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Systematic Review

Toxicity, normal tissue and dose-volume planning parameters for radiotherapy in soft tissue sarcoma of the extremities: A systematic review of the literature

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ABSTRACT

Background: Patients with soft tissue sarcoma of the extremities (STSE) are left with high incidence of toxicities after Radiotherapy (RT). Understanding the normal tissue dose relationship with the development of long-term toxicities may enable better RT planning in order to reduce treatment toxicities for STSE. This systematic review of the literature aims at reporting the incidence of acute and late toxicities and identifying RT delineation guidance the normal tissues structures and dose-volume parameters for STSE.

Methods: A literature search of PUBMED-MEDLINE for studies that reported data on RT toxicity outcomes, delineation guidelines and dose-volume parameters for STSE from 2000 to 2022. Data has been tabulated and reported.

Results: Thirty of 586 papers were selected after exclusion criteria. External beam RT prescriptions ranged from 30 to 72 Gy. The majority of studies reported the use of Intensity Modulated RT (IMRT) (27%). Neo-adjuvant RT was used in 40%. The highest long-term toxicities were subcutaneous and lymphoedema, reported when delivering 3DCRT. IMRT had a lower incidence of toxicities. Normal tissue outlining such as weight-bearing bones, skin and subcutaneous tissue, corridor and neurovascular bundle was recommended in 6 studies. Nine studies recommended the use of dose-volume constraints, but only one recommended evidence-based dose-volume constraints.

Conclusion: Although the literature is replete with toxicity reports, there is a lack of evidence-based guidance on normal tissue and dose-volume parameters and strategies to reduce the normal tissues irradiation when optimising RT plans for STSE are poor compared to other tumour sites.

Soft tissue sarcoma incidence was approximately 7% in 2019. In 2019, 4,295 new cases were registered in the United Kingdom (UK) and there was a 5% increase trend in their incidence since 2013. [1,2,3] Localised disease is potentially curable with 5-year survival rates of 60% in high-grade disease.[4].

Radiotherapy (RT) is often used in the management of STSE, either as neo-adjuvant, adjuvant or primary definitive treatment. [5] For large, deep-seated resectable high-grade tumours, RT is recommended in the neo-adjuvant or adjuvant setting in combination with surgery to achieve local control rates of greater than 80%.[6] International guidelines recommend neo-adjuvant RT, allowing smaller volumes to be treated to lower total radiation doses.[7,8] Adjuvant RT translates to similar local control rate when compared to neo-adjuvant therapy but with reduced incidence of late complications.[6] In selected cases where tumours may cause significant symptoms affecting limb function or demonstrate less radiosensitivity with a propensity to grow marginally during RT, surgery followed by post-operative RT is preferred, with the expectation that patients are at increased risk of long-term side-effects.

Long-term side-effects are defined as late complications causing persistent damage and developing from 3 months to years after RT. [9] These RT long-term side-effects include joint stiffness, tissue fibrosis, bone fractures and lymphoedema in the context of STSE. [6] Clinical trials, such as the SR2 have reported an incidence of tissue fibrosis in 48.2% and 31.5% of patients, joint stiffness in 23.2% and 17.8% of patients and lymphoedema in 23.2% and 15.5% of

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patients who received post-operative and pre-operative RT, respectively.[10] The CRUK VorteX trial, comparing standard against reduced post-operative RT target volumes, has recently reported grade 2 + late toxicity rates of about 50%, including subcutaneous (47% in standard arm and 41% in the experimental arm), bone (11% versus 15%) and joint (18% for both arms) toxicities.[11] Importantly, such complications can cause impairment of normal limb function which significantly impact on patients' quality-of-life.

