PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Simões, Rita; Gulliford, Sarah; Seddon, Beatrice; Dehbi, Hakim-Moulay; Robinson, Martin; Forsyth, Sharon; Hughes, Ana; Gaunt, Piers; Nguyen, Thuy-Giang; Elston, Stephanie; Mohammed, Kabir; Zaidi, Shane; Miles, Elizabeth; Hoskin, Peter; Harrington, Kevin; Miah, Aisha

VERSION 1 – REVIEW

REVIEWER	Domschikowski, Justus University Hospital Schleswig Holstein
REVIEW RETURNED	02-Feb-2024

GENERAL COMMENTS	Thank you for this protocol. Could you please describe your rationale for including palliative radiotherapy in the validation cohort since the parameters in cohort A were not derived from this patient cohort or dosing regime. Can you further elaborate your plan in assessing toxicities. From my understanding it is at least partially a PRO and thus should be reported according CONSORT PRO extension or SPIRIT PRO extension.

REVIEWER	Smolle, Maria Medical University of Graz
REVIEW RETURNED	13-Mar-2024

GENERAL COMMENTS	Herein, the authors present an interesting study protocol exploring a research question of evident clinical need in patients with extremity soft tissue sarcoma. The aims of the study are clearly stated. However, there are – amongst other small issues – inconsistencies between the protocol and appendices that need clarification by the authors. Please find below major comments and minor comments that may be addressed to improve the study protocol's quality and eventually research findings: Major comments: - Given that only 56 patients had received preoperative radiotherapy in the PredicT A cohort, the authors should consider omitting these patients from their analyses, as the preoperative clinical setting is different to a postoperative situation.

	- How will the authors ensure that patients in PredicT B are distributed equally to one of the three treatment arms (i.e. preoperative, postoperative, palliative radiotherapy)? Furthermore, which number of patients do the authors estimate will be eligible for one of the research arms? Considering that neoadjuvant radiotherapy is more and more established as “first choice” treatment in patients with extremity soft tissue sarcoma, it may be expected that only a small number of patients will receive adjuvant radiotherapy. - The study protocol is inconsistent regarding the recruitment period of patients in PredicT B. On page 9 of the submission file, the authors state that 150 patients will be recruited within 27 months, whilst on page 12 of the submission file, they write about 18 months. Please provide consistent numbers. Similarly, there are discrepancies between the protocol and the appendix regarding statistical analyses in PredicT B: On page 9 of the submission file the authors state that multivariate models will be used to predict “…if dose-volume and toxicity relationships are similar in the validation cohort when compared to PredicT A analyses”. On page 47 of the submission file, the authors write that “There is no plan to fit multivariate model.“ Please clarify. Minor comments: - The authors should be consistent with the writing of “PredicT”, as they sometimes write “Predict”. - The “Methods and analysis” section of the abstract is written in a confusing way, as it is unclear whether the statistical model will derive from the PredicT A or PredicT B (although it can be assumed that the model will be generated on the former cohort). Please clarify. - Thorough revision in English grammar and writing is recommended, as several errors appear throughout the manuscript that impair its readability.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Justus Domschikowski, University Hospital Schleswig Holstein
Comments to the Author:
Dear Author,

Thank you for this protocol.
Could you please describe your rationale for including palliative radiotherapy in the validation cohort since the parameters in cohort A were not derived from this patient cohort or dosing regime.

Thank you for your thoughtful observations. The outcomes and toxicities of palliative radiotherapy for soft tissue sarcoma of the extremities are insufficiently documented, and we aim to address this gap.

High-dose palliative radiotherapy doses are marginally lower than pre-operative doses and are biologically calculated to be equivalent to pre-operative radiotherapy. Including the high-dose

palliative spectrum allows us to further test our hypothesis while also reporting the incidence and severity of toxicities.

Can you further elaborate your plan in assessing toxicities. From my understanding it is at least partially a PRO and thus should be reported according CONSORT PRO extension or SPIRIT PRO extension.

Many thanks for your comment.

Although our study is not a randomised controlled study we are following CONSORT PRO extension checklist. We have added a sentence describing this and detailed the specific toxicity scales for clinician-reported and patient-reported outcomes to the methodology section. We have also detailed the patient- and clinician-reported outcome measures that we will be used.

Reviewer: 2
Dr. Maria Smolle, Medical University of Graz
Comments to the Author:
Herein, the authors present an interesting study protocol exploring a research question of evident clinical need in patients with extremity soft tissue sarcoma. The aims of the study are clearly stated. However, there are – amongst other small issues –inconsistencies between the protocol and appendices that need clarification by the authors. Please find below major comments and minor comments that may be addressed to improve the study protocol's quality and eventually research findings:

Major comments:

- Given that only 56 patients had received preoperative radiotherapy in the PredicT A cohort, the authors should consider omitting these patients from their analyses, as the preoperative clinical setting is different to a postoperative situation.

