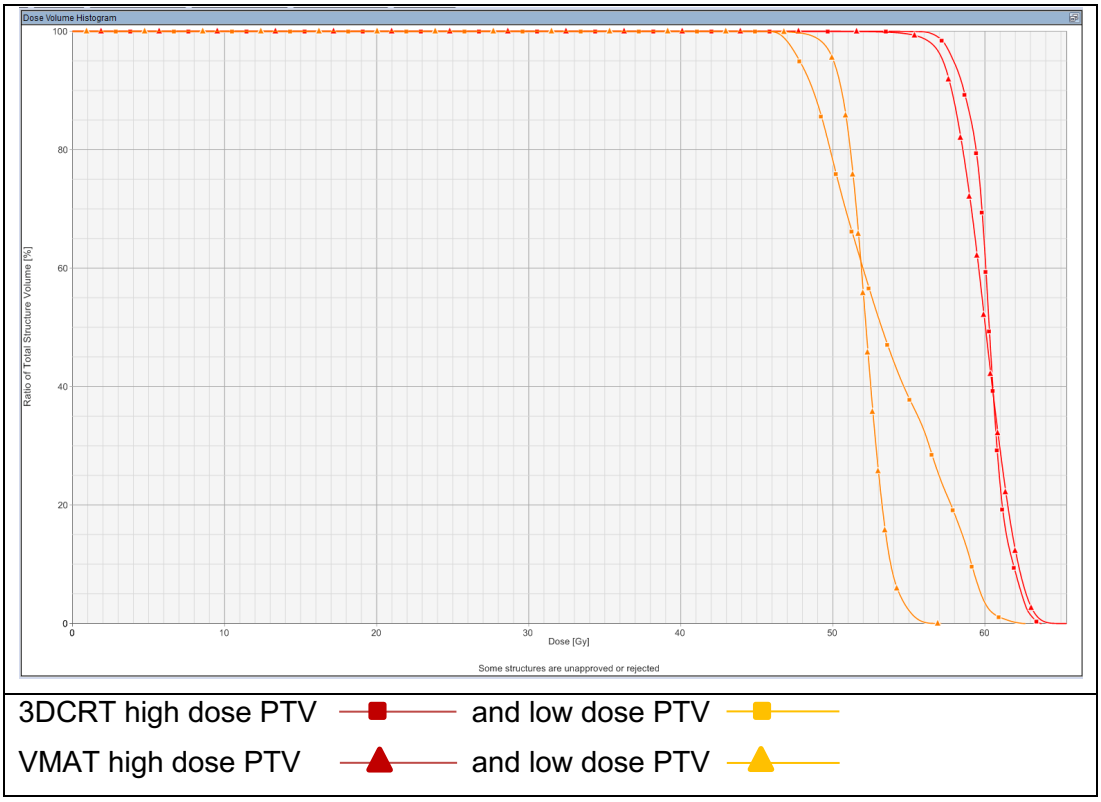
The D95% was slightly low at 92% in one case with 3DCRT. There was a hotspot of 109% in one other case with 3DCRT. VMAT plans met all the dose constraints as specified for IMRT plans in ICRU report 83.(28) The D95% of at least 95%, the traditional measure of 3DCRT plans, was not reliably met by the VMAT plans, with the value ranging from 93% to 96.5%. Homogeneity was excellent for both techniques in all cases. Typical PTV dose volume histograms (DVH) for 3DCRT and VMAT are shown in Figure 3.6.

The median change between paired VMAT and 3DCRT results for individual cases, as assessed by the Wilcoxon signed-rank non-parametric test, was not statistically significant for any of the PTV dose parameters.

Table 3.3 Dose-volume parameters for PTV coverage

Dose parameter	PTV coverage target value	3DCRT		VMAT	
		Median	Range	Median	Range
High dose PTV $D_{98\%}$ [%]	≥ 90%	95	90-99	92	90–95.5
$D_{95\%}$ [%]	≥ 95%	96	92-99	94	93–96.5
$D_{50\%}$ [%]	= 100%	101	100-103	100	100-100.7
$D_{2\%}$ [%]	≤ 107%	104	102-109	105	102.7–106
Maximum dose [Gy]		62	51.5–70	62	51.70–70.9
Minimum dose [Gy]		43.6	19-56	44	28-53.7
Low dose PTV $D_{98\%}$ [%]	≥ 90%	92.35	87-96	92.4	90-97.1
$D_{50\%}$ [%]	= 100%	98.3	95.7-103	99.4	97.9-101
Maximum dose [Gy]		62	60.8-69	57.95	56.1-68
Minimum dose [Gy]		41.45	10-46	41	27-47.4
Inhomogeneity coefficient	≤ 0.17	0.09	0.05-0.16	0.13	0.07-0.15
D98% = percentage dose to 98% of the volume; D95% = percentage dose to 95% of the volume; D50% = percentage dose to 50% of the volume; D2% = percentage dose to 2% of the volume					

Figure 3.6 Example of VMAT and 3DCRT PTV dose volume histograms (FLG3, Anterior thigh)



3.4.3 Monitor Units

The median monitor units for VMAT plans was 371 (range 271-533), and for 3DCRT it was 393 (range 192-495). The median increase in monitor units with VMAT, between paired plans for individual cases, was 86 (range -180 to 292), and this was not statistically significant ($0.10<p<0.20$). There was a decrease seen in 6 cases.

3.4.4 Normal tissue sparing

3.4.4.1 Normal soft tissue outside the PTV

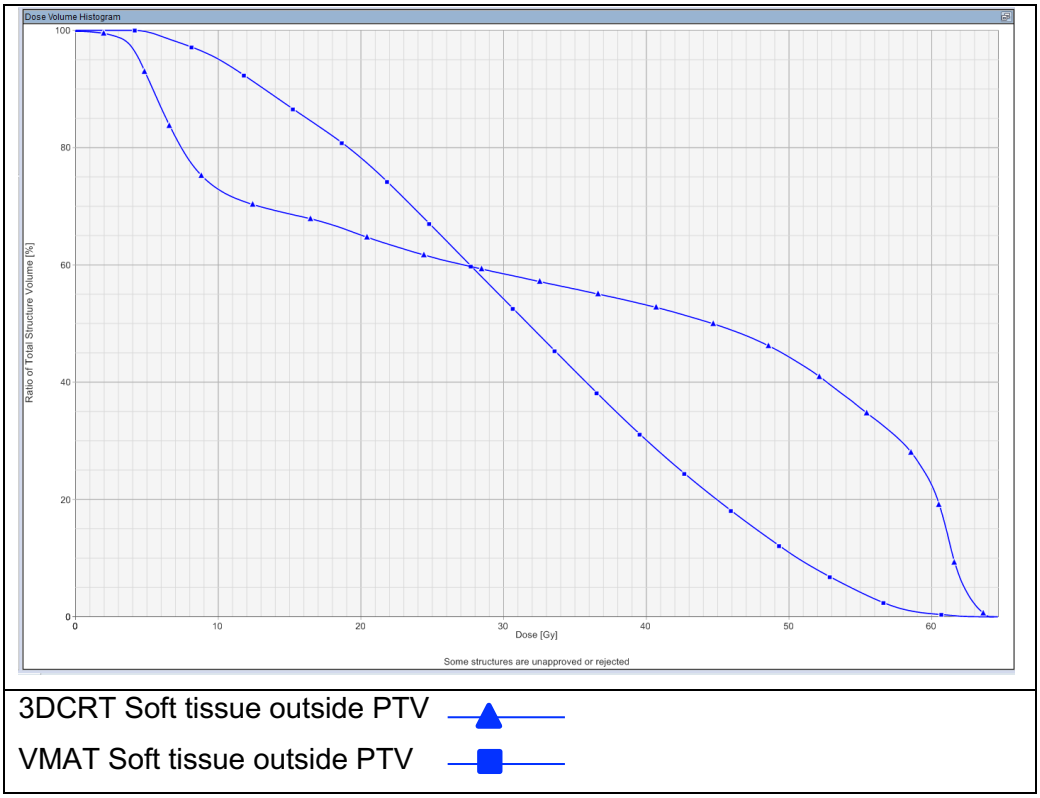
VMAT resulted in a reduction in the volume of normal soft tissue receiving moderate to high radiotherapy doses (Table. 3.4). The median percentage reduction in V30Gy was 15%, V40Gy 46%, V50Gy 78% and V60Gy 98%. This was statistically significant for doses above 30Gy with the mean crossover value of the curves for the two techniques at 27Gy (range 6 – 41Gy). The reduction in the volume of normal soft tissue receiving radiotherapy dose was seen to extend to lower dose levels in upper extremity sites. The curves crossed at a median dose of 18.5Gy (range 7.6-23) for upper limb sites, and 31.5Gy (range 6-41) for lower limb sites.

The volume receiving low doses below the crossover value, increase with VMAT, with a median percentage increase of 13% in V20Gy. This was borderline significant ($0.05 < p < 0.1$). An example case is given in Figure 3.7.

Table 3.4 Dose-volume parameters for soft tissue outside PTV

	3DCRT Median (range)		VMAT Median (range)		Comparison between paired data Median (range)	*p* value
Dose/ volume parameter	Percentage volume (%)	Absolute volume (cm^3)	Percentage volume (%)	Absolute volume (cm^3)	Change in soft tissue volume with VMAT (%)	
Soft tissue V_{60Gy}	5 (0-22)	99 (0-830)	0.4 (0-7)	10 (0-202)	-98 (-100 to -38)	$0.001 < p < 0.005$
Soft tissue V_{50Gy}	11 (1-53)	237 (7-3434)	2.2 (0-19	33 (0-666)	-78 (-100 to -29)	$p<0.001$
Soft tissue V_{40Gy}	35 (8-74)	387 (80-4883)	14 (9-33)	246 (33-1610)	-46 (-76 to +13)	$p<0.001$
Soft tissue V_{30Gy}	40 (11-82)	457 (107-5441)	35 (17-54)	496 (64-3545)	-15 (-54 to +91)	$0.02 < p < 0.05$
Soft tissue V_{20Gy}	48 (15-92)	511 (140-6295)	56 (29-78)	999 (107-6815)	+13 (-33 to +153)	$0.05 < p < 0.1$
Maximum dose (Gy)	61Gy (52-70Gy)		61Gy (51-70Gy)		-	$p>0.2$
Mean dose (Gy)	25Gy (0.2-44Gy)		25Gy (16-31Gy)		-	$p>0.2$
V60Gy = volume receiving 60Gy; V50Gy = volume receiving 50Gy; V40Gy = volume receiving 40Gy; V30Gy = volume receiving 30Gy; V20Gy = volume receiving 20Gy						

Figure 3.7 Example of dose volume histogram curves for soft tissue outside the PTV (FLG4, Posterior thigh)



3.4.4.2 Corridor

VMAT plans achieved the target of V20Gy <50% in all but one case where it was 55%. This was a proximal adductor thigh case in close proximity to pelvic organs and the corridor V40 was 8%. (Table 3.5)

Table 3.5 Dose-volume parameters for the corridor

	V5Gy (%)	V10Gy (10%)	V20Gy (%) Aim for <50% as per RTOG0630	V40Gy (%)
Median	90	50	6	0
Range	(26 – 100)	(0 – 89)	(0 – 55)	(0 – 8)

3.4.4.3 Bone dose

The results are presented in Table 3.6 and an example of a dose-volume histogram (DVH) of bone dose is shown in Figure 3.8.

Whole bone V40Gy was slightly but statistically significantly reduced by a median 14% ($p<0.001$) with VMAT in all but five cases. The target of <64% was achieved in 90% of cases with VMAT, compared with 75% of cases with 3DCRT.

The dose constraint of whole bone mean dose ≤37Gy was achieved in 90% with VMAT and 86% with 3DCRT, with a borderline significant median reduction of 5% between paired plans favouring VMAT.

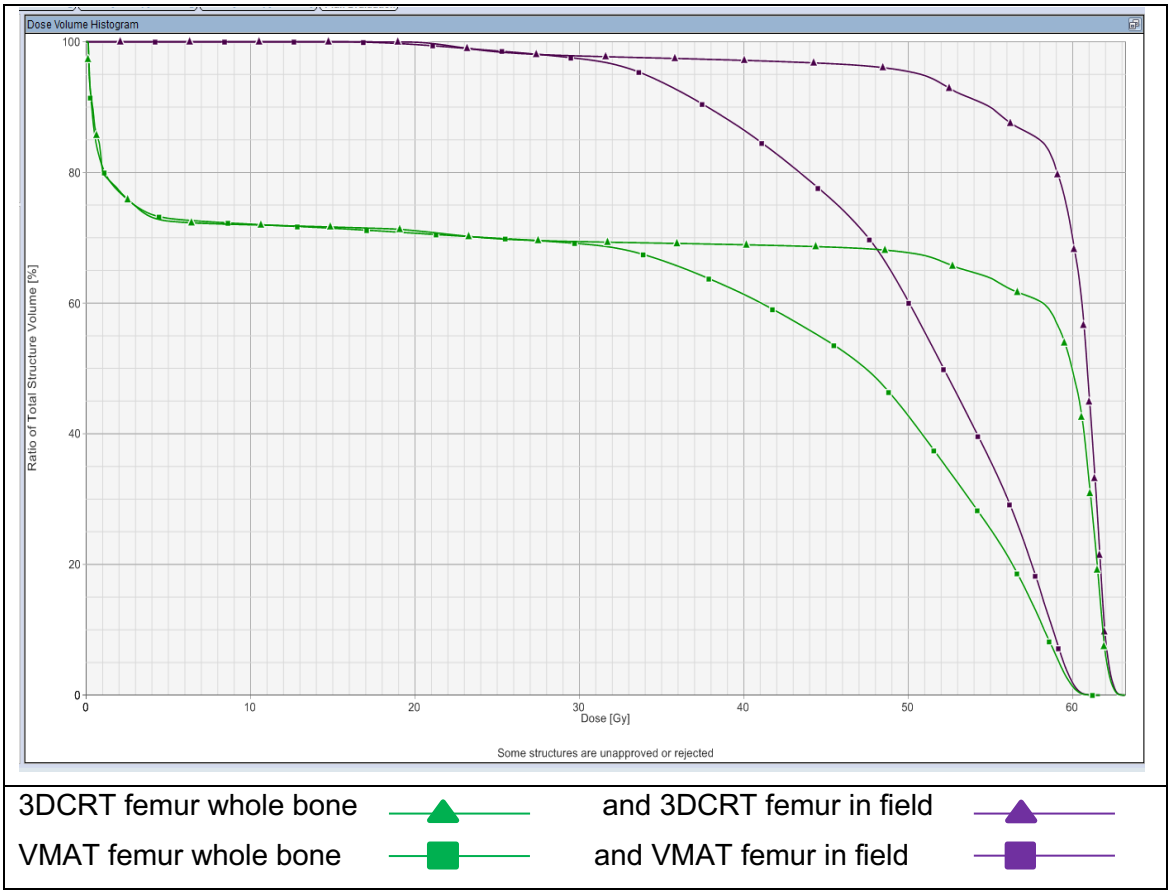
Both techniques achieved the whole bone maximum dose constraint of <59Gy in half of cases (11/21 3DCRT cases and 10/21 VMAT cases). There was a median 3% increase in the peak dose with VMAT.

The volume of bone in the treatment field receiving 50Gy was significantly reduced with VMAT to 29% compared to 57% with 3DCRT ($p<0.001$). The target of <50% was met by 76% of VMAT plans and 48% of 3DCRT plans. Reduction of hotspots in femoral head or head of humerus was possible for all 4 applicable cases with VMAT.

Table 3.6 Dose-volume parameters for bone

Dose parameter	Target	3DCRT		VMAT		Comparison between paired data Median (range)	*p* value
		Median	Range	Median	Range	Change in bone volume with VMAT (%)	
Whole Bone V_{40Gy} (%)	<64%	36	0-78	35	0-65	-14 (-81 to 92)	<0.001
	Target achieved:	16 cases (76%)		19 cases (90%)			
Bone in field V_{50Gy} (%)	<50%	57	0-95	29	0-90	-25 (-100 to 5500)	<0.001
	Target achieved:	10 cases (48%)		16 cases (76%)			
Whole bone maximum dose (Gy)	<59Gy	61	4-69	61	18-70	3 (-3 to 374)	0.001 < p < 0.005
	Target achieved:	11 cases (52%)		10 cases (48%)			
Whole bone mean dose (Gy)	<37Gy	23	1-42	26	2-40	-5 (-41 to 102)	0.05 < p < 0.1
	Target achieved:	18 cases (86%)		19 cases (90%)			
Femur head/ humerus head V60Gy (%)	<5%	3.5	0-17	0	0-5	-	-
	Target achieved:	4/4 cases (100%)		2/4 cases (50%)			
V50Gy = volume receiving 50Gy; V40Gy = volume receiving 40Gy							

Figure 3.8 Example of dose volume histogram curves for bone (FLG4, Posterior thigh)



3.4.4.4 Contralateral limb

In five cases the PTV involved the trunk or contralateral proximal leg and this could not be avoided. In the remaining 16 cases the median dose to the contralateral limb/ trunk was 3Gy (range 0-7Gy) with VMAT compared to 1.6Gy (range 0.1 – 3.5Gy) with 3DCRT.

3.4.4.5 Other normal tissue doses

These are summarised in Table 3.7. The advantage of VMAT is in reducing the high doses. Brachial plexus maximum dose was reduced in one case. Small bowel space, rectum, perineum and testicular maximum dose was reduced. Mean doses to these structures were similar. Lung and anal canal maximum and mean doses were similar.

Table 3.7 Maximum and mean doses for pelvic and thoracic organs

Organ/ parameter	Number of cases	3DCRT		VMAT	
		Median (Gy)	Range (Gy)	Median (Gy)	Range (Gy)
Brachial plexus Maximum dose	1	46		27	
Brachial plexus Mean dose		5		12	
Lung Maximum dose	3	3	1-13	3	2-9
Lung Mean dose		0.3	0.1-0.4	0.3	0.1-2
Small bowel space Maximum dose	3	58	50-63	44	9-63
Small bowel space Mean dose		3	2-4	2	1-9
Rectum Maximum dose	3	56	1-63	42	4-65
Rectum Mean dose		6	1-43	12	3-41
Anal canal Maximum dose	3	7	1-57	11	3-17
Anal canal Mean dose		4	1-24	7	2-10
Perineum Maximum dose	4	43	20-62	18	6-36
Perineum Mean dose		5	1-11	4	2-8
Testes Maximum dose	2	15	4-21	8	5-10
Testes Mean dose		3	3-3	3	3-3

3.4.5 Feasibility of VMAT for different anatomical subsites.

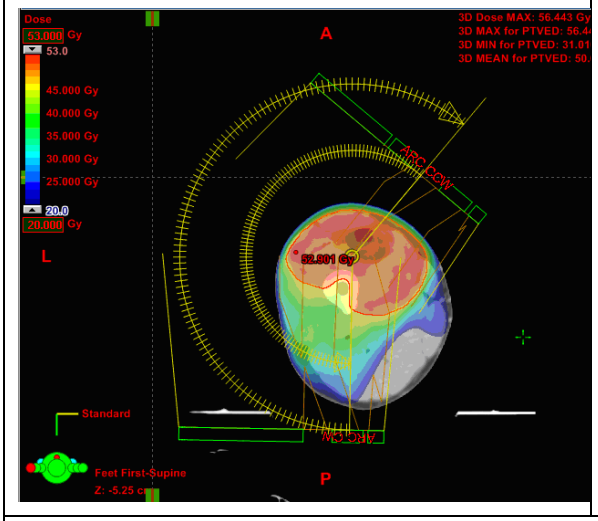
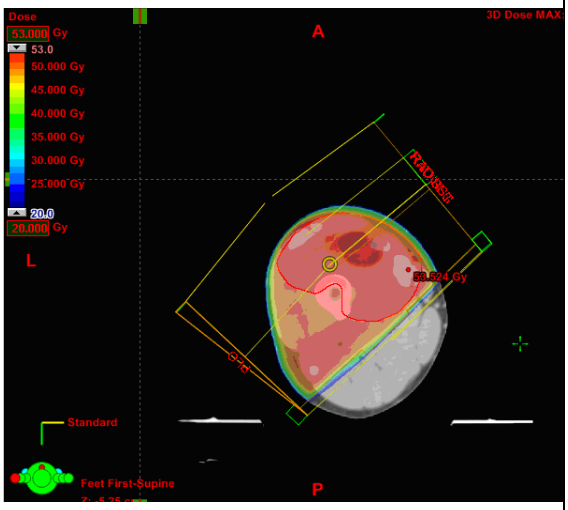
The different sites are discussed below with illustrative screen shots of the plans. In the dose colour-wash images high doses are reflected as red colour spectrum, medium dose as green and low dose as blue spectrum.

3.4.5.1 Anterior Thigh

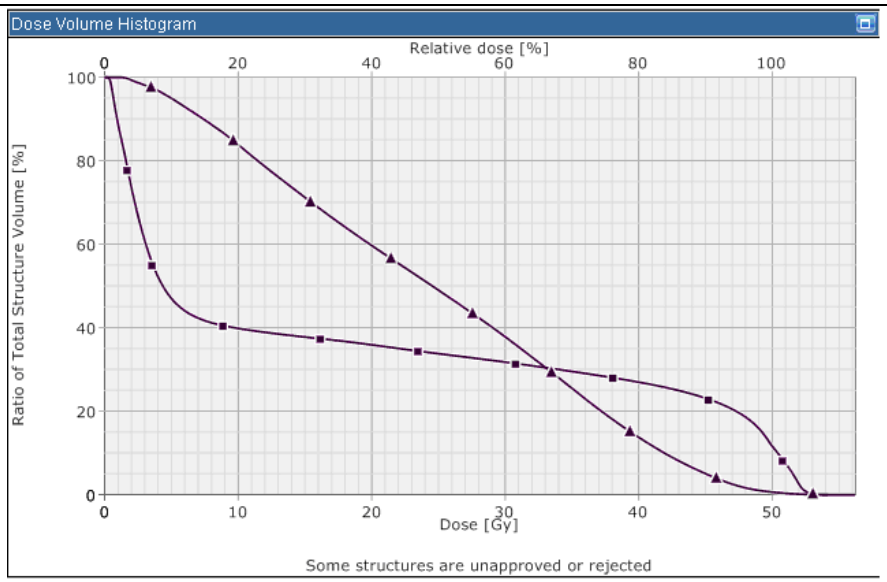
There was a large proximal thigh, a mid-thigh and a distal thigh tumour in this group. Two were treated post-operatively to 60Gy and 66Gy respectively, and one pre-operatively. VMAT plans were feasible for all, using two lateral partial arcs. PTV coverage was good. An example anterior thigh case is given in Figure 3.9.

It was difficult to spare bone in the treatment field even with VMAT, because the PTV was in contact with >50% of bone circumference in two cases and 100% in the third. The mean dose constraint to the whole bone was achievable for all with VMAT, and the V50Gy to bone in field was 45% for one of the cases. It was possible to spare the corridor with both VMAT and 3DCRT. Sparing of soft tissue outside the target was superior for VMAT. The least benefit in soft tissue sparing was seen for a small lateral tumour as the dose distribution was similar to that with 3DCRT fields.

Figure 3.9 Anterior thigh plan comparison and DVH (FLG1, pre-operative radiotherapy).

VMAT*	3DCRT*
	

*Dose colour-wash lower limit set at 20Gy



VMAT soft tissue outside PTV

3DCRT soft tissue outside PTV

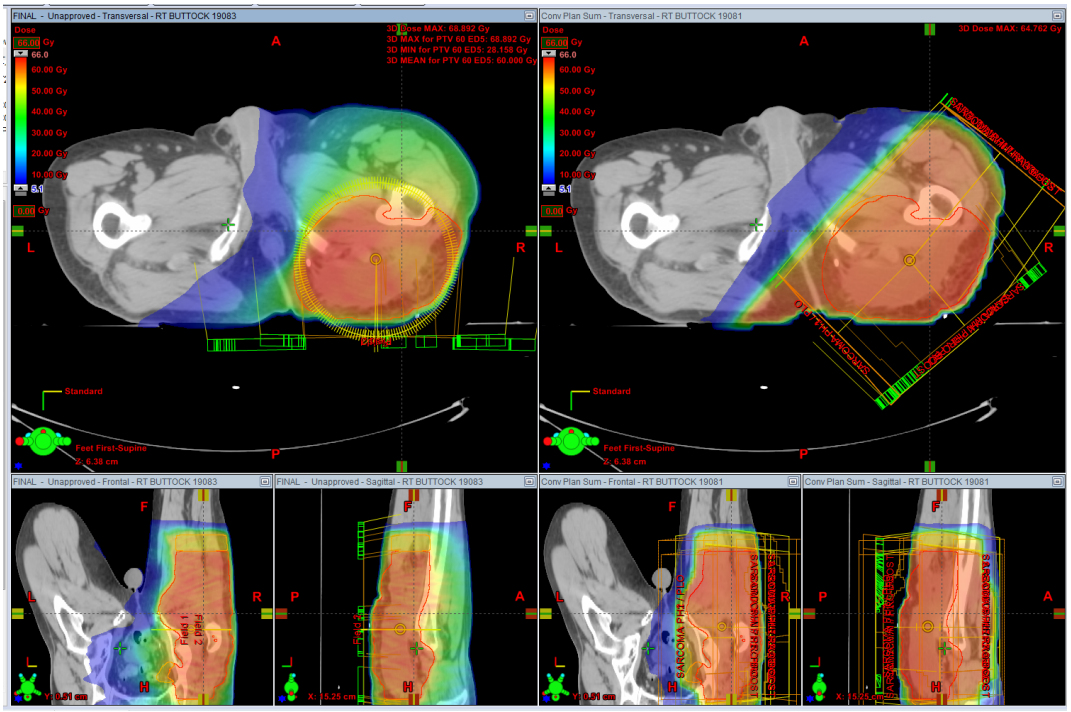
3.4.5.2 Posterior thigh

This site included a large proximal posterior thigh/buttock tumour treated post-operatively, and two mid posterior thigh cases, one pre-operative and one post-operative. VMAT plans were feasible with two partial arcs, but PTV coverage was challenging for the two large tumours especially at the posterior-medial aspect of the target. However, the PTV planning targets were met for 3DCRT and VMAT in all cases.

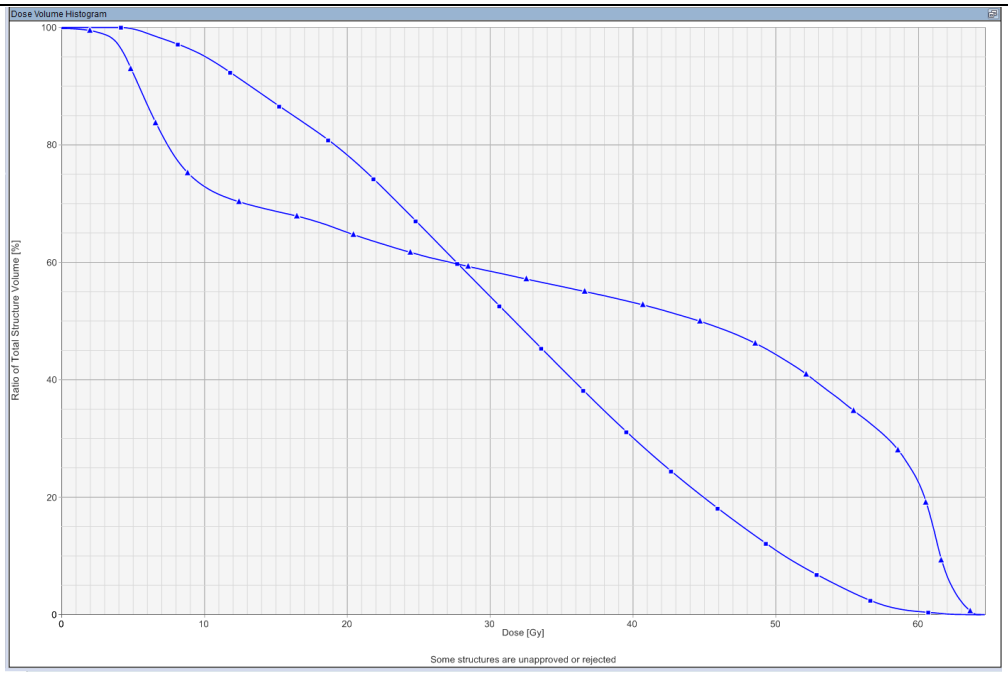
Bone sparing and soft tissue sparing with VMAT was good in the two mid-thigh cases. It was challenging in the case with a large proximal buttock tumour filling the posterior compartment and in contact with 100% of the bone circumference. Competing priorities in this case were the sparing of genitalia and pelvic organs. Soft tissue sparing and perineum dose was superior for VMAT, but the other organ doses could not be improved on. This case is shown in Figure 3.10.

Figure 3.10 Proximal posterior thigh plan comparison and DVH (FLG4, post-operative radiotherapy)

VMAT* 3DCRT*



* Dose colour-wash lower limit set at 5.1Gy



VMAT soft tissue outside PTV

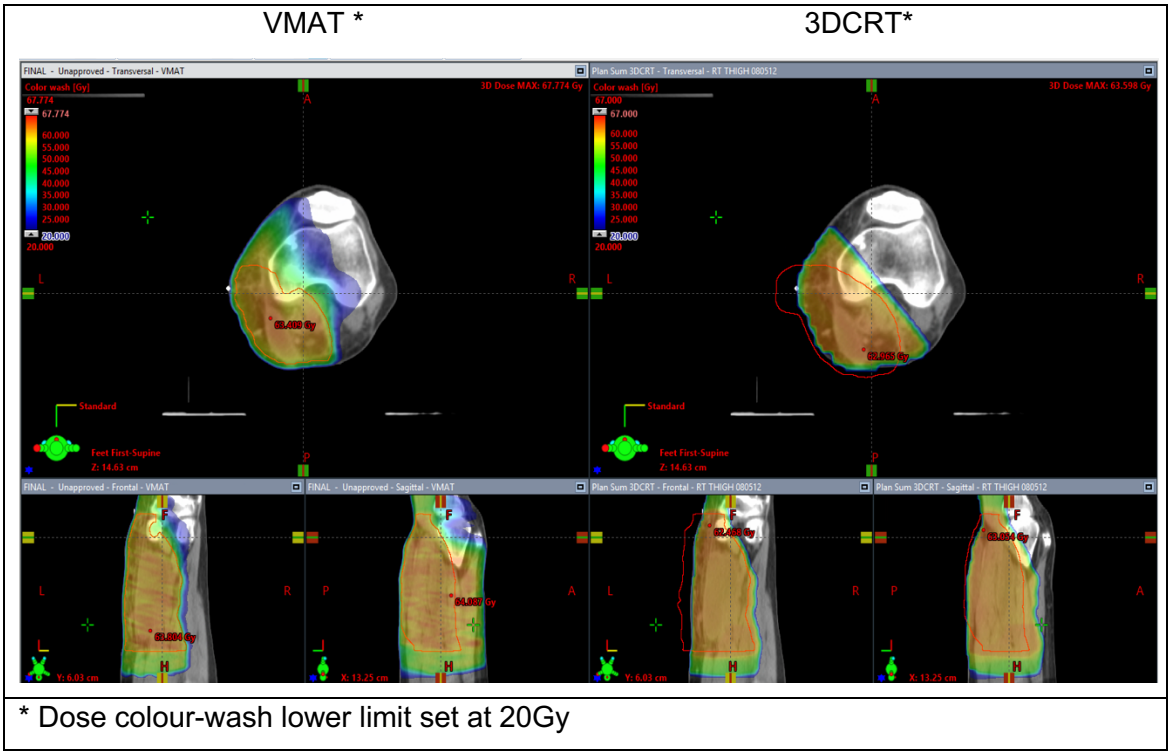
3DCRT soft tissue outside PTV

3.4.5.3 Adductor compartment thigh

At this site there were two large tumours and one smaller superficial tumour, all treated post-operatively. VMAT plans were feasible for all, using two partial arcs for the larger tumours, and only one arc in the smaller tumour. PTV coverage with VMAT was challenging for the proximal tumour in close proximity to pelvic organs, and it was difficult to reduce the dose to these. Bone sparing was difficult in two cases where the PTV wrapped around 50% of the bone circumference, but all parameters were met except maximum dose to bone.

The dose distributions were not dissimilar to the 3DCRT plans for the deep and large tumours at this site in order to spare a lateral corridor. Beam entry angles were limited to avoid the pelvis and contralateral leg.

Figure 3.11 Adductor thigh plan comparison and DVH (FLG7, post-operative radiotherapy).