Understanding the normal tissue dose relationship with the development of long-term toxicities may enable better radiotherapy planning in order to reduce treatment toxicities. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC), is an expert consensus defining radiation dose levels delivered to a defined volume of normal tissue which may predict for specific RT-related toxicities, often referred as dose-volume constraints. When applying these to the radiotherapy planning processes, the dose to specific neighbouring normal tissue structures can be significantly reduced.[12] The use of such strategies with modern RT optimisation techniques has reduced the development of late side-effects, such as dry mouth and diarrhoea for tumour types such as head and neck or prostate cancers.[13,14,15] Strategies to reduce the radiation dose to the normal tissues of the extremities have not been included in such expert consensus as QUANTEC. Dickie and colleagues studied the dose–effect for bone fractures and identified that when a dose-volume constraint of V40 < 64% is applied to the femur the risk of fracture appears to be reduced. This in conjunction with keeping the mean dose to the femur below 37 Gy and maximum dose below 59 Gy were game changers in RT for STSE.[16] Unfortunately, this effort has not been made possible yet for the other normal tissue toxicities, such as fibrosis or lymphoedema. Historically a normal tissue corridor consisting of a longitudinal strip of skin and subcutaneous tissue was defined and the dose it received was restricted. In an effort to translate this to modern techniques, such as Intensity modulated RT (IMRT), it has been recommended that no more than 50% of the normal tissue corridor volume receives 20 Gy to avoid lymphoedema or normal tissue fibrosis.[17] The definition of this avoidance structure however lacks consistent guidelines and can vary in its definition, shape and size from patient-to-patient. It also does not correlate to an organ or a specific normal tissue structure. On other hand applying a V50%<20 Gy when doing rotational IMRT may be challenging due to the low-dose bath associated with the technique delivery. There is an unmet need in knowing which normal soft tissues irradiation will most likely be associated with the development of toxicities, such as fibrosis or oedema.

The aims of this systematic review of the literature are:

- To review the incidence of acute and late toxicities after neo-adjuvant and adjuvant external beam RT delivered to patients with STSE;
- To identify delineation guidance the normal tissues structures which are associated with the development of acute and late toxicities;
- To identify dose-volume parameters applied to specific normal tissue structures and subsequent reporting of normal tissue toxicities.

Methods

Protocol and registration

Studies were identified following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [18] The protocol for this systematic review was registered with PROSPERO (CRD42021286246).

Study identification and search strategy

Pubmed-MEDLINE was used using search terms '((((radiotherapy) OR (radiation therapy)) AND (soft tissue sarcoma)) AND (toxicity) AND ((dose) OR (dosimetry)))' and also '((radiotherapy dose constraints) OR (radiotherapy dose-volume constraints)) AND (extremities)'. Both literature searches were limited to publications from 1st of January 2000 and 9th of August 2022.

The references for all selected papers were searched to ensure that all the relevant papers were included. Duplicates were removed.

Study selection

Studies written in English, involving human adult patients treated for STSE with external beam RT were eligible. Studies describing side-effects to the normal tissues of the extremities following RT and/or providing outlining guidance for these normal tissue structures were also considered. Any paper describing dose-volume relationships or constraints to the normal tissues of the extremities was included. Table 1 shows the exclusion criteria.

Abstracts were independently screened by two reviewers (RS, YA). Eligibility of the papers was also checked independently by the same two reviewers, with any discrepancies discussed between the two reviewers. A third reviewer (ABM) was available to adjudicate in case of disagreement. The references of all included papers were checked for additional papers.

Data extraction and synthesis

The following data were reported and tabulated for each study included: author, year, journal, country of study, radiotherapy technique, type of study, Phase I, II or III, soft tissue sarcoma histopathology, adults versus children, treatment intention, number of patients included in the study, total prescribed dose and number of fractions, patient positioning and immobilisation, anatomical location, organs at risk or normal tissue outlining guidance, toxicity grade scales used, acute and late toxicities reported (above grade 2 and in percentage, %), dose-volume constraints or planning thresholds and patient reported outcome measures in the studies.

Data analyses

The radiosensitivity, α/β for each sarcoma histological subtype is unknown. The literature has reported in the range of 3–5. The equivalent dose at 2 Gy per fraction (EQD2) was calculated using an α/β ratio of 3 and 5 for all the studies in order to obtain a comparable prescription referential.[19,20] The average of the toxicities above grade 2 in percentage (%) by reported technique was calculated.

Quality assessment of the studies

The quality assessment of the studies was performed using the MINORS-validated instrument for the selected studies.[21] MINORS is designed to assess the methodological quality of non-randomized studies, whether comparative or non-comparative.

Results

Study selection

Five-hundred and ninety-six papers were searched. Based on the exclusion criteria stated on section Table 1, 30 papers were eligible. Fig. 1 details the rationale for the paper exclusion.

Table 1
Literature exclusion criteria.