Thank you very much for your comments. We appreciate the opportunity to clarify the details in the PredicT A section. It appears this section might have been misunderstood. In this section, we analysed data from two UK clinical trials: VorteX and IMRiS. Within the VorteX trial, 216 patients received post-operative radiotherapy. In the IMRiS trial, a total of 168 patients were treated, with 112 receiving pre-operative radiotherapy and 56 receiving post-operative radiotherapy. To improve clarity, we have revised this section, and the changes are highlighted in yellow below.

Furthermore, we wish to emphasise the significance of analysing a range of doses, from high-dose palliative to pre-operative and post-operative treatments, to capture a comprehensive range of doses and clinical scenarios. This approach will aid in determining dose-volume constraints and understanding the impact of various clinical, treatment, and patient factors that may contribute to toxicities.

'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 post-operative radiotherapy improved limb function without compromising local control for STSE.12 Two hundred and sixteen patients were recruited between 2008 and 2013. The co-primary 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 (RTOG clinician-reported scoring system), overall level of limb function (measured with two general questions in TESS), as well as disease-free and overall survival. Patients were randomized to either the control arm to receive a 2-phase radiotherapy technique of 50 Gy in 25 fractions followed by a boost of 16 Gy in 8 fractions or the research arm, which consisted of 66 Gy in 33 fractions to the reduced boost volume. 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 pre-operative and 56 patients received post-operative 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 (measured with the TESS score), time to local recurrence, disease-free and overall survival. IMRT was delivered either pre-operatively as 50 Gy in 25 fractions or post-operatively as 60 Gy in 30 fractions or 66 Gy in 33 fractions (for patients with positive resection margins).'

- How will the authors ensure that patients in PredicT B are distributed equally to one of the three treatment arms (i.e. preoperative, postoperative, palliative radiotherapy)? Furthermore, which number of patients do the authors estimate will be eligible for one of the research arms? Considering that neoadjuvant radiotherapy is more and more established as "first choice" treatment in patients with extremity soft tissue sarcoma, it may be expected that only a small number of patients will receive adjuvant radiotherapy.

Many thanks for this. Perhaps it has not been clear in the protocol that our study is a cohort study and does not stratify or randomise patients in different arms. The study overall aims are to describe the incidence of radiotherapy toxicities and to develop dose-volume constraints for the normal tissues in patients who receive pre or post-operative radiotherapy. In the UK, the ratio between pre-operative to post-operative radiotherapy is approximately 50:50 and we have been observing this is the recruited patients.

- The study protocol is inconsistent regarding the recruitment period of patients in PredicT B. On page 9 of the submission file, the authors state that 150 patients will be recruited within 27 months, whilst on page 12 of the submission file, they write about 18 months. Please provide consistent numbers. Similarly, there are discrepancies between the protocol and the appendix regarding statistical analyses in PredicT B: On page 9 of the submission file the authors state that multivariate models will be used to predict "…if dose-volume and toxicity relationships are similar in the validation cohort when compared to PredicT A analyses". On page 47 of the submission file, the authors write that "There is no plan to fit multivariate model." Please clarify.

Many thanks for highlighting this. 27 has been incorrectly typed.

"There is no plan to fit multivariate model." has been left incorrectly from the previous protocol version. Both incorrections have now been removed.

Minor comments:

- The authors should be consistent with the writing of “PredicT”, as they sometimes write “Predict”. This has now been corrected. Many thanks

- The “Methods and analysis” section of the abstract is written in a confusing way, as it is unclear whether the statistical model will derive from the PredicT A or PredicT B (although it can be assumed that the model will be generated on the former cohort). Please clarify. Many thanks for highlighting that the abstract was not clear. It has now been amended.

- Thorough revision in English grammar and writing is recommended, as several errors appear throughout the manuscript that impair its readability.

Many thanks for this. We can confirm that we have reviewed the manuscript to ensure that English grammar is correct.

Reviewer: 1
Competing interests of Reviewer: no competing interets

Reviewer: 2
Competing interests of Reviewer: I have no conflicts of interest to declare.

VERSION 2 – REVIEW

REVIEWER	Domschikowski, Justus University Hospital Schleswig Holstein
REVIEW RETURNED	02-Jul-2024

GENERAL COMMENTS	Thank you for your clarifications. From my point of view no other revisions are necessary.

REVIEWER	Smolle, Maria Medical University of Graz
REVIEW RETURNED	14-Jun-2024

GENERAL COMMENTS	The authors have addressed all comments raised, provided explanations to open questions, and have revised the protocol where necessary. I have no further suggested improvements.