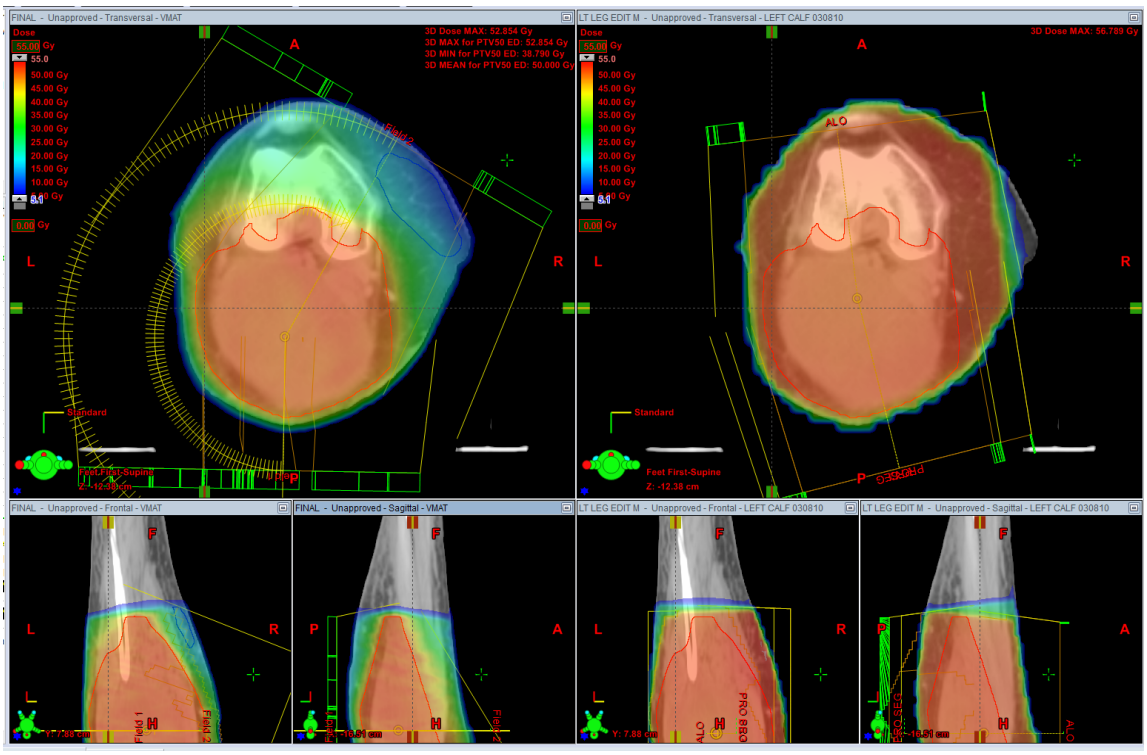
* Dose colour-wash lower limit set at 20Gy

3.4.5.4 Calf

There were two popliteal fossa tumours and one mid-calf tumour. All three were treated pre-operatively. 3DCRT planning had been with anterior – posterior fields or a lateral opposed field pair with the contralateral leg positioned on a bridge. VMAT was feasible and PTV coverage was easily achieved with two partial lateral arcs. The positioning of the contralateral leg on a high bridge limited beam angles and there was risk of collision with the gantry. A low bridge was advantageous as it increased the potential beam angles posterior-medially.

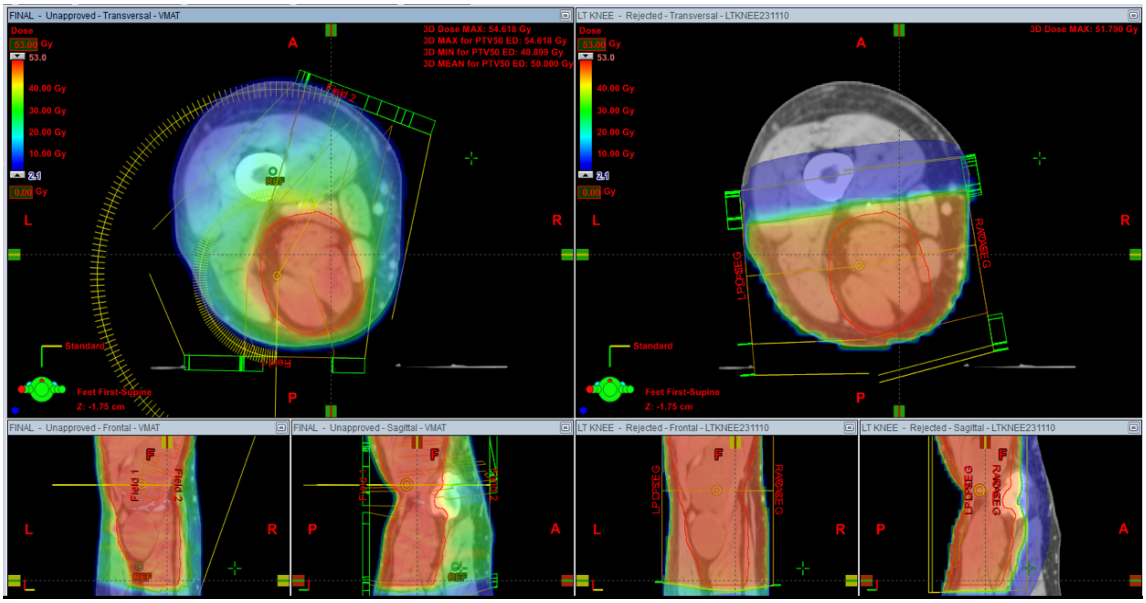
Soft tissue and bone sparing with VMAT were superior to 3DCRT even where PTV wrapped around >50% of the bone and some additional sparing of the knee joint and patella tendon was possible. Examples of VMAT compared with both a lateral opposed 3DCRT plan and an anterior-posterior opposed plan are shown in Figures 3.12 and 3.13.

Figure 3.12 Calf plan comparison (FLG11, pre-operative radiotherapy).



* Dose colour-wash lower limit set at 5.1Gy

Figure 3.13 Calf plan comparison (FLG12, pre-operative radiotherapy).

VMAT *	3DCRT*
	

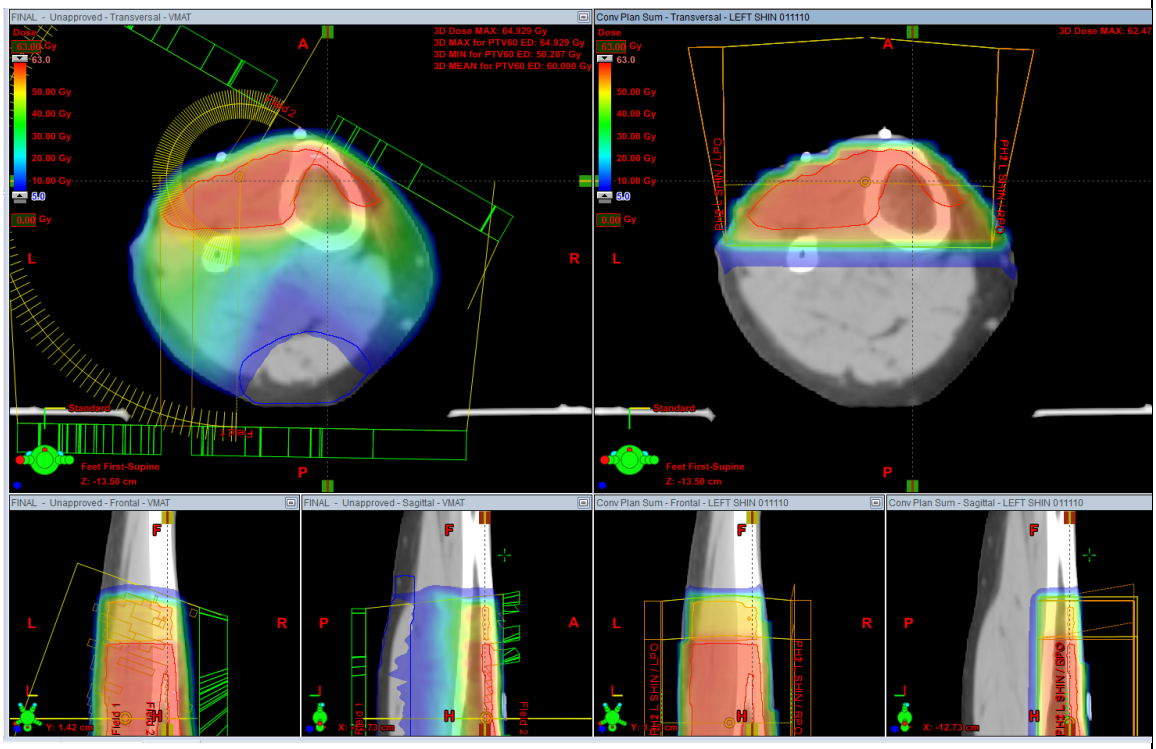
* Dose colour-wash lower limit set at 2.1Gy

3.4.5.5 Shin

In this group there were two distal tumours just proximal to the ankle, and one proximal shin case. Two were treated post-operatively and one pre-operatively. VMAT was feasible with one or two partial arcs and good resulting PTV coverage.

It was easy to spare the corridor and meet the soft tissue parameters, but for superficial tumours there was no significant benefit with VMAT in sparing soft tissue outside the PTV. Bone was more difficult to spare especially where PTV wrapped around it. VMAT gave better sparing of the knee and ankle joints than 3DCRT. Figure 3.14 demonstrated the bone sparing achieved with VMAT compared to a lateral pair of fields, and also shows the low dose bath.

Figure 3.14 Shin plan comparison (FLG13, post-operative radiotherapy).



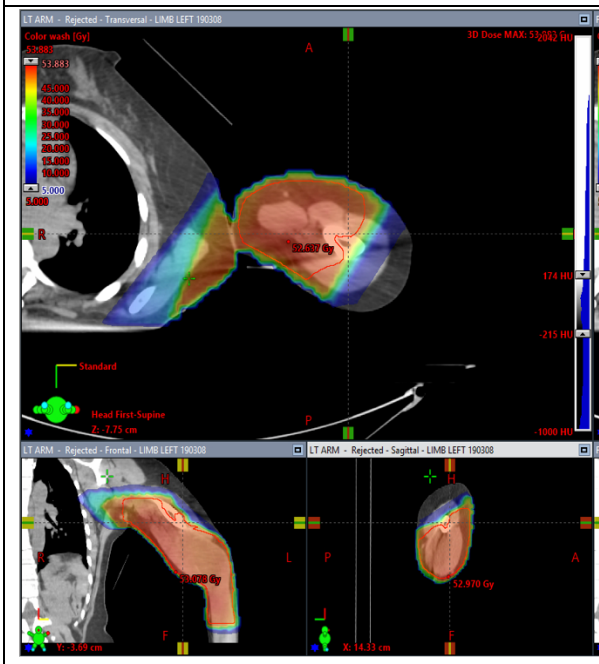
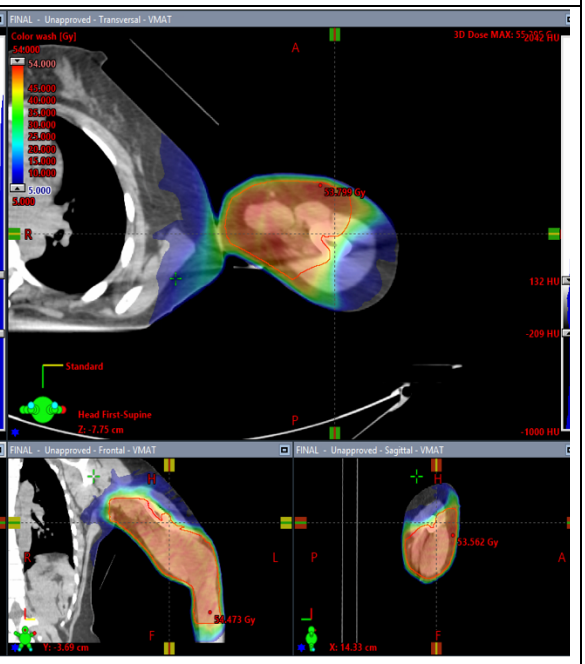
* Dose colour-wash lower limit set at 5.0Gy

3.4.5.6 Upper arm

One case was located in the proximal upper arm and two were near the elbow. Two were treated preoperatively and one post-operatively. VMAT plans were feasible with two lateral arcs and a couch/ floor rotation in all three, with good PTV coverage.

Corridor and soft tissue sparing were good with VMAT. Bone sparing depended on the circumference of bone in contact with the PTV. Lung doses were acceptably low. An example is given in Figure 3.15.

Figure 3.15 Upper arm plan comparison (FLG19, pre-operative radiotherapy).

3DCRT*	VMAT*
	

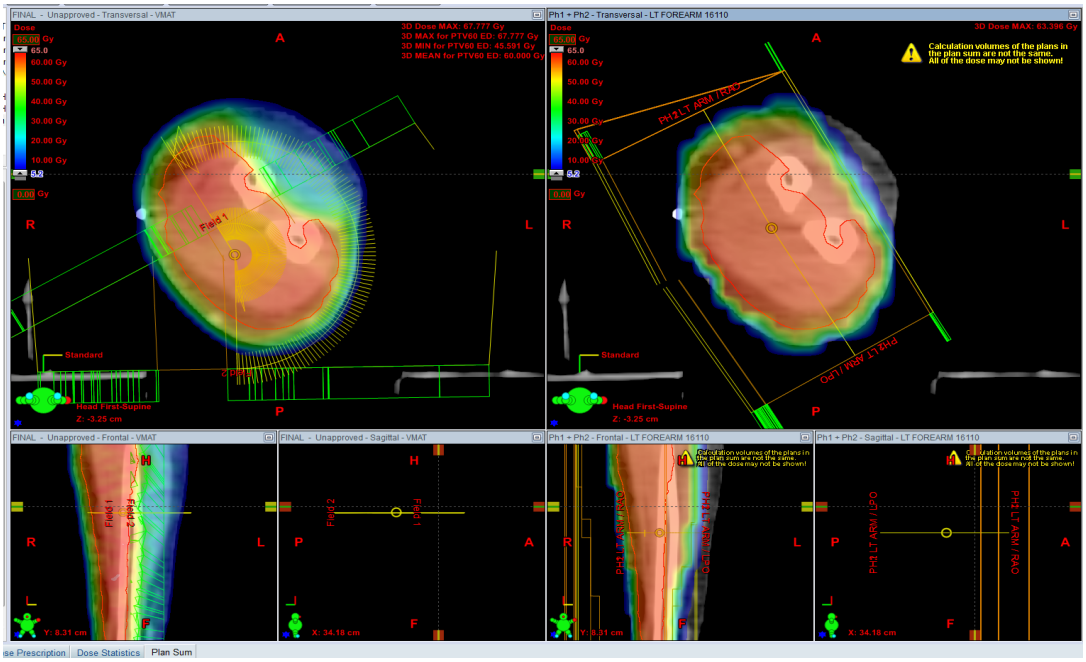
* Dose colour-wash lower limit set at 5.0Gy

3.4.5.7 Forearm

The three cases represented the proximal, mid and distal forearm. One was treated preoperatively and two postoperatively. VMAT plans were feasible using one or two partial arcs and achieved good PTV coverage.

This was subjectively the site that benefitted least from VMAT in terms of normal tissue sparing, probably because the forearm is the smallest of all the limb sub-sites. Corridor and soft tissue sparing were possible, but the dose distribution was not dissimilar to an anterior-posterior 3DCRT field pair. The tumours were typically wrapped around the radius and/or ulna which made it difficult to reduce bone dose, although bone dose was still lower than with 3DCRT. (Figure 3.16)

Figure 3.16 Forearm plan comparison (FLG21, post-operative radiotherapy).

VMAT*	3DCRT*
	

* Dose colour-wash lower limit set at 5.2Gy

3.5 Discussion

3.5.1 Feasibility and site-specific solutions

This double planning study has demonstrated that VMAT is a feasible technique to treat extremity soft tissue sarcomas. This was the case for all limb subsites, including the upper extremity, and in both the pre-operative and post-operative setting. Upper extremity sites had not previously been explored in any published double planning studies. In this study there was excellent PTV coverage as well as normal tissue sparing.

There was benefit to VMAT for anterior, posterior and medial thigh sites. Beam angles were however limited in the latter and particularly where PTV is in proximity to pelvic structures. In the lower leg, VMAT was particularly useful for calf sites. The value was less pronounced when treating the shin, where the dose distribution was not dissimilar to 3DCRT with opposed lateral fields. VMAT did offer some bone sparing in these cases but with low dose bath to much of the calf.

The heterogeneity of these tumours in terms of anatomical location, size and relationship with adjacent normal structures was again observed, and no formal site-specific solutions emerged. Plans were individualised for each case. Two lateral partial arcs were sufficient to achieve the planning targets in the majority of cases. A single partial arc could be sufficient in a proportion of small shin and forearm targets.

3.5.2 Potential challenges delivering VMAT and points to consider

3.5.2.1 Position of the contralateral leg

The position of the contralateral leg for lower limb sites is an important consideration. For 3DCRT the leg may be raised on a bridge to allow opposed lateral radiotherapy fields to the treated leg. Replicating this position may allow more entry and exit angles for VMAT for posterior and medial targets but could equally limit the anterior angles and also risk potential collision between couch and gantry. All cases in this planning study could be treated with either one or two lateral arcs. It therefore should be acceptable to position the contralateral leg on the couch in a neutral position, which is also likely to be the most reliably reproducible position. Dose to the contralateral leg was acceptably low, although in contrast to the 3DCRT plans, were slightly higher.

3.5.2.2 Monitor Units

It was possible to achieve acceptable PTV coverage without an increase in monitor units for the cases in this double planning study, on average 371 MU for VMAT compared to 393 MU for 3DCRT. This makes VMAT an attractive choice of IMRT technique in view of the concerns raised around fixed field IMRT with generally increased monitor units and estimated 0.25% additional increased risk of second malignancy because of this effect.(31) One of the planning studies of fixed field IMRT reports that the average MU used were 774 for the fixed field IMRT plans compared to 336 MU for 3DCRT plans.(77)

3.5.3 Dosimetric comparison

3.5.3.1 Target coverage

VMAT plans met all the dose constraints as specified for IMRT plans in ICRU report 83. (28). Homogeneity was acceptable for both techniques and was not statistically significantly different.

3.5.3.2 Normal soft tissue outside PTV in the treated limb

VMAT reduced the volume of normal tissue receiving moderate to high doses. This was statistically significant for all doses above 30Gy, and more marked for the very high dose range. This benefit was also seen with fixed field IMRT with significant reduction in V55 reported in one study, and a 78% reduction in V63 in another. (76, 77). This may translate into reduced late effects such as fibrosis and oedema and will be evaluated in the IMRiS study.

Maximum and mean doses to normal soft tissue were not significantly altered ($p>0.2$), reflecting the increase in normal tissue volume receiving low doses with VMAT. This was also seen in the published IMRT studies. (77, 83) The V20 was not significantly increased with VMAT in this comparison. The clinical relevance of the low dose bath below 20Gy in adult patients is likely limited to the risk of second malignancies in long term survivors which is modelled to be a 0.5% increase for VMAT and a 0.75% increase for fixed field IMRT.(31)

3.5.3.3 Corridor

The target of keeping the volume of the corridor receiving 20Gy below 50% was achievable in all but one case. During VMAT planning the position of the corridor was moved on occasion to improve the plan. The corridor is an optimisation structure rather than a true organ at risk, and the clinical relevance of this constraint has not been

established. It is used in the RTOG0630 trial and was subsequently included in the IMRiS protocol where its value will be prospectively explored.

3.5.3.4 Other normal soft tissues

The dose to the contralateral limb was acceptably low with VMAT. The maximum dose to the perineum, genitalia, pelvic organs and brachial plexus was reduced with VMAT.

3.5.3.5 Bone

VMAT was superior to 3DCRT to spare dose to the bones for endpoints clinically relevant to predict bone fracture risk in a retrospective review. (51) In this study, VMAT plans were able to achieve the bone tolerance targets of V40Gy <64% and bone mean dose ≤37Gy in 90% of cases. The V40Gy <64% was only met in 76% with 3DCRT, and the difference was statistically significant, as also seen for fixed field IMRT.(78) Whole bone mean dose was borderline significantly reduced with VMAT in the current series. A significant reduction was also seen in published fixed field IMRT series.(77, 78) In addition, the volume of bone in the treatment field receiving 50Gy was significantly reduced with VMAT to 29% compared to 57% with 3DCRT ($p<0.001$), and VMAT achieved the whole bone maximum dose constraint <59Gy in all but two cases where the PTV was in contact with a significant proportion of the bone circumference.

3.5.4 Conclusion

This planning study has demonstrated that VMAT is a feasible technique to treat extremity soft tissue sarcomas of upper and lower limbs in the pre-operative and post-operative setting. Target coverage was excellent and there was improved bone and normal soft tissue sparing in the medium to high dose ranges compared to 3DCRT. This dosimetric advantage may translate into a reduction in long term treatment related toxicity such as fibrosis, joint stiffness and lymphoedema. The clinical implication of the low dose bath seen with all IMRT techniques remains poorly understood in the adult population and is likely to be a small increased risk of second malignancies in long term survivors.

The experience gained in planning these cases with an IMRT technique was used in the development of the IMRiS trial. The normal tissue constraints used were demonstrated as achievable in the majority of cases and were included in IMRiS. Specific experience using VMAT was used to implement this as the preferred IMRT technique for treating extremity soft tissue sarcomas at UCLH.

4 Chapter 4 Double planning study comparing VMAT and PBT for the treatment of pelvic Ewing sarcoma

4.1 Introduction and literature review

The planning study discussed in Chapter 3 demonstrated the potential of VMAT to improve dose distributions, reducing the moderate to high doses to normal tissues while maintaining excellent target coverage in extremity sarcomas. This led to the question of whether advanced radiotherapy techniques offer similar benefits to improve the therapeutic ratio for sarcomas at other challenging anatomical sites? How effectively could it do the same for Ewing sarcoma in the pelvis?

4.1.1 Radiotherapy in the treatment of pelvic Ewing sarcoma

Radiotherapy is an important modality in the local treatment of the primary tumour in Ewing sarcoma, either in the pre-operative or post-operative setting or as definitive treatment for tumours that are not amenable to surgery. (13, 86-88) The recommended dose ranges from 45Gy to 66Gy depending on the timing of radiotherapy in relation to surgery. The average radical dose is around 55Gy.(87, 89)

Ewing sarcomas arising in the pelvis and in the spine are particularly challenging to treat with 3DCRT due to the proximity of sensitive normal tissues including the small bowel, spinal cord and genitalia. In children there are additional considerations about bone and soft tissue growth impairment and secondary cancers. At these sites, the challenge is dual: to reduce the dose to normal tissues but also to improve the coverage of the target to the optimal dose. An audit of 24 patients with pelvic (20 patients) and spinal (4 patients) Ewing sarcoma treated curatively with 3DCRT at UCLH between 2002 and 2012 highlighted this challenge: The optimal dose could safely be delivered in only 67% of cases because of the limitations of 3DCRT (unpublished data). The concern is that suboptimal doses may negatively impact local tumour control.

4.1.1.1 Side effects of 3DCRT in pelvic Ewing sarcoma

Indelicato et al reported a series of 75 patients with Ewing sarcoma, including 26 pelvic tumours, treated before 2007. Six patients developed fractures, having received doses

ranging from 50.4 to 60Gy in conventional 1.8 to 2Gy fractionation, and in 5 of these the radiotherapy field included the whole bone or pelvis. Other significant late complications seen in the pelvis included one case of haemorrhagic cystitis requiring cystectomy and one of osteoradionecrosis resulting in hip replacement. There were also two radiation induced osteosarcomas of the pelvis that developed at 7 and 17 years after treatment.(87) Paulino et al reported another retrospective series of 76 cases treated between 1976 and 2001, including only 13 pelvic tumours. Radiotherapy-related side effects at 5 years were seen in 12 of 24 patients (50%) who had received radiotherapy. Pelvic late effects included decreased hip rotation and flexion, and lumbar scoliosis.(90)

In the German CESS86 Ewing sarcoma trial, which recruited patients prior to 1991, radiotherapy was given post-operatively to 45Gy or definitively to 60Gy. Grade 3 to 4 late effects were seen in 4 of 44 patients treated to 60Gy: two patients developed chronic radiation proctitis for which one needed a colostomy; two patients developed pathological fractures and one vaginal stenosis.(91)

Fuchs et al published a retrospective series of 41 long-term survivors (minimum 20 years follow up) treated between 1960 and 1980 at the Mayo clinic, of whom 37 patients received radiotherapy. Twenty percent of cases were located in the pelvis. The majority (59%) had long-term treatment complications, with the complication rate increasing with time. Thirteen of the radiotherapy patients (35%) had late radiotherapy-related complications: two major wound complications requiring hip disarticulation, three with pulmonary fibrosis, two radiation induced cancers, two with neuropathy, two with leg length discrepancy, and one patient with femoral head necrosis requiring hip replacement.(92)

These studies all indicate relatively high rates of long-term radiotherapy complications in this young population treated with 3DCRT.

4.1.1.2 Pelvic radiotherapy and female fertility

Future fertility and premature menopause are important considerations when treating young patients with curative intent. Both chemotherapy with alkylating agents and radiotherapy contribute to gonadal dysfunction. Radiation effect on the ovaries depends on dose and the patients' age, with the risk of ovarian dysfunction increasing exponentially with rising age and radiation dose.(93-95) In young male patients sperm banking is offered, and this can be done without causing any delay to starting cytotoxic chemotherapy. The situation is more complex for female patients. Various techniques

including oocyte cryopreservation, ovarian tissue cryopreservation and embryo freezing are possible to preserve fertility, but these require invasive procedures and all inevitably cause a delay in initiating cancer treatment.(96) Ovarian transposition or translocation is used to surgically move one or both ovaries away from the target in an attempt to reduce the ovarian dose.(97) In addition to ovarian dysfunction, female patients treated with pelvic radiation are at risk of uterine dysfunction that could lead to complications in future pregnancies such as vascular insufficiency, placental problems, miscarriage, preterm labour, low birth weight, and placental abnormalities. (94, 98, 99) There are however very limited data regarding outcomes after treatment with advanced radiotherapy techniques, and no clear tolerance dose limit that would ensure normal uterine function.

4.1.2 Standard practice in the UK

Until recently, the standard approach to treat pelvic Ewing sarcoma has been with 3DCRT. Certainly, this was the case across NHS centres at the time of this work. As IMRT became more accessible in the UK, and the potential dosimetric benefit was demonstrated in other tumour sites, individual Ewing sarcoma cases were treated on an ad hoc basis. Cases were selected depending on limited clinical experience of the dosimetric effect and the availability of IMRT at specific centres, with no robust evidence base upon which to guide decision-making. In addition, since 2008, selected Ewing sarcoma patients have been able to access proton beam therapy (PBT) through NHS England Overseas Programme funding for treatment abroad.

4.1.2.1 Eligibility criteria for NHS funded PBT via the NHS England Overseas Programme

The eligibility criteria have since been extended, but in 2012 these were very limited. (75) Cases were only considered for curative indications, with a good life expectation of at least 40% 5-year survival and a WHO performance status 0-1. There should be no evidence of distant metastasis with the exception of rhabdomyosarcoma and Ewing's Tumours when this was confined to the lung and good partial response was evident at the initial radiological reassessment after chemotherapy. Eligible tumour types and sites at the time are listed below:

Adult

- base of skull & spinal chordoma
- base of skull chondrosarcoma
- spinal & paraspinal bone and soft tissue sarcomas

Paediatric

- base of skull & spinal chordoma
- base of skull chondrosarcoma
- base of skull, spinal & paraspinal bone and soft tissue sarcomas
- orbital rhabdomyosarcoma
- parameningeal rhabdomyosarcoma
- retinoblastoma
- pineal
- sarcomas arising from the pelvis (pelvic Ewing sarcomas)
- central optic path and selected low grade glioma.

Adult patients with pelvic Ewing sarcoma were not routinely eligible for PBT at the time. For ineligible patients or those not able to travel abroad for any reason, either 3DCRT or IMRT were used. The criteria have since been updated to include patients up to the age of 24 with diagnoses on the paediatric indications list, but many adult patients older than 24 years remain ineligible.

4.1.3 Evidence for the use of PBT – general aspects

The evidence base for the use of PBT is growing. Many poorly understood aspects remain that may have implications for the biological effect of protons, but the main benefits that triggered the implementation of PBT internationally and the development of a UK proton service, are the physical properties of this particle and the consequent dosimetric effect. With PBT there is a significant reduction in the volume of normal tissue exposed to low doses compared to 3DCRT or IMRT.(83, 100, 101) This has the potential to reduce the late side effects of radiotherapy, as well as the risk of radiotherapy-induced second cancers.(36, 37, 102) These benefits are particularly important for paediatric malignancies, as reflected in the proton panel eligibility criteria, and despite the lack of long-term clinical outcome data, PBT has become the treatment of choice for many paediatric indications.(39) A further benefit is that PBT can enable delivery of higher prescription doses while maintaining safe normal tissue doses in certain cancers requiring high radiotherapy doses (such as chordomas and chondrosarcomas), with the potential to improve cancer outcomes and toxicity profiles (103).

4.1.4 Evidence for the use of advanced techniques (IMRT and PBT) in pelvic Ewing sarcoma

The literature on advanced radiotherapy techniques in patients with pelvic Ewing sarcoma consists of three heterogenous retrospective series (one used PBT and two used IMRT), and two small planning studies, and is described below. The total number of pelvic tumours in the retrospective series' combined is 36, and the data are therefore at most anecdotal, but they do indicate the kind of late effects patients experienced after this treatment.

4.1.4.1 Evidence for IMRT in Ewing sarcoma (particularly pelvic tumours)

There are 2 retrospective series that include patients treated with IMRT.
The first series reporting on 31 paediatric and adolescent patients treated for a heterogenous group of tumours with IMRT between 1991 and 2008 in Heidelberg included 5 patients with Ewing sarcoma, one located in the pelvis. The following late effects were seen: scoliosis (1), sensory change in the forearm (1), enophthalmia (1), with a median follow up of 34 months (range 1 - 68).(104)

A second series of 60 patients with Ewing sarcoma, treated at Memorial Sloan Kettering hospital between 1990 and 2004, included 26 patients (43%) treated with IMRT. Actuarial 3-year local control rate was 77%. The radiotherapy technique (2D vs. 3DCRT vs. IMRT) had no impact on local control rates. Median dose was 51Gy (range 30 to 60Gy). There were 15 pelvic cases in this series. Median follow up was 41 months (6 months to 14 years). Late effects included: growth retardation of the treated extremity (2), death from pulmonary fibrosis 17 months after radiotherapy (1), and further minor musculoskeletal effects.(105) An update of this series was subsequently published to include patients treated up to 2012 at which point 109 patients were included. Median follow up was slightly longer at 4.8 years (range 1 to 17.5 years.) Thirty-three pelvic tumours represented 30% of the cohort. The median dose was 55.8Gy (range, 27–66Gy). IMRT was used in 58% reflecting the increase in use of IMRT during this period. The 5-year local failure rate was 18%. Involved surgical margins was the only predictive factor for local failure. 5-year event free survival was 36%, and 5-year overall survival was 54%. Pelvic site, tumour size and histopathologic response to chemotherapy were prognostic. There was one case of radiotherapy-related lung cancer 13 years after treatment. This paper did not comment on other late effects of radiotherapy.(13)

4.1.4.2 Evidence for PBT in Ewing sarcoma (particularly pelvic tumours)

A retrospective review of 30 children with Ewing sarcoma treated with PBT at Massachusetts General Hospital between 2003 and 2009 included only five pelvic tumours. Three-year actuarial event free survival, local control, and overall survival rates for the series were 60%, 86%, and 89%, respectively. The median prescribed dose was 54Gy (range 45 to 59.4Gy) delivered in 1.8Gy per fractions. Median follow up was 38.4 months (range 17.4 months to 7.4 years). The authors reported that PBT was well tolerated with a low incidence of side effects. Five patients had a grade 3 acute skin reaction. Late effects observed included five spinal deformities, one leg length discrepancy, one case of telangiectasia with nose bleeds, two patients with eye lid late effects, two with endocrine deficiencies and unilateral high frequency hearing loss in one.(106)

4.1.4.3 Planning studies in Ewing sarcoma of PBT and IMRT

Mounessi et al published the only planning study in this population, of 8 pelvic Ewing sarcoma cases that were double planned with 3DCRT and IMRT and demonstrated a dosimetric advantage of fixed field IMRT over 3DCRT. Doses ranged from 45 to 59.4Gy with a median dose of 54Gy. IMRT achieved statistically significant reductions in the volume of rectum receiving doses above 45Gy, the mean and maximum dose to small bowel, as well as the volume of small bowel receiving more than 20Gy. There was no significant difference in bladder dose between the two techniques. A larger volume of normal tissue received low doses (V2Gy) with IMRT.(107)

A single planning study of IMRT compared with PBT included 3 paediatric pelvic sarcomas (1 osteosarcoma, 1 rhabdomyosarcoma and 1 Ewing sarcoma) treated to moderate doses ranging from 36 to 45Gy, lower than the average dose used to treat pelvic Ewing sarcoma. 3DCRT, fixed field IMRT and single field PBT plans were compared. All 3 techniques achieved good target coverage. There was a reduction in dose to the ovaries with PBT. The percentage bowel dose was not significantly different between techniques at 30Gy, 40Gy and 45Gy. IMRT was superior for bladder sparing. Spinal cord dose was lowest with PBT. The dose to femoral heads with all techniques was close to 0%.(108)

The literature indicates that both IMRT and PBT achieve good local tumour control rates, with dosimetric advantages for IMRT over 3DCRT. There is also some limited evidence for additional advantages to PBT for normal tissue sparing, but given the limited studies to date, there was a need for more work to compare these techniques in the setting of pelvic Ewing sarcoma and clarify the relative benefits of IMRT and PBT.

4.2 Background and purpose of this study

It is clear that 3DCRT is not a reliable technique to deliver the required radiotherapy dose for a significant proportion of patients, but the published retrospective series and planning studies offer a very limited understanding of the relative value of different advanced radiotherapy techniques in this patient population. At the time of this study, paediatric patients treated with curative intent and adults with paraspinal tumours were being offered PBT based on modelling studies and assumed anticipated benefits. However, there was not a clear understanding of how IMRT and PBT compared dosimetrically. In addition, the value of IMRT for the remaining patients not eligible for PBT, particularly pelvic tumours, was also not clear. This lack of evidence meant that access to IMRT across the UK varied between centres. Furthermore, with the increasing use of PBT internationally, it was unlikely that there would be future prospective studies of IMRT in this setting.

