

BMJ Open Predicting radiotherapy response, Toxicities and quality-of-life related functional outcomes in soft tissue sarcoma of the extremities (PredicT) using dose-volume constraints development: a study protocol

Rita Simões ,^{1,2,3,4} Sarah Gulliford,^{3,5} Beatrice Seddon,³ Hakim-Moulay Dehbi,⁶ Martin Robinson,⁷ Sharon Forsyth,⁸ Ana Hughes,⁹ Piers Gaunt,⁹ Thuy-Giang Nguyen,² Stephanie Elston,² Kabir Mohammed,² Shane Zaidi,^{1,2} Elizabeth Miles,⁴ Peter Hoskin,¹⁰ Kevin Harrington,¹¹ Aisha Miah^{1,2}

To cite: Simões R, Gulliford S, Seddon B, *et al.* Predicting radiotherapy response, Toxicities and quality-of-life related functional outcomes in soft tissue sarcoma of the extremities (PredicT) using dose-volume constraints development: a study protocol. *BMJ Open* 2024;**14**:e083617. doi:10.1136/bmjopen-2023-083617

► Prepublication history for this paper are available online. To view these files, please visit the journal online (<https://doi.org/10.1136/bmjopen-2023-083617>).

Received 22 December 2023
Accepted 16 July 2024



© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Rita Simões;
rita.simoes@nhs.net

ABSTRACT

Introduction Radiotherapy improves local tumour control in patients with soft tissue sarcoma of the extremities (STSE) but it also increases the probability of long-term toxicities such as tissue fibrosis, joint stiffness and lymphoedema. The use of radiation dose and volume thresholds, called dose constraints, may potentially reduce the development of toxicities in STSE. The aim of this study is to determine predictors of radiotherapy-related side effects for STSE.

Methods and analysis Predicting radiotherapy response, Toxicities and quality-of-life related functional outcomes in soft tissue sarcoma of the extremities (PredicT) is a multicentre observational study comprising two cohorts (PredicT A and B). PredicT A, a retrospective analysis of the UK VortX (NCT00423618) and IMRIS clinical trials (NCT02520128), is aimed at deriving a statistical model for development of dose-volume constraints. This model will use receiving operator characteristics and multivariate analysis to predict radiotherapy side effects and patient-reported outcomes. PredicT B, a prospective cohort study of 150 patients with STSE, is aimed at testing the validity of those dose-volume constraints. PredicT B is open and planned to complete recruitment by September 2024.

Ethics and dissemination PredicT B has received ethical approval from North West - Liverpool Central Research Ethics Committee (20/NW/0267). Participants gave informed consent to participate in the study before taking part. We will disseminate our findings via publications, presentations, national and international conference meetings and engage with local charities.

Trial registration number [NCT05978024](https://www.clinicaltrials.gov/ct2/show/study?term=NCT05978024).

INTRODUCTION AND RATIONALE

Soft tissue sarcoma of the extremities (STSE) accounted for 1% of all malignancies arising in adults, with 3272 cases in the UK in 2010.^{1–3} Localised disease is potentially curable, with

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This is a national study of the prediction of radiotherapy outcomes for patients with soft tissue sarcoma of the extremities (STSE).
- ⇒ A model for radiotherapy outcome prediction will be created using high-quality data generated from two prospective studies: UK VortX and IMRIS clinical trials.
- ⇒ The model validity will be tested in a prospective study, called Predicting radiotherapy response, Toxicities and quality-of-life related functional outcomes in soft tissue sarcoma of the extremities – cohort B (PredicT B).
- ⇒ PredicT is the first study to identify specific normal tissues at risk of developing toxicities which can predict STSE radiotherapy outcomes.

5-year survival rates of 60% in high-grade disease.⁴

Radiotherapy, when delivered as an adjunctive treatment improves the local tumour control rates. However, it also increases the probability of patients experiencing acute and late toxicities. The development of toxicities may be dependent on anatomical location, tumour size, treated volume, radiation dose and fractionation, as well as the intrinsic radiosensitivity of the normal tissues surrounding the tumour.⁵ The scheduling of radiotherapy also plays an important role. Neoadjuvant radiotherapy is associated with higher chances of postoperative wound complications, whereas adjuvant radiotherapy results in worsening limb function due to the

high probability of late toxicities caused by delivering a higher total dose to a larger volume.⁶