Article exclusion criteria
1. Publications that did not study soft tissue sarcomas of the extremities
2. No Radiotherapy or historic radiotherapy techniques such as 2D RT or cobalt-60
3. No mention of external beam radiotherapy toxicities, dose-volume parameters to normal tissues or only visceral toxicities reported
4. Pre-clinical studies or studies not conducted in humans
5. Papers not written in English or access to abstract only
6. Duplicates
7. Case reports
8. Radiation enhancers toxicity-related studies

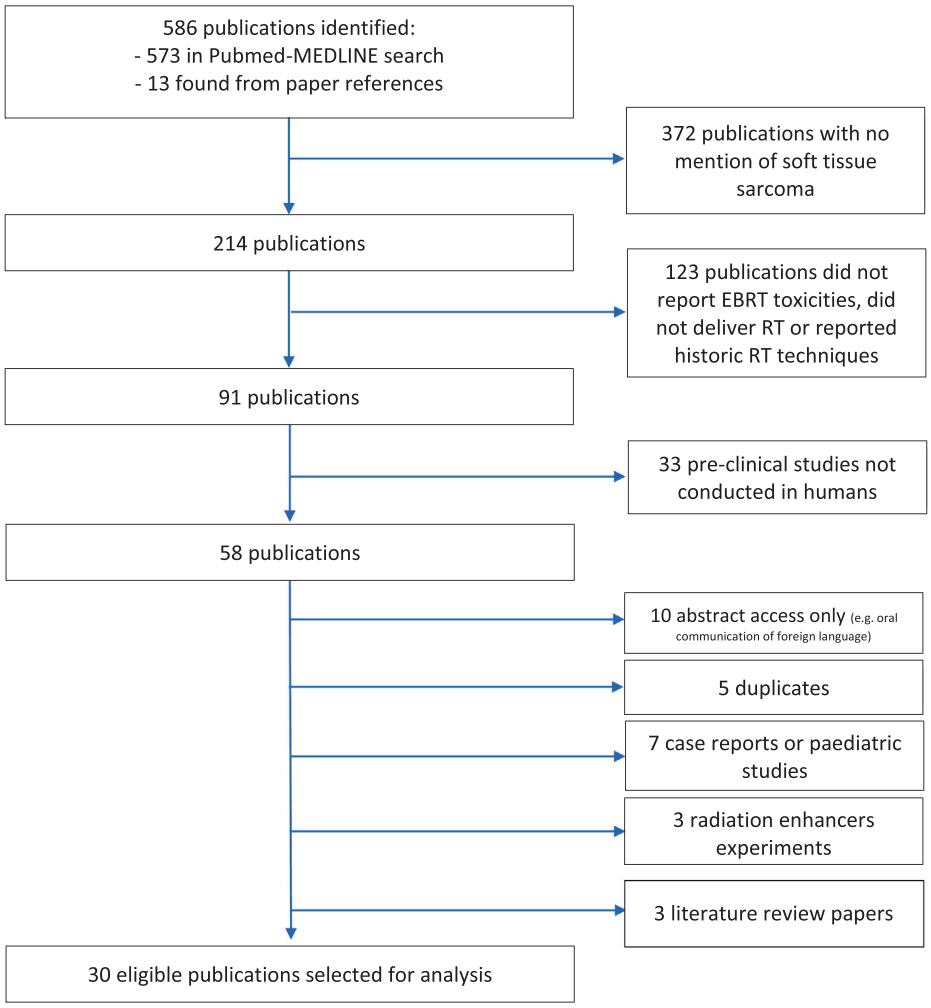

Fig. 1. PRISMA diagram demonstrating the rationale for the paper exclusion.

Study characteristics

The majority of the studies identified in the search were not specific to soft tissue sarcoma (63%). Approximately 21% of the papers did not report on external beam radiotherapy (EBRT), did not deliver RT or reported historic RT techniques. Other criteria that led to exclusion were: studies not conducted in humans or pre-clinical (33), access to abstract only (10), duplicated papers (5), case reports or paediatric studies (7). All the relevant references found in three literature review papers were included in the analysis.

A summary of the studies is provided in Table 2. Of the 30 studies analysed, IMRT was used in 8 (27%) papers. Also, 8 studies included patients treated either with 3DCRT or IMRT. Six (20%) studies analysed used 3D conformal RT (3DCRT). The RT technique was not specified in 5 papers (17%). Other techniques were used in 3 studies (10%) such as a combination of 3DCRT and 2DRT and stereotactic body RT (SBRT). These studies included 2669 patients in total, specifically 1196 and 1107 patients were treated with adjuvant and neo-adjuvant RT, respectively. It was not possible to track the regimen for 366 patients with STSE as it was stated in the studies that both regimens could be used. Neo-adjuvant RT was used in 12 studies (40%). Adjuvant RT was used in 10 studies (33%), adjuvant and neo-adjuvant RT was used also in 10. On average 89 patients (range: 10–319) were treated in each study to a prescription dose ranging from 30 Gy to 72 Gy. Neo-adjuvant studies used.