The IMRiS trial was being developed to prospectively investigate IMRT in UK patients with extremity soft tissue sarcomas. A second cohort was included in the protocol to explore the value of IMRT in pelvic and spinal Ewing sarcomas and generate the necessary evidence to implement IMRT in a quality assured setting across the country for these patients (Chapter 5).(56)

This planning study was thus undertaken for several reasons:

- To assess the feasibility of PBT as well as VMAT, the preferred IMRT technique at UCH, in pelvic Ewing sarcoma and to explore the benefits and limitations of each technique
- To facilitate and inform development of a prospective trial protocol (IMRiS) in this patient cohort
- To compare VMAT dosimetrically with PBT
- To assess the value of VMAT and PBT to limit doses to adjacent normal structures while optimising target volume coverage
- To gain experience of PBT planning in anticipation of opening one of the two planned NHS proton beam facilities at UCLH.

4.3 Materials and methods

This double planning study was developed in Spring 2014. Ethics approval was granted by the Proportionate Review Sub-committee of the NRES Committee London – Bloomsbury.

4.3.1 Study aim

- To assess feasibility of VMAT and PBT as treatment for Ewing sarcoma of the pelvis
- To compare dosimetry of IMRT and PBT in treatment of Ewing sarcoma of the pelvis
- To compare the ability of PBT and VMAT to deliver the prescribed dose to CTV or PTV
- To compare ability of IMRT and PBT to achieve fertility preservation in female patients by sparing of ovaries and uterus
- To compare the ability of IMRT and PBT to reduce dose to the small bowel, rectum, bladder and femoral head and neck.

4.3.2 Study design

A double planning study using anonymised radiotherapy planning datasets from cases previously treated at UCLH to generate and compare VMAT and PBT plans for comparison.

4.3.3 Study endpoints

- PTV coverage (D100%, D98%, D95%, D2%) of VMAT plans
- CTV coverage of PBT plans (CTV mean dose)
- Homogeneity of dose
- Normal tissue dose/volume parameters
    - Bowel space V_{45Gy}
    - Bowel space mean dose
    - Rectum V_{50Gy}
    - Bladder V_{50Gy}
    - Femoral head mean dose
    - Ovarian mean dose
    - Uterus mean dose
    - Vagina mean dose

4.3.4 Case selection

Cases were identified from a retrospective clinical database of patients treated with radiotherapy for sarcomas at UCLH.

Inclusion criteria

- Patients treated for primary Ewing sarcoma of the pelvis with 3DCRT plans
- Only female patients were included to enable evaluation of the ability of VMAT and PBT to reduce dose to the ovaries and uterus.

Exclusion criteria

- Large volume metal implants or fixation devices in the target area or near sensitive structures where there would be uncertainty about the ability of the planning system to calculate the dose accurately
- Where the 3DCRT CT and plan data could not be retrieved from the archive

4.3.5 Plan generation

Radiotherapy planning scan datasets were retrieved from the UCLH radiotherapy department archive of *Oncentra Masterplan v4.1*, anonymised and imported into the *Varian Eclipse v10* planning system. The original CT dataset and original contours outlining the target volumes and organ at risk volumes were included. Normal tissue structures were outlined by myself, and I generated the VMAT plans in collaboration with senior radiotherapy physicists Rachel Bodey and Chris Stacey. The identical CT dataset and structure sets were also imported to *Varian Eclipse v10* with *Proton Convolution Superposition version 11.0.31* algorithm. Pencil beam proton plans were generated by Richard Amos, senior proton radiotherapy physicist.

4.3.5.1 Target volumes

The original 3DCRT GTV and CTV were used. The volumes were evaluated to confirm that they conformed to standard practice and the IMRiS trial protocol.(56, 89)

GTV (gross tumour volume)

This was outlined based on the pre-treatment maximum tumour extent at presentation prior to any chemotherapy or surgery. A reconstructed GTV was created in patients treated post-operatively, taking changes in normal anatomy after surgery into account.

CTV (clinical target volume)

This volume included the GTV with a margin for suspected microscopic extension

Pre-operative or definitive radiotherapy:

The CTV was created by adding a margin of 1.5 to 2 cm around the GTV in all directions, taking patterns of spread and intact skin, fascial barriers and bone into account. The skin was only included if it was involved.

Post-operative radiotherapy:

The post-operative CTV was created by adding a margin of 1.5 to 2 cm around the reconstructed GTV in all directions taking patterns of spread and intact skin, fascial barriers and bone into account. It was extended to include all areas at risk of microscopic spread or surgical contamination. This included metallic prostheses, drain sites and surgical scars.

PTV (planning target volume)

The PTV margin to take into account uncertainties in set-up and patient movement, was created by expanding the relevant CTV in all directions with a body-site specific margin that depended on the immobilisation used and departmental set-up reproducibility, 5mm in this case.

VMAT PTV:

The original 3DCRT PTV was edited, cropping it to 5mm within skin/body as per standard VMAT planning practice.

PBT uncertainty margin:

The traditional concept of PTV as defined for photon radiotherapy (27, 84) does not apply in the same way to PBT. The uncertainties are different and include not only daily positioning and motion errors but also uncertainty around beam range that is specific to each individual proton beam within the plan. The range uncertainty is influenced by the different density tissues the beam travels through with changes in patient positioning and organ motion. For the purpose of this planning study, the 5mm lateral PTV margin was taken into account to guide the width of the PBT beams but the plans were not optimised to the original PTV. Beam angles were chosen to minimise the risks of range uncertainty. The final plan was optimised in a robust way to take the range uncertainty with potential setup errors in different directions into account.(109, 110)

4.3.5.2 Dose prescription

A prescription dose of 54Gy in 30 fractions of 1.8Gy per fraction was used in this study. This is consistent with standard practice for post-operative and definitive radiotherapy for Ewing sarcoma.

- VMAT plans were prescribed to the mean PTV volume
- PBT plans were prescribed to mean CTV volume and dose is expressed in Cobalt Gy Equivalent (CGE) to reflect the proton Relative Biological Effectiveness (RBE) of 1.1.(111)

4.3.5.3 Normal tissue structures and dose constraints

The normal structures and organs at risk (OAR) outlined are shown in Table 4.1. Dose constraints were according to accepted QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic)(25) and Emami guidelines(23, 24) as well as specific literature on constraints for the femoral head and neck and reproductive organs. No constraint was applied to the cauda equina and sacral nerve roots as the prescription dose was within the tolerance of these tissues. (23)

The planning goals were to optimise target coverage while limiting the dose to the normal tissues as much as possible and certainly within the constraints for acceptable incidence of late effects.

Table 4.1 Normal tissue structures and dose constraints

Normal tissue/ OAR	**Outlining definition**	**Absolute and ideal dose constraints**
Bowel space	The entire axial peritoneal space in which bowel loops can move (whole space not covered by planning scan in all cases)	V_{45Gy} <195cc (absolute limit), predicts <10% acute toxicity (112) There is a volume effect. Aim for low dose and small volume *Constraints to a specific volume of the whole small bowel, as per Emami et al, were not useful as the entire small bowel space was not always available if planning scans only included a part of it.(23, 24)*
Rectum	From the recto-sigmoid junction to the anal verge	V_{50Gy} < 50% (24, 113)
Bladder	Entire organ	V_{50Gy} ≤ 50% (114)
Femoral head	From the top of the femur to just below the lesser trochanter	Mean dose <40Gy (115)
Ovary (bilateral)	Entire organ	Aim for no dose If complete avoidance not possible the aim for Mean dose <4Gy (95, 97) to at least one of the 2 ovaries Literature suggests late effects may develop after very small doses <2Gy(94)
Uterus	Entire organ	Aim for mean dose <10Gy *No agreed limit in the literature. Aim for as low a dose and as small a volume as possible (94)*
Vagina	Entire organ	*No agreed limit in the literature. Avoid as much as possible*
Normal tissue outside target (integral dose)	External body contour minus PTV	As low as possible

4.3.6 Data collection

Dosimetric data:

- PTV coverage parameters of VMAT plans as per the study endpoints (section 4.3.3)
- CTV coverage parameters of PBT plans (CTV mean dose)
- Homogeneity of dose according to the formula:

  Inhomogeneity coefficient = (D2% - D98%) / D50%

  Where D2% = the dose to 2% of the PTV (hotspot); D98%= the dose to 98% of the PTV (cold spot); D50% = the dose to 50% of the PTV
  A result of $\leq$0.17 indicates acceptable homogeneity

- Normal tissue dose/volume parameters for bowel space, rectum, bladder, femoral heads, ovaries, uterus and vagina as per the study endpoints (section 4.3.3)
- Integral dose

Qualitative data:

- Advantages and challenges of PBT and VMAT at this site
- Qualitative plan assessment performed by myself with input from the physics team and Dr Beatrice Seddon (MD supervisor)

Statistical considerations

Data were entered into an Excel spreadsheet. Dose volume parameter results were evaluated using the Wilcoxon signed-rank non-parametric test for paired data. Statistical significance was defined as a p-value <0.05 and borderline significance as p-value >0.5 and <0.1.

4.4 Results

4.4.1 Cases

Ten female patients with pelvic primary Ewing sarcoma treated between September 2006 and December 2014 were included. The median age was 19 (range 16-34). Nine had originally received definitive radiotherapy and one neo-adjuvant treatment prior to surgery. This patient received 50.4Gy, but for the purposes of this study was planned to 54Gy as for the definitive radiotherapy cases.

The cases are shown in Table 4.2. The volume of the CTV ranged from 216.9 cm^3 to 1318.7 cm^3 (median 786.6; mean 748.4). One patient with an ipsilateral proximal femoral replacement after resection of a pubic ramus tumour was included as the prosthesis was just adjacent to CTV but not within it. Three patients had ovarian transposition of one or both ovaries prior to radiotherapy. The right ovary was in the PTV target in 2 patients and was therefore not defined as a separate normal tissue structure in these cases. Three patients with tumours of the iliac bone had a pelvic spacer inserted to move the small bowel away from the target.

Table 4.2 Pelvic Ewing sarcoma planning cases

Case	Site	Laterality	CTV volume (cm^3)	VMAT PTV volume	Ovarian transposition	Notes
1	Ilium	Across midline, predominant on left	930.35	1348.17	No	Spacer used
2	Ischium	Unilateral	979.92	1362.74	Yes (both)	
3	Ischium	Across midline	915.06	1320.29	No	
4	Pubic ramus	Unilateral	216.92	413.59	Yes (right ovary)	Ipsilateral proximal femoral prosthesis
5	Ilium	Unilateral	1318.7	1737.83	No (right ovary in PTV)	Spacer used
6	Sacrum	Across midline	338.94	790.91	Yes (both)	
7	Sacrum	Across midline	356.67	607.25	No	
8	Sacrum	Across midline	1222.31	1558.58	No	
9	Ilium	Unilateral	658.07	952.94	No (right ovary in PTV)	Spacer used
10	Sacroiliac joint	Unilateral	547.29	828.52	No	

4.4.2 Planning technique

4.4.2.1 VMAT

VMAT plans were created using two full or partial arcs, using an iterative inverse planning approach. The planning goal was to reduce the dose to normal structures as much as possible without compromising target coverage.

4.4.2.2 PBT

PBT plans were generated using an intensity modulated proton therapy (IMPT) technique with multi-field optimization of two or three pencil beam scanning fields. Dose was prescribed and reported to the mean CTV volume. A positional uncertainty of 5 mm and proton range uncertainty of 3.5% were used to robustly analyse the CTV coverage with the majority of potential CTV worse case scenarios adequately covered by the 95% isodose. Robustness was assessed for 12 potential situations: positive and negative shifts in x (anterior/posterior), y (lateral), and z (cranio-caudal) directions as well as a 3% increase or decrease in Hounsfield numbers for each shift. Dose is reported as Cobalt Grey Equivalent (CGE) for a proton Relative Biological Effectiveness (RBE) of 1.1 reflecting a 10% increase in biological effect.(111)

Dose-colourwash images of the 10 cases are presented in Figure 4.1

4.4.3 Target dose parameters and homogeneity

Plans were visually assessed for acceptable dose distributions as well as dosimetrically analysed. The results are presented in Table 4.3. PTV coverage was acceptable for all cases and plans met all the dose constraints as specified for IMRT plans in ICRU report 83 (28), and according to robust analysis for the PBT plans. Homogeneity was excellent with both techniques.

Table 4.3 Target coverage and homogeneity of VMAT and PBT radiotherapy plans

VMAT PTV coverage			
Dose parameter	PTV coverage target value	Coverage achieved	
		Median	Range
$D_{98\%}$ [%]	≥ 90%	95	94-96
$D_{95\%}$ [%]	≥ 95%	96	96-97
$D_{50\%}$ [%]	= 100%	100	100-101
$D_{2\%}$ [%]	≤ 107%	103	103-104
Inhomogeneity coefficient	≤ 0.17	0.09	0.08-0.1
PBT CTV coverage			
Inhomogeneity coefficient	≤ 0.17	0.02	0.02-0.1
CTV mean dose [CGE]		55.3	55.0 – 55.8
D98% = percentage dose to 98% of the volume; D95% = percentage dose to 95% of the volume; D50% = percentage dose to 50% of the volume; D2% = percentage dose to 2% of the volume			

Figure 4.1 Dose-colourwash images for VMAT and IMPT radiotherapy plans

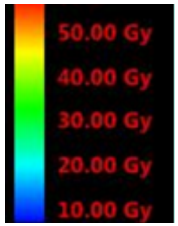
Colour wash lower dose cut-off in these images:
Case 1: 6.4Gy
Case 6: 5.8Gy

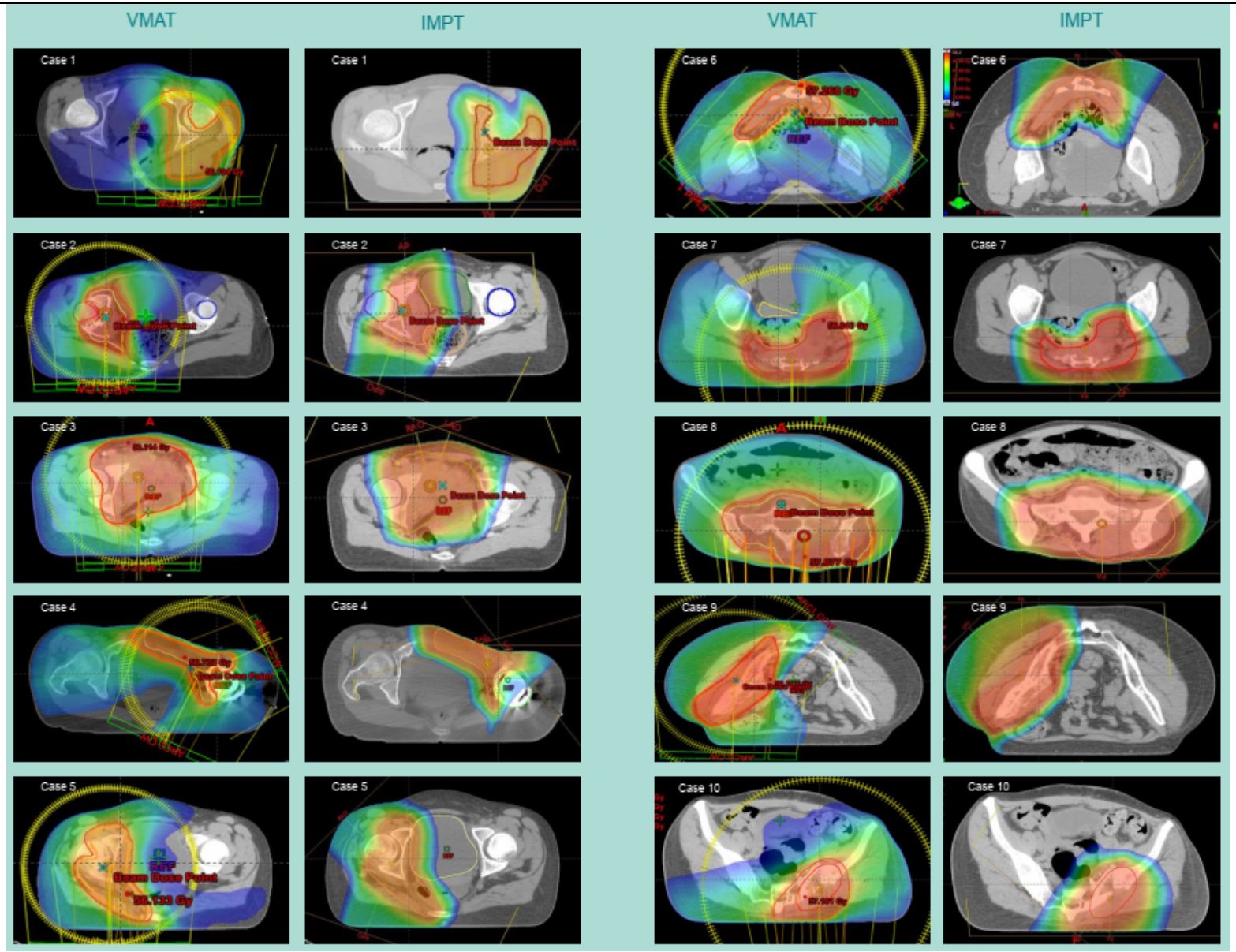
Case 2: 5.7Gy
Case 7: 10.8Gy

Case 3: 5.7Gy
Case 8: 12.4Gy

Case 4: 10.6Gy
Case 9: 10.3Gy

Case 5: 6.1Gy
Case 10: 5.8Gy





4.4.4 Normal tissue sparing

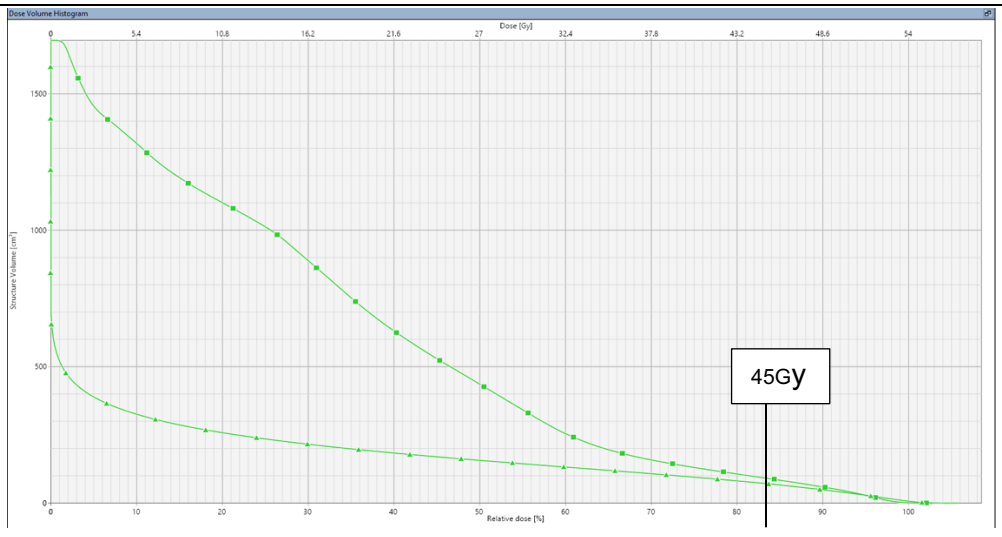
Bowel space

There was no significant difference in the volume of small bowel receiving 45Gy or more between techniques, with PBT achieving a non-significant median reduction in the V_{45Gy} of 13.8% compared with VMAT ($p<0.2$), and an increase seen in three of the cases with PBT. Both techniques were able to keep below the target volume of V_{45Gy} <195cm^3 without the need to compromise PTV coverage. The mean bowel dose was significantly reduced with PBT ($p<0.001$). Results are shown in Table 4.4 and an example Dose-Volume Histogram for one of the cases is shown in Figure 4.2.

Table 4.4 Dose-volume parameters for bowel space

Dose parameter	Target	PBT		VMAT		Comparison between paired data	
		Median	Range	Median	Range	Median difference (%) (range)	*p* value
Bowel space V_{45Gy} (cm^3)	<195cm^3	14.6	0-181	21.5	0.4-182	13.8% reduction with PBT (-18 to 100)	>0.2
	Target achieved	All cases		All cases			
Bowel space mean dose (Gy)	-	1.5	0-6	6	1-18	67% reduction with PBT (23 to 100)	<0.001
V45Gy = volume receiving 45Gy							

Figure 4.2 Example of dose volume histogram curves for bowel space (Case 1)



Rectum

There was no significant difference in V50Gy to the rectum between the two techniques (p>0.2). In three cases the V50Gy was lower with VMAT, and in seven it was lower with PBT. Both techniques met the target for all cases. Results are shown in Table 4.5 and in the Dose-Volume Histogram in Figure 4.3.

Table 4.5 Dose-volume parameters for rectum

Dose parameter	Target	PBT		VMAT		Comparison between paired data	
		Median	Range	Median	Range	Median difference (%) (range)	*p* value
Rectum V_{50Gy} (%)	<50%	10.5	0-37	12.2	0-39	0% (-75 to 25)	>0.2
	Target achieved	All cases		All cases			
V50Gy = volume receiving 50Gy							

Bladder

There was a non-significant increase (median 4.9%) in bladder V50Gy with PBT (p<0.2). Although the V50Gy was lower with VMAT in the majority of cases, VMAT could not achieve the target in one case when the V50Gy was 62%. Results are shown in Table 4.6 and in the Dose-Volume Histogram in Figure 4.3.

Table 4.6 Dose-volume parameters for bladder

Dose parameter	Target	PBT		VMAT		Comparison between paired data	
		Median	Range	Median	Range	Median difference (%) (range)	*p* value
Bladder V_{50Gy} (%)	<50%	2.5	0-47	1.1	0-62	4.9% increase with PBT (-92 to 283)	>0.2
	Target achieved	All cases		9 cases 90%			
V50Gy = volume receiving 50Gy							

Femoral heads

Summative results for 19 femoral heads in 10 patients are given in Table 4.7, excluding the one proximal femoral replacement. It was possible to limit the mean dose to <40Gy in all cases with both techniques. PBT avoided any dose to 11 femoral heads in nine patients. An example Dose-Volume Histogram for bilateral femurs is included in Figure 4.3.

Table 4.7 Dose to femoral heads

Dose parameter	Target	PBT		VMAT		Comparison between paired data	
		Median	Range	Median	Range	Median difference (%) (range)	*p* value
Femoral head mean dose (Gy)	<40Gy	0	0-37.8	7.2	0.3-37.3	100% reduction with PBT (-1.3 to 100)	<0.001
	Target achieved	All cases		All cases			
Complete avoidance	Achieved	11 femoral heads In 9 patients received 0.0Gy		2 femoral heads in 1 patient received ≤0.7Gy *(the target was above the level of the femoral heads)*			

Ovaries

Ovarian dose is shown in tables 4.8 and 4.9. PBT was able to limit the dose to <4Gy for at least one ovary in all patients and was able to achieve an even lower dose of <2Gy for at least one ovary in all patients (Table 4.9). VMAT could achieve <4Gy to at least one ovary in 9 patients. The Dose-Volume Histogram for the ovaries in Case 1 is included in Figure 4.3.

Table 4.8 Dose to ovaries

Dose parameter	Target	PBT		VMAT		Comparison between paired data	
		Median	Range	Median	Range	Median difference (%) (range)	*p* value
Ovarian mean dose (Gy)	<4Gy to at least one ovary	0	0-17.1	3.9	0.3-28.4	100% reduction with PBT (29 to 100)	<0.001
	Target achieved:	All cases		9 cases			
Complete avoidance	achieved:	11 ovaries* in 8 patients received 0.0Gy		2 ovaries** in 2 patients received <0.5Gy			
*three ovaries in 2 patients were transposed out of pelvis **ovaries transposed out of pelvis							

Table 4.9 Individual ovarian doses

Case	Site	Ovaries	Right ovary		Left ovary	
			Mean dose VMAT (Gy)	Mean dose PBT (CGE)	Mean dose VMAT (Gy)	Mean dose PBT (CGE)
1	Ilium	Not transposed	3.9	0.0	22.4	3.2
2	Ischium	Both ovaries transposed out of pelvis	0.3	0.0	0.9	0.0
3	Ischium	Not transposed	5.9	4.2	3.9	1.8
4	Pubic ramus	Right ovary transposed out of pelvis	0.4	0.0	28.4	17.1
5	Ilium	No Right ovary structure as in PTV	-	-	3.8	0.0
6	Sacrum	Both ovaries transposed	3.2	0.0	3.4	0.0
7	Sacrum	Not transposed	3.6	0.0	5.5	0.0
8	Sacrum	Not transposed	4.5	0.1	4.3	0.2
9	Ilium	No Right ovary structure as in PTV	-	-	2.8	0.0
10	Sacroiliac joint	Not transposed	3.6	0.0	7.4	2.1

Uterus and vagina

Doses to the uterus and vagina are summarised in Table 4.10 and illustrated in Figure 4.3. Both VMAT and PBT were able to limit the mean dose to the uterus to ≤10Gy in eight patients. There was however a significant reduction in mean dose to the uterus of 40% with PBT ($0.02<p<0.05$) and the mean dose with PBT was <8Gy in all eight patients. The dose was lower with VMAT in one case (11Gy vs, 18Gy with PBT). Vaginal dose was significantly reduced with PBT ($p<0.001$).

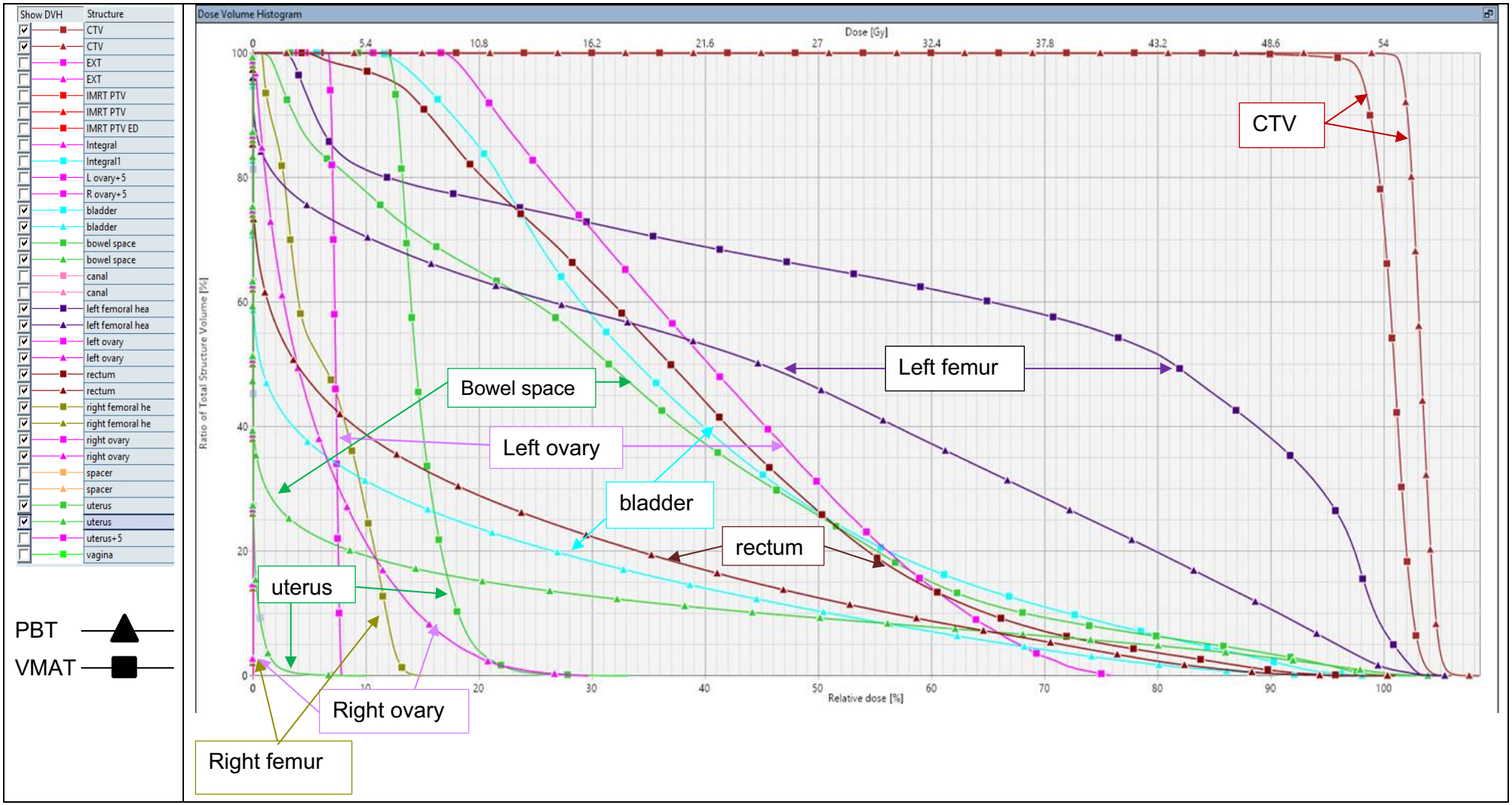
Table 4.10 Dose to uterus and vagina

Dose parameter	PBT		VMAT		Comparison between paired data	
	Median	Range	Median	Range	Median difference (%) (range)	*p* value
Uterus mean dose (Gy)	5.1	0.1-22.2	8.2	6.8-22.4	40% reduction with PBT (-59 to 99)	$0.02<p<0.05$
Vagina mean dose (Gy)	0.6	0-48.2	8.2	0.6-50.4	89% reduction with PBT (1.8 to 100%)	$p<0.001$

Integral dose

The mean integral dose to the normal tissue volume outside the VMAT PTV was compared to the dose to the same volume from PBT. The median was 9.3Gy (range 5.6 to 13) with VMAT and 5Gy CGE (range 1.2 to 14.2) with PBT. The result indicates a median decrease of 45% with PBT ($p<0.006$).

Figure 4.3 Dose volume histogram for Case 1 – Left ilium tumour crossing midline. Ovaries not transposed. Spacer used.



4.5 Discussion

This chapter has described a planning study comparing VMAT and PBT for Ewing sarcoma of the pelvis, comparing target (PTV and CTV) coverage, and also dose-volume parameters in a number of relevant normal tissues to assess the respective abilities of the two techniques to spare normal tissues in this young population.

4.5.1 Case selection

It was challenging to find eligible patients in the retrospective database due to the rarity of pelvic Ewing sarcoma, the narrow inclusion criteria and the change in practice with young patients going abroad for PBT from 2008. The database went back to 2002, but electronically stored radiotherapy datasets were not available prior to 2006 due to a departmental change in radiotherapy planning system. The final ten patients represented the heterogeneous case mix seen in the clinic. Tumours were laterally located or crossing midline and varying in size, three patients had ovarian transposition and three had pelvic spacers inserted.

4.5.2 Feasibility and target coverage

One of the aims of the study was to assess if these techniques would make it possible to deliver the required radiotherapy dose to the target, as this was historically achievable in only 67% of patients treated with 3DCRT. Both VMAT and PBT could achieve acceptable target coverage for all patients in this study, independent of tumour size, or location in the pelvis. This was consistent with the fixed field IMRT in planning study by Mounessi, previously discussed.(107) This has important implications for local control outcomes and indicates that advanced techniques are more reliable to deliver optimal doses to ensure optimal local control outcomes in these patients for whom radiotherapy is frequently used as definitive treatment. IMRT appears as effective as PBT to deliver the necessary radiation dose, which will be reassuring for patient not eligible for PBT or who are unable to travel to receive this.

4.5.3 Normal tissue sparing

4.5.3.1 Bowel space

The small bowel is frequently the most important dose limiting structure for pelvic radiotherapy. At a prescription dose of 54Gy it is anticipated that some target compromise may be required to keep the bowel dose acceptably low. The evidence suggests that the higher doses are more relevant for developing early and late effects as per the QUANTEC (112) review that sets a target of less than 195cm^3 of the bowel space to receive ≥45Gy. The Emani guidelines concur and suggest aiming even lower with ≤5% of the whole potential bowel space receiving ≥50Gy or more.(24) It is therefore reassuring that both VMAT and PBT were able to achieve the 45Gy target in all cases in this study without the need to compromise the tumour target coverage. The median bowel volume receiving ≥45Gy was much lower than the 195cm^3 target for both techniques, at 21.5cm^3 and 14.6cm^3 for VMAT and PBT, respectively. There was no statistically significant difference demonstrated between the two techniques at this dose level. If the bowel is immediately adjacent to or in the target volume, the dose to bowel will be the same with both techniques. The mean bowel dose was significantly lower with PBT compared with VMAT, at 1.5CGE and 6Gy respectively, representing a 67% reduction in mean bowel dose. The clinical significance of this is likely to be important in the paediatric population, but at these low absolute doses, may have less long-term implications for adults.

4.5.3.2 Rectum

The literature on rectal late effects indicates that the high doses are relevant for late effects such as proctitis, bleeding and fistulation.(24, 113) There was no difference in the volume of rectum receiving ≥50Gy between the two techniques, and the target of V_{50Gy} <50% was easily achieved with both techniques. The PBT and VMAT results of 10.5% (range 0-37%) and 12.2% (range 0-39%) respectively, were consistent with that seen by Mounessi et al for fixed field IMRT where the mean volume was 7% (range 0–40.51%).(107)

4.5.3.3 Bladder

The volume of the bladder receiving 50Gy was slightly lower with VMAT, with a median V_{50Gy} of 1.1% (range 0-62%) and 2.5% (range 0-47%) for VMAT and PBT respectively, although this was not statistically significant. In one case, VMAT could not achieve the target of <50%, in a patient with a large tumour of the ischium and an extensive intra-pelvic soft tissue mass that crossed midline. The V_{50Gy} was 62% with VMAT and 47%

with PBT in this case. The median bladder V_{50Gy} for both VMAT and PBT in our study was substantially lower compared to 19.72% (range 0–56.63%) with fixed field IMRT in the Mounessie series.(107) It is not clear why this was higher using fixed field IMRT in that study, where no significant difference from 3DCRT was seen.