High-grade radiation-induced fibrosis of normal tissues surrounding the tumour is an important irreversible late side effect, manifesting as soft tissue contracture, pain in the treated area and associated gait (lower limb) or dexterity (upper limb) problems. This can significantly impact normal activities of daily living and health-related quality-of-life. It can occur in months or years after treatment and may worsen over time. The SR.2 phase III trial, conducted by from the National Cancer Institute of Canada Clinical Trials Group, compared preoperative radiotherapy in STSE with postoperative radiotherapy in STSE and reported the incidence on late toxicities. Tissue fibrosis occurred in 48.2% and 31.5%, joint stiffness was observed in 23.2% and 17.8% and lymphoedema was reported in 23.2% and 15.5% of the patients receiving postoperative and preoperative radiotherapy, respectively.⁵

Radiotherapy techniques have evolved to improve the therapeutic index. However, there is a dearth of dose-volume constraint guidelines relating to normal tissue structures within the extremities and linking them to the incidence and severity of acute and late toxicities.⁷ For example, modern radiotherapy planning for STSE is still performed by sparing the normal tissue corridor, which is defined by a longitudinal strip of skin and subcutaneous tissue away from the planning target volume (PTV); this corridor will vary in its location within the extremity and unrelated to any specific anatomical structure. Historically, to avoid lymphoedema or normal tissue fibrosis, it has been recommended that no more than 50% of the normal tissue corridor volume receives 20 Gy.⁸ The definition of this avoidance structure is inconsistent and does not correspond to a specific, anatomical structure.

Dose-volume constraints to reduce the dose to the whole femur have been proposed by Dickie *et al* and have been used for radiotherapy plan optimisation for over a

decade.⁹ As a result, an incidence of bone fractures lower than 5% has been reported in recent studies.^{10 11}

Addressing uncertainties and developing dose-volume constraints to specific normal tissue structures, such as neurovascular bundle (NVB), subcutaneous tissue and muscle compartments (MC), is likely to reduce the severity of toxicities and improve functional outcomes of patients with STSE.

Predicting radiotherapy response, Toxicities and quality-of-life related functional outcomes in soft tissue sarcoma of the extremities (PredicT) is an observational non-interventional study reporting and recording the toxicities and outcomes of patients receiving preoperative, postoperative or palliative radiotherapy for STSE. Clinical and radiotherapy plan data will be collated to determine the relationship between radiation dose delivered to specific normal tissue structures and the incidence and severity of toxicities.

DESIGN

The PredicT Study is composed of two patient cohorts: PredicT A and PredicT B (figure 1).

PredicT A is a retrospective analysis of 384 patients recruited in the Vortex and IMRiS UK trials. It aims to develop a radiation dose-volume constraint model to predict predefined late toxicities. PredicT B is a multi-centre, prospective observational cohort reporting the severity and frequency of toxicities in 150 patients with STSE. This cohort will test the radiation dose-volume constraints defined in PredicT A.

Overall study objective

The objective of this study was to develop predefined dose-volume constraints for radiotherapy planning purposes to help deliver radiation to the tumour site and minimise dose to other normal tissue anatomical sites, consequently predicting severity and frequency of toxicities.