Table 2
Summary of the eligible studies. (Abbreviations in table: 2-Dimensional radiotherapy (2DRT), 3-Dimensional Conformal Radiotherapy (3DCRT), Intensity modulated radiotherapy (IMRT), Randomised clinical trial (RCT) followed by phase (I, II, III, or IV), Non-randomised clinical trial (NRCT) followed by phase (I, II, III).

Author	Year	journal	Treatment intention	Radiotherapy technique	Prescription dose	No of fractions	EQD2 ($\alpha\beta = 3$)	EQD2 ($\alpha\beta = 5$)	Type of study	No of STSE patients	Adults vs Children	Country of study	MINORS score
Di Brina, L. et al.[22]	2019	Br J Radiol	Adjuvant	IMRT & 3DCRT	60 to 70 Gy	30 to 35	60 to 70 Gy	60 to 70 Gy	Retrospective	109	Adults	Italy	8
Wang, D. et al.[17]	2015	Journal of Clinical Oncology	adjuvant and neo-adjuvant	IMRT & 3DCRT	50 Gy + Boost if + margin	25 fractions + 8 EBRT or 4 HDR	50 Gy	50 Gy	NRCT II	79	Adults	USA and Canada	13
Peeken, J. et al.[23]	2019	Radiat Oncol.	Neo-adjuvant	Helical IMRT	50 Gy	25	50 Gy	50 Gy	Retrospective	41	Adults	Germany	7
Kubicek, G. et al.[24]	2018	Am J Clin Oncol.	Neo-adjuvant	SBRT	35 Gy to 40 Gy	5	56 Gy to 64 Gy	50 to 57.1 Gy	Retrospective	14	Adults	USA	9
Devisetty, K. et al.[25]	2011	Int J Radiat Oncol Biol Phys	Neo-adjuvant	not specified	20 Gy	10 to 16	15.2 Gy to 20 Gy	16 Gy to 20 Gy	Retrospective	22	Both	USA	10
Wang J. et al.[26]	2015	Onco Targets Ther.	Adjuvant	IMRT	50 Gy ph1 + 10–16 Gy ph2	25 + 10–16	50 Gy to 66 Gy	50 Gy to 66 Gy	Retrospective	51	Both	China	10
Stewart, A. et al.[27]	2009	Radiother Oncol.	Adjuvant	IMRT & 3DCRT	50 Gy + 16 Gy for 3DCRT; 62.5 Gy with SIB	25 + 8	50 Gy to 68.8 Gy	50 Gy or 66.9 Gy	Prospective dosimetric	10	Not stated	UK	6
Kim Y. et al.[28]	2016	Anticancer Res	Adjuvant	not specified	46 Gy to 60 Gy	23 to 30	46 Gy to 60 Gy	46 Gy to 60 Gy	Retrospective	17	Both	Republic of Korea	10
Kalbasi A. et al.[29]	2020	Clin Cancer Res.	Neo-adjuvant	IMRT	30 Gy	5 fraction	82.8 Gy	72.3 Gy	NRCT II	43	Adults	USA	14
Davis, A. et al.[30]	2005	Radiother Oncol.	adjuvant and neo-adjuvant	3DCRT	50 Gy or 66–70 Gy	25 or 33–35 fractions	50 Gy, 66 to 70 Gy	50 Gy, 66 to 70 Gy	RCT III	190	Adults	Canada	12
O'Sullivan, B.et al.[31]	2013	Cancer	Neo-adjuvant	IMRT	50 Gy	25	50 Gy	50 Gy	NRCT II	59	Adults	Canada	13
Felderhof, J. et al.[4]	2013	Acta Oncol.	Adjuvant	3DCRT	60 to 66 Gy	30 to 33 fractions	60 to 66 Gy	60 to 66 Gy	Retrospective	118	Adults	The Netherlands	11
McGee, L. et al.[32]	2012	Int J Radiat Oncol Biol Phys.	Adjuvant	not specified	mean RT dose 65 Gy	not mentioned	N/A	N/a	Retrospective	173	Adults	USA	10
Pak, D. et al.[33]	2012	Int J Radiat Oncol Biol Phys	adjuvant and neo-adjuvant	3DCRT & 2DRT	45 to 50.4 Gy	25 to 28 fractions	43.2 Gy to 48.3 Gy	43.7 to 49 Gy	Retrospective	223	Adults	USA	9