4.5.3.4 Femoral heads

Fractures and osteoradionecrosis are the most consistently reported late effects in this population in the retrospective literature from the 3DCRT era.(87, 91, 92) Guidelines from this period simply suggest that the whole femoral head should not receive more than 50 – 52Gy.(23, 24) The target of mean dose <40Gy to avoid fractures is used in the IMRiS trial discussed in chapter 5 (56), and derives from one dosimetric paper describing 4 patients with femoral fracture after surgery and radiotherapy for soft tissue sarcoma. All patients with fractures received >40Gy in that series.(115) In the current study, PBT was superior to VMAT to completely avoid femoral heads, with PBT avoiding delivering any dose to 11 femoral heads in 10 patients. The remaining eight femoral heads received between 1.7 and 37.8Gy. The single proximal femoral replacement prosthesis was excluded from the analysis. VMAT could not completely avoid dose to femoral heads except in one patient with a relatively small tumour around the left sacroiliac joint, above the level of the femoral heads, where the mean dose was 0.3Gy and 0.7Gy to the femoral heads. The remaining 17 received between 2.3 and 37.3Gy with VMAT. This complete sparing of the femoral heads with PBT is likely to benefit growing children, and younger adults at risk of late fractures, although it is less clear if this avoidance of low doses has clinical benefit in older adult patients,

4.5.3.5 Female reproductive organs

Ovaries are very radiosensitive, and infertility and early menopause can result from very low radiotherapy doses. The literature suggests that doses should be kept below 5Gy and ideally below 2Gy.(94, 95, 97). This study demonstrated that PBT was able to completely avoid direct dose to at least one ovary in all patients. There are theoretical concerns that neutron scatter produced during PBT treatment delivers an additional radiation dose to the patient, but this has been modelled to be lower with pencil beam scanning techniques compared to passive scatter fields in paediatric patients receiving cranio-spinal irradiation.(116) VMAT was able to limit the ovarian dose to at least one ovary to <4Gy in nine patients, and to < 2Gy in two of these. This indicates that while PBT is superior to VMAT in completely avoiding dose to at least one ovary, nevertheless VMAT can contribute to ovarian preservation in patients not eligible or able to undergo PBT.

Uterine function preservation following radiotherapy is complex. There is a correlation between eventual uterine size and the age at the time of radiotherapy due to growth impairment in young patients. The uterine function also depends on maintaining a healthy endometrium to ensure embryo implantation, and to prevent early pregnancy loss. Vascular effects can influence placental function, and this may be a problem at lower delivered radiotherapy doses. Even if ovarian function is preserved thereby avoiding premature menopause, the uterus may not be able to sustain a normal future pregnancy.(94, 98, 99) There is no agreed safe uterine dose in the literature. Reducing the dose to as low as possible seems the safest way to ensure a normal future pregnancy. The results in this study indicate that PBT was more effective in achieving lower doses, limiting the uterine dose to <8Gy in 8 cases. VMAT limited the dose to ≤10Gy in the same 8 patients. There was a significant reduction in mean dose to the uterus of 40% with PBT. Completely avoiding radiation to the uterus was impossible in this study with either technique. Vaginal dose was also reduced with PBT compared to VMAT in this study. Overall, PBT seem superior to VMAT in optimising the chances of maintaining normal uterine function following pelvic radiotherapy.

4.5.3.6 Integral dose

The mean dose to normal tissues outside the PTV was significantly lower with PBT compared with VMAT in this study, in keeping with our understanding of PBT dose distribution and the anticipated low dose bath seen with VMAT. This is important in young adults and children to reduce the risk of radiation-induced malignancies (37, 38, 102), but may have less clinical benefit in older adult patients.

4.5.4 How does PBT and VMAT compare in pelvic Ewing sarcomas?

Both PBT and VMAT achieved good PTV/CTV coverage, and were equally effective in this respect. Normal tissue doses close to or in the range of the prescription dose were very similar with both techniques as was demonstrated for the V_{50Gy} for the rectum and bladder. These are the clinically relevant doses for late effects in adults, and both techniques were able to achieve the target with ease. Both techniques could also limit the femoral head doses to acceptable levels, although PBT was able to completely avoid dose to a significant proportion of femoral heads particularly contralateral to the target, which is likely to be particularly important in growing children.

PBT is superior to completely avoid dose to at least one ovary in all patients, which has significant implications for future fertility options in young patients. Complete avoidance was not possible with VMAT despite the use of ovarian transposition in three of the cases in this study. The position of the ovaries when transposed was however not chosen with this technique in mind in this retrospective series, and there may still be a role for this if the likely beam angles and low dose bath is taken into account when deciding where to position the ovaries.

The increase in integral dose observed with VMAT compared to PBT is of concern for the development of second cancers in young patients treated with curative intent.

4.5.5 Conclusion

The planning study presented here uniquely compares two advanced radiotherapy techniques specifically for the treatment of pelvic Ewing sarcoma. Both techniques resulted in excellent sparing of bowel, rectum and bladder. PBT offered superior sparing of femoral heads, uterus, vagina and ovaries in this group of young female patients. This dosimetric advantage may translate into a reduction in long term treatment related toxicity such as infertility, early menopause, the ability to sustain a future pregnancy, bone growth, osteoradionecrosis and bone fracture. The reduction in integral dose is clinically relevant for young patients in reducing the risk of secondary malignancies and who may suffer from the late effects of low doses such as growth delay.

The eligibility criteria for UK patients to have PBT have been expanded since this work. The age limit for paediatric indications, including all Ewing sarcoma except for extremity tumours, is now up to 24 years old, recognising the importance of using PBT to reduce late toxicity in the young adult population.(117) Patients with metastatic disease outside the lungs, or those older than 24 years, are not routinely eligible for PBT. These patients should be offered IMRT as a feasible alternative to deliver the required radiotherapy doses to the target to optimise local control, with the potential to reduce late effects.

IMRT will be evaluated prospectively in patients with spinal and pelvic Ewing sarcoma within the UK national IMRiS trial. The development of the trial is discussed in Chapter 5.

5 Chapter 5 IMRiS: A phase II study of intensity modulated radiotherapy (IMRT) in primary bone and soft tissue sarcoma

The radiotherapy planning studies described in Chapters 3 and 4 demonstrate the dosimetric advantages of advanced radiotherapy techniques in extremity sarcomas and pelvic Ewing sarcoma. Does this dosimetric benefit translate into clinical benefit? The IMRiS trial was developed to answer this question. (Full title *IMRiS: A phase II study of intensity modulated radiotherapy (IMRT) in primary bone and soft tissue sarcoma)*

I developed the study protocol with Dr Beatrice Seddon who is also the Chief Investigator for the study. The study is registered with the National Institute of Health Research (NIHR), *Clinical trials.gov,* number NCT02520128.(56)

IMRiS was developed in parallel with the investigational work described in this thesis, as a multi-centre non-randomised prospective phase II trial to investigate the feasibility, efficacy and toxicity of IMRT in three cohorts of patients with soft tissue sarcoma and primary bone sarcoma:

- Cohort 1: Patients with limb/limb girdle soft tissue sarcoma receiving (neo)-adjuvant radiotherapy
- Cohort 2: Patients with Ewing sarcoma of the spine/pelvis receiving definitive radical or (neo)-adjuvant radiotherapy
- Cohort 3: Patients with non-Ewing primary bone sarcomas of the spine/pelvis receiving definitive radical or adjuvant radiotherapy

The results from the late effects survey and planning studies described in Chapters 2,3 and 4 informed the protocol, radiotherapy guidelines and quality assurance programme for cohorts 1 (extremity soft tissue sarcoma) and 2 (pelvic and paraspinal Ewing sarcoma).

The aim in developing IMRiS was three-fold:

- To investigate IMRT prospectively in patients with sarcoma
- To give sarcoma patients and centres across the UK access to treatment with IMRT
- To allow treatment in a standardised and quality assured way across the UK

5.1 Rationale for developing a clinical trial to investigate IMRT in patients with sarcoma

5.1.1 Cohort 1: Patients with limb/limb girdle soft tissue sarcoma receiving (neo)-adjuvant radiotherapy

The literature on late effects of treatment in this group of patients has been reviewed in Chapter 2. The late effects survey we completed described the burden of late effects from surgery and 3DCRT and identified a correlation with the volume of tissue irradiated to the prescription dose. The planning study in Chapter 3 demonstrated the dosimetric advantage of VMAT, a rotational IMRT technique, to reduce the high doses to normal soft tissue and bone outside the target. This effect was also demonstrated for fixed field IMRT in other planning studies.(76-78) The lack of prospective evidence for the use of IMRT in this group of patients, and the limited resource in the NHS setting, meant that the standard practice to treat extremity soft tissue sarcomas in the UK was 3DCRT. A clinical trial was needed to investigate the potential of IMRT to reduce the late effects of treatment and improve functional outcomes.

5.1.2 Cohort 2: Patients with Ewing sarcoma of the spine/pelvis receiving definitive radical or (neo)-adjuvant radiotherapy

The literature on late effects of radiotherapy in patients with Ewing sarcoma is summarised in Chapter 4. The double planning study we performed demonstrated the dosimetric benefits of PBT and VMAT in patients with pelvic Ewing sarcoma. This effect has also been shown for fixed field IMRT in one study.(107) There have been no clinical trials prospectively investigating IMRT in Ewing sarcoma, and Cohort 2 of IMRiS was developed to prospectively assess the target dose coverage achieved at challenging sites in the pelvis and spine, and to establish the side effects of treatment.

5.1.3 Cohort 3: Patients with non-Ewing's primary bone sarcomas of the spine/pelvis receiving definitive radical or adjuvant radiotherapy

The third cohort was included to assess the feasibility of IMRT to enable dose escalation at challenging sites in bone sarcomas that require high radiation doses. Tumours include osteosarcoma, chondrosarcoma, other rare high-grade bone sarcomas and chordoma. Radiotherapy is used as adjuvant treatment to surgery for resectable bone sarcomas, and sometimes as definitive or palliative treatment where resection is not possible or anticipated to lead to unacceptable morbidity.(15, 18, 118, 119) The dose used to treat osteosarcoma in the adjuvant setting is 60 to 66Gy and the

ideal dose for prolonged tumour control in patients treated with radiotherapy alone is at least 70Gy.(18, 20, 120). A retrospective review of 22 radio-resistant pelvic and spinal bone sarcomas treated at UCH with 3DCRT showed that the intended dose (60-66Gy) could be prescribed in only 14% of cases (unpublished data).

There are data on the use of PBT either alone or in combination with photons to treat osteosarcoma with a promising 5 year local control rate of 72% in patients treated to a mean dose of 68.4Gy.(19) Doses up to 77Gy have been used safely in a phase II study of spinal bone sarcomas.(120) Combined PBT and photons , PBT alone and carbon ion radiotherapy are reported to achieve excellent 5 year local control rates in excess of 89% in extracranial chordoma at doses above 70Gy.(41, 43, 121-123) The results with PBT in the presence of metal implant is however significantly worse as reported in series from the Paul Scherrer Institute where the 5 year local control was 100% without surgical stabilization, compared to less than 60% with metal implants.(122)

There is very little published on the use of IMRT in this setting. IMRT resulted in similar dose conformality as PBT in a planning study of five paraspinal sarcomas (124) and doses of up to 70Gy were achievable with stereotactic IMRT in a series of 35 paraspinal malignancies including 14 sarcomas.(125) Results were poor for sacral chordoma treated with IMRT in a series of 34 patients where the 5 year local control rate was 27% (126), but the median dose was 66Gy in this study which is lower than that used in the PBT series mentioned above.

Cohort 3 of IMRiS was developed to prospectively investigate the target dose coverage achievable with IMRT in the pelvis and spine and the side effects of treatment in this setting.

5.2 Trial summary

The trial schema taken from the protocol is shown in Figure 5.1 and a summary of the trial design in Table 5.1. Radiotherapy in the trial is delivered with fixed field IMRT, or rotational IMRT techniques. The prescription dose for each cohort is shown in Figure 5.2.

The primary endpoint in Cohort 1 is late toxicity (≥ Grade 2 soft tissue fibrosis at 2 years after radiotherapy). The primary endpoint for Cohorts 2 and 3 is dosimetric (target coverage), and late effects data are collected as part of the secondary endpoints. The full protocol is attached in Appendix 4.

Figure 5.1 IMRiS Trial Schema *(from IMRiS protocol version 3.0, 14.1.2019)*

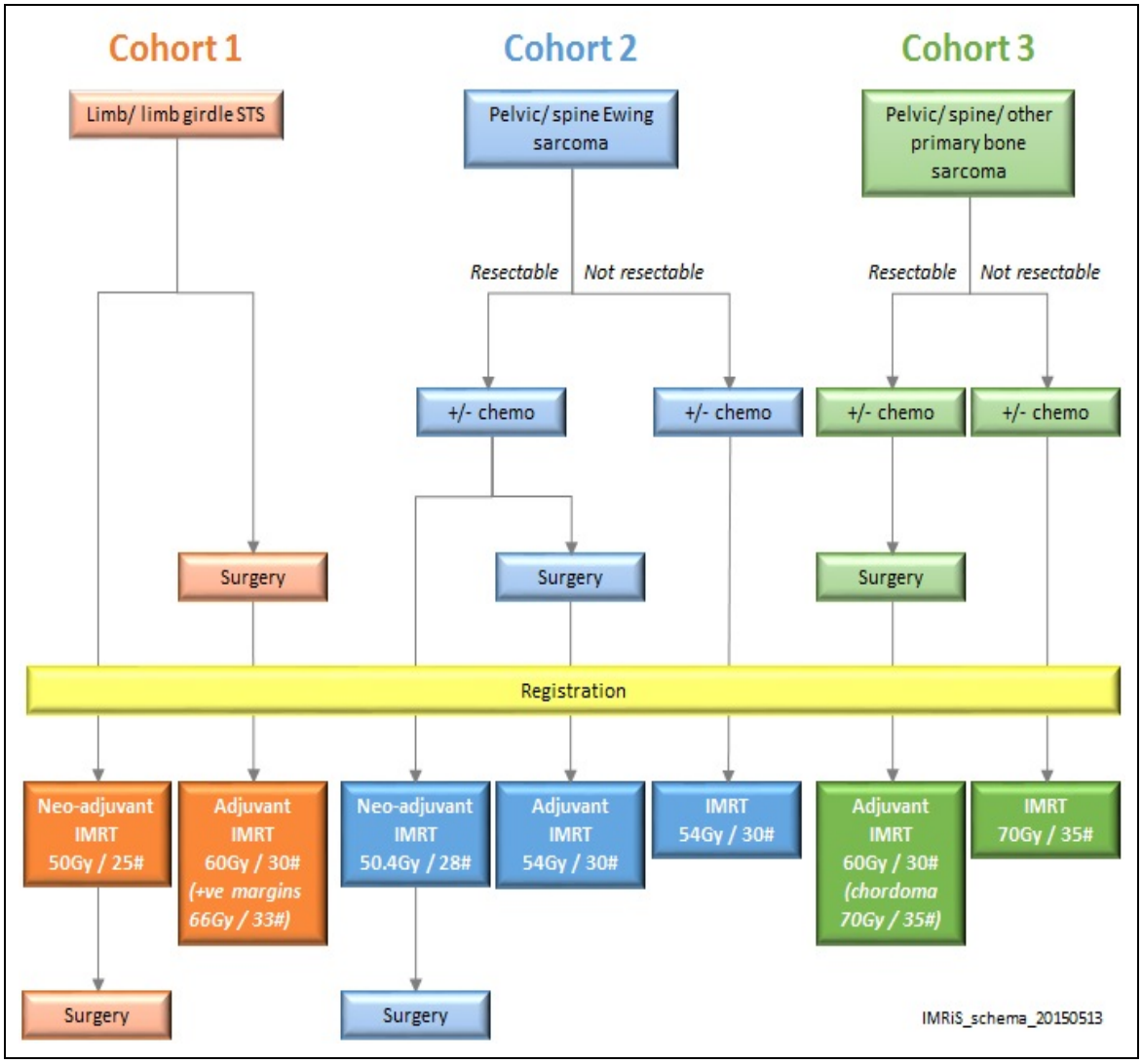


Table 5.1 IMRiS Trial Design summary *(from IMRiS protocol version 3.0, 14.1.2019)*

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); patient reported quality of life; 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:
	  ○ soft tissue sarcoma of the upper or lower limb or limb girdle, *or*
	  ○ Ewing's sarcoma of bone arising in the pelvis or spine,
	  or
	  ○ 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 week • 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

5.3 Comments on sample size

Each cohort is analysed separately. The goal is to recruit 188 patients over 2 and a half years: 167 in Cohort 1, nine patients in Cohort 2 and 12 patients in Cohort 3.

5.3.1 Cohort 1: Patients with limb/limb girdle soft tissue sarcoma receiving (neo)-adjuvant radiotherapy

The minimum rate of grade 2 or more late soft tissue fibrosis at two years after 3DCRT is estimated at approximately 30% as per the CAN-NCIC-SR2 trial pre-operative radiotherapy arm (52) and the retrospective series presented in Chapter 2. A sample size of 138 patients is needed to demonstrate a reduction to 20% using IMRT (85 % power and 5% significance level). To account for deaths and loss to follow up, the total number of patients required was estimated at 143. Due to higher than anticipated recruitment numbers this target has since been extended to 167.

5.3.2 Cohort 2: Patients with Ewing's sarcoma of the spine/pelvis receiving definitive radical or (neo)-adjuvant radiotherapy

The endpoint in Cohort 2 is dosimetric target coverage. The historical data from UCLH indicate that it was possible to deliver the ideal prescription dose to <70% of patients using 3DCRT (UCLH retrospective data, unpublished). It is likely that all patients in the trial will be prescribed the ideal dose but that it would not necessarily be possible to deliver this to the whole PTV in all cases. Areas overlapping with critical normal tissue organs at risk will be treated to a lower dose within the IMRT plan. The proportion of the PTV affected in this way depends on the site (spine more likely than pelvis), the size of the tumour and the prescribed dose.

The data presented in Chapter 4 demonstrate that all patients with pelvic Ewing sarcoma in the double planning study could be treated to 54Gy with VMAT, with 95% of the PTV receiving at least 95% of the dose. Additional historical cases treated with IMRT at UCLH were individually reviewed in addition to estimate the likely target coverage that could be expected at different sites (Table 5.2). The primary endpoint for Cohorts 2 was derived taking these historical data into account and in context of what would be deemed a clinically relevant 95% PTV coverage.

Table 5.2 Target coverage with IMRT in individual cases

Case	Histology	Site	Prescription	Percentage of IMRT PTV receiving 95% dose
1	Ewing sarcoma	Sacrum	54Gy	95.7
2	Ewing sarcoma	Cervical spine	50.4Gy	98.7
3	Ewing sarcoma	Thoracic spine	54Gy	81.5
4	Chordoma	Sacrum	70Gy	83.6

It was anticipated that only a small number of patients nationally would be recruited to Cohort 2 as the majority of adult and paediatric patients with paraspinal Ewing sarcoma, and paediatric patients with pelvic Ewing sarcoma treated with curative intent, were eligible to have PBT.

To demonstrate an increase in the proportion of patients receiving at least 95% optimal dose to the target from 70% to 95% using IMRT, 9 patients were required (with a 20% significance level and 80% power calculation). All patients would be assessable at the planning stage for the primary endpoint.

5.3.3 Cohort 3: Patients with non-Ewing's primary bone sarcomas of the spine/pelvis receiving definitive radical or adjuvant radiotherapy

Historical data from UCLH indicated that 14% of patients could be treated to doses ranging from of 60 to 66Gy with 3DCRT and no patients were treated to 70Gy (unpublished data). It is anticipated that with the use of IMRT it will be possible, and clinically relevant, to deliver the indicated dose in the majority of cases (at least 50%), although areas of the PTV overlapping with critical structures will inevitably receive less than the prescription dose. 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 (Table 5.2).

To demonstrate that 50% of patients could receive 95% of the dose to 80% of the PTV using IMRT, 12 patients were required (10% significance level and 80% power calculation). The primary endpoints for cohort 3 will similarly be assessed before treatment, therefore all patients will be assessable.

5.4 Protocol development

5.4.1 Peer review

The trial proposal was reviewed by the NCRI (National Cancer Research Institute) Sarcoma Clinical Studies Group in November 2012 and the CT Rad (Clinical and Translational Radiotherapy Research) Working Group in February 2013. NIHR Radiotherapy Trials Quality Assurance group (RTTQA) is responsible for the Radiotherapy Quality Assurance for the trial.

5.4.2 Sponsor

The CR UK (Cancer Research UK) and UCL (University College London) Cancer Trials Centre (CTC) was approached in January 2013 and agreed to sponsor the trial. The IMRiS team at the CTC contributed to protocol development, statistical input, funding and ethics applications.

5.4.3 Interest and eligibility survey

A questionnaire was sent to sarcoma centres across the UK in Spring 2013 to gage interest, to establish the numbers of patients that would potentially be eligible for the trial, the current techniques used and potential access to IMRT at each centre. The minority (30%) routinely used IMRT at the time.

5.4.4 Patient group input

The National Cancer Research Institute Consumer Liaison Group, UCLH sarcoma user group and CT Rad consumers contributed to reviewing the trial and the patient information sheets and consent forms.

5.4.5 Translational research

After discussion with Professor Catharine West, Professor of Radiation Biology at the University of Manchester, it was decided to approach all patients taking part in IMRiS for inclusion in the RAPPER project (Radiogenomics: Assessment of Polymorphisms for Predicting the Effects of Radiotherapy) (127, 128) run by Professor West. This is a UK study collecting blood samples from patients enrolled in national radiotherapy trials. The UK VORTEX trial (a randomized controlled multicenter phase 3 trial of VOlume of postoperative Radiation Therapy given to adult patients with EXtremity soft tissue sarcoma) treated with 3DCRT (46), had already contributed 206 samples to the

RAPPER biobank and the RAPPER study was starting to identify common single nucleotide polymorphisms (SNPs) associated with radiotherapy toxicity in other cancers. Those associated with overall toxicity or fibrosis endpoints would be potential candidates to explore in the VORTEX and IMRiS sarcoma trials.

5.4.6 Funding

An outline application for a Late Phase Study funding award was submitted to Cancer Research UK's Clinical Trials Awards and Advisory Committee (CTAAC) in August 2013. Feedback from the committee was taken into account and a full application was submitted in December 2013. A Full Project Grant was awarded in July 2014 (reference C2921/A17558).

5.4.7 Research ethics approval

An Integrated Research Approval System (IRAS) ethics application was submitted in August 2015. NHS Health Research Authority Research Ethics Committee approval was granted October 2015

5.5 Radiotherapy Quality Assurance

The NIHR Radiotherapy Trials Quality Assurance group (RTTQA) was involved throughout the trial development, protocol development and designing the radiotherapy guidelines and Quality Assurance (QA) program for the trial. RTTQA provide input into the Trial Management Group (TMG) and the on-going quality assurance for the trial, including central prospective review of IMRT plans. Prospective central review of target delineation is done by myself and Dr Seddon.

5.5.1 Pre-trial Quality Assurance

5.5.1.1 Facility questionnaire

A facility questionnaire was sent out to centres across the UK that had expressed an interest in taking part in the trial. Information was gathered on equipment, technique, immobilisation, imaging protocol and on treatment verification protocols and numbers of patients treated.

5.5.1.2 Limb immobilisation workshop

A workshop was subsequently held to address limb sarcoma immobilisation and patient set up, attended by radiographers, physicists and clinicians from 23 centres. The robustness of the immobilisation techniques was assessed. Results were used to inform the radiotherapy guidelines for the trial and tailor QA support for centres. This was subsequently presented as a poster at the ESTRO (European Society for Radiotherapy and Oncology) conference in 2016 (129) and published in Radiography journal in 2019.(130) (Appendix 3)

5.5.1.3 Target outlining workshop

An outlining workshop was held to establish current practice and reach consensus on target delineation and the draft planning guidelines amongst clinicians from participating centres. Three benchmark planning cases were created and sent to relevant centres prior to the workshop, one example case for each cohort. The soft tissue sarcoma case was completed by all centres. The bone sarcoma cases (cohorts 2 and 3) were completed by clinicians from the five UK bone sarcoma centres.

5.5.1.4 Pre-trial QA pack

A pre-trial QA pack was prepared that included:

- The radiotherapy target definition and planning guidelines, also appended to the protocol (Appendix 4)

- Outlining benchmark cases, one for each cohort, to be completed by each treating clinician prior to enrolling patients in the trial. Target and organs at risk outlining are centrally reviewed:
    - *Cohort 1 (Extremity soft tissue sarcoma):* Proximal thigh sarcoma for post-operative radiotherapy to 60Gy.
    - *Cohort 2 (Ewing sarcoma):* Thoracic spine Ewing sarcoma treated to 54Gy
    - *Cohort 3 (Other high grade bone sarcomas/Chordoma):* High grade pleomorphic bone sarcoma grade 3 of the left hemi-sacrum crossing the midline, treated to 70Gy

A review of the conformality of target outlining for the cohort 1 benchmark case was subsequently presented at the ESTRO conference in 2017 (131). (Appendix 3)

- Planning benchmark cases, to be completed by each centre for each IMRT technique they are planning to use (fixed field IMRT, VMAT or Tomotherapy) prior to enrolling patients in the study
    - *Cohort 1 (Extremity soft tissue sarcoma):* One thigh sarcoma case treated with pre-operative radiotherapy to 50Gy
    - *Cohort 2 and 3 (pelvis and spinal bone sarcomas):* One case with grade 2 chondrosarcoma of the sacrum treated with radical radiotherapy as sole modality to 70Gy

5.5.2 On-trial Quality Assurance

5.5.2.1 Prospective case review

- Cohort 1 (Extremity soft tissue sarcoma): The first patient entered into Cohort 1 from each centre is prospectively reviewed for target volumes as well as the IMRT plan. Subsequent patients are reviewed retrospectively.
- Cohorts 2 and 3 (pelvic and spinal bone sarcomas): Target volumes and IMRT plans for all cases are prospectively reviewed prior to starting treatment on the trial.
- Dosimetric data is collected for all recruited patients

5.6 Trial setup and progress

Recruitment opened in March 2016 and will close in December 2019. The trial will close in July 2020. The 18 centres where IMRiS is open, in the order of site activation from top to bottom, are listed in Table 5.3.

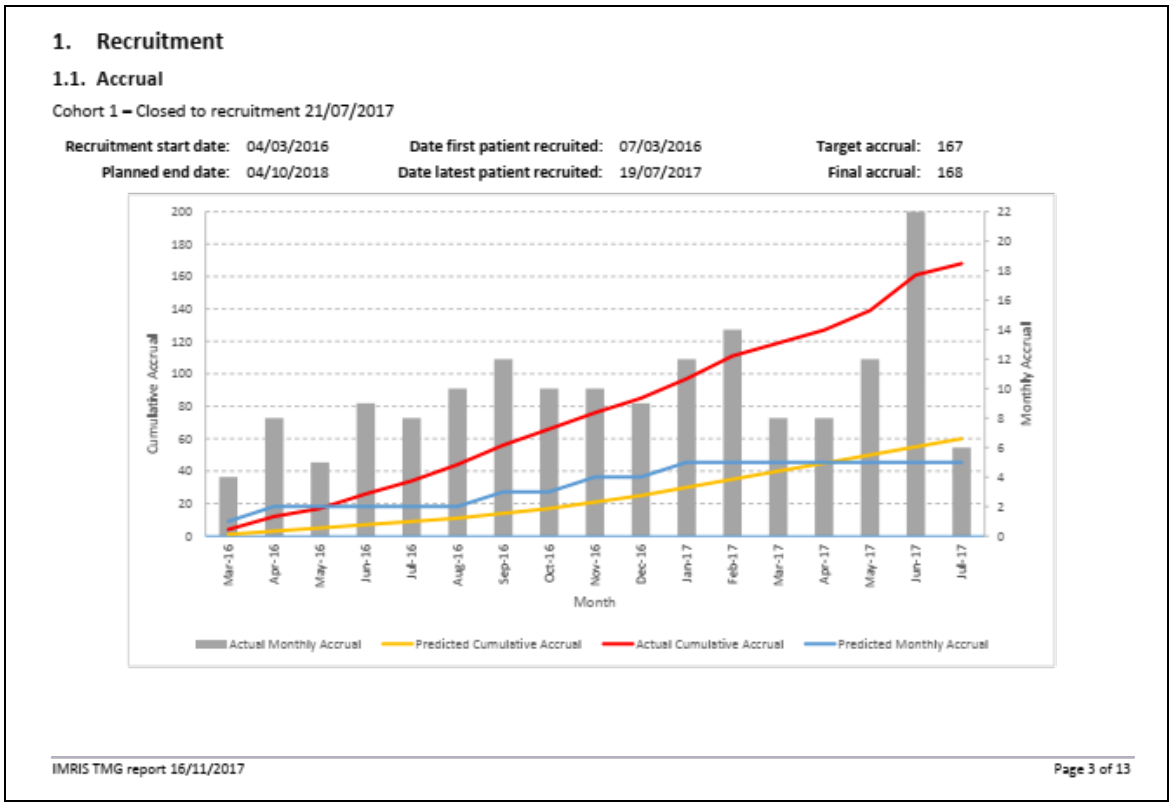
Table 5.3 IMRiS sites and open cohorts

	Cohort 1	Cohort 2	Cohort 3
UCLH	X	X	X
Norfolk and Norwich	X		
Cheltenham General Hospital	X		
Addenbrooke's, Cambridge Centre	X	X	X
Churchill Hospital, Oxford	X	X	X
Royal Marsden Hospital, Fulham Road	X		
University Hospitals Southampton	X		
Nottingham University Hospitals	X		
Royal Devon & Exeter Foundation Trust	X		
University Hospitals Coventry	X		
Christie Hospital, Manchester	X	X	X
Plymouth Hospitals NHS Trust	X		
University Hospitals Birmingham	X	X	X
Royal Preston	X		
Weston Park, Sheffield	X	X	
Leicester Royal Infirmary	X		
Bristol Haematology and Oncology Centre	X		
St Luke's Hospital, Dublin	X		
Beatson, WOSCC, Glasgow		X	

Cohort 1 recruited rapidly between March 2016 and July 2017 and recruited to target and on time. Indeed, recruitment was so successful that a decision was made to increase recruitment from 143 patients to 167 patients, to give late opening centres the opportunity to enter patients into the study. (Figure 5.2)

Cohorts 2 and 3 have recruited more slowly, as anticipated, given the rarity of these patients, and the fact that many patients were eligible for PBT. However, the cohorts have recruited fully, with recruitment completed in December 2019.

Figure 5.2 IMRiS Cohort 1 recruitment graph *(from IMRiS TMG report 16/11/2017)*



5.7 Related projects

5.7.1 Dosimetric analysis and late effects

Rita Simoes, NCRI RTTQA Group Radiographer, is a PhD student studying the identification of dose-volume parameters for radiotherapy in relation to toxicity levels in patients with soft tissue sarcomas. This project will use the radiotherapy QA data held with the RTTQA group for IMRiS cohort 1 and data held for the VORTEX trial.(46)

5.8 Presentations and publications arising from IMRiS

- Simões R, Miles E, Le Grange F, Bhat R, Seddon B. PO-1023: Quality assurance for IMRiS phase II study of IMRT in sarcomas: a survey of limb immobilisation. Radiotherapy and Oncology. 2016;119:S495-S6. Poster, ESTRO, May 2016 (Appendix 3)
- Simões R, Yang H, Patel R, Le Grange F, Beare S, Miles E, Seddon B. A novel and objective plan evaluation for limb sarcomas IMRT in the IMRiS phase II trial. Oral presentation by Rita Simoes, ESTRO, May 2017
- Yang H, Simões R, Le Grange F, Forsyth S, Eaton D, Seddon B. PO-0742: Target delineation conformity in extremity STS within the UK phase II multi-centre IMRiS trial. Radiotherapy and Oncology. 2017;123:S390-S1. Poster, ESTRO, May 2017 (Appendix 3)
- Simoes R, Yang H, Le Grange F, Forsyth S, Seddon B. Planning benchmark cases for IMRiS phase II trial: Will different optimisation techniques in bone sarcomas impact on clinical outcomes?; Oral presentation by Rita Simoes, UK Radiological & Radiation Oncology Congress (UKRO), July 2018
- Simões R, Miles E, Yang H, Le Grange F, Bhat R, Forsyth S, et al. IMRiS phase II study of IMRT in limb sarcomas: Results of the pre-trial QA facility questionnaire and workshop. Radiography, https://doi.org/10.1016/j.radi.2019.08.006. (Appendix 3)

6 Chapter 6 Summary and conclusions

6.1 Summary of the key results

6.1.1 Late effects of 3D conformal radiotherapy in extremity bone and soft tissue sarcomas

The late effect survey set out to describe the pattern of late normal tissue effects and patient reported outcomes after radical radiotherapy in patients with extremity sarcoma and to explore potential risk factors for late treatment related toxicity. Results demonstrated that 49% of patients live with RTOG grade 2 or greater late effects, and 15% have significant long-term sequelae (any late effect ≥ grade 3). Soft tissue fibrosis of grade 2 or greater was present in 30%. A third of patients with lower extremity tumours walked with an abnormal gait and 24% needed a walking aid. Long-term pain was a feature in 41% and 38% reporting regular use of analgesia. Pain was inversely related to functional outcome and quality of life. A third of patients surveyed had functional (TESS) scores below 80 (out of maximum 100) and 35% reported a negative impact on their quality of life after treatment. Patients with larger tumours, lower limb site, older age at the time of radiotherapy, complex surgery, post-operative radiotherapy and wound complications were at a higher risk of significant late effects in this study. Late effects correlated strongly with functional outcomes. This data highlighted that a reduction in the volume of normal tissue that receives high radiation doses may improve the late effects profile of radiotherapy in this setting. Although many of the risk factors identified are patient- and disease-specific and cannot be changed (age, tumour site, tumour size, the need for complex surgery), the data raise the awareness of which patients are at higher risk of late toxicity, and this can be taken into account in the clinic when management plans are made.