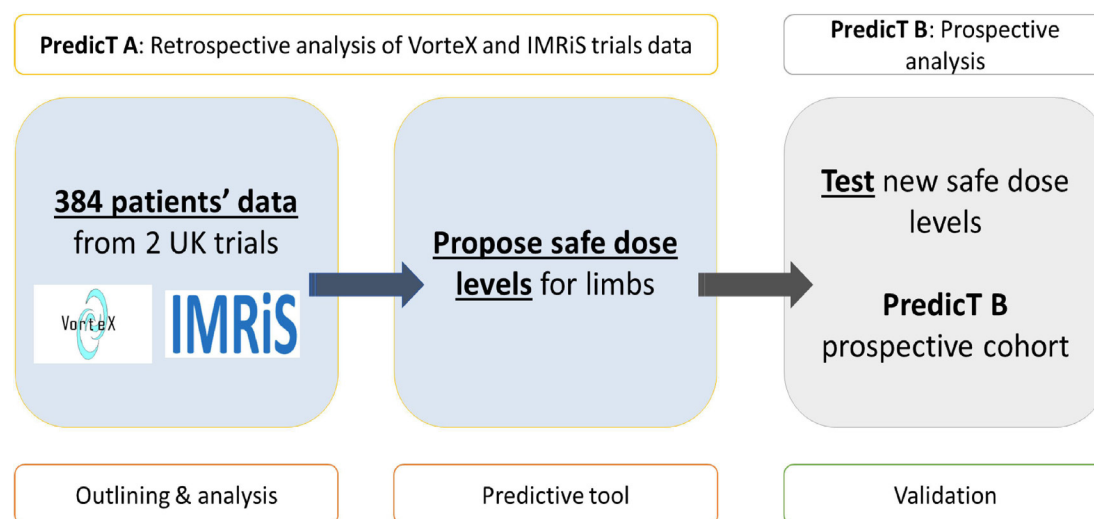


Figure 1 Predicting radiotherapy response, Toxicities and quality-of-life related functional outcomes in soft tissue sarcoma of the extremities (PredicT) Study flow chart.

METHODOLOGY AND ANALYSIS

The manuscript adheres to the Consolidated Standards of Reporting Trials' Patient-Reported Outcomes extension guidelines.¹²

PredicT A

PredicT A represents the largest radiotherapy STSE cohort of patients accrued as part of two UK clinical trials, VortEX and IMRiS.

The VortEX (NCT00423618) phase III randomised trial investigated whether a reduced volume of postoperative radiotherapy improved limb function without compromising local control for STSE.¹³ 216 patients were recruited between 2008 and 2013. The coprimary endpoints were limb function (measured with the patient-reported Toronto Extremity Salvage Score (TESS)) and time to local recurrence. Secondary endpoints included evaluation of soft tissue and bone toxicity (Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (RTOG/EORTC) scoring system), overall level of limb function as well as disease-free survival and overall survival. Patients were randomised to either the control arm to receive a two-phase radiotherapy technique of 50 Gy in 25 fractions followed by a boost of 16 Gy in eight fractions or the research arm, which consisted of 66 Gy in 33 fractions to the reduced boost volume. Three-dimensional (3D) conformal radiotherapy or intensity-modulated radiotherapy (IMRT) were permitted.

The IMRiS (NCT02520128) phase II trial studied the feasibility of delivering IMRT in three sarcoma cohorts. Specifically, the STSE cohort recruited 168 patients, of which 112 patients received preoperative radiotherapy and 56 patients received postoperative radiotherapy. Recruitment was completed in July 2017. The primary endpoint was the rate of high-grade fibrosis at 2 years. Secondary endpoints were the incidence of other high-grade toxicities, patient-reported limb function and quality-of-life, time to local recurrence and disease-free and overall survival. IMRT was delivered either preoperatively as 50 Gy in 25 fractions or postoperatively as 60 Gy in 30 fractions or 66 Gy in 33 fractions (for patients with positive resection margins).¹⁴

For both clinical trials, the acute and late clinician-reported toxicities were reported according to the RTOG/EORTC scoring system¹⁵; Stern's scale for lymphoedema reporting⁸; and Common Terminology Criteria for Adverse Events (CTCAE).¹⁶

Standardised scoring scales that were used for patient-reported outcomes are TESS¹⁷; EORTC Quality-of-Life Questionnaire C-30¹⁸; and Musculoskeletal Tumor Society (MSTS).¹⁷

PredicT A objectives

Primary objective

The primary objective was to identify specific dose-volume constraints for anatomical regions of interest, within the normal tissue of the limb but lying outside the

clinical target volume, that can predict for the frequency and intensity of radiotherapy-related side effects in STSE.

Secondary objectives

Secondary objective were:

- To identify anatomical regions of interest within the normal tissues in limbs in which delivery of high-dose radiotherapy may result in specific toxicities, such as fibrosis and lymphoedema.
- To define dose-volume constraints for lymphoedema, fibrosis, bone fracture and joint stiffness.

Patient population

PredicT A is a retrospective analysis of all 384 patients recruited as part of the VortEX and IMRiS clinical trials.

PredicT B

PredicT B (NCT05978024) (figure 2) is a multicentre, prospective cohort study. Radiotherapy is delivered per local clinical protocols. Figure 2 summarises the recommended techniques, as well as Radiotherapy (RT) dose schedules. Patients will be followed up during RT and at 3, 6, 12 and up to 24 months post RT. The protocol and consent form are provided in online supplementary material.