Koseła-Paterczyk, H. et al.[34]	2014	Eur J Surg Oncol	Neo-adjuvant	3DCRT	25 Gy	5 (consecutive days)	40 Gy	35.7 Gy	Prospective observational	235	Adults	Poland	9
Cai, L. et al.[35]	2013	Rare Tumors	adjuvant and neo-adjuvant	not specified	50 Gy or 64 Gy	25 or 32 fractions	50 or 64 Gy	50 or 64 Gy	Retrospective	109	Adults	Switzerland	10
Brodowicz, T. et al.[36]	2000	Sarcoma	Adjuvant	3DCRT	51 Gy	30 (twice during 3 weeks)	47.9 Gy	48.8 Gy	RCT II	46	Adults	Austria	12
Dogan, ÖY. et al.[37]	2019	Acta Ortop Bras.	Adjuvant	not specified	50 Gy phase 1, 60–70 Gy boost	25 to 35	50, 60 to 70 Gy	50, 60 to 70 Gy	Prospective observational	114	Adults	Turkey	10
O'Sullivan, B. et al.[6]	2002	Lancet	adjuvant and neo-adjuvant	3DCRT	50 Gy or 66 Gy	25 or 33 fractions	50 or 66 Gy	50 or 66 Gy	RCT III	190	Adults	Canada	13
Baldini, EH. et al.[38]	2013	Ann Surg Oncol.	adjuvant and neo-adjuvant	IMRT & 3DCRT	50 Gy	25	50 Gy	50 Gy	Prospective observational	103	Adults	USA	11
DeLaney, T. et al.[39]	2007	International Journal of Radiation Oncology Biology Physics	adjuvant and neo-adjuvant	not specified	50 Gy, 60 Gy or 66 Gy for + margins	25. 30 or 33	50, 60 or 66 Gy	50, 60 or 66 Gy	Prospective observational	105	Both	USA	10
Lansu, J. et al.[40]	2020	JAMA Oncology	Neo-adjuvant	IMRT	36 Gy	13	36 Gy	36 Gy	NRCT II	79	Adults	Europe and USA	14
Alektiar, K. et al.[41]	2008	Journal of Clinical Oncology	adjuvant and neo-adjuvant	IMRT	50 Gy or 60 to 66 Gy	25 to 33	50, 60 or 66 Gy	50, 60 or 66 Gy	Prospective observational	41	Adults	USA	12
Folkert, M. et al.[42]	2014	Journal of Clinical Oncology	adjuvant and neo-adjuvant	IMRT & 3DCRT	50 Gy or 63 Gy	Not stated	N/a	N/a	Retrospective	319	Adults	USA	10
Hong, L. et al.[43]	2004	Int J Radiat Oncol Biol Phys	Adjuvant	IMRT & 3DCRT	63	37	59.2 Gy	60.3 Gy	Retrospective	10	Adults	USA	7
Dickie, C. et al.[16]	2009	Int J Radiat Oncol Biol Phys	Adjuvant	3DCRT	Not stated	Not mentioned	N/a	N/a	Retrospective	74	Adults	Canada	10
Van Meekeren, M. et al.[44]	2021	Acta Oncol	Neo-adjuvant	IMRT & 3DCRT	36 Gy or 50 Gy	25 or 18	36 or 50 Gy	36 or 50 Gy	NRCT II	25	Adults	Netherlands and United Kingdom	13
Bedi, M. et al.[20]	2021	Advances in Radiation Oncology	Neo-adjuvant	IMRT & 3DCRT	35 Gy	5	70 Gy	60 Gy	NRCT II	32	Adults	USA	11
Lawless, A. et al.[45]	2022	Practical Radiation Oncology	Neo-adjuvant	IMRT	50 Gy	25	50 Gy	50 Gy	Retrospective	20	Adults	Australia	5
Casey, D et al.[46]	2021	Ann Surg Oncol	adjuvant and neo-adjuvant	IMRT	50 Gy or 63 Gy	25 or 35	50 Gy or 60.5 Gy	50 or 61.2 Gy	Retrospective	145	Adults	USA	9

Table 3
Summary of grade 2 or above toxicities grouped by RT technique(2DRT, 3DCRT and IMRT) for the neo and adjuvant treatment settings. Minimum and maximum toxicity incidence (in %) are presented for cases where there are a minimum of studies.