6.1.2 Planning study comparing VMAT with 3DCRT in extremity sarcomas

The planning study comparing VMAT to 3DCRT in extremity soft tissue sarcomas explored the value of VMAT to achieve a reduction in normal soft tissue and bone outside the target that receive high doses of radiation. The results demonstrated that VMAT is a feasible technique to treat both upper and lower extremity sarcomas. VMAT reduced the volume of normal tissue receiving moderate to high doses. The reduction was statistically significant for all doses above 30Gy, and more marked for the very high dose range. This effect may reduce the risk of significant late effects and improve

long term functional outcomes. The clinical benefit of the dosimetric advantage seen is currently under investigation in the IMRiS phase II trial.

6.1.3 Double planning study comparing VMAT and PBT for the treatment of pelvic Ewing sarcoma

The effect of VMAT and PBT on the therapeutic ratio in patients with pelvic Ewing sarcoma was explored in a double planning study. Both techniques were shown to be feasible in this setting to deliver 54Gy in 30 fractions to the target while limiting dose to adjacent normal tissues to an acceptable level. This rate of effective dose delivery had not been possible in the era of 3DCRT, and this improved dose delivery may also have a positive effect on local control outcomes. There was no significant difference in the volume of small bowel receiving 45Gy or more, or the volume of the rectum and bladder receiving 50Gy or more between the two techniques. PBT was able to completely avoid irradiating the contralateral femoral head in all cases. Complete avoidance of at least one ovary was possible with PBT in 80% of cases and mean dose of less than 2Gy delivered in the remaining two patients. VMAT could limit the dose to one ovary to less than 4Gy in 90% of patients. While PBT is currently used for the majority of paediatric patients, and some adult patients with paraspinal tumours, this planning study demonstrates that VMAT is an acceptable alternative treatment that delivers the required dose safely for patients not receiving PBT for whatever reason. The superior physical dose distribution of PBT may have a positive impact on fertility preservation and premature menopause in young female patients. The low dose volume of normal tissues outside the PTV was significantly less with PBT, and this may have implications for children and younger adults treated with curative intent to reduce the risk of late radiation induced malignancy.

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

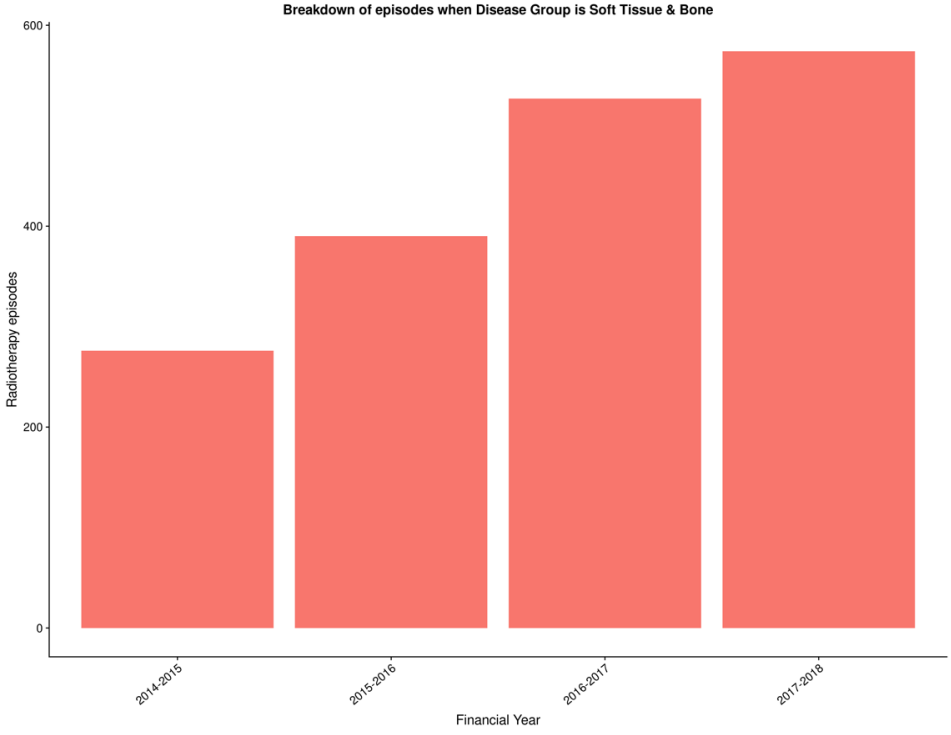
The data gathered through the late effects survey, and the experience with VMAT in the two planning studies, were used in the development of the IMRiS phase II trial protocol, and radiotherapy planning and QA guidelines. The trial is investigating IMRT prospectively in patients with sarcoma. It aims to answer the question whether the dosimetric benefit seen with advanced radiotherapy techniques in the planning studies will translate into clinical benefit, to reduce long term side effects in extremity sarcomas and to improve target coverage for bone sarcomas.

6.2 Changes in practice since the experimental work was completed

6.2.1 The use of IMRT in the UK

A second aim of the IMRiS trial was to give sarcoma patients and centres across the UK access to treatment with IMRT in a standardised and quality assured setting. Figure 6.1 shows the increase in the use of IMRT to treat sarcomas during the study period. The number of IMRT courses in England has doubled from around 300 to almost 600 a year. It is not possible to comment if this is solely the effect of the IMRiS trial or partly due to the eventual roll-out of new technologies such as IMRT to rarer tumour groups, although it should be noted that IMRiS was opened in 18 centres around the whole of the UK, and almost all contributed patients to cohort 1 (extremity soft tissue sarcomas). This suggests that it is likely that the opening of IMRiS has contributed to at least some of the observed increase of IMRT courses for sarcoma. Undoubtedly IMRiS has contributed to a quality assured implementation of IMRT. Delegates from 23 centres attended the pre-trial workshops, centres agreed a national approach to IMRT target delineation in soft tissue and bone sarcomas, and the trial opened with central quality assurance of all target and organ at risk delineations and IMRT plans.

Figure 6.1 Number of IMRT episodes to treat sarcoma in England



National Cancer Registration and Analysis Service (NCRAS) data from the Radiotherapy Dataset (RTDS) on radiotherapy activity in hospitals in England, available from https://www.cancerdata.nhs.uk/radiotherapy

6.2.2 Access to PBT for patients in the UK

The eligibility criteria for UK patients to have NHS-funded PBT have been expanded since this work. The age limit for paediatric indications, including all Ewing sarcoma (extremity tumours excluded), is now up to 24 years old.(117) This effectively means that more young patients treated with curative intent will be eligible for PBT. This is encouraging in view of the results of the pelvic double planning study that demonstrated the potential benefits of PBT to prevent early menopause, maintain fertility, and reduce the risk of late radiation induced malignancies. The first UK NHS PBT facility opened in Manchester at the Christie Hospital in December 2018 and a second facility is planned to open in London at UCLH in 2020. This will make it possible for many eligible patients who would have been unable to travel abroad for personal or other reasons, to access PBT closer to home.

Patients with Ewing sarcoma and metastatic disease outside the lungs, or those older than 24 years, are not currently eligible for NHS-funded PBT. The results from the planning study have given a clear understanding of the comparative ability of PBT and IMRT to delivery optimal treatment dose to the target, and indicate that these patients should be offered IMRT as a feasible alternative to PBT to optimise local tumour control, without the risk of significant bowel side effects. Target coverage and late effects data are being collected prospectively for these patients within the IMRiS trial.

Adult patients with sacral and spinal chordoma and other high-grade spinal bone sarcomas are now eligible for adjuvant PBT. More recently patients with sacral chordoma with a good five-year survival expectation are being considered for definitive PBT in line with international practice. It is not yet clear if local control outcomes in the latter group will be any better with PBT compared to IMRT. Earlier poor local control results with photons date back to the 3DCRT era and suboptimal treatment delivery. If IMRT can deliver the required dose to the target as effectively as PBT, the difference in local control may be small at best. A prospective trial comparing the two technologies is not possible in such a rare tumour where long term follow up is required. IMRiS aims to answer the question of what dose coverage is achievable with IMRT without unacceptable risk of toxicity. Data on local control and late effects will also be collected prospectively. The SACRO study (Sacral Chordoma: Surgery Versus Definitive Radiation Therapy in Primary Localized Disease), a multinational prospective cohort study of local management (surgery or radiotherapy) is also collecting data on the outcomes of current practice in this rare disease (*clinical trials.gov* number NCT02986516).

6.3 Limitations and strengths of the research

The research presented here reflects the challenge of undertaking studies in rare tumours which rely heavily on retrospective data analysis and frequently can include only small numbers.

The late effects survey collected data on tumour, patient and treatment specifics retrospectively from patient records, and captured details of early wound complications as reported retrospectively by patients. There is a high chance that some side effects were under-reported because of this. If this is the case, then the results may underestimate the magnitude of the problem of treatment-related side effects and particularly wound complications (<6% in this study) in this population. External data from the literature suggest that this is the case with, for example, a much higher incidence of wound complications reported in the CAN-NCIC-SR2 trial of pre-operative radiotherapy compared to post-operative radiotherapy, 35% and 17% respectively.(6) Wound complication outcomes are being collected prospectively in the IMRiS study. The data on late effects and functional outcomes is being collected in real time and is therefore expected to be more robust.

Both planning studies included a relatively small number of cases, 15 and 10 for the extremity sarcoma and pelvic Ewing sarcoma studies, respectively. These are not unusual numbers for planning studies in radiotherapy. It is very difficult to know how best to power this type of feasibility study as the expected differences will vary significantly at different dose levels and for different techniques. For example, a big difference was anticipated at the low dose levels between VMAT and PBT, but a smaller effect at the high dose levels. For VMAT and 3DCRT, a big difference at high dose levels was anticipated. The number of 15 cases was selected for the extremity planning study as it was felt that at least three cases from each subsite was needed to comment meaningfully on the feasibility of this technique for extremity sarcoma as a heterogenous group (in terms of anatomical size/site) of tumours, and also to comment on the individual subsites. As such, this cohort was larger than any of the published planning studies in extremity sarcomas. The decision for 10 cases included in the planning study of VMAT and PBT in pelvic Ewing sarcoma was pragmatic, in that it was not possible to identify more than 10 cases that met the eligibility criteria and for which the complete planning dataset was available. The study may have been underpowered to detect subtle differences at the high dose levels because of this. Dose-volume

results for the normal tissues were well within tolerance for both techniques, however, and it is unlikely that such subtle differences would have a true clinical impact.

Limiting the eligibility criteria to young female patients for the pelvic Ewing sarcoma planning study, removed potential confounding factors of a more heterogeneous population that may have diluted the results and hindered their interpretation. While the question arises as to whether the superior high dose conformality seen with VMAT and PBT and the ability to deliver the required dose will also be applicable to male patients, it is likely to be the case, as for male patients there are fewer competing priorities for intra-pelvic organs for the optimisation software to consider.

The patients included in the pelvic planning study were 16 years old or older and plans were created as for adult patients that are no longer growing. For example, no attempt was made to apply a minimum homogenous dose across bone growth plates or vertebrae. These results should therefore not be extrapolated to the paediatric Ewing sarcoma population without taking this into account.

The dose used in the pelvic planning study was 54Gy, which was chosen as a frequently used dose as reflected by the literature, and the standard dose in the adjuvant as well as definitive setting in UK practice. These results may therefore not apply to patients treated to higher doses as is sometimes the case. The IMRiS trial allows for these higher doses and will report on the dose that can be safely achieved in such cases.

There was no attempt made to comment on the difference in skin dose between techniques in either planning study. This was because of the uncertainty in modelling the skin dose with VMAT.(28) Another area of uncertainty is the soft tissue corridor in extremity sites. A clinician defined corridor structure with a tolerance of $\leq$50% receiving 20Gy, was decided on, based on the approach used in the RTOG 0630 trial of image guided radiotherapy (58), and is also used in the IMRiS trial. There is no specific guidance on how to delineate this structure and the target dose-volume parameter has not been clinically validated. The incidence of oedema in RTOG0630 was acceptably low (5.3%). Experience during the VMAT planning study indicates that this structure should be utilised as an optimisation structure to drive high dose away from a specific longitudinal area of the limb. The clinical outcome and incidence of oedema with this approach will be reported by IMRiS, and correlation with the size and volume of the corridor structure will be explored.

Objective parameters were used to evaluate the target coverage achieved with the various technologies under investigations. There is, however, also a more subjective component to radiotherapy plan evaluation which requires visual evaluation of the 3D dose distribution in relation to the specific anatomy. All plans were assessed visually by myself, Dr Seddon and an experienced physicist in an attempt to remove potential bias from this subjective assessment.

The quality of the PBT planning was evaluated according to robustness of clinical target volume (CTV) coverage. At the time this was still a somewhat controversial approach and made it difficult to comment quantitively on some aspects of plan comparison such as PTV coverage and dose conformality around the target compared to VMAT. Plans were robustly and visually assessed, as would be done in clinical practice to decide the most appropriate and acceptable final plan, and it is unlikely that the lack of quantitative comparison would have materially affected the outcomes of the study. Robust optimisation has gained popularity and is the preferred approach that will be used for planning at the clinical PBT facility at UCLH.

Arguably the most important caveat with any pre-clinical research, is the uncertainty around whether the potential benefits identified will translate in clinical benefit. IMRT has been demonstrated to improve the late effects profile in head and neck, breast and prostate cancer in clinical trials. (29, 30) Planning studies in radiotherapy can be practice changing, and IMRT has been rolled out to many other tumour sites without additional prospective clinical evidence. A modelled improvement of the therapeutic index is unlikely to have a detrimental effect in practice. The dosimetric benefit to reduce dose to future skin flaps in extremity sarcomas using IMRT did not, however, translate into a significant reduction in wound complications in a phase II study.(78, 82)

Advances in radiotherapy technology has historically been incorporated into clinical practice without randomised prospective evidence in many instances. In the era of advanced radiotherapy technologies, with potential economic impact and limited resource, it is important to generate the evidence to support the use of new technologies in specific tumour sites and anatomical locations.(132) It is especially importance to test the principle in rare cancers. The preclinical results presented in this thesis are now being clinically tested in the prospective IMRiS trial.

6.4 Suggestions for future research

Strategies to reduce the volume of normal tissue receiving radiation dose can influence the therapeutic index. The work in this thesis has focussed on how advanced radiotherapy technologies may be used to achieve this in specific patient groups and has demonstrated the dosimetric benefit. Integrating new technologies into clinical practice creates a significant learning curve, and many factors interplay. There is still a lot of work to do to optimise the use of these new technologies for clinical benefit.

The possibility of dose escalation along the spine and in the pelvis with IMRT is being addressed in the high-grade bone sarcoma and chordoma cohort of the IMRiS phase II trial. We are planning to double plan cases retrospectively with PBT to understand how the two technologies compare in this situation.

Prospective collection of outcome and toxicity data for patients treated with PBT will be very important and will be embedded in the UK PBT treatment programme. This is a rare opportunity for collaboration and to capture data for the majority of patients treated nationally in a uniform way. This will provide useful information on the outcomes of the current standard indications of PBT. Other non-standard indications will need to be explored in a research setting, initially in planning studies followed by clinical cohort studies. One such question is regarding the potential benefit of PBT to improve outcomes in proximal medial thigh tumours. In the planning study presented in this thesis, the dose distributions with VMAT were sometimes similar to those resulting from 3DCRT, as entry dose through the lateral thigh had to be avoided to spare the corridor. More proximally VMAT was better able to reduce dose to pelvic organs and genitalia in most cases. This is a site recognised to be at high risk of wound complications, and so it is possible that the anticipated higher skin dose from PBT may out-weigh any dosimetric advantage in clinical practice.

Wound complications correlated strongly with radiotherapy late effects in the late effects survey presented here. Finding ways to reduce the incidence of wound complications should be a focus of future research. A large retrospective review of all extremity sarcoma cases treated with surgery at the Royal National Orthopaedic Hospital, with or without radiotherapy, is currently underway, auditing wound complications as one of the outcomes. Potential factors that could be explored in future research may emerge from these data.

The IMRiS and VORTEX trial radiotherapy plan data held by the RTTQA group is an important resource for evaluation of dosimetric parameters in extremity sarcomas, and their protential correlation with clinical outcomes and late effects. This project will be undertaken by Rita Simoes from the RTTQA group as part of her PhD research.

Other research on optimising the therapeutic index through radiobiological factors is currently underway. The Dose REduction in pre-operative radiotherapy for MYxoid liposarcomas (DOREMY) trial is one example (clinicaltrials.gov number NCT02106312). Several studies are exploring concurrent immune therapy with radiotherapy in early phase research.(133) Biomarkers of normal tissue and tumour radio sensitivity is being explored through the UK national RAPPER project (Radiogenomics: Assessment of Polymorphisms for Predicting the Effects of Radiotherapy).(127, 128)

6.5 Concluding remarks

The current radiotherapy research climate in the UK has made it possible to move sarcoma radiotherapy research onto the national agenda, with quality assured national prospective clinical trials in this rare disease through the VORTEX and IMRiS trials. It will be possible to collect PBT outcomes data in sarcoma patients prospectively on a national level in the UK as part of the national PBT treatment programme. The recent initiative to develop a national network in radiobiology and radiation oncology research (RadNet) from Cancer Research UK is making unprecedented funding opportunities available to researchers in this field.

The results of the IMRiS trial are eagerly awaited. Building on the results of the planning studies presented here, it is anticipated that IMRiS will provide valuable insights into whether IMRT will result in clinical benefit for patients with sarcoma.

7 Bibliography

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8 Appendix 1: LERTiSS protocol including data collection tools

Late Effects of Radiotherapy in Sarcoma Survey (LERTiSS)

A survey of late normal tissue effects and functional outcomes following radical radiotherapy in patients with limb/limb girdle bone and soft tissue sarcoma

Protocol v1.1

Sites and Contacts

Sites		
University College Hospital	University College London Hospitals NHS Foundation Trust and the London Sarcoma Service	250 Euston Road London NW1 2PG
Investigators		
Dr Beatrice Seddon	University College London Hospitals NHS Foundation Trust and the London Sarcoma Service	Tel: 020 3447 9866 beatrice.seddon@uclh.nhs.uk
Dr Franél le Grange	University College London Hospitals NHS Foundation Trust and the London Sarcoma Service	Tel: 020 3447 9866 franel.legrange@uclh.nhs.uk
Dr Anna Cassoni	University College London Hospitals NHS Foundation Trust and the London Sarcoma Service	Tel: 020 3447 9087 anna.cassoni@uclh.nhs.uk

Survey Summary

Late Effects of Radiotherapy in Sarcoma Survey (LERTiSS)

A survey of late normal tissue effects and functional outcomes following radical radiotherapy in patients with limb/limb girdle bone and soft tissue sarcoma

Aim: To assess and document the late side effects and functional outcomes of patients with limb/limb girdle bone and soft tissue sarcoma treated with radical radiotherapy within the London and South East Sarcoma Network centres. The data will be used as a historical reference as our practice evolves, and when new techniques are evaluated for introduction at our respective institutions.

Primary objectives:

- To evaluate late radiotherapy toxicities, limb functionality and overall level of disability

Secondary objectives:

- To correlate the incidence of late radiotherapy toxicities with radiotherapy plan parameters and dosimetric data
- To correlate late toxicity scores with limb functionality and overall disability
- To identify any subgroups at greater risk of developing late treatment related toxicity
- To establish a benchmark of outcomes of current treatment practice

Primary endpoints and outcome measures:

- Incidence of grade 2 or greater radiotherapy toxicity, as measured by the RTOG/EORTC late effects scoring system [1] and the LENT/SOMA score[2], in patients seen at the following time intervals following radiotherapy:
    - 1 to 2 years
    - 2 to 5 years
    - 5 to 10 years
- Limb functionality measured by the Toronto Extremity Salvage Score (TESS) [3]
- Overall disability measured through the general questions on the Toronto Extremity Salvage Score (TESS) [3]

Secondary endpoints and outcome measures:

- Correlation between radiotherapy plan and dosimetric parameters and grade 2 or greater late toxicity (RTOG and individual SOM scores)
- Correlation between grade 2 or greater late toxicity (RTOG and individual SOM scores) and TESS score
- Comparison of individual SOM scores (pain, fracture, fibrosis, oedema, joint movement) with results from the 2001 RMH survey.

Methods: A cross-sectional survey of patients, who have completed radical radiotherapy at least 12 months ago, will be carried out prospectively over a minimum period of twelve months. Data on late toxicity, limb functionality and overall disability will be collected when patients attend for routine follow up appointments. Data on disease and treatment specifics will be collected retrospectively from patient notes and radiotherapy plans.

Inclusion criteria:

- Histological confirmed soft tissue sarcoma or bone sarcoma
- Tumours of upper and lower limbs/limb girdles
- Previous treatment with radical radiotherapy (dose ≥45Gy EQD2)
- Minimum of 12 months interval since completion of radiotherapy
- Age 18 years or older
- **Exclusion criteria:**
- Patients with active locally recurrent disease
- Inability to give informed consent to the survey
- Inability to understand and complete the TESS questionnaire

Contents

1. Introduction

Background

Current practice

The current standard treatment for the local management of adult extremity Soft Tissue Sarcomas (STS) involves limb-sparing surgery with adjuvant radiotherapy in patients deemed at high risk of local disease recurrence.[4-6] This combined modality treatment achieves equivalent local control outcomes to surgical amputation with published local control rates of greater than 80% reported in recent series and a large systematic review.[5, 7-13] Radiotherapy may be given in the pre-operative or post-operative setting with external beam radiotherapy or brachytherapy, alone or in combination. There is limited information on the role of adjuvant radiotherapy for soft tissue sarcomas at other sites, including uterine leiomyosarcoma[6, 14, 15] and retroperitoneal sarcomas, where it may be used in highly selected cases.[6, 15] Radiotherapy is used in the combined modality treatment of bone and soft tissue Ewing's sarcoma. These tumours are considered to be radiosensitive and radiotherapy is used as definitive local treatment for inoperable tumours or as adjuvant to surgery in cases at high risk of local relapse.[19-22]

Indications for adjuvant radiotherapy of soft tissue sarcomas include tumour size more than 5cm, histological high grade tumours (Trojani grades 1 and 2), inadequate surgical margins, tumours involving the anatomical deep compartment, and cases where initial surgery was incomplete and a second procedure was required to achieve complete resection (R0). Radiotherapy is given in the preoperative setting in tumours of borderline resectability to improve the likelihood of complete surgical resection.

Three-dimensional conformal CT based external beam radiotherapy planning is our current standard practice for the treatment of extremity STS. Conventional three dimensional external beam radiotherapy plans for the treatment of limbs typically consist of an opposed pair of fields optimised and angled to spare a longitudinal corridor of normal tissue, and to minimise radiation dose to the weight-bearing bones, joint spaces and remaining normal tissues. The prescribed dose for soft tissue sarcomas in the preoperative setting is 50Gy in 25 fractions. In the post-operative setting the dose is 60 to 66Gy in 30 to 33 fractions, delivered in 1 or 2 phases. There is inevitably a significant volume of normal tissue that receives radiation doses close to the prescription dose or even higher due to dose hot spots created by the opposed fields.

Late effects of radiotherapy

The published data on late radiotherapy effects on normal tissues in patients with extremity sarcoma focuses mainly on the incidence of bone fracture which is reported at a rate of 4% - 8.6% at 5 years.
Several risk factors for fracture have been identified although these findings are not consistent across studies. Reported risk factors include periosteal stripping, radiation dose of 60Gy or above, female gender, age greater than 50 years, additional treatment with chemotherapy, anterior thigh tumours, marginal or intralesional resection, volume of bone receiving more than 40Gy, and higher maximum and mean dose to bone.[7, 24-28]

The reported range in incidence of other late effects include peripheral neuropathy 4%[7], joint stiffness 7 – 23%[7, 29], fibrosis 31- 48%[29], oedema 8 -23%[7, 25, 29], decrease in range of motion 32%, joint contracture 20%, decrease in muscle strength 20%, soft tissue induration 57% and long term pain 7%.[25] Reported risk factors for significant late soft tissue toxicity include the field size, more than 50% of the joint space in the radiation portal, the volume of tissue irradiated to more than 55Gy, the volume and dose to hot spots, and the total radiation prescription dose.[11] Additional side effects including bone growth defects and secondary malignancies have been described in the paediatric population.[30]

Fibrosis, joint stiffness and oedema have been shown to impact significantly on functional outcomes in a prospective study comparing pre-operative and post operative radiotherapy.[29]

New directions in radiotherapy delivery

Ongoing developments in radiotherapy aim to improve the effectiveness of treatment while limiting radiotherapy related side effect. There is limited published data on the use of novel radiotherapy technologies and techniques including Intensity Modulated Radiotherapy (IMRT) for extremity sarcomas. Planning studies have shown that IMRT can produce more conformal dose distributions with improved sparing of the bone, more homogeneous dose distributions, and reduction of the hot spots in the remaining normal tissues and skin.[31-33]
The ability of IMRT to reduce the volume of normal tissues receiving high radiation doses could potentially also lead to a reduction in late toxicity. A small prospective trial of surgery and IMRT in 41 patients with soft tissue sarcoma showed a 5 year actuarial local control rate of 94% at a median follow-up of 35 months, with an acceptable toxicity profile (bone fracture 4.8%).[34, 35]

Rationale

This service evaluation is aimed at assessing the late side effects and functional outcomes of patients with sarcoma of the limb/limb girdle treated with radiotherapy within the London and South East Sarcoma Network sarcoma centres. The data collected will establish a benchmark of long term outcomes of our current practice. The results from this survey will be interpreted in conjunction with retrospectively collected local control and survival data for the same period.

There is a need to improve long term functional outcomes for patients as highlighted in the *'Improving Outcomes: A Strategy for Cancer'* document published by the Department of Health in January 2011[36] and the recently published '*NHS Outcomes Framework 2012/2013'.* [37] Radiotherapy is an important component of multi modality treatment of sarcomas. Combined radiotherapy and surgery for patients with extremity soft tissue sarcoma has been established as the standard of care with excellent local control results, but at the price of long term side effects and loss of function. Data on functional outcomes from this survey will guide the planning of support services for these patients.

The potential of new technologies such as IMRT and IGRT to reduce the associated late tissue effects from this treatment needs to be evaluated in the clinical setting and this is the focus of ongoing research. Data on radiotherapy toxicities and functional outcomes will be used as a benchmark for comparison when advanced radiotherapy techniques, including IMRT and rotational arc therapy are evaluated for introduction at our respective institutions. The aim of this survey is to determine the incidence of late radiotherapy toxicities and functional outcomes in this cohort of patients and to correlate this to radiation dosimetric parameters. This is anticipated to facilitate the development of dose volume constraints when determining optimal class solutions for IMRT and rotational arc therapy.

2. Objectives

Primary objectives

- To evaluate late radiotherapy toxicities, limb functionality and overall level of disability

Secondary objectives

- To correlate the incidence of late radiotherapy toxicities with radiotherapy plan parameters and dosimetric data
- To identify any subgroups at greater risk of developing late treatment related toxicity
- To establish a benchmark of outcomes of current treatment practice

3. Outcome measures

Primary endpoints and outcome measures

- Incidence of grade 2 or greater radiotherapy toxicity, as measured by the RTOG/EORTC late effects scoring system [1] and the LENT/SOMA score[2], in patients seen at the following time intervals following radiotherapy: ○ 1 to 2 years ○ 2 to 5 years ○ 5 to 10 years

  The time from radiotherapy will be measured from the first day of treatment.

- Limb functionality as measured by the Toronto Extremity Salvage Score (TESS) [3]
- Overall disability as measured through the general questions on the Toronto Extremity Salvage Score (TESS) [3]

Secondary endpoints and outcome measures

- Correlation between dosimetric parameters and grade 2 or greater late toxicity (RTOG and individual SOM scores)
- Correlation between grade 2 or greater late toxicity (RTOG and individual SOM scores) and TESS score

4. Study Design

This is a prospective service evaluation study that will be carried out over twelve months. This period may be extended to allow data capture on maximum eligible patients. This will be a cross-sectional survey of patients attending sarcoma outpatient clinics for routine follow-up appointments. Patients will be clinically assessed for late toxicity and will be asked to complete a questionnaire on limb functionality and overall disability.

Patient selection

Patients will be recruited from the Sarcoma follow-up clinics at UCLH. The maximum interval between follow-up appointments usually does not exceed 12 months and it is anticipated that this period should allow assessment of most eligible patients.

Eligibility criteria

Inclusion criteria:

- Histological confirmed soft tissue sarcoma or bone sarcoma
- Tumours of upper and lower limbs/limb girdles
- Previous treatment with radical radiotherapy (≥45Gy EQD2)
- Minimum of 12 months interval since completion of radiotherapy
- Age 18 years and older

Exclusion Criteria:

- Patients with active locally recurrent disease
- Inability to give informed consent to the survey
- Inability to understand and complete the TESS questionnaire

Data collection

- Data will be collected at one clinic visit for each patient during the survey period.
- Data will be collected by:

- Co-investigators and clinical oncology SpRs (clinical evaluation of late toxicity)
- Research nurses (completion of questionnaires)

- Data will be collected on: (Appendix 1 and 2)
  - Patient details (demographic information, performance status at presentation, co-morbidities, current disease status, current systemic therapy) ○ Tumour details (site, histology, grade, size, depth, surgical margins) ○ Treatment details
    - Surgical procedures, wound complications
    - Radiotherapy plan parameters and dosimetric information (technique, field size, PTV volume, whether PTV crossed a joint, treatment dose and fractionation, PTV dose coverage, and the dose to normal tissues including bone and soft tissue outside the PTV)

- Late radiotherapy toxicity will be graded and documented according to the RTOG/EORTC scales [1] (Appendix 3) and selected criteria from the LENT/SOMA scales [2] (Appendix 4)
- Limb functionality and overall disability will be assessed with the Toronto Extremity Salvage Score (TESS). This short patient-completed questionnaire is specific to either upper or lower limb function, and measures the patient reported degree of disability affecting routine daily activities.[3, 38] (Appendix 5 and 6)

Statistical considerations

This is an observational study and the results will be descriptive. Data will be processed using Microsoft Excel software and commercially available statistical software.

The primary analysis will describe the incidence and severity of late toxicities observed. The rates of grade 2 or greater toxicities in patients seen at different time intervals following radiotherapy will be compared using chi-square tests. The degree of functional impairment and overall disability at different time intervals will be compared using t-tests or Wilcoxon rank sum tests depending on the data distribution.

The secondary analysis will explore associations between late toxicity and radiotherapy dosimetric parameters, as well as that between late toxicity and functional outcomes. Appropriate parametric or non-parametric statistical tests will be used depending on the distribution of the data.

5. Ethical Considerations

The study is a service evaluation and it does not involve an intervention in patient management. We estimate that it will have a minimal impact on patients' time. Informal questioning about functional levels and disability form part of routine clinical review and the TESS questionnaire has been developed and validated to provide a formal tool of reporting functional outcomes in this population group. The questionnaire is simple and can be completed in less than 15 minutes.

The study proposal has been reviewed by UCLH Research and Development department. It has been classified as audit/ service evaluation, and formal ethical approval is not required.

Patient informed consent

The nature and purpose of the survey will be explained to the patient by the clinician and the patient will be provided with an information sheet prior to giving consent. (Appendix 7 and 8)

Confidentiality

The personal data collected and all documents in this survey will be regarded as strictly confidential.
Data will be anonymised prior to presentation or publication of the results.

6. Financial considerations

This survey can be achieved within the scope of the current clinical follow-up pathway and will not require additional visits, time or resources.

7. Publication policy

Results from this survey will be collated and may be presented at scientific meetings or published in scientific journals. The manuscript will be prepared by a writing group, appointed from amongst the collaborators. All participating centres and investigators will be acknowledged in this publication. Authorship will depend on participation in the survey, contribution of patient data to the results, and contribution to the manuscript preparation. Data relating to this survey must not be reported or published without prior consultation with the other collaborators.

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Proforma for data collection in clinic

Late Effects of Radiotherapy in Sarcoma

*A separate form to be completed for each treatment site.

Centre _____ Date seen in clinic _____ Form completed by

_____ **PATIENT DATA:**

Name _____ Hospital no _____ Date of birth

_____

Current PS: 0 1 2 3 4 PS at presentation: 0 1 2 3 4

Is the patient currently on systemic treatment? No / Yes

Regimen _____

Relevant co-morbidities (e.g. diabetes, vascular insufficiency, cardiac failure, hip/knee replacement, etc) _____

Gait: normal / abnormal

Walking aid: yes / no Aid: _____ When used:

_____ **SURGERY:**

Date	Site	Complications

Surgery involved: Prosthesis: □ Skin graft: □ Musculoskeletal flap: □ Motor nerve damage: □

Periosteal stripping: □ Resection of deep vein: □

Wound complications requiring readmission to hospital within 120 days of surgery: yes / no

Details:

_____

_____ Other Comments:

_____

RTOG/EORTC late toxicity assessment form

*A separate form to be completed for each treatment site.

Patient name:		Date assessed:	
Hospital number:		Treatment Site:	
Centre:			

ORGAN TISSUE	0	Grade 1	Grade 2	Grade 3	Grade 4	5
SKIN	None	Slight atrophy Pigmentation change Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration	DEATH DIRECTLY RELATED TO RADIATION LATE EFFECTS
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosia) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic Slight field contracture <10% linear reduction	Severe induration and loss of subcutaneous tissue Field contracture >10% linear measurement	Necrosis	
BONE	None	Asymptomatic No growth retardation Reduced bone density	Moderate pain or tenderness Growth retardation Irregular bone sclerosis	Severe pain or tenderness Complete arrest of bone growth Dense bone sclerosis	Necrosis/ Spontaneous fracture	
JOINT	None	Mild joint stiffness Slight limitation of movement	Moderate stiffness Intermittent or moderate joint pain Moderate limitation of movement	Severe joint stiffness Pain with severe limitation of movement	Necrosis/ Complete fixation	

Selected LENT SOMA scales

*A separate form to be completed for each treatment site. Indicate the grade (0 – 4) for each parameter.