Clinicians should aim for RT to start within 4 weeks of registration and no longer than 12 weeks after surgery. 3D conformal radiotherapy or IMRT techniques are permitted. The radiation dose is delivered:

- Preoperatively as 50 Gy in 25 daily fractions, delivered in 5 fractions per week over 5 weeks.
- Postoperatively as 60/66 Gy (R0/R1) in 30/33 daily fractions to the high-dose PTV and 52.2/43.46 Gy in 30 daily fractions to the low-dose PTV treated concurrently, or in a two-phase technique of 50 Gy in 25 daily fractions then 10–16 Gy in 5–8 fractions delivered 5 times per week over 6 or 6½ weeks.
- Palliatively as 30–36 Gy in 10–12 daily fractions; 40 Gy in 15 daily fractions; 36 Gy in 6 fractions delivered once a week; and 25 Gy in 5 daily fractions ($\alpha/\beta=3$ Gy).

Clinician-reported toxicity scales used in PredicT B are RTOG/EORTC scoring system¹⁵; Stern's scale for lymphoedema reporting¹⁹; and CTCAE.¹⁶

Standardised scoring scales that were used for patient-reported outcomes for functional outcomes and quality-of-life are TESS¹⁷; EORTC Quality-of-Life Questionnaire C-30¹⁸; EORTC Quality-of-Life Fatigue Module FA-12¹⁸; and MSTS.¹⁷

PredicT B objectives

Primary objective

The primary objective is to report the frequency and intensity of radiotherapy-related toxicities in STSE.

Secondary objective

The secondary objective is to test the validity of specific dose-volume constraints for normal tissue structures within the normal tissue of the limb, predicting the

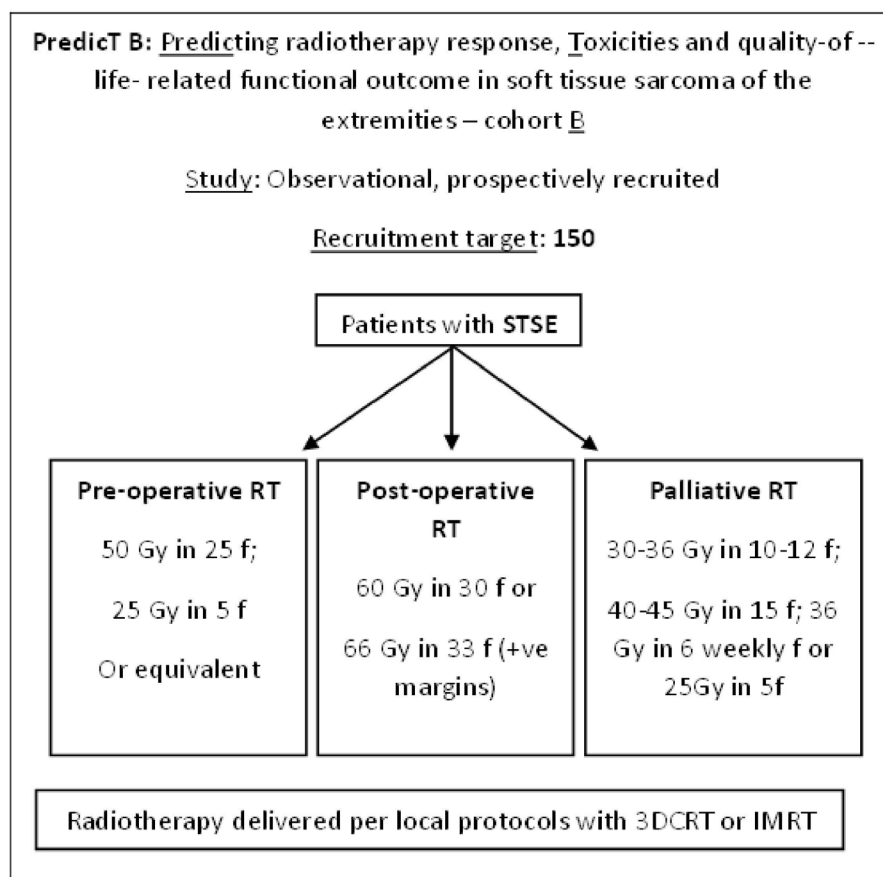


Figure 2 PredicT B summary. IMRT, intensity-modulated radiotherapy; STSE, soft tissue sarcoma of the extremities, 3DCRT, Three dimensional Radiotherapy.

frequency and intensity of radiotherapy-related toxicities for lymphoedema, fibrosis, bone fracture and joint stiffness.