		Moderate to major wound complications	Acute skin toxicity (dermatitis)	Acute Pain	Late skin toxicity	Bone fracture	Lymphoedema	Tissue fibrosis	Joint stiffness	Joint range of motion decreased	Joint arthralgia	Subcutaneous toxicity	Osteonecrosis	Peripheral nerve damage ≥ grade 2	Fatigue
Ajuvant or Neo-adjuvant 2DRT or 3DCRT	Pak D. et al.[33] §					4.0%									
Adjuvant 3DCRT	Davis, A. et al.[30]*¥						23.2%		23.2%			48.2%			
	Felderhof, J. et al.[4]¦	7.6%	87.0%				25.4%	15.3%	4.2%		0.8%				4.2%
	Brodowicz T et al.[36]¢§	2.2%	10.9%			0.2%	0.2%								
	Di Brina, L. et al.[22]*¦		60.5%					7.6%					2.8%		
	O'Sullivan, B. et al.[6]*	17.0%	68.1%												
	min	2.2%	10.9%				0.2%	7.6%	4.2%						
	max	17.0%	87.0%				25.4%	15.3%	23.2%						
Neo-adjuvant 3DCRT	Davis, A. et al.[30]*¥						15.5%		17.8%			31.5%			
	Koseła-Paterczyk H.[34] et al.*	21.1%					22.5%	12.2%							
	O'Sullivan, B. et al.[6]*	35.0%	36.4%												
	min	21.1%					15.5%								
	max	35.0%					22.5%								
Adjuvant and Neoadjuvant 3DCRT	Jacob R. et al.[47]*¤	32.4%	78.4%		24.3%		10.8%		10.8%		13.5%	27.3%			
	Folkert, M. et al.[42]¦	17.5%	48.7%			9.1%	14.9%		11.0%					1.6%	
Neo-adjuvant 3DCRT or IMRT	Wang, D. et al.[17] *¥	36.6%						5.3%	3.5%			5.3%			
	Baldini EH et al.[38]¤	35.0%													
	van Meekeren, M. et al.[44]¦¤	28.0%	0.0%				0.0%	4.0%		0.0%					0.0%
	Bedi, M. et al.[20]¦¤	25.0%	15.6%					34.5%							
	min	25.0%						4.0%							
	max	36.6%						34.5%							
Adjuvant IMRT	Di Brina, L. et al.[22]*¦		49.3%					11.3%							
	Wang J. et al.[26]¦						5.9%		13.8%						
Adjuvant or Neo-adjuvant IMRT	Folkert, M. et al.[42]¦	19.0%	31.5%			4.8%	7.9%		14.5%					3.5%	
	Alektiar, K. et al.[41]¦	9.7%				4.8%	12.2%		17.1%					3.3%	
	Casey, D et al.[46]§					4.9%									
	min	9.7%				4.8%	7.9%		14.5%					3.3%	
	max	19.0%				4.9%	12.2%		17.1%					3.5%	
Neo-adjuvant IMRT	Peeken J. et al.[23]¦¤	36.8%	20.0%	27.5%	5.0%		7.5%		2.5%		2.5%				12.5%
	Kalbasi A. et al.[29]*¥¦¤	32.0%					4.0%	11.0%	11.0%						
	O'Sullivan, B.[31]*¥¦¤	30.5%	1.9%			0.0%	11.1%		5.6%			9.3%			
	Lansu, J. et al.[40]*¥	17.0%					6.0%	9.0%	1.0%						
	min	17.0%	1.9%				4.0%	9.0%	1.0%						
	max	36.8%	20.0%				11.1%	11.0%	11.0%						
Neo-adjuvant SBRT	Kubicek, G. et al.[24]¦¡	28.5%	28.0%				0.0%	0.0%	0.0%						
Technique not specified	Devisetty, K. et al.[25]¡	36.0%				10.0%									
	Kim Y. et al.[28]¦¤					11.8%									
	McGee L. et al.[32]¦	3.4%	1.1%			6.3%									
	Cai, L. et al.[35]¦	38.0%			16% combined with lymphoedema)		16% (combined with skin toxicity)		2.5%			16% (but mixed with lymphoedema and skin toxicities			
	DeLaney, T. et al.[39] ¤	17.5%				2.8%									

Toxicity scales:*Acute and late morbidity EORTC/RTOG criteria; ¤- NCIC late limb oedema scale and/or wound complications; §- Not specified; ¥ - Stern's scale; ¦- CTCAE; ¢- WHO (for chemotherapy); ¡-own scoring scale.