Patient name:		Hospital number:	

1. Muscle / Soft tissue						
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Score
Subjective Pain	None	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating	
Function	None	Interferes with athletic recreation	Interferes with work	Interferes with daily activity	Complete lack of function	
Objective Oedema	None	Present/ asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction	
Mobility & extremity function	None	Present/ asymptomatic	Symptomatic	Secondary dysfunction	No mobility, frozen	
Fibrosis	None	Detectable	≤20% of muscle	>20% - 50% of muscle	>50% of muscle	
Atrophy	None	≤10%	>10% - 20%	>20% - 50%	>50%	
Contraction	None		≤10% linear field	>10% - 30% linear field	>30% linear field	
Management Pain	None	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention	
Oedema	None		Compression	Medical intervention	Surgical intervention	
Mobility & extremity function	None	Occasional physiotherapy	Intermittent physiotherapy	Persistent physiotherapy/ medical intervention	Surgical intervention	
Fibrosis	None	Occasional physiotherapy	Intermittent physiotherapy		Surgical intervention	
Atrophy	None		Intermittent physiotherapy		Surgical intervention	
Total muscle/ soft tissue SOM score:						
LENT score = Total muscle/ soft tissue SOM score divided by 12:						

2. Skin / Subcutaneous tissue

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Score
Subjective Scaliness/ Roughness	None	Present/ asymptomatic	Symptomatic	Requires constant attention		
Sensation	None	Hypersensitive, pruritus	Intermittent pain	Persistent pain	Debilitating dysfunction	
Objective Oedema	None	Present/ asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction	
Alopecia (scalp)	None	Thinning	Patchy, permanent	Complete, permanent		
Pimentation change	None	Transitory, slight	Permanent, marked			
Ulcer/ necrosis	None	Epidermal only	Dermal	Subcutaneous	Bone exposed	
Telangiectasia	None	Minor	Moderate <50%	Gross ≥50%		
Fibrosis/ scar	None	Present/ asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction	
Atrophy/ Contraction (depression)	None	Present/ asymptomatic	Symptomatic/ <10%	Secondary dysfunction/ 10% - 30%	Total dysfunction/ >30%	
Management Dryness	None		Intermittent medical intervention	Medical intervention		
Sensation	None		Intermittent medical intervention	Continuous medical intervention		
Ulcer	None		Intermittent medical intervention	Medical intervention	Surgical intervention/ amputation	
Oedema	None		Intermittent medical intervention	Medical intervention	Surgical intervention/ amputation	
Fibrosis/ scar	None		Intermittent medical intervention	Medical intervention	Surgical intervention/ amputation	
Total skin/ subcutaneous SOM score:						
LENT score = Total skin/ subcutaneous SOM score divided by 14:						

3. Peripheral Nerves

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Score
Subjective Pain	None	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating	
Strength	None		Detectable weakness	Persistent weakness	Paralysis, transverse myelitis	
Sensory	None	Occasional paresthesia, hyperesthesia	Intermittent paresthesia	Persistent paresthesia	Paralysis	
Motor paresis	None	Occasional	<50% decrease from base line capabilities	≥50% decrease from base line capabilities	Paralysis	
Objective Motor dysfunction	None	<20% loss	20% – 30% loss	>30% - 50% loss	>50% loss	
Sensory dysfunction	None	Paresthesia	Vibration decrease	Decrease to pin prick	Complete anaesthesia	
Reflex	None	Decrease deep tendon reflex	Absent deep tendon reflex			
Management Pain	None	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention	
Motor dysfunction	None			Physical or medical intervention	Surgical intervention	
Sensory dysfunction	None			Physical or medical intervention	Surgical intervention	
Sensory	None				Neurosurgical intervention	
					Total peripheral nerve SOM score:	
					LENT score = Total peripheral nerve SOM score divided by 11:	

4. Mature bone (excluding mandible)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Score
Subjective Pain	None	Occasional & minimal	Intermittent & tolerable	Persistent & intense	Refractory & excruciating	
Function	None	Interferes with athletic recreation	Interferes with work	Interferes with daily activity	Complete lack of function	
Joint movement	None	Stiffness interfering with athletic recreation	Stiffness interfering with work	Stiffness interfering with daily activity	Complete fixation. Necrosis	
Objective Fracture	None			Partial thickness	Full thickness	
Mucosa soft tissue	None			Sequestration		
Skin over bone	None	Erythema	Ulcer	Sinus	Fistula	
Joint movement	None	<10% decrease	>10% - 30% decrease	>30% – 80% decrease	>80% decrease	
Management Pain	None	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention	
Function	None	Occasional physiotherapy	Intermittent physiotherapy	Persistent physiotherapy or medical intervention	Surgical intervention	
Joint movement	None	Occasional physiotherapy	Intensive physiotherapy	Corrective Surgery		
Total mature bone SOM score:						
LENT score = Total mature bone SOM score divided by 10:						

Seen by: Name _____ Signature _____ Date _____

Upper Extremity TESS questionnaire

Late effects of Radiotherapy in Sarcoma

(Davis 1996)(68)

General Guidelines

This questionnaire is designed as a measure of physical disability for patients undergoing limb salvage surgery for musculoskeletal tumours. It is a self-administered questionnaire. There is an upper extremity and lower extremity version of the questionnaire. Total completion time of the questionnaire averages 10 minutes.

Scoring

Each question is a measure of the difficulty that the individual has performing the task. The total potential score for an item is a perfect performance score (ie. 5).

The scale has been designed to allow individuals to respond to a non-applicable category on an item if it is not something they perform in their everyday life. Consequently, a total questionnaire score, if desired, would be a standardized score ranging from 0 to 100 calculated by:

$$\frac{\textit{sum of the item scores - \# items}}{\textit{possible score range}} \; X\ 100\%,$$

where, *sum of the item scores* = sum of difficulty responses

 # items = items completed excluding the N/A response items

possible score range = (5 x #items) - (1 x #items)

Upper Extremity TESS questionnaire

Patient name:		Hospital number:	
Date form completed:		Centre:	

Please complete the following questions. Put 'X' beside the most appropriate answer:

A. Please state your current work status:

- ☐ Employed / self-employed full-time
- ☐ Employed / self-employed part-time
- ☐ Unemployed
- ☐ Retired
- ☐ Student
- ☐ Disabled

B. If you are employed / self-employed, please give your current job title / role at work:

_____

C. Describe your leisure activities (ie sports, reading, gardening, etc)

_____

_____

D. Are you:

- ☐ Right handed
- ☐ Left handed
- ☐ Ambidextrous

E. Do you take any of the following pain medication?

- ☐ None
- ☐ Anti-inflammatory pain killers e.g. ibuprofen, diclofenac
- ☐ Mild pain killers e.g. paracetamol, Co-codamol
- ☐ Strong pain killers e.g. morphine, oxycodone

Upper Extremity TESS questionnaire

Patient name:		Hospital number:	

F. How frequently do you take pain medication?

- ☐ Occasionally / not every day
- ☐ Once a day
- ☐ Twice a day
- ☐ Three times a day or more
- ☐ Not applicable

G. Do you think that the treatment you had has had an impact on your lifestyle and your ability to perform your daily activities?

- ☐ Yes
- ☐ No

H. If you are worse, how much worse are you?

- ☐ Not applicable, treatment had no impact
- ☐ Almost the same, no real change
- ☐ A little worse
- ☐ Moderately worse
- ☐ A lot worse
- ☐ A great deal worse

If you are better, how much better are you?

- ☐ Not applicable, no impact
- ☐ Almost the same, no real change
- ☐ A little better
- ☐ Moderately better
- ☐ A lot better
- ☐ A great deal better

I. Are these changes acceptable in your opinion?

- ☐ Yes
- ☐ No
- ☐ Not applicable

Upper Extremity TESS questionnaire

Patient name:		Hospital number:	

The following questions are about activities commonly performed in daily life. Each question asks that you mark each item (as in the examples below) opposite the description that best describes your ability to perform each task during the **past week**. Some activities will be extremely easy for you to do, others will be extremely difficult or impossible.

EXAMPLE:

Peeling vegetables is:

1____impossible to do
2____extremely difficult
3____moderately difficult
4____a little bit difficult
5____not at all difficult
00___This task is not applicable to me

You should choose the response "impossible to do...." if the activity is **something that you normally do** in your daily activities but are **now unable to do** because of physical limitations such as weakness, stiffness or pain.

If you do not perform an activity as part of your normal lifestyle you would choose the response "00" to indicate that the item is not applicable.

Mark all items ensuring that you choose the description that most accurately describes your abilities in the **past week.**

1) Putting on a pair of trousers is:

1____impossible to do
2____extremely difficult
3____moderately difficult
4____a little bit difficult
5____not at all difficult
00___This task is not applicable to me

Upper Extremity TESS questionnaire

Patient name:		Hospital number:	

2) Tying shoe laces is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

3) Putting on a pair of socks or stockings is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

4) Showering is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

5) Dressing my arms and upper body is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

Upper Extremity TESS questionnaire

Patient name:		Hospital number:	

6) Buttoning a shirt is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

7) Tying a tie or a bow at the neck of a blouse is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

8) Putting on make-up or shaving is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

9) Brushing your teeth is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

Upper Extremity TESS questionnaire

Patient name:		Hospital number:	

10) Brushing your hair is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

11) Doing light household chores is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

12) Gardening is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

13) Preparing and serving meals is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

Upper Extremity TESS questionnaire

Patient name:		Hospital number:	

14) Cutting food while eating is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

15) Drinking from a glass is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

16) Performing heavy household chores is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

17) Going shopping is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

Upper Extremity TESS questionnaire

Patient name:		Hospital number:	

18) Giving or receiving change (ie. coins or notes) is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

19) Carrying a shopping bag or briefcase is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

20) Lifting a box to an overhead shelf is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

21) Turning a key in a lock is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

Upper Extremity TESS questionnaire

Patient name:		Hospital number:	

22) Pushing or pulling open a door is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

23) Writing is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

24) Picking up small items is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

25) Completing my usual duties at work is: (Work includes a job outside the home or as a homemaker.)

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

Upper Extremity TESS questionnaire

Patient name:		Hospital number:	

26) Working my usual number of hours is: (Working includes both a job outside the home and as a homemaker.)

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

27) Participating in my usual leisure activities is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

28) Socialising with friends and family is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

29) Participating in my usual sporting activities is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

Upper Extremity TESS questionnaire

Patient name:		Hospital number:	

1. Considering all the activities in which I participate in daily life, I would rate my ability to perform these activities during the past week as:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

2. I would rate myself as being:

1____completely disabled

2____severely disabled.

3____moderately disabled.

4____mildly disabled.

5____not at all disabled

Please comment below on any activities you find difficult to perform or on any other difficulties you experience due to the problem you currently have in your arm that you feel are important and have not been asked about in this questionnaire

_____

_____

_____

_____

Please check to make sure that you have not missed any questions.

Thank you for taking the time to answer these questions.

Lower Extremity TESS questionnaire

Late effects of Radiotherapy in Sarcoma

(Davis 1996)(68)

General Guidelines

This questionnaire is designed as a measure of physical disability for patients undergoing limb salvage surgery for musculoskeletal tumours. It is a self-administered questionnaire. There is an upper extremity and lower extremity version of the questionnaire. Total completion time of the questionnaire averages 10 minutes.

Scoring

Each question is a measure of the difficulty that the individual has performing the task. The total potential score for an item is a perfect performance score (ie. 5).

The scale has been designed to allow individuals to respond to a non-applicable category on an item if it is not something they perform in their everyday life. Consequently, a total questionnaire score, if desired, would be a standardized score ranging from 0 to 100 calculated by:

$$\frac{\textit{sum of the item scores - \# items}}{\textit{possible score range}} \; X\ 100\%,$$

where, *sum of the item scores* = sum of difficulty responses

 # items = items completed excluding the N/A response items

possible score range = (5 x #items) - (1 x #items)

Lower Extremity TESS questionnaire

Patient name:		Hospital number:	
Date form completed:		Centre:	

Please complete the following questions. Put 'X' beside the most appropriate answer:

A. Please state your current work status:

- ☐ Employed / self-employed full-time
- ☐ Employed / self-employed part-time
- ☐ Unemployed
- ☐ Retired
- ☐ Student
- ☐ Disabled

B. If you are employed / self-employed, please give your current job title / role at work:

_____

__

C. Describe your leisure activities (ie sports, reading, gardening, etc)

_____

_____

____

D. Do you take any of the following pain medication?

- ☐ None
- ☐ Anti-inflammatory pain killers e.g. ibuprofen, diclofenac
- ☐ Mild pain killers e.g. paracetamol, Co-codamol
- ☐ Strong pain killers e.g. morphine, oxycodone

Lower Extremity TESS questionnaire

Patient name:		Hospital number:	

F. How frequently do you take pain medication?

- ☐ Occasionally / not every day
- ☐ Once a day
- ☐ Twice a day
- ☐ Three times a day or more
- ☐ Not applicable

G. Do you think that the treatment you had has had an impact on your lifestyle and your ability to perform your daily activities?

- ☐ Yes
- ☐ No

H. If you are worse, how much worse are you?

- ☐ Not applicable, treatment had no impact
- ☐ Almost the same, no real change
- ☐ A little worse
- ☐ Moderately worse
- ☐ A lot worse
- ☐ A great deal worse

If you are better, how much better are you?

- ☐ Not applicable, treatment had no impact
- ☐ Almost the same, no real change
- ☐ A little better
- ☐ Moderately better
- ☐ A lot better
- ☐ A great deal better

I. Are these changes acceptable in your opinion?

- ☐ Yes
- ☐ No
- ☐ Not applicable

Lower Extremity TESS questionnaire

Patient name:		Hospital number:	

The following questions are about activities commonly performed in daily life. Each question asks that you mark each item (as in the examples below) opposite the description that best describes your ability to perform each task during the **past week**. Some activities will be extremely easy for you to do, others will be extremely difficult or impossible.

EXAMPLE:

Riding a bicycle is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

You should choose the response "impossible to do...." if the activity is **something that you normally do** in your daily activities but are **now unable to do** because of physical limitations such as weakness, stiffness or pain.

If you do not perform an activity as part of your normal lifestyle you would choose the response "00" to indicate that the item is not applicable.

Mark all items ensuring that you choose the description that most accurately describes your abilities in the **past week.**

1) Putting on a pair of trousers is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

Lower Extremity TESS questionnaire

Patient name:		Hospital number:	

2) Putting on shoes is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

3) Putting on a pair of socks or stockings is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

4) Showering is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

5) Light household chores such as tidying and dusting are:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

Lower Extremity TESS questionnaire

Patient name:		Hospital number:	

6) Gardening is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

7) Preparing meals is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

8) Going shopping is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

9) Heavy household chores such as vacuuming and moving furniture is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

Lower Extremity TESS questionnaire

Patient name:		Hospital number:	

10) Getting in and out of the bath is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

11) Getting out of bed is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

12) Rising from a chair is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

13) Kneeling is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

Lower Extremity TESS questionnaire

Patient name:		Hospital number:	

14) Bending to pick something up off the floor is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

15) Walking upstairs is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

16) Walking downstairs is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

17) Driving is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

Lower Extremity TESS questionnaire

Patient name:		Hospital number:	

18) Walking within the house is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

19) Walking outdoors is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

20) Sitting is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

21) Walking up or down hills or a ramp is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

Lower Extremity TESS questionnaire

Patient name:		Hospital number:	

22) Standing is:

1____impossible to do
2____extremely difficult
3____moderately difficult
4____a little bit difficult
5____not at all difficult
00___This task is not applicable to me

23) Getting up from kneeling is:

1____impossible to do
2____extremely difficult
3____moderately difficult
4____a little bit difficult
5____not at all difficult
00___This task is not applicable to me

24) Getting in and out of a car is:

1____impossible to do
2____extremely difficult
3____moderately difficult
4____a little bit difficult
5____not at all difficult
00___This task is not applicable to me

25) Participating in sexual activities is:

1____impossible to do
2____extremely difficult
3____moderately difficult
4____a little bit difficult
5____not at all difficult
00___This task is not applicable to me

Lower Extremity TESS questionnaire

Patient name:		Hospital number:	

26) Completing my usual duties at work is: (Work includes both a job outside the home and as a homemaker.)

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

27) Working my usual number of hours is: (Working includes both a job outside the home and as a homemaker.)

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

28) Participating in my usual leisure activities is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

29) Socialising with friends and family is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

Lower Extremity TESS questionnaire

Patient name:		Hospital number:	

30) Participating in my usual sporting activities is:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

00___This task is not applicable to me

1. Considering all the activities in which I participate in daily life, I would rate my ability to perform these activities during the past week as:

1____impossible to do

2____extremely difficult

3____moderately difficult

4____a little bit difficult

5____not at all difficult

2. I would rate myself as being:

1____completely disabled

2____severely disabled.

3____moderately disabled.

4____mildly disabled.

5____not at all disabled

Please comment below on any activities you find difficult to perform or on any other difficulties you experience due to the problem you currently have in your leg that you feel are important and have not been asked about in this questionnaire

_____

_____

_____

Please check to make sure that you have not missed any questions.

Thank you for taking the time to answer these questions.

LERTiSS Patient information sheet

A survey of late side effects of radiotherapy used for the treatment of sarcoma

You are being invited to take part in a survey. Before you decide it is important for you to understand why the survey is being done and what it will involve. Please take time to read the following information carefully and ask one of the doctors or nurses on the sarcoma team if there is anything that is not clear, or if you would like further information. It is important that you read and understand this information sheet before you decide whether or not to take part.

Why have I been chosen and what is the purpose of the survey?

You have been invited to take part in this survey because in the past you have had radiotherapy as part of the treatment for sarcoma. It is important that we monitor any side effects of the treatment and whether it has any impact on activities of every day life. This will help us to understand the long term effects of treatment and guide us when we try to reduce and prevent side effects in future. We are asking everyone who has had radiotherapy as part of their treatment for sarcoma to take part.

Do I have to take part in the survey?

Your participation is entirely voluntary. If you choose to take part you may withdraw at any time. You do not have to give any reason for your decision. This will not affect any care or treatment that you might have in future.

What will happen to me if I take part?

You will see one of the doctors on the sarcoma team as normal. You will be asked to sign a consent form before you take part in the survey. You will be asked about the effects of the radiotherapy on the area of your body that was treated and your doctor will examine you as normal, including the area where you were treated. The questions and the examination will be no more than is usually done at your clinic visits. The findings will be formally recorded on a data sheet and in your case notes. In addition you will be asked to complete a short questionnaire about any effect from the treatment on your routine daily activities. This questionnaire should not take more than 10 to15 minutes to complete.

Will my taking part in this survey be kept confidential?

All your details will be treated as strictly confidential and will be covered under the Data Protection Act 1998. Any information that leaves the hospital will have your personal details including your name and address removed.

What will happen to the results of the survey?

The results of this survey will be used to guide the future development of our radiotherapy service for patients with sarcoma. The results may be presented at a meeting or published in a medical journal. If you would like a summary of the results when available, please inform your doctor.

Contact for further information

You will be given a copy of this information sheet and the signed copy of the consent form for you to keep. Please feel free to ask any further questions of the doctors and nurses looking after you before deciding to take part in this survey.

Contact Name _____
Contact Number _____

LERTiSS Patient consent form

A Survey of late side effects of radiotherapy used for the treatment of sarcoma

• I confirm that I have read and understood the Patient Information Sheet and I have had the opportunity to ask questions and discuss the study.	☐
• I understand that I am taking part voluntarily and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
• I understand that sections of my medical notes which identify me by name may be looked at by responsible individuals at UCLH and the RMH where it is relevant to my taking part in this study. I give permission for these individuals to have access to my records. However, I understand that I will not be identified by name in any reports or publications resulting from this study.	☐
• I agree to take part in the '*Survey of late normal tissue effects and functional outcomes following radical radiotherapy in patients with limb/limb girdle bone and soft tissue sarcoma'*	☐

_____	_____	_____
Name of patient	Signature	Date
_____	_____	_____
Name of person taking consent	Signature	Date

9 Appendix 2 LERTiSS statistical analysis data

Figure 9.1 Univariate analysis of RTOG late effects scores

Continuous variables																												
	RTOG >= 2				RTOG >= 3				RTOG subcuta >= 2				RTOG subcuta >= 3				RTOG skin >= 3				RTOG bone = 4				RTOG joint >= 3			
	OR	LL	UL	p-value	OR	LL	UL	p-value	OR	LL	UL	p-value	OR	LL	UL	p-value	OR	LL	UL	p-value	OR	LL	UL	p-value	OR	LL	UL	p-value
Age at start of radiotherapy (for an increase in 10 years)	1.1	1.0	1.3	0.07	0.97	0.80	1.18	0.78	1.2	1.0	1.4	0.02	0.8	0.6	1.1	0.14	1.0	0.8	1.3	0.88	1.0	0.7	1.6	0.91	0.8	0.5	1.1	0.16
Time from end of radiotherapy (for an increase of 5 years)	0.9	0.7	1.3	0.71	1.40	0.95	2.06	0.10	0.9	0.6	1.3	0.56	1.1	0.6	2.0	0.72	1.1	0.6	1.9	0.76	1.9	0.9	3.9	0.12	1.8	1.0	3.2	0.07
Tumour size (for an increase of 5cm)	1.5	1.2	2.1	0.00	1.78	1.27	2.50	0.00	1.6	1.2	2.1	0.00	1.7	1.1	2.6	0.02	1.4	0.9	2.3	0.12	1.6	0.8	3.0	0.22	3.3	1.8	6.1	0.00
Categorical variables																												
	RTOG >= 2				RTOG >= 3				RTOG subcuta >= 2				RTOG subcuta >= 3				RTOG skin >= 3				RTOG bone = 4				RTOG joint >= 3			
	OR	LL	UL	p-value	OR	LL	UL	p-value	OR	LL	UL	p-value	OR	LL	UL	p-value	OR	LL	UL	p-value	OR	LL	UL	p-value	OR	LL	UL	p-value
ECOG performance status at the time of radiotherapy				0.08				0.43				0.08				0.84				0.05				0.46				0.49
0	1.0	.	.		1.00	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
1	1.8	0.9	3.7		1.73	0.75	3.97		2.0	1.0	4.1		1.3	0.4	4.2		2.9	1.0	8.2		2.0	0.3	11.1		0.5	0.1	3.7	
2	3.3	0.6	16.7		0.82	0.10	6.93		2.6	0.6	10.8		1.8	0.2	15.6		1.0	.	.		1.0	.	.		2.7	0.3	25.0	
Presence of any comorbidities that may affect limb function				0.36				0.66				0.79				0.40				0.79				0.01				0.43
No	1.0	.	.		1.00	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	1.4	0.7	2.6		1.21	0.51	2.86		1.1	0.6	2.2		0.5	0.1	2.5		0.8	0.2	3.0		9.5	1.7	53.4		0.5	0.1	3.7	
Dominant arm involved (upper limb sites only)				0.90				0.67				0.52				.				0.67				.				0.13
No	1.0	.	.		1.00	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	0.9	0.3	2.8		0.73	0.17	3.09		1.6	0.4	6.4		1.0	.	.		1.5	0.2	9.8		1.0	.	.		0.2	0.0	2.0	
Site (upper vs lower limb)				0.08				0.59				0.01				0.54				0.67				0.67				0.01
Upper	1.0	.	.		1.00	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Lower	1.7	0.9	3.1		0.80	0.36	1.78		2.5	1.2	5.4		1.5	0.4	5.3		0.8	0.3	2.3		1.6	0.2	13.7		0.2	0.1	0.7	
Location relative to the deep fascia				0.13				0.03				0.10				0.04				0.63				.				.
Deep	0.5	0.1	2.0		1.00	.	.		0.6	0.1	3.2		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Superficial	1.7	0.9	3.1		0.42	0.14	1.25		1.9	1.0	3.6		0.2	0.0	1.4		0.7	0.2	2.7		1.0	.	.		1.0	.	.	
Number of surgical procedures				0.27				0.26				0.95				0.20				0.36				0.02				0.61
zero-one operation	1.0	.	.		1.00	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
More than one operation	1.3	0.8	2.3		1.50	0.74	3.05		1.0	0.6	1.7		0.5	0.2	1.5		0.6	0.2	1.8		8.8	1.0	76.8		0.7	0.2	2.8	
Wound complications				0.01				0.41				0.00				0.04				0.89				.				0.50
No	1.0	.	.		1.00	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	5.9	1.3	27.0		1.81	0.47	6.93		5.7	1.7	19.0		5.3	1.3	21.9		1.2	0.1	9.6		1.0	.	.		2.3	0.3	19.6	
Complex surgery				0.01				0.00				0.11				0.33				0.42				0.00				0.00
No	1.0	.	.		1.00	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	2.3	1.3	4.1		3.73	1.78	7.81		1.6	0.9	2.9		1.7	0.6	5.1		1.5	0.5	4.4		13.3	1.5	116.4		9.6	1.9	47.7	
(Neo)adjuvant chemotherapy				0.37				0.00				0.48				0.02				0.03				0.83				0.00
No	1.0	.	.		1.00	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	1.4	0.7	2.9		3.52	1.53	8.09		1.3	0.6	2.9		4.0	1.4	11.7		3.6	1.3	10.5		1.3	0.1	11.2		18.5	4.5	75.9	
Timing of radiotherapy				0.08				0.64				0.65				0.50				.				0.85				.
Post-operative	1.0	.	.		1.00	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Pre-operative	0.5	0.2	1.1		0.77	0.25	2.36		0.8	0.4	1.9		1.6	0.4	6.0		1.0	.	.		1.2	0.1	11.0		1.0	.	.	
Radiotherapy field crossing a joint				0.46				0.53				0.58				0.23				0.10				0.94				0.10
No	1.0	.	.		1.00	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	1.2	0.7	2.1		0.79	0.38	1.65		0.9	0.5	1.5		0.5	0.2	1.5		0.4	0.2	1.2		0.9	0.1	6.7		3.4	0.7	16.6	
Radiotherapy dose groups				0.11				0.10				0.21				0.04				0.05				0.53				0.08
< 60Gy	1.0	.	.		1.00	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
60Gy	0.9	0.5	1.6		0.56	0.25	1.27		0.9	0.5	1.9		0.3	0.1	1.1		0.7	0.2	2.5		1.9	0.2	16.7		0.3	0.1	1.2	
>60Gy	2.0	0.8	5.1		1.45	0.51	4.11		1.9	0.8	4.8		1.6	0.5	5.9		3.2	0.8	12.3		1.0	.	.		1.4	0.3	6.8	
Muscle flap				0.08				0.71				0.05				0.94				0.88				.				.
No	1.0	.	.		1.00	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	2.5	0.9	7.4		0.76	0.17	3.48		2.8	1.0	7.5		0.9	0.1	7.5		0.9	0.1	6.9		1.0	.	.		1.0	.	.	
Skin graft				0.12				0.79				0.25				.				0.39				.				.
No	1.0	.	.		1.00	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	2.3	0.8	6.8		0.82	0.18	3.77		1.8	0.7	5.1		1.0	.	.		2.1	0.4	10.3		1.0	.	.		1.0	.	.	
Bone prosthesis or fixation				0.00				0.00				0.23				0.00				0.28				0.00				0.00
No	1.0	.	.		1.00	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	4.3	1.5	11.8		10.31	4.13	25.78		1.7	0.7	4.1		3.7	1.1	12.7		2.2	0.6	8.4		21.1	3.6	122.4		23.4	5.4	101.7	
Gender				0.37				0.22				0.04				0.31				0.22				0.48				0.64
Female	1.0	.	.		1.00	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Male	0.8	0.5	1.3		0.64	0.31	1.31		0.6	0.3	1.0		0.6	0.2	1.7		0.5	0.2	1.5		0.5	0.1	3.1		0.7	0.2	2.7	

Figure 9.2 Univariate analysis of SOM late effects scores

Continuous variables																				
	SOM fibrosis >= 2				SOM oedema >= 2				SOM pain >= 2				SOM pain >= 3				SOM joint >= 2			
	OR	LL	UL	p-value	OR	LL	UL	p-value	OR	LL	UL	p-value	OR	LL	UL	p-value	OR	LL	UL	p-value
Age at start of radiotherapy (for an increase in 10 years)	1.1	1.0	1.4	0.11	1.1	0.9	1.3	0.57	1.0	0.8	1.2	0.81	0.8	0.5	1.1	0.18	0.7	0.5	0.8	0.00
Time from end of radiotherapy (for an increase of 5 years)	1.0	0.7	1.4	0.90	1.3	0.8	2.0	0.32	1.0	0.6	1.5	0.96	0.4	0.1	1.7	0.13	1.8	1.2	2.7	0.01
Tumour size (for an increase of 5cm)	1.7	1.2	2.2	0.00	1.6	1.1	2.4	0.01	1.5	1.1	2.1	0.02	1.8	1.0	3.2	0.05	2.2	1.5	3.2	0.00
Categorical variables																				
	SOM fibrosis >= 2				SOM oedema >= 2				SOM pain >= 2				SOM pain >= 3				SOM joint >= 2			
	OR	LL	UL	p-value	OR	LL	UL	p-value	OR	LL	UL	p-value	OR	LL	UL	p-value	OR	LL	UL	p-value
ECOG performance status at the time of radiotherapy				0.30				0.52				0.02				0.37				0.11
0	1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
1	1.6	0.8	3.5		1.8	0.7	4.6		1.8	0.7	4.6		1.3	0.1	12.4		1.0	0.3	3.2	
2	2.3	0.5	9.9		1.3	0.2	11.3		9.1	2.1	40.0		7.6	0.7	82.3		5.8	1.3	26.9	
Presence of any comorbidities that may affect limb function				0.65				0.65				0.10				0.67				0.58
No	1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	1.2	0.6	2.6		1.3	0.5	3.3		2.0	0.9	4.4		1.4	0.3	7.4		1.3	0.5	3.5	
Dominant arm involved (upper limb sites only)				0.48				0.57				0.67				.				0.40
No	1.0	.	.		1.0	.	.		1.0	.	.		.	.	.		1.0	.	.	
Yes	1.7	0.4	8.2		2.0	0.2	23.6		1.5	0.2	9.8		.	.	.		0.5	0.1	2.5	
Site (upper vs lower limb)				0.11				0.08				0.09				.				0.18
Upper	1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Lower	1.9	0.8	4.3		2.7	0.8	9.2		2.2	0.8	6.0		1.0	.	.		0.5	0.2	1.3	
Location relative to the deep fascia				0.63				0.23				0.66				.				0.07
Deep	0.4	0.0	3.3		1.8	0.4	9.0		1.0	.	.		1.0	.	.		1.0	.	.	
Superficial	1.0	0.5	2.2		0.4	0.1	1.5		1.2	0.5	2.8		1.0	.	.		0.2	0.0	1.7	
Number of surgical procedures				0.42				0.01				0.17				0.03				0.35
zero-one operation	1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
More than one operation	0.8	0.4	1.5		0.3	0.1	0.8		1.6	0.8	3.3		5.3	1.0	26.8		1.5	0.7	3.4	
Wound complications				0.01				0.69				0.49				0.06				0.54
No	1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	5.0	1.6	15.5		0.7	0.1	5.4		1.6	0.4	6.2		6.7	1.2	36.9		1.7	0.3	8.1	
Complex surgery				0.19				0.51				0.00				0.01				0.00
No	1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	1.6	0.8	3.0		0.7	0.3	1.9		4.0	2.0	8.3		8.2	1.6	41.6		7.8	3.0	19.8	
(Neo)adjuvant chemotherapy				0.20				0.07				0.16				0.93				0.00
No	1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	1.7	0.8	3.9		2.6	1.0	6.6		1.9	0.8	4.7		0.9	0.1	7.6		12.8	5.2	31.9	
Timing of radiotherapy				0.96				0.67				0.43				0.10				0.09
Post-operative	1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Pre-operative	1.0	0.4	2.4		0.8	0.2	2.7		1.5	0.6	3.6		3.9	0.9	17.0		0.2	0.0	1.8	
Radiotherapy field crossing a joint				0.50				0.51				0.31				0.11				0.01
No	1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	0.8	0.4	1.5		0.8	0.3	1.8		0.7	0.3	1.4		0.3	0.1	1.5		3.7	1.3	10.3	
Radiotherapy dose groups				0.02				0.32				0.48				0.25				0.00
< 60Gy	1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
60Gy	0.6	0.3	1.2		1.2	0.4	3.5		0.6	0.3	1.3		0.3	0.1	1.2		0.2	0.1	0.5	
>60Gy	1.8	0.7	4.6		2.5	0.7	9.1		0.7	0.2	2.3		0.4	0.0	4.2		0.7	0.2	2.1	
Muscle flap				0.15				0.46				0.40				0.11				0.32
No	1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	2.2	0.8	6.3		0.5	0.1	3.9		1.7	0.5	5.5		4.8	0.9	25.9		2.0	0.5	7.7	
Skin graft				0.32				0.51				0.03				.				.
No	1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	1.8	0.6	5.4		0.5	0.1	4.2		3.6	1.2	10.5		1.0	.	.		1.0	.	.	
Bone prosthesis or fixation				0.31				0.36				0.00				0.22				0.00
No	1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Yes	1.6	0.6	4.2		1.8	0.5	5.6		4.8	1.9	11.8		3.2	0.6	16.6		21.8	8.0	59.7	
Gender				0.90				0.05				0.16				0.57				0.92
Female	1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.		1.0	.	.	
Male	1.0	0.6	1.9		0.4	0.2	1.0		0.6	0.3	1.2		0.7	0.2	2.8		1.0	0.4	2.2	

10 Appendix 3 Publications and posters arising from this thesis

10.1 Late effects of 3D conformal radiotherapy in extremity bone and soft tissue sarcomas (LERTiSS)

10.1.1 Interim analysis poster presented at ASCO in September 2014 and CTOS in October 2014

Royal National Orthopaedic Hospital NHS Trust

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LATE EFFECTS OF RADIOTHERAPY IN EXTREMITY SARCOMAS (abstract #3145)

F le Grange†, A Cassoni†, AA Kirkwood*, B Seddon†

†University College London Hospitals; *CR UK and UCL Cancer Trials Centre

BONE CANCER RESEARCH TRUST

This research project was supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

BACKGROUND

Radiotherapy (RT) for extremity sarcomas

RT is an important component of multi modality treatment of sarcomas. Combined RT and surgery has been established as the standard of care for extremity soft tissue sarcoma with excellent local control results, but at the price of long term side effects and loss of function. RT is used in the combined modality treatment of Ewing sarcoma. It is not routinely used to treat other bone sarcomas, but may be used in individual cases [1-3].