Exploratory objectives

The exploratory objectives are:

- ▶ To explore the effect of RT technique, schedule, tumour size and anatomical location in the development of acute and late toxicities.
- ▶ To determine quality-of-life related functional outcomes and explore correlations with dose-volume parameters for patients who received preoperative, postoperative or palliative radiotherapy for STSE.

Patient population

PredicT B inclusion, exclusion and subject withdrawn criteria are listed in the following sections.

Inclusion criteria

- ▶ Histopathological diagnosis of soft tissue sarcoma of the upper or lower limb or limb girdle.
- ▶ Patients receiving preoperative (neoadjuvant), post-operative (adjuvant) or palliative radiotherapy.
- ▶ Patients receiving radiotherapy planned as per local protocols (neoadjuvant chemotherapy will be allowed).
- ▶ WHO performance status 0–2.
- ▶ Aged ≥16 years.

- ▶ Patients fit enough to undergo radiotherapy and willing to attend follow-up visits, during 2 years.
- ▶ Female patients of childbearing potential and male patients with partners of childbearing potential must agree to use adequate contraception methods, which must be continued for 3 months after the treatment.
- ▶ Capable of giving written informed consent.

Exclusion criteria

- ▶ Previous radiotherapy to the same site.
- ▶ Pregnancy.
- ▶ Patients with concurrent or previous malignancy that could compromise assessment of primary and secondary endpoints of the trial.

Subject withdrawal criteria

- ▶ Patients expressing a wish to withdraw from the study will be asked if data up to that point can be used and they will be withdrawn in line with procedures for reporting study withdrawal. Withdrawal data instigated by the investigator or the patient will be collected and reasons for withdrawal will be recorded during this study.
- ▶ The investigators will try to replace patients who are withdrawn while study recruitment is open, to allow for a 2-year follow-up. After recruitment is completed,

patients who are withdrawn will not be replaced by other individuals.

As this is an observational study, patients will not experience a change in their regular standard of medical care if there is a study withdrawal.

Radiotherapy quality assurance (RTQA)

PredicT A

A comprehensive RTQA programme for Vortex and IMRT trials was designed and implemented by the National Radiotherapy Trials Quality Assurance (RTTQA) Group, including pre-accrual and per-accrual components. For pre-accrual, QA centres completed the following exercises prior to site activation: (1) process documents, (2) benchmark outlining cases, (3) benchmark planning cases and (4) dosimetry audit (subject to prior RTTQA accreditation). On-trial QA included prospective case review of contouring and planning for the first preoperative and postoperative case from each centre, followed by retrospective review of all cases.

PredicT B

PredicT B is a non-interventional, prospective cohort study where patients receive standard-of-care radiotherapy. Therefore, an RTQA programme is not required but internal institutional peer review is performed. Radiotherapy CT scan, structures, dose plan, replan, cone-beam CT scan and diagnostic imaging (where applicable) are anonymised and centrally uploaded in RTTQA systems for review and analyses.

Statistical analyses

Hypothesis

We hypothesise that in PredicT B patients' radiation treatment plans that indicate the dose to organs-at-risk in the extremities will fail the dose constraints derived in PredicT A will have higher incidences of toxicities than patients whose treatment plans meet the constraints.

PredicT A: Development of dose–volume constraints predictive model

Patients' characteristics, tumour locations, histological subtype, toxicities and Patient Reported Outcome Measures (PROMs) will be collated with radiotherapy plan datasets.

Normal tissue structures will be defined anatomically for lower limb STSE using anatomy references for^{20–22}: MC; NVB; subcutaneous tissue; bones; and joints.

All cases will have the aforementioned normal tissues outlined retrospectively. An outlining training programme is ongoing and this is backed up by outlining peer-review and an ongoing interobserver variability study.

The radiotherapy dose–volume parameters for each predefined normal tissue structure will be exported from the treatment planning system. The database will be merged with a toxicity database including the following per patient entries: patient identification, dose–volume histogram (DVH) parameters for each normal tissue, treatment technique, side effect measures (clinician-reported

RTOG and PROMs), patient characteristics and comorbidities (eg, diabetes, hypertension, smoking habits).