Table 4
Outlining guidance provided in the studies.

Author	Technique	Weight-bearing bone	Partial bone	Other bones	Skin	Subcutaneous tissue	Normal tissue corridor	Joints	Neurovascular bundle
Di Brina, L. et al[22]	IMRT & 3DCRT	Outlined, definition not provided							
Wang, D. et al.[48]	IMRT & 3DCRT	Outlined, definition not provided					Longitudinal strip of skin and subcutaneous tissue		
Stewart A. et al.[27]	IMRT & 3DCRT	Outlined, definition not provided					The volume of a 2 cm thick band that covered 30% of the limb circumference at 180 degrees from the centre of the PTV over the length of PTV was contoured		Contoured from pelvic brim to mid knee joint; definitions not provided
O'Sullivan, B.[31]	IMRT	Outlined, definition not provided		All bones contoured; definitions not provided	skin and subcutaneous tissues required to close the future resection site; The future scar a surgical skin flap was outlined by the surgeon and marked with radio-opaque markers to guide delineation in the CT scan.				
McGee L. et al.[32]	not specified		Femur outlined partially, definition not provided	Uninvolved bones outlined; definitions not provided				Entire joint space was excluded from the radiotherapy fields	Uninvolved neurovascular outlined; definitions not provided
Pak D. et al.[33]	3DCRT & 2DCRT	Femur auto-contoured using thresholds of 150 to 3,000 and manually edited where required	Femoral neck was contoured from the lateral border of the femoral head to the intertrochanteric line. The intertrochanteric region of the femur was contoured from the tip of the greater trochanter superiorly to the bottom of the lesser trochanter inferiorly, and the subtrochanteric region from the bottom of the lesser trochanter superiorly to 5 cm inferiorly. The body of the femur was then contoured from the inferior border of the subtrochanteric region to the most inferior beam field edge.						
Lawless, A. et al.[45]	IMRT			Any bone in field outlined			Normal tissue structure used, no further guidance on how to outline it		

on average a RT prescription dose of 62 Gy (EQD2 calculated, ranging from 20 to 60 Gy) and adjuvant prescriptions were on average 62 Gy (ranging from 50.4 to 72 Gy). EQD2 for these studies are presented in Table 2.

Normal tissue toxicities

Table 3 summarises toxicities grade 2 or above (grade 2 +) by technique and treatment intention. Some of the studies reported toxicities combined for the radiotherapy regimen and/or technique. Minimum and maximum dose are presented for each group sorted by regimen and technique. Mean and standard deviation were not calculated. Overall, neo-adjuvant IMRT studies report lowest incidences of grade 2 + dermatitis, lymphoedema, tissue fibrosis and joint stiffness. The only study utilising neo-adjuvant SBRT reported lower wound complications, lymphoedema, tissue fibrosis and joint stiffness compared to neo-adjuvant IMRT. The highest toxicities reported tended to be for 3DCRT either in the neo-adjuvant or adjuvant setting. IMRT studies reported a larger number of toxicity endpoints than 3DCRT studies.

Normal tissue outlining and dose-volume constraints

Seven studies (Table 4) reported the outlining of normal tissue structures.[22,17,27,31,32,33,45] There is a consensus on the outlining of bony structures for all studies. One study provided outlining guidance for the skin and subcutaneous tissues involved in the surgical resection with a surgeon. Three studies reported outlining of a normal tissue corridor, defined as longitudinal strip of normal tissue with at least 2 cm diameter. This concept developed from the application of 2DRT. Two studies outlined the neurovascular bundle however guidance on how to reproduce these outlines was not provided. One study outlined joint space, but outlining guidance was not provided.

Dose-volume constraints were reported in 9 studies (Table 5), with only Dickie et al. deriving dose-volume constraints based on reported toxicities.[16] These dose-volume constraints were used across seven studies. The remaining 8 studies were studies reporting on dosimetry outcomes such or planning recommendations published