3D conformal CT-based RT (3DCRT)

3DCRT is the current standard approach to extremity sarcomas at UCLH. In order to achieve adequate radiation doses to the tumour with this technique, large volumes of normal tissue must also be treated, potentially increasing the risk of side effects.

Late treatment toxicity

The data on late treatment toxicity following 3DCRT are mainly retrospective and reported incidence and prognostic factors vary across series [4-7]. Evidence from a prospective trial suggests a correlation with timing of RT, treated volume and dose. Rates of significant fibrosis (≥ grade 2) were related to poorer limb function [8].

Introducing new RT technologies

The potential of new technologies such as IMRT and IGRT to reduce the associated late tissue effects from RT is the focus of ongoing research. Data from this survey will be used as a benchmark for comparison when advanced radiotherapy techniques, including IMRT, are evaluated for introduction at UCLH.

PURPOSE/ OBJECTIVES

- Document late normal tissue effects and patient reported outcomes after radical RT in patients with extremity bone and soft tissue sarcoma.
- Establish a benchmark of outcomes of current treatment practice
- Identify any subgroups at greater risk of developing late treatment related toxicity

RESULTS

- Survey period: August 2012 - March 2013
- RT was given between 1991- 2012.
- Data collected on 161 cases

Missing data are not shown in the tables

PATIENT CHARACTERISTICS		Years
Age at start of RT	median (range)	51 (13 - 88)
Age at survey	median (range)	55 (19 - 91)
		N (%)
Sex	Female	83 (52)
	Male	78 (48)
Performance status prior to RT	0	99 (61)
	1	31 (19)
	2	6 (4)
Current performance status (ECOG)	0	119 (74)
	1	24 (15)
	2	6 (4)
	3	4 (2)
Time lapse since RT	<2 years	35 (22)
	2-5 years	75 (46)
	>5 years	51 (32)
Disease status at survey	Disease free	145 (90)
	Distant relapse	14 (9)
Receiving chemotherapy at survey	No	154 (96)
	Yes	7 (4)
Comorbidities that may affect limb function	No	130 (81)
	Yes	31 (19)

MATERIALS/ METHODS

- Prospective cross-sectional survey of patients who completed RT (≥45Gy EQD2) to a limb ≥12 months earlier
- Exclusion criteria:
  - Active local recurrence
  - Amputation of the treated limb
- Disease and treatment specifics collected retrospectively
- Endpoints:
  - Late toxicity (RTOG/EORTC)
  - Patient reported limb functionality -Toronto Extremity Salvage Score (TESS)

RESULTS

DISEASE CHARACTERISTICS		N (%)
Limb affected	Upper	39 (24)
	Lower	122 (76)
Dominant hand affected (upper limb site N=39)	No	17 (14)
	Yes	17 (14)
Tumour site	Shoulder girdle	6 (4)
	Upper arm	11 (7)
	Elbow	4 (3)
	Forearm	12 (7)
	Wrist/hand	6 (4)
	Buttock	10 (6)
	Popliteal fossa	10 (6)
	Thigh	77 (48)
	Calf	12 (7)
	Shin	5 (3)
	Ankle/foot	8 (5)
Site in relation to deep fascia	Deep	110 (68)
	Superficial	37 (23)
Tumour type	Soft tissue	147 (91)
	Bone sarcomas*	14 (9)
Tumour size (median 7.5cm; range 1 – 28cm)	<5cm	32 (20)
	5-10cm	74 (46)
	>10cm	46 (29)
Stage at presentation	M0	154 (96)
	M1	7 (4)

**Bone sarcoma types (number): Ewing sarcoma (5), osteosarcoma (6), leiomyosarcoma (1), malignant fibrous histiocytoma (1), giant cell tumour (1)*

LATE EFFECTS SCORES

RTOG ≥ Grade 2 late effects observed in 50%
RTOG ≥ Grade 3 late effects observed in 28%
Fracture rate was 2%
Subcutaneous fibrosis ≥ Grade 2 seen in 28%

CORRELATION BETWEEN LATE EFFECTS AND TESS score

Higher RTOG scores were associated with a lower TESS score. The same trend was seen accross all scores, and was statistically significant for all except skin toxicity.

Subcutaneous fibrosis ≥Grade 2 was associated with a mean TESS score of 71.3 (range 10 - 97.5) compared to TESS score 85.0 (range14.7 – 100) for <Grade 2 toxicity *(p=0.002)*.

Presented at: ASTRO 56th Annual Meeting, September 14-17, 2014, San Francisco.

Contact: franel.legrange@uclh.nhs.uk

TREATMENT CHARACTERISTICS		N (%)
Number of surgical procedures to the RT site	None	3 (2)
	One	102 (63)
	More than one	56 (35)
Complex surgery†	Yes	41 (26)
	No	117 (74)
Wound complications (<3 months of surgery; requiring admission)	Yes	14 (9)
	No	144 (91)
(Neo)adjuvant chemotherapy	Yes	27 (17)
	No	134 (83)
Timing of RT	Post-operative	137 (85)
	Pre-operative	21 (13)
	Sole modality	3 (2)
RT dose (EQD2 with an α/β=3)	<60Gy	38 (23)
	60Gy	96 (60)
	>60Gy	26 (16)
Field length (median 21.9cm; range 8-40cm)	<20cm	59 (37)
	20 – 30cm	68 (42)
	30 – 40cm	25 (16)
RT fields cross a joint	Yes	74 (46)
	No	77 (48)

†Involving (number): skin graft (10), muscle flap (11), bone prosthesis or internal fixation (17), bone resection without prosthesis (2), joint fusion (1), vascular graft (1), tendon resection (2), motor nerve resection (4)

RTOG LATE EFFECTS SCORES

Results shown as number (percentage), N=161

RTOG score	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Highest RTOG score overall	13 (8)	67 (42)	51 (32)	22 (14)	6 (4)
Individual scores:					
Skin	22 (14)	80 (50)	40 (25)	15 (9)	2 (1)
Subcutaneous	38 (24)	76 (47)	32 (20)	13 (8)	0 (0)
Bone	148 (92)	6 (4)	1 (1)	1 (1)	3 (2)
Joint	120 (75)	22 (14)	9 (6)	7 (4)	1 (1)

POTENTIAL PROGNOSTIC FACTORS

Correlation with RTOG late effects ≥ Grade 2

Factor	Univariate analysis OR (95%CI)	Univariate analysis p-value	Multivariate analysis* OR (95%CI)	Multivariate analysis* p-value
Tumour size (for an increase in 5cm)	1.46 (1.03 – 2.06)	*0.03*	3.16 (1.36 – 7.30)	*0.007*
Wound complications	2.75 (0.83– 9.18)	*0.099*	14.6 (1.47 – 145.42)	*0.022*
Complex surgery	2.83 (1.33 – 6.00)	*0.007*	5.45 (1.24 – 23.96)	*0.025*
RT dose (for an increase in 5Gy)	1.21 (0.91 – 1.62)	*0.19*	2.84 (1.10 – 7.36)	*0.032*
Dose (in groups)				
RT dose <60Gy	1.00	*0.07*		
RT dose 60Gy	0.75 (0.35 – 1.61)			
RT dose >60Gy	2.13 (0.74 – 6.11)			
Age at time of RT (for an increase of 10 years)	1.10 (0.94 – 1.30)	*0.24*	1.31 (0.97-1.77)	*0.08*

**Multivariate model included: age at RT, gender, PS at RT, Site (lower or upper limb), tumour size, tumour location (deep or superficial), number of operations (0-1 or 1+), wound complications, complex surgery, neo-adjuvant chemo, RT timing, whether the field crossed a joint, field length, dose and time since RT*

PATIENT REPORTED FUNCTIONAL STATUS + QUALITY OF LIFE		Score
TESS score (out of 100)	median (range)	88.88 (10-100)
TESS QOL questions (out of 10)	median (range)	9 (3-10)
		N (%)
Gait (lower limb tumours, N=122)	Normal	80 (66)
	Abnormal	29 (24)
Walking aid required (lower limb tumours, N=122)	No	87 (71)
	Yes	28 (23)
Work status	Full time employed	57 (35)
	Part time employed	25 (15)
	Student	1 (1)
	Retired	47 (29)
	Unemployed	16 (10)
	Disabled	9 (6)
Regular analgesia use	Yes	57 (36)
	No	97 (60)
Type of analgesia used	Mild (paracetamol, codeine)	29 (18)
	Non-steroidal anti inflammatory	21 (13)
	Opioid	7 (4)
Treatment had a negative impact on lifestyle	Yes	69 (43)
	No	87 (54)
Negative impact on lifestyle acceptable or not (N=69)	Acceptable	49 (71)
	Not acceptable	10 (14)

CONCLUSIONS

- The data present patients treated with 3DCRT over a 21 year period.
- The incidence of late effects and impact on QOL was significant:
  - 43% reported a negative impact on their lifestyle after treatment
  - 50% had ≥grade 2 late effects
  - 28% had ≥grade 3 late effects
  - Late effects observed correlated with poor limb function
- Potential prognostic factors for the development of late effects emerged but need to be interpreted with caution in this small series
- The results presented provide benchmark data for future research and introduction of more conformal RT techniques

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10.2 Planning study comparing VMAT with 3DCRT for soft tissue sarcomas of the extremities

10.2.1 Poster presented at CTOS in November 2013 and oral presentation at BSG in February 2014

UCL HOSPITALS

TREATMENT PLANNING COMPARISON OF THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY (3D-CRT) AND VOLUMETRIC MODULATED ARC THERAPY (VMAT) FOR EXTREMITY SOFT TISSUE SARCOMA (abstract #1773035)

This research project was supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

the london sarcoma service

F le Grange, C Stacey, B Seddon. University College Hospital, London, UK

INTRODUCTION

Conventional three-dimensional conformal radiotherapy (3DCRT) is used routinely to treat extremity soft tissue sarcomas (STS). In order to achieve adequate radiation doses to the tumour, large volumes of normal tissue often receive high radiation doses. Evidence suggests that late toxicity and limb function are related to treatment volumes and radiation dose. Rates of significant fibrosis (≥ grade 2) relating to poorer long term limb function have been observed in up to 31% of patients receiving pre-operative radiotherapy and in 48.2% after post-operative radiotherapy [1]. Intensity modulated radiotherapy (IMRT) offers potential advantages in therapeutic ratio, allowing delivery of high doses to tumours while reducing the dose in surrounding normal tissues. Planning studies have shown a dosimetric advantage to fixed field IMRT compared to 3DCRT in lower limb (thigh) STS [2-5].

OBJECTIVES

This study aimed to test the feasibility of volumetric modulated arc therapy (VMAT), a rotational IMRT technique, and to compare it dosimetrically to 3D-CRT, in both upper and lower limb STS.

METHODS

21 patients with extremity STS treated with 3D-CRT were included. There were 3 cases from each of the following sites: anterior, medial and posterior thigh, shin, calf, upper arm and forearm. All patients underwent a planning CT scan in supine position with customised immobilisation devices. The phase 1 and 2 3D-CRT targets and doses were adapted to allow for a simultaneous integral boost technique with VMAT.

CLINICAL TARGET VOLUME (CTV) DEFINITION

The gross tumour volume (GTV) was defined with reference to the diagnostic MRI, operative note and pathology report.

Pre-operative radiotherapy:

3D-CRT	VMAT
CTV = GTV+ 2cm axial and 3 to 5cm superior/ inferior margins*	CTV as for 3D-CRT

Post-operative radiotherapy:

3D-CRT	VMAT
CTV2 = Tumour bed + 2cm margin in all dimensions*	HD-CTV (high dose CTV) as for CTV2
CTV1 = Tumour bed + 2cm axial and 5cm superior/ inferior margins*	LD-CTV (low dose CTV) as for CTV1 with CTV2 subtracted

**Adjusted to account for patterns of spread and intact bone/ fascial planes*

A 7mm setup margin was added to each CTV to create the respective planning target volume (PTV).

RADIOTHERAPY PRESCRIPTION

INDICATION	3D-CRT at 100%	VMAT to the mean PTV
Pre-operative (9 cases)	50Gy/25# (2Gy fractions)	50Gy/25# (2Gy fractions)
Post-operative (11 cases)	PTV1: 50Gy/25# PTV2: 10Gy/5# or	HD-PTV: 60Gy/30# LD-PTV: 52.2Gy/30# or
Post-operative (1 case)	PTV1: 50Gy/25# PTV2: 16Gy/8# Consecutive boost, 2Gy fractions	HD-PTV: 66Gy/33# LD-PTV: 53.46Gy/33# Simultaneous integral boost, equivalent 2Gy fractions (EQD2)

VMAT PLANNING

The original 3D-CRT plans were imported from Oncentra Masterplan v4.1 to Varian Eclipse v10 where VMAT plans were produced. PTV dose targets were according to ICRU 83 [5]. Additional structures, including a normal soft tissue corridor, were define as required for VMAT optimisation and for DVH (dose-volume histogram) generation. The PTV was edited to within 5mm of the skin surface to avoid errors from the optimisation algorithm.

ORGAN AT RISK (OAR) DOSE CONSTRAINTS

According to published data on the risk factors for late radiotherapy toxicity and QUANTEC guidelines [1,6-8]. Planning objectives were to limit dose to bone and soft tissue outside the PTV.

PLAN COMPARISON

The 3D-CRT plans were recalculated in Eclipse for the purpose of plan comparison. Plans were compared for target coverage, dose/volume parameters and homogeneity.

RESULTS

Radiotherapy plans meeting the target dose constraints were produced for all cases demonstrating the feasibility of the technique in extremity STS. Median monitor units for VMAT was 371 (range 271-533) and for 3DCRT it was 393 (range 192-495) (0.1<p<0.2).

BONE DOSE

BONE DOSE CONSTRAINT	3D-CRT	VMAT	*p* value
Whole bone V_{40Gy}[a] < 64%	Achieved in 76%	Achieved in 90%	
Mean dose < 37Gy	Achieved in 85%	Achieved in 90%	
Bone in field V_{50Gy}[b]	Median 57% (Range 0-95)	Median 29% (Range 0-90)	*p*<0.001

[a]V40Gy = volume receiving 40Gy; [b]V50Gy = volume receiving 50Gy

TARGET VOLUME (PTV) COVERAGE

DOSE PARA-METER	AIM	3DCRT Median cover achieved (%)	3DCRT Range	VMAT Median cover achieved (%)	VMAT Range
HD-PTV					
$D_{98\%}$[a] [%]	≥ 90%	95	90-99	92	90–95
$D_{95\%}$[b] [%]	≥ 95%	96	92-99	94	93–96
$D_{50\%}$[c] [%]	= 100%	101	100-103	100	100-100.7
$D_{2\%}$[d] [%]	≤ 107%	104	102-109	105	102–106
LD-PTV					
$D_{98\%}$[a] [%]	≥ 90%	92	87-96	92	90-97
$D_{50\%}$[c] [%]	= 100%	98	95-103	99	97-101
Inhomogeneity coefficient[e]	≤ 0.17	0.09	0.05-0.16	0.13	0.07-0.15

[a]D98% = percentage dose to 98% of the volume; [b]D95% = percentage dose to 95% of the volume; [c] D50% = percentage dose to 50% of the volume; [d]D2% = percentage dose to 2% of the volume; [e]Inhomogeneity coefficient = (D2%-D98%)/D50%

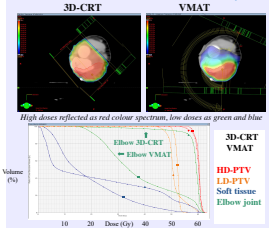
NORMAL TISSUE DOSES

VMAT resulted in a significant reduction in the volume of normal soft tissue outside the PTV receiving moderate to high doses, and an increase in the volume receiving doses below a mean of 27Gy (range 6-41).

Dose/ volume parameter	3D-CRT Percentage volume (%)	3D-CRT Absolute Volume (cm^3)	VMAT Percentage volume (%)	VMAT Absolute volume (cm^3)	Percentage change in absolute soft tissue volume with VMAT (%)	*p* value
Soft tissue V_{60Gy}[a]	4.6 (0-22)	99.0 (0-830)	0.4 (0-7.1)	10.25 (0-202.9)	-98 (-100 to -38)	*p*<0.001
Soft tissue V_{50Gy}[b]	11 (1.4-53)	237 (6.5-3434)	2.2 (0-19.1)	33 (0.05-666)	-78 (-100 to -29)	*p*<0.001
Soft tissue V_{40Gy}[c]	35 (8-74)	387 (80-4883)	14.4 (8.6-33)	246 (33-1610)	-45 (-75 to +12)	*p*<0.001
Soft tissue mean dose	24.7Gy (0.2-43.6Gy)		24.9Gy (16-31Gy)		-	*p*>0.2

All values expressed as median (range). Soft tissue = normal tissue outside the PTV to 2cm above and below PTV excluding bone; [a]V60Gy = volume receiving 60Gy; [b]V50Gy = volume receiving 50Gy; [c]V40Gy = volume receiving 40Gy; [d]V30Gy = volume receiving 30Gy; [e]V20Gy = volume receiving 20Gy

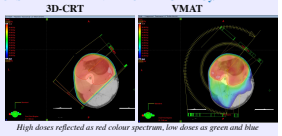
CASE EXAMPLE: UPPER ARM with DVH. 60Gy/30#



High doses reflected as red colour spectrum, low doses as green and blue

3D-CRT
VMAT
HD-PTV
LD-PTV
Soft tissue
Elbow joint

CASE EXAMPLE: ANTERIOR THIGH. 50Gy/25#



High doses reflected as red colour spectrum, low doses as green and blue

CONCLUSION

- VMAT is feasible in this setting, achieving equivalent PTV coverage to 3D-CRT. The dose distributions with VMAT are highly conformal, sparing significant volumes of normal tissue that would otherwise receive high doses with 3D-CRT.
- The soft tissue and bone sparing advantage seen with VMAT was apparent in upper and lower extremity STS.
- This dosimetric advantage has the potential to translate into a reduction in long term treatment related toxicity and improved limb function.

Presented at: CTOS 18th Annual Meeting, October 30th to November 2nd, 2013, New York, NY

Contact: franel.legrange@uclh.nhs.uk

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University College London Hospitals NHS Foundation Trust

10.3 Double planning study comparing VMAT and PBT for the treatment of pelvic Ewing sarcoma

10.3.1 Oral presentation at BSG in February 2016 and poster at PTCOG in May 2016

University College London Hospitals NHS
NHS Foundation Trust

uclh

Dosimetric comparison of intensity-modulated proton therapy (IMPT) and volumetric-modulated arc therapy (VMAT) treatment plans for Ewing sarcoma of the pelvis.

Franél le Grange[1], Richard A. Amos[2], Rachel Bodey[2] and Beatrice Seddon[1]
Departments of [1]Oncology and [2]Radiotherapy Physics, University College London Hospitals NHS Foundation Trust, London, UK.

Objective

To compare IMPT and VMAT for pelvic Ewing sarcoma; to assess potential to limit dose to normal structures.

Methods

Ten female patients (median age 20 years) treated with RT for pelvic Ewing sarcoma were selected. Robust IMPT and VMAT plans [54.0 Gy(RBE) in 28 fractions] were produced for each case. Plans were independently calculated to remove bias. Planning objectives were to limit dose to surrounding normal structures. Dosimetric parameters were compared and evaluated using Wilcoxon signed-rank non-parametric test for paired data.

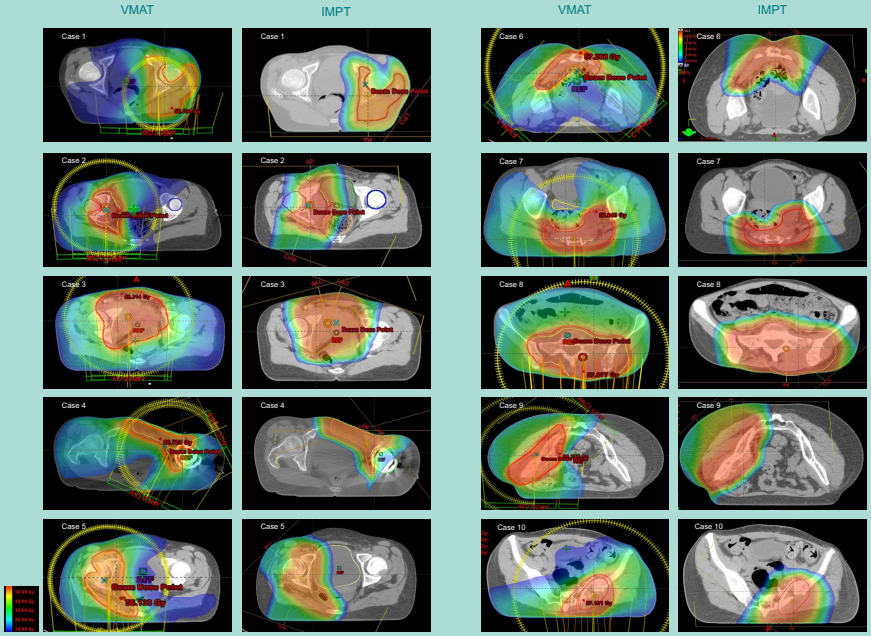

Figure 1: Representative slices of VMAT and IMPT plans. VMAT technique: 2 partial/full arcs; 5mm PTV expansion from CTV. IMPT technique: Multi-field optimization with 2 or 3 pencil beam scanning fields; positional uncertainty of 5 mm and proton range uncertainty of 3.5% used to robustly cover the CTV.

Results

Both techniques gave acceptable target coverage [95% of PTV received 95% dose for all VMAT; median CTV 55.3 Gy(RBE) for IMPT]. No significant difference for bowel V_{45Gy} [13.8% reduction with IMPT; p>0.2]. Mean bowel dose reduced by 66.7% (p<0.001). Rectum and bladder V_{50Gy} did not differ significantly. IMPT reduced dose (p<0.001) to bilateral femoral heads [0.0 – 37.8 Gy(RBE)]. IMPT reduced uterus mean dose by 40.4% [median 5.2 Gy(RBE) vs. 8.2 Gy; p<0.001] and vagina by 89.3% (p<0.001). Mean dose to ovaries reduced from 3.9 Gy [0.3 – 28.4 Gy] with VMAT to 0.0 Gy(RBE) [0.0 – 17.1 Gy(RBE)] with IMPT (p<0.001).

Conclusions

Both techniques resulted in excellent sparing of bowel, rectum, and bladder. IMPT offered superior sparing of femoral heads, uterus, vagina, and ovaries in this group of young female patients. This dosimetric advantage may translate into a reduction in long term treatment related toxicity such as infertility, early menopause, and spontaneous fracture.

10.4 Publications and presentations arising from IMRiS

10.4.1 Pre-trial QA survey of limb immobilisation in the UK – poster presented at ESTRO 2016 (129)

Pre-trial quality assurance for IMRiS phase II study of IMRT in sarcomas: a survey of limb immobilisation across the UK

Rita Simões[1], Elizabeth Miles[1], Franel Le Grange[2], Reshma Bhat[3], Beatrice Seddon[2]

[1]National Radiotherapy Trials Quality Assurance Group, Mount Vernon Hospital, London , UK ;
[2]University College of London Hospital, London, UK; [3] Cancer Research UK & UCL Cancer Trials Centre, London, UK;

RTTQA Radiotherapy Trials Quality Assurance

IMRiS

PURPOSE/ OBJECTIVE

Soft tissue sarcomas are rare malignancies, commonly arising in limbs, with an annual incidence of 3,298 cases in the UK in 2010. Their rarity leads to a lack of published data and experience in limb immobilisation for radiotherapy planning. The IMRiS trial is a phase II study of intensity modulated radiotherapy (IMRT) in primary bone and soft tissue sarcoma, opened in March 2016. As part of a pre-trial quality assurance (PT QA) programme, we report on UK status of limb soft tissue sarcoma (LSTS) immobilization techniques and its impact on treatment quality within this multi-centre trial.

METHODS

A facility questionnaire was circulated to 29 IMRiS centres to investigate variation in immobilisation devices, planning techniques, and imaging protocols used. A workshop was held to address LSTS immobilisation and patient setup. Centres attending the workshop were requested to prepare a short presentation describing their current immobilisation practice. Robustness of patient set-up at each centre was evaluated based on the following criteria: previously performed set-up audits, calculation of margins based on the audit, frequency of imaging, and number of patients treated per centre per annum. Centres were required to have either implemented daily imaging or performed an internal treatment setup audit as well as treating a minimum of 15 patients per year.

RESULTS

Twenty-seven questionnaires were returned. The workshop had 32 attendees, 20 of these were RTTs specialised in the pre-treatment area, 7 treatment RTTs, 3 physicists and 2 clinicians , from 23 centres.

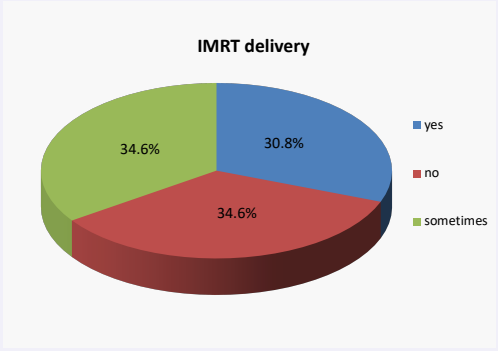

Figure 1. Percentage of IMRT delivery across the 27 IMRiS centres

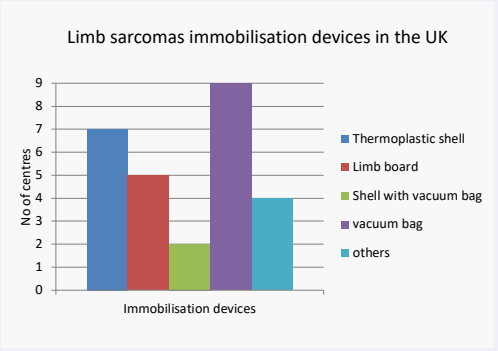

Figure 2. Immobilisation devices used for LSTS.

Only 8 responders routinely treated their patients with IMRT, mandatory in the IMRiS trial (see Figure 1). The most commonly used immobilisation devices are summarized in Figure 2, with vacuum bags being the most popular. 'Others' included in-house developed and customisable devices and common positioning pads. Nine centres had audited their local setup. However, only 4 had used their analysis to calculate setup margins (based on systematic and random errors). Sixteen centres did not state whether a setup audit had been carried out.

All centres follow the national minimum recommendation from 'On target: ensuring geometric accuracy in radiotherapy'[1] to perform imaging on fractions 1 to 3 and then weekly (see Figure 3). Six centres performed daily imaging, 3 of which routinely treated LSTS with IMRT. On average, centres were treating 24 patients per year (range 3-53), and 18 departments treated at least 15 patients a year. Based on our criteria for robustness, 8 centres were found to be at an acceptable level. Four of these used IMRT techniques and 5 had already implemented daily imaging.

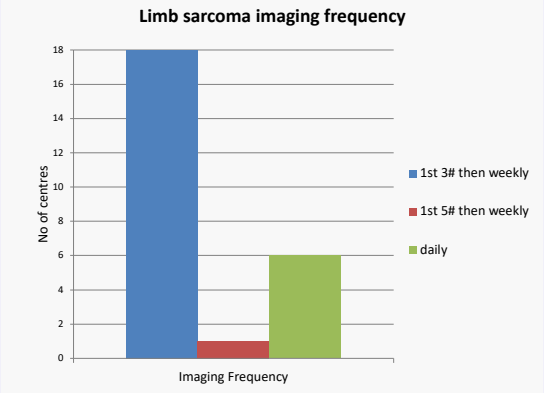

Figure 3. Imaging frequency for LSTS before IMRiS protocol implementation.

CONCLUSION

The results from the facility questionnaire and workshop demonstrate variations in treatment modality, immobilisation devices used and imaging frequency in potential IMRiS centres. Seventy percent of participating centres are now implementing or further developing their IMRT technique in order to treat LSTS within the study. This has required a change in treatment delivery modality (from 3DCRT to IMRT) in 9 centres. Comprehensive PT QA is required to ensure quality in a trial to be run at centres with such different levels of experience and ensure reliable trial outcomes. Robustness of patient setup is vital to decrease variability arising from different immobilisation devices and ensure the reproducibility of treatment. The PT QA program encourages centres to assess robustness of setup through audit and calculation of centre specific margins. The majority of centres will need to review treatment verification as daily imaging is mandated for the trial. We anticipate that centres with less robust setup systems may need more support to safely implement IMRiS. In response to this, a discussion group will be created to allow centres to share their experience.

ACKNOWLEDGEMENTS

The authors would like to thank all IMRiS trial centres who completed the facility questionnaire and attended the immobilisation workshop, as part of the pre-trial QA programme and submitted it to the National Radiotherapy Trials Quality Assurance Group. This trial is funded by Cancer Research UK (C2921/A17558) and conducted by the CR UK & UCL Cancer Trials Centre; ClinTrials.gov NCT02520128.

[1] 'On target: ensuring geometric accuracy in radiotherapy.' The Royal of Radiologist; Institute of physics and Engineering in Medicine; Society and College of Radiographers.

UCL Cancer Research UK and UCL Cancer Trials Centre

CANCER RESEARCH UK

10.4.2 Pre-trial QA survey of limb immobilisation in the UK - paper published in *Radiographer* in September 2019 (130)

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IMRiS phase II study of IMRT in limb sarcomas: Results of the pre-trial QA facility questionnaire and workshop

R. Simões [a, *], E. Miles [a], H. Yang [a], F. Le Grange [b], R. Bhat [c], S. Forsyth [c], B. Seddon [b]

[a] National Radiotherapy Trials Quality Assurance Group, Mount Vernon Hospital, London, UK
[b] University College of London Hospital, London, UK
[c] Cancer Research UK & UCL Cancer Trials Centre, London, UK

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ABSTRACT

Introduction: Soft tissue sarcomas of the extremities (STSE) are rare malignancies. We report current UK practice for immobilisation of soft tissue sarcoma of STSE, as part of the initial study set-up within the IMRiS trial, a phase II study of intensity modulated radiotherapy (IMRT) in primary bone and soft tissue sarcoma.
Methods: A facility questionnaire (FQ) was circulated to 29 IMRiS centres investigating the variation in immobilisation devices, planning techniques, and imaging protocols. A workshop was held to address concerns raised by centres. It focused on STSE immobilisation and patient set-up. Robustness of patient set-up at each centre was evaluated based on the following criteria: evidence of local set-up audit, calculation of margins based on set-up audit results, imaging frequency, and number of patients treated per centre per annum.
Results: Twenty-seven (93%) questionnaires were returned. 30% (8/27) of responders routinely treated STSE with IMRT. The remaining 70% (19/27) had little or no experience with IMRT for STSE. Vacuum bags were the most frequent immobilisation device (9/27), followed by thermoplastic shells (7/27). Nine centres had audited their local set-up; however, only 4 had calculated margins in response to the results. Ten centres were classified as having high level of robustness.
Conclusions: Immobilisation devices and planning techniques for STSE are inconsistent across centres. Robustness of set-up is an important tool to ensure quality of results in a multicentre trial setting with such different levels of experience. The IMRiS trial Quality Assurance programme encourages centres to assess robustness of set-up through local audit and subsequent calculation of treatment margins.
Implications for practice: This is the first study that used robustness criteria to tailor QA support to individual centres.

Introduction

Soft tissue sarcomas (STS) are rare tumours, representing 1% of all malignant neoplasms. The incidence of STS in 2010 was 3298.[1] STS arise in soft tissues connecting and surrounding other organs of the body, such as fat, muscle, blood vessels, deep skin tissues, tendons and ligaments. Although they can arise in any part of the body, they frequently develop in the extremities.[2]

Radiotherapy is often used in the management of these malignancies, either in the pre-operative, post-operative or definitive setting.[3] Three-dimensional conformal radiotherapy (3DCRT) is currently the most frequently used radiotherapy treatment technique for soft tissue sarcomas of the extremities (STSE), planned typically with at least two radiotherapy treatment fields. As STSE planning target volumes (PTV) are often large with irregular shape, 3DCRT has limitations in shaping the dose distribution to such target volumes whilst keeping the surrounding normal tissues within tolerance dose limits, in an attempt to avoid the development of serious side-effects.[4] PTV coverage is often compromised when sparing organs at risk (OAR) such as bone within the treatment field, which can impact on the efficacy of treatment.

Intensity Modulated Radiotherapy (IMRT) is a high-precision radiotherapy planning technique delivering highly conformal treatment by varying radiation beam fluency. IMRT allows

* Corresponding author.
E-mail address: rita.simoes@nhs.net (R. Simões).