An atlas of complication incidence (ACI) described by Jackson *et al*²³ will be used in order to visualise the incidence of grade 2 and above (grade 2+) toxicities. A specific ACI will be created for each normal tissue, summarising the DVH for all patients and the incidence of grade 2+ toxicities. Each ACI will show a grid of boxes with increments of volume (in cc or percentage of volume) on the y-axis and dose (in Gy) on the x-axis. The DVH for each patient will be overlaid and the number of patients whose DVHs pass through each box will be calculated. The incidence of toxicity related to the patients whose DVH passes through each box will also be calculated. This analysis will identify dose–volume regions associated with toxicities.^{24–26} Subgroup analyses will be performed to identify if different associations are detected between patients undergoing postoperative versus preoperative radiotherapy and patients undergoing IMRT or 3 dimensional radiotherapy (3DCRT).

Receiving operator characteristics (ROC) analysis will be used to find optimal dose–volume thresholds (also known as constraints) that best discriminate between patients with and without toxicity (eg, lymphoedema, fibrosis) in the PredicT A dataset. The volumes receiving each specified dose will be ranked (smallest to largest) for all patients and each possible threshold will be considered, generating the areas under the curve (AUC). Only AUC with lower CIs > 0.5 ($p < 0.05$ compared with chance) will be used to find optimal thresholds using the Youden index. In parallel, multivariate analysis (MVA) will be performed.²⁷ The associations between dose–volume variables, comorbidities and radiation-induced grade 2+ toxicities will be tested.

PredicT B: Prediction validity of frequency and intensity of radiotherapy toxicities in STSE

The validity of the dose–volume constraints identified in the PredicT A cohort will be tested in PredicT B. Specifically, patients will be divided into those meeting or not meeting constraints and comparisons of toxicity levels between both groups will be carried out.²⁸ In parallel, a similar MVA will be performed in this cohort to assess if dose–volume and toxicity relationships are similar in the validation cohort when compared with PredicT A analyses. The recruitment of the 150 patients is planned for 18 months across three centres. Patients will be followed up during RT and at 3, 6, 12 and up to 24 months post RT.

PredicT B sample size and power calculation

The primary endpoint is descriptive of toxicity rates as observed in patients recruited in the study. Published studies^{6,7} reported toxicity rates of around 40%, the rate in our patient sample $n=126$ is expected to be within two-sided 95% CI $\pm 8.6\%$. The study has also, therefore, been powered for the main secondary endpoint (endpoint 2). It has been assumed that the incidence of RTOG grade 2+ subcutaneous tissue fibrosis would be greater for patients whose radiation

treatment plan did not meet the radiotherapy dose–volume constraints compared with those for whom it did. We, therefore, aim to find differences in toxicity levels between two groups of patients: (1) patients not exceeding the previously defined dose–volume constraint and (2) patients exceeding the previously defined dose–volume constraints. Dose–volume constraints of interest will be defined in the PredicT A cohort. To detect a difference in toxicity rate of 30% between patients treated with a dose below and above a specific constraint (assuming 70% probability of grade 2+ toxicity in patients above constraint and 40% for patients below), using the 126 patients sample size with assumed ratio of 2:1 between patients below (84 patients) and above (42 patients) the constraint. This secondary endpoint will have 90% power to detect difference in the toxicity rate between the two groups at two-sided 5% significance level. The difference in toxicity rate between groups (30%) has been assumed by using a preliminary review of available Vortex trial toxicity outcome reports. Assuming 19% dropout rate during the 2-year follow-up, recruitment will continue until 150 (additional 24) patients are recruited.

Interim analysis

A preliminary analysis including the calculation of ACl, ROC and MVA for PredicT A is planned when data from 30% (115 patients) of the sample has been retrospectively outlined.

Patient and public involvement

Two patients who had a previous diagnosis of STSE and who received radiotherapy are members of the steering committee. They were involved in the design, study analyses and dissemination plan.

Planned timeline

PredicT A analysis started in June 2021 and was planned to be finalised by May 2024. PredicT B recruited its first patient on 16 April 2021. As of 19 September 2023, the study was open in three centres and is expected to complete recruitment by September 2024.

ETHICS APPROVAL

PredicT A retrospective analyses have been reviewed and received approval from the Cancer Research UK Clinical Trials Unit (University of Birmingham, Birmingham) and Cancer Research UK & UCL Cancer Trials Centre (London). Collaborations have been established with the sponsors for both Vortex and IMRIS clinical trials, and data-sharing agreement has been put in place. PredicT B has received ethical approval from North West - Liverpool Central Research Ethics Committee (20/NW/0267). Participants gave informed consent to participate in the study before taking part.

Author affiliations

¹Institute of Cancer Research, London, UK

²Royal Marsden Hospital, London, UK

³University College London Hospital NHS Foundation Trust, London, UK

⁴National Radiotherapy Trials Quality Assurance Group, Mount Vernon Hospital, Northwood, UK

⁵University College London, London, UK

⁶Institute of Clinical Trials and Methodology, University College London, London, UK

⁷University of Sheffield, Sheffield, UK

⁸Cancer Research UK & UCL Cancer Trials Centre, University College London, London, UK

⁹CRUK Clinical Trials Unit, University of Birmingham, Birmingham, UK

¹⁰University of Manchester, The Victoria University of Manchester Campus, Manchester, UK

¹¹Targeted Therapy Team, The Institute of Cancer Research, London, UK

X Rita Simões @RitaLSimoes

Acknowledgements We would like to acknowledge the trial management groups for Vortex, IMRIS and PredicT B, as well as the trials units, namely, Cancer Research UK Clinical Trials Unit, Cancer Research UK & UCL Cancer Trials Centre and Sarcoma Unit, Royal Marsden NHS Foundation Trust.

Contributors RS is the guarantor. Conceptualisation: RS, SG and AM. Methodology: RS, SG, AM, KM, H-MD, BS and MR. Software: RS and SG. Validation and visualisation: RS, SG and AM. Formal analysis: RS, SG and H-MD. Investigation: RS, SG, H-MD, AH, PG, SF, SE, T-GN, AM and SZ. Data curation: RS, AH, PG, SF, SE, T-GN and SZ. Writing—original draft and project administration: RS. Writing—review and editing: RS, SG, EM, PH, KH, AM, BS, MR and SZ. Supervision: AM, SG, KH and PH. Funding acquisition: RS and AM.

Funding RS is a clinical doctoral research fellow funded by Higher Education England and the National Institute for Health and Care Research (NIHR), award number CDR-2018-04-ST2-004. KH and AM are supported in part by National Health System funding to the NIHR Biomedical Research Centre for Cancer at The Royal Marsden Hospital and The Institute of Cancer Research. PH is supported by NIHR Manchester Biomedical Research Centre. National Radiotherapy Trials Quality Assurance Group is funded by NIHR.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methodology and analysis section for further details.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Rita Simões <http://orcid.org/0000-0003-3874-3128>

REFERENCES

- 1 Cancer research UK. Soft tissue sarcoma incidence statistics. 2010. Available: <http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/soft-tissue-sarcoma/incidence#heading=Zero>
- 2 NHS digital. Detailed statistics get out programme>sarcoma, Available: <https://www.cancerdata.nhs.uk/getdataout/sarcoma>
- 3 Francis M, Charman J, Lawrence G. "Bone and soft tissue sarcomas UK incidence and survival: 1996 to 2010. National cancer intelligence," 2010. *Pub Heal Engl* 2013;2. Available: <http://ncin.org.uk/view?rid=2353>
- 4 Felderhof JM, Creutzberg CL, Putter H, *et al*. Long-term clinical outcome of patients with soft tissue sarcomas treated with limb-sparing surgery and postoperative radiotherapy. *Acta Oncol* 2013;52:745–52.
- 5 Davis AM, O'Sullivan B, Turcotte R, *et al*. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. *Radiother Oncol* 2005;75:48–53.
- 6 O'Sullivan B, Davis AM, Turcotte R, *et al*. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet* 2002;359:2235–41.