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1078-8174/

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10.4.3 Pre-trial QA exercise of target delineation – poster presented at ESTRO 2017

Target delineation conformity in extremity Soft Tissue Sarcoma within the multi-centre UK phase II IMRiS trial

H. Yang[1], R. Simões[1], F. Le Grange[2], S. Forsyth[3], D. Eaton[1], B. Seddon[2]

[1]National Radiotherapy Trials Quality Assurance (RTTQA) Group, Mount Vernon Cancer Centre, London, UK; [2]University College Hospital, London, UK; [3]Cancer Research UK & University College London Cancer Trials Centre, London, UK

PURPOSE

Accurate target volume delineation is essential in the use of intensity-modulated radiotherapy, where its role in the treatment of bone and soft tissue sarcoma (STS) is being investigated for the first time within the UK in IMRiS, a prospective multi-centre phase II trial of IMRT in primary bone and STS.

As part of radiotherapy trials quality assurance, we determined the conformity of volume delineation of an extremity STS benchmark training case in the post-operative setting, and report target outlining variation in relation to the trial protocol.

METHODS

The clinical history, operation/histology reports, pre-operative magnetic resonance imaging and planning scans of the training case were made available to participating clinicians, who submitted outlines based on the protocol. Both first and re-submissions were evaluated by two clinicians, where GTV, CTV_6000 and CTV_5220 were compared to the reference contours. The volumes were quantitatively assessed using Dice Similarity Coefficient (DSC) as: $DSC = \frac{2|A \cap B|}{|A| + |B|}$, where A and B represent regions of interest. Individual feedback based on trial protocol variations was provided for all submissions.

RESULTS

There was a total of 25 submissions from 23 centres. Delineation of GTV, CTV_6000 and CTV_5220 were deemed unacceptable according to the protocol in 5(20%), 10(40%) and 5(20%) submissions respectively.

Table 1 details the unacceptable variations from the protocol. All unacceptable GTV contours failed to reconstruct the pre-operative disease in its entirety. Incorrect margin expansion constituted the majority of the unacceptable submissions for both CTVs.

CTV_5220 was incorrectly positioned in 5 submissions due to the contouring inaccuracies of GTV/CTV_6000. Other variations in the inclusion of the scar/seroma were seen where it was not fully encompassed axially (CTV_6000: 8 submissions, CTV_5220: 6 submissions), and where CTV_6000 was extended beyond margins longitudinally to include it (5 submissions). In addition, some volumes were tapered where the anatomical planes were not followed lengthwise (CTV_6000: 5 submissions, CTV_5220: 13 submissions).

The mean DSCs were systematically lower for the unacceptable contours compared to accepted contours for GTV, CTV_6000 and CTV_5220 (table 2).

Volumes (and brief description from trial protocol)	Unacceptable variations from trial protocol	No. of cases (total 25)
GTV (Reconstructed pre-operative GTV)	Based on post-operative appearance only; pre-operative disease not taken into account	1 (4%)
	Based on post-operative appearance radially; pre-operative disease taken into account for superior/inferior extent but not radially	1 (4%)
	Based on post-operative appearance; pre-operative disease taken into account partially for radial extent but not superiorly/inferiorly	4 (16%)
CTV_6000 (From GTV with margin of 2cm radially, superiorly and inferiorly)	Pre-operative GTV not fully encompassed	3 (12%)
	Incorrect margin expansion (from post-operative appearance)	5 (20%)
	Incorrect margin (<2cm isotropic margin)	5 (25%)
	Incorrect margin (>2cm isotropic margin)	1 (4%)
CTV_5220 (From GTV with margin of 2cm radially and 5cm superior and inferiorly, excludes CTV_6000)	Incorrect margin (<5cm superior/inferior from GTV)	3 (12%)
	Incorrect margin (>5cm superior/inferior from GTV)	1 (4%)
	Volume too narrow due expansion from CTV_6000, where CTV_6000 was tapered longitudinally	1 (4%)

Table 1. Description of volumes from guidelines and rates of unacceptable outlining variations from trial protocol.

Target Volume	Outlining Variation	Mean	Minimum	Maximum	*p*-value (equality of means)
GTV	Unacceptable	0.61	0.55	0.66	< 0.001
	Acceptable	0.77	0.60	0.81	
CTV_6000	Unacceptable	0.75	0.53	0.82	0.036
	Acceptable	0.82	0.77	0.89	
CTV_5220	Unacceptable	0.15	0.02	0.36	0.002
	Acceptable	0.43	0.11	0.64	

Table 2. Dice similarity coefficient for unacceptable vs acceptable outlining variation for the target volumes.

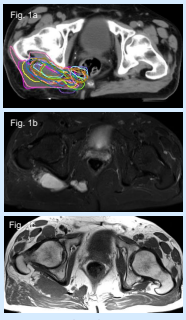

Figure 1a) GTV outlining variation on an axial CT slice. 1b-c) Pre-operative MRI on equivalent axial slice, T2-weighted fat suppressed and T1-weighted respectively.

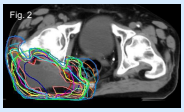

Figure 2. CTV_6000 outlining variation on an axial CT slice.

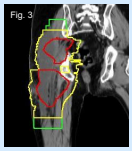

Figure 3. Reference volumes in the coronal plane. GTV – red; CTV_6000 – yellow; CTV_5220 – green.

There were five re-submissions after feedback, for which all target volumes had either acceptable, or no variation from the protocol (mean DSC GTV: 0.75, CTV_6000: 0.83, CTV_5220: 0.48).

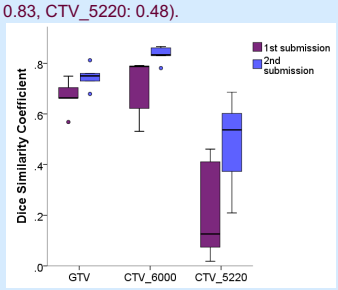

Figure 4. Comparison of the Dice similarity coefficient for the five cases requiring re-submission.

CONCLUSION

High numbers of unacceptable variations from the trial protocol were seen in the first submission of the training case; the adherence to the protocol improved following individualised feedback. As the outlining of both CTVs is dependent on the accuracy of the reconstructed GTV in the post-operative setting, this should be done with particular care, with the aid of surgical reports and diagnostic imaging. These results emphasise the importance of robust QA programmes for pre-trial preparation and training prior to patient recruitment.

ACKNOWLEDGEMENTS

The authors would like to thank all IMRiS trial centres who completed the QA programme and submitted their benchmark cases for review.
This trial is funded by Cancer Research UK (C2921/A17558) and conducted by the CR UK & UCL Cancer Trials Centre; ClinTrials.gov NCT02520128.

10.4.4 Pre-trial QA plan evaluation of the benchmark planning case (Cohort 1) - Oral presentation by Rita Simoes at ESTRO 2017(134)

patient. On average CyberArc decreased treatment times by 1.76x ± 0.23x for the prostates cases and 1.62x ± 0.13x for brain patients, not taking into consideration the gantry speed limitations. Staying within the tolerance of the machine speed specifications, the average time decrease was 1.56x ± 0.19x for prostate patients and 1.39x ± 0.11x for brain patients.

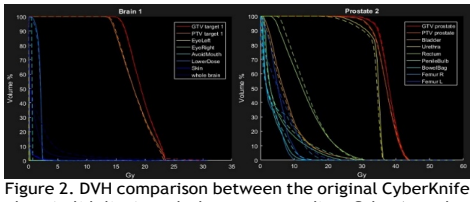

Figure 2. DVH comparison between the original CyberKnife plan (solid line) and the corresponding CyberArc plan (dashed line).

Conclusion

CyberArc is able to deliver plans that are dosimetrically comparable to their CyberKnife counterparts, while reducing treatment times considerably.

OC-0448 Near real-time automated dose restoration in IMPT to compensate for daily tissue density variations

T. Jagt[1], S. Breedveld[1], S. Van de Water[1], B. Heijmen[1], M. Hoogeman[1]
[1]*Erasmus MC Cancer Institute, Radiation Oncology, Rotterdam, The Netherlands*

Purpose or Objective

Intensity-modulated proton therapy (IMPT) allows for very localized dose deposition, but is also highly sensitive to daily variations in tissue density along the pencil beam paths, induced for example by variations in organ filling. This potentially results in severe deviations between the planned and delivered dose. To manage this, we developed a fast dose restoration method that adapts the treatment plan in near real-time.

Material and Methods

The dose restoration method consists of two steps: (1) restoration of the geometrical spot positions (Bragg peaks) by adapting the energy of each pencil beam to the new water equivalent path length (Figure 1), and (2) re-optimization of pencil beam weights by minimizing the dosimetric difference with the planned dose distribution, using a fast and exact quadratic solver.

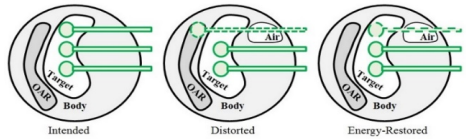

Figure 1 Restoring spot positions. Left: The intended spot positions. Middle: An air cavity causes a displacement and a change in spot shape (not depicted). Right: The energy of the pencil beam has been adapted to restore the spot position.

The method was evaluated on 10 prostate cancer patients, using 8-10 repeat CT scans; 1 for planning and 7-9 for restoration. The scans were aligned based on intra-prostatic markers. Prostate, lymph nodes and seminal vesicles were delineated as target structures. Dose was prescribed according to a simultaneously integrated boost scheme assigning 74 Gy to the high-dose planning target volume (PTV) (prostate + 4 mm) and 55 Gy to the low-dose PTV (lymph nodes and seminal vesicles + 7 mm).

Results

While substantial dose deviations were observed in the repeat CT scans without restoration, clinically acceptable dose distributions were obtained after restoration (Figure 2). This resulted in PTV $V_{95\%} \geq 98\%$ and $V_{107\%} \leq 2\%$ for all scans. For the bladder, the differences between the restored and intended treatment plans were below 2 Gy and 2%-point. The rectum differences were below 2 Gy and 2%-point for 90% of the scans. In the remaining scans the rectum was filled with air and partly overlapped with the PTV, resulting in unavoidably higher rectum doses.

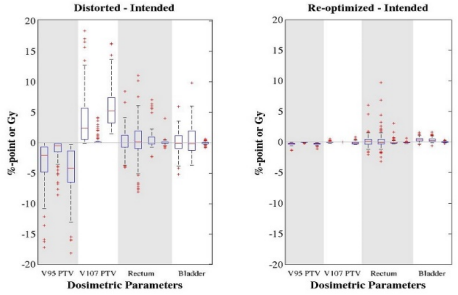

Figure 2 Boxplots showing differences in dosimetric parameters between the distorted and intended (left) and re-optimized and intended dose distributions (right) for all 80 scans. Left to right, rectum parameters: D_{mean}, V_{45Gy}, V_{60Gy}, V_{75Gy} and bladder parameters: D_{mean}, V_{45Gy}, V_{65Gy}.

The mean time needed for energy adapta tion was 5.4 seconds (3.5-10.6). The re-optimization time was on average below 5 seconds (maximum 9.0). T he most time consuming and currently limiting operation was calculating the dose distribution matrix (average 4.3 minutes (2.4-9.6)), performed once betw een the two steps.

Conclusion

The impact of density variations on the penci l beam path in IMPT can be reduced by performing an automated dose restoration consisting of a water equivalent path length correction of the pencil beams, followed by a re-optimization of the pencil beam weights.

Proffered Papers: Planning and quality assurance

OC-0449 A novel and objective plan evaluation for limb sarcomas IMRT in the IMRiS phase II trial

R. Simões[1], H. Yang[1], R. Patel[1], F. Le Grange[2], S. Beare[3], E. Miles[1], B. Seddon[2]
[1]*Mount Vernon Cancer Centre, National Radiotherapy Trials Quality Assurance RTTQA Group, London, United Kingdom*
[2]*University College Hospital, Sarcoma Unit, London, United Kingdom*
[3]*University College of London, Cancer Research UK & University College London Cancer Trials Centre, London, United Kingdom*

Purpose or Objective

IMRiS (Clinicaltrials.gov id:NCT02520128) is a multicentre phase II trial of intensity modulated radiotherapy (IMRT) in soft tissue and bone sarcomas. IMRT was implemented in the UK for limb soft tissue sarcomas (STS) in the context of this trial, which opened to recruitment in March 2016. As limb STS volumes are very variable, there are several ways of optimising the plans. It is often difficult to assess plan quality without understanding fully if the presented plan has been well optimised. We describe novel metrics used to evaluate IMRT plan quality for limb STS.

Material and Methods

A case of liposarcoma of the left thigh was available to the 29 IMRiS participating centres. The prescription was 50Gy in 25 fractions. The clinical target volumes and the

11 Appendix 4 IMRiS protocol

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:	3
Protocol version date:	14/01/2019

Protocol version 3, 14/01/2019

Authorisation signatures

Name & Role:	Signature:	Date authorised:
Chief Investigator: Dr Beatrice Seddon Consultant Clinical Oncologist	[redacted]	06/03/2019
For the Sponsor: Professor Jonathan Ledermann Director, UCL CTC	[redacted]	11/03/2019
Miss Laura White Clinical Trials Group Manager, UCL CTC	[redacted]	06/03/19

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 9281

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
Mr Chris Stacey	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

Mr Ihtisham Malik	Trial Coordinator	CR UK & UCL Cancer Trials Centre
Dr Hakim-Moulay Dehbi	Trial Statistician	CR UK & UCL Cancer Trials Centre

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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.

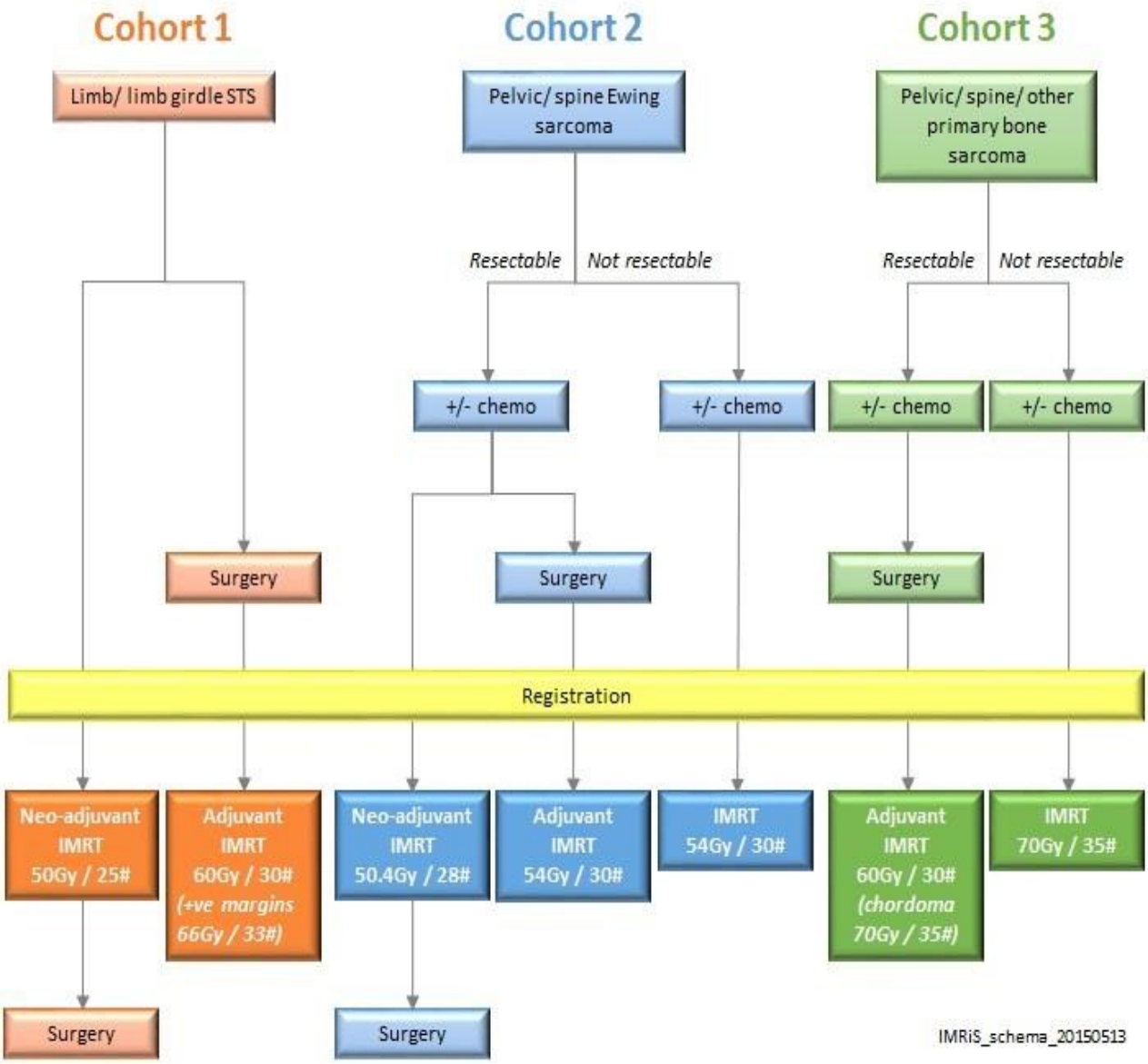
Primary endpoint:	Cohort 1: The rate of grade 2 or more late soft tissue fibrosis at 2 years following RT as assessed by RTOG late radiation morbidity criteria. Cohort 2: (Ewing's sarcoma of the spine/pelvis): The proportion of patients in whom 90% of the plan PTV receives 95% of the optimal prescription 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 week • 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 preoperatively 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 ***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

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.
Coinvestigators 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 all 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 preregistration 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 neoadjuvant chemotherapy prior to surgery, radiotherapy should be planned with reference to the baseline pre-chemotherapy MRI when the tumour was at it's 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

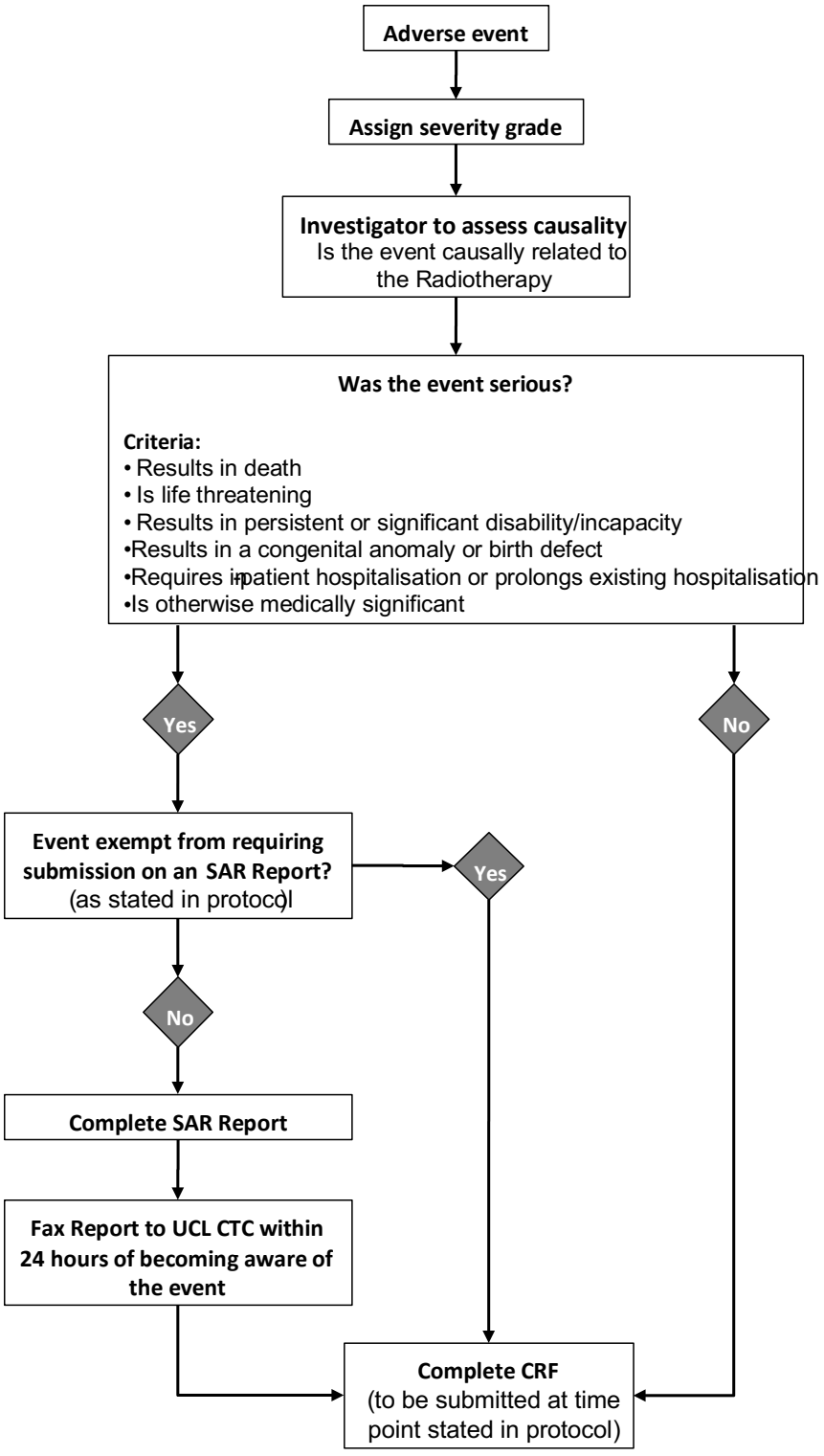
For this trial, the following events are exempt from requiring submission on a SAR Report, but must be recorded on the relevant forms of the trial eCRF:

- 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 noncompliance 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 postoperative 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.
- 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.

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 preoperative 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

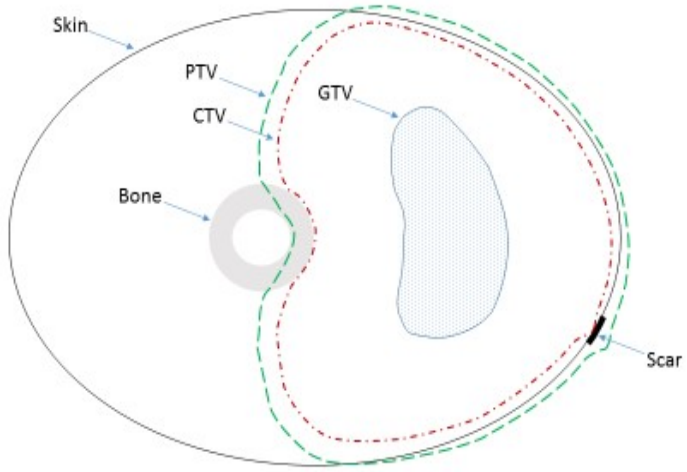


Fig. 1b

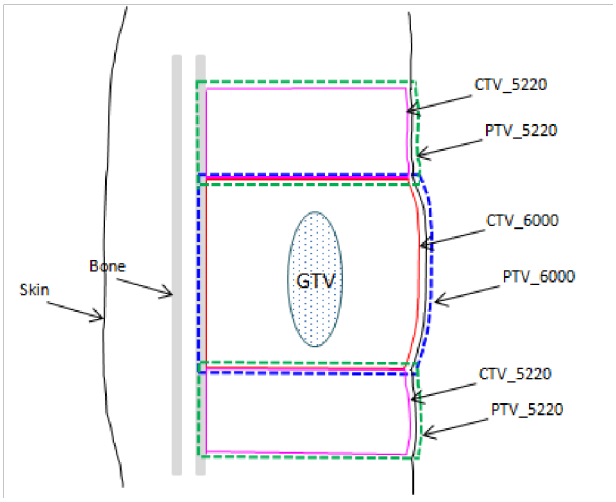
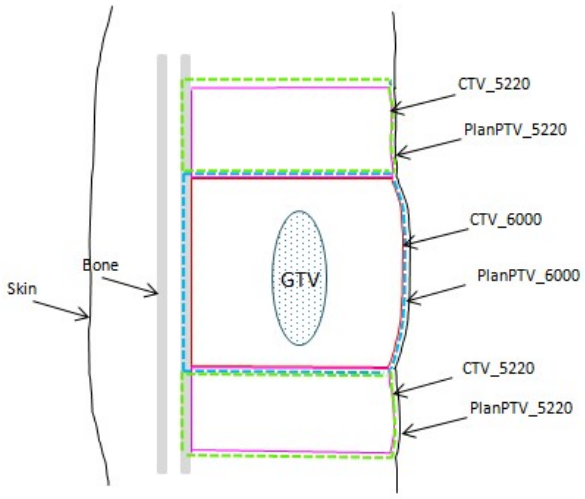


Fig. 1c



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

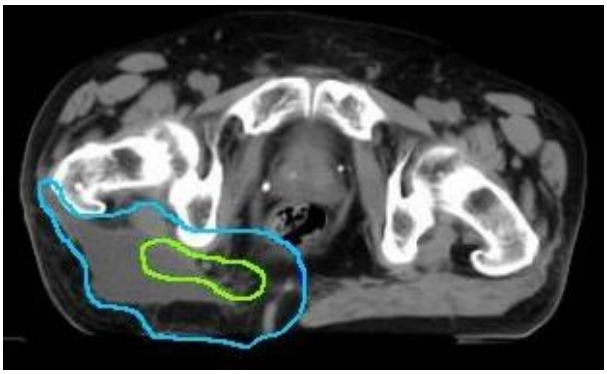


Fig. 2b

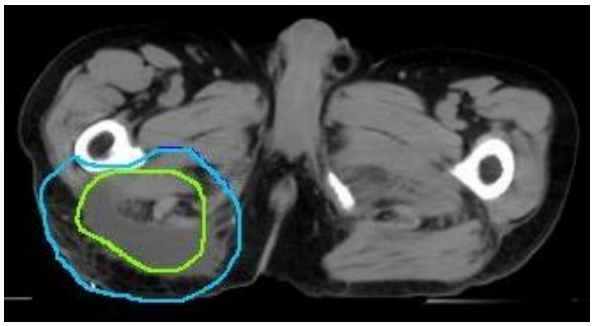
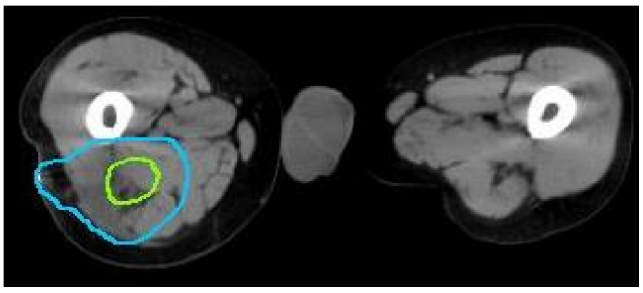


Fig. 2c



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

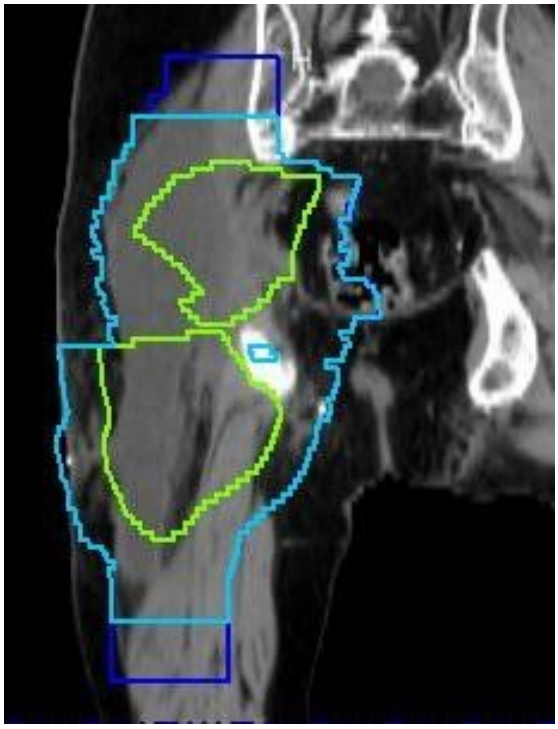


Fig. 3b

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, twothirds, 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 nearminimum 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 setup and patient/organ motion.

Fig. 4a

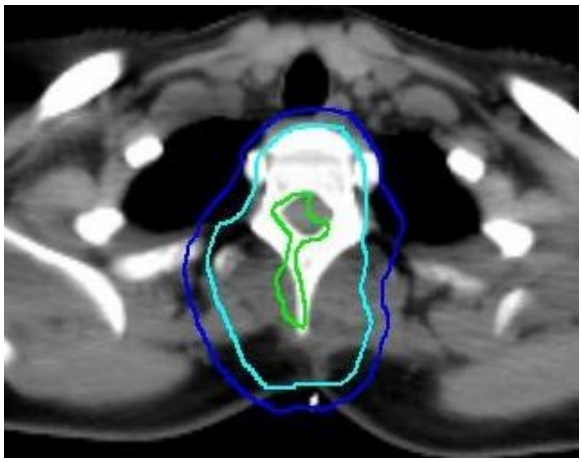


Fig. 4b

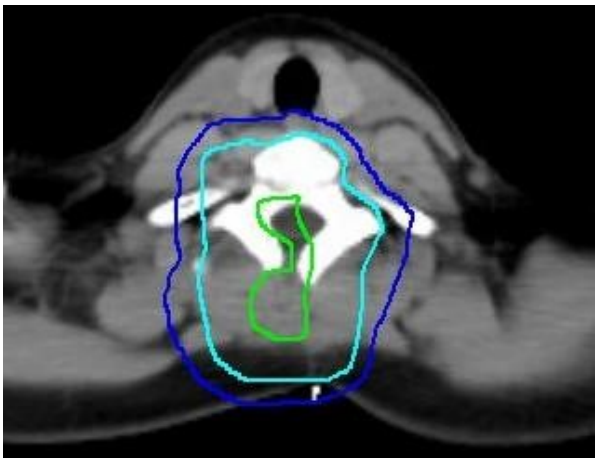
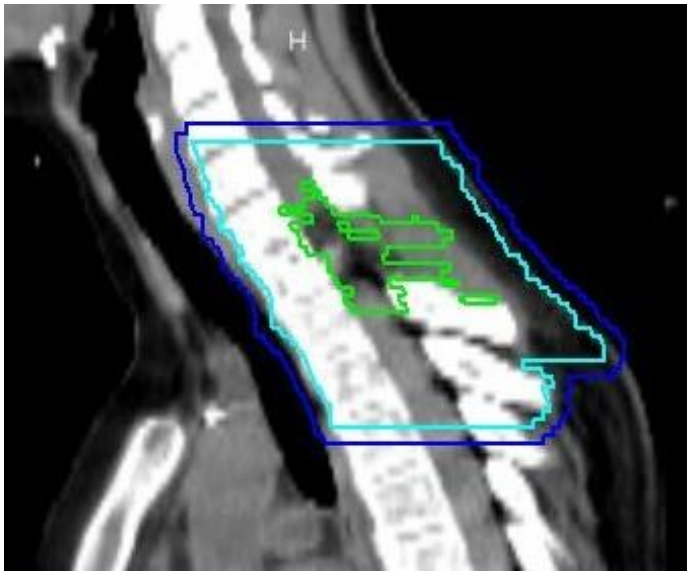


Figure 5. Post-surgical sagittal planning CT slices following decompression of C7/T1 and chemotherapy for Ewing's sarcoma of the spine at C7/T1. Green – GTV; Turquoise – CTV_5400; Dark Blue – PTV_5400.

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>
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<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 anorectal 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 nearminimum 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 preoperative 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 subvolumes (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

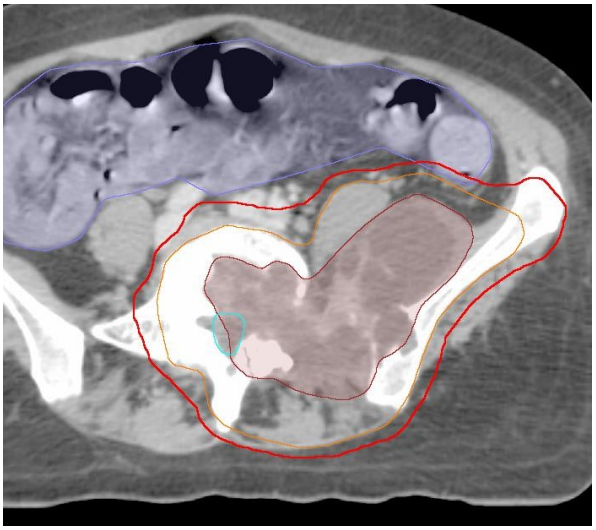
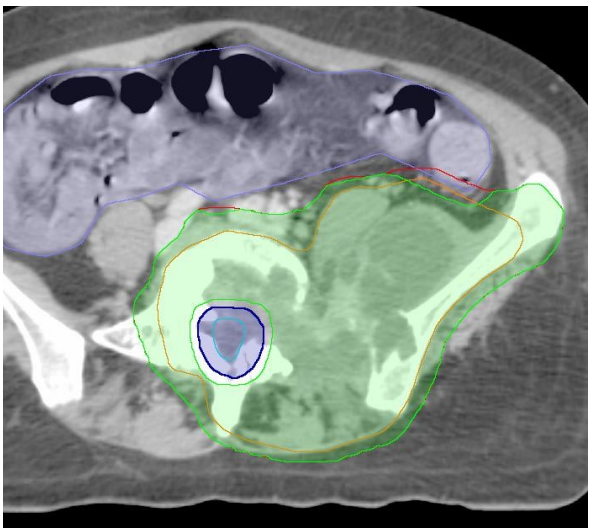


Fig. 6b



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

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<tr><th>OAR</th><th>Volume and dose constraint</th></tr>
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Max dose (D0.1cc) < 65 Gy</td></tr>
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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
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<tr><td>BowelSpace [74]</td><td>Keep as low as possible.
Volume outside PlanPTV receiving >45Gy should be <195cm^3 (grade 2 toxicity) [89]
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</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 anorectal 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)	ɔn of Trial Treatment (28 days after last fraction of RT)	~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/discomfo 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.