- 7 Simões R, Augustin Y, Gulliford S, *et al.* Toxicity, normal tissue and dose-volume planning parameters for radiotherapy in soft tissue sarcoma of the extremities: A systematic review of the literature. *Radiother Oncol* 2023;186:S0167-8140(23)00277-3.
- 8 Wang D, Zhang Q, Eisenberg BL, *et al.* Significant reduction of late toxicities in patients with extremity sarcoma treated with image-guided radiation therapy to a reduced target volume: results of radiation therapy oncology group RTOG-0630 trial. *J Clin Oncol* 2015;33:2231-8.
- 9 Dickie CI, Parent AL, Griffin AM, *et al.* Bone fractures following external beam radiotherapy and limb-preservation surgery for lower extremity soft tissue sarcoma: relationship to irradiated bone length, volume, tumor location and dose. *Int J Radiat Oncol Biol Phys* 2009;75:1119-24.
- 10 Folkert MR, Singer S, Brennan MF, *et al.* Comparison of local recurrence with conventional and intensity-modulated radiation therapy for primary soft-tissue sarcomas of the extremity. *J Clin Oncol* 2014;32:3236-41.
- 11 Gurusamy VM, Al-Hammadi N, Caparrotti P, *et al.* Real-world clinical outcomes with daily image-guided IMRT in extremity soft tissue sarcomas. *Cancer Treat Res Commun* 2022;33:100655.
- 12 Calvert M, Blazeby J, Altman DG, *et al.* Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA* 2013;309:814-22.
- 13 Robinson MH, Gaunt P, Grimer R, *et al.* Vortex trial: a randomized controlled multicenter phase 3 trial of volume of postoperative radiation therapy given to adult patients with extremity Soft Tissue Sarcoma (STS). *Int J Radiat Oncol Biol Phys* 2016;96:S1.
- 14 Seddon B, Grange FL, Simões R, *et al.* The IMRIS Trial: A Phase 2 Study of Intensity Modulated Radiation Therapy in Extremity Soft Tissue Sarcoma. *Int J Radiat Oncol Biol Phys* 2024.
- 15 Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31:1341-6.
- 16 Trotti A, Colevas AD, Setser A, *et al.* CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 2003;13:176-81.
- 17 Ploetze KL, Dalton JF, Calfee RP, *et al.* Patient-reported outcomes measurement information system physical function correlates with Toronto extremity salvage score in an orthopaedic oncology population. *J Orthop Translat* 2019;19:143-50.
- 18 Kaasa S, Bjordal K, Aaronson N, *et al.* The EORTC core quality of life questionnaire (QLQ-C30): validity and reliability when analysed with patients treated with palliative radiotherapy. *Eur J Cancer* 1995;31A:2260-3.
- 19 Wang D, Zhang Q, Eisenberg B, *et al.* Significant reduction of radiation related morbidities in the extremity sarcoma patients treated with image guided radiation therapy to reduced target volume: results of RTOG 0630. *Int J Radiat Oncol Biol Phys* 2013;87:S63.
- 20 Moeller TB, Reif E. *Pocket atlas of sectional anatomy: computed tomography and magnetic resonance imaging Vol 3 Spine, extremities, joints.* Germany: Thieme, 2007.
- 21 Lengelé B, Scalliet P. Anatomical bases for the radiological delineation of lymph node areas. Part III: Pelvis and lower limbs. *Radiother Oncol* 2009;92:22-33.
- 22 Drake RL. Gray's atlas of anatomy. *Clin Anat* 2008.
- 23 Jackson A, Yorke ED, Rosenzweig KE. The atlas of complication incidence: A proposal for a new standard for reporting the results of radiotherapy protocols. *Semin Radiat Oncol* 2006;16:260-8.
- 24 Gulliford SL, Ghose S, Ebert MA, *et al.* Radiotherapy dose-distribution to the perirectal fat space (PRS) is related to gastrointestinal control-related complications. *Clin Transl Radiat Oncol* 2017;7:62-70.
- 25 Montovano M, Zhang M, Oh P, *et al.* Incidence and dosimetric predictors of radiation-induced gastric bleeding after chemoradiation for esophageal and gastroesophageal junction cancer. *Adv Radiat Oncol* 2021;6:100648.
- 26 Murray J, Gulliford S, Griffin C, *et al.* Evaluation of erectile potency and radiation dose to the penile bulb using image guided radiotherapy in the CHHiP trial. *Clin Transl Radiat Oncol* 2020;21:77-84.
- 27 Otter S, Schick U, Gulliford S, *et al.* Evaluation of the risk of grade 3 oral and pharyngeal dysphagia using atlas-based method and multivariate analyses of individual patient dose distributions. *Int J Radiat Oncol Biol Phys* 2015;93:507-15.
- 28 Gulliford SL, Foo K, Morgan RC, *et al.* Dose-volume constraints to reduce rectal side effects from prostate radiotherapy: evidence from MRC RT01 Trial ISRCTN 47772397. *Int J Radiat Oncol Biol Phys* 2010;76:747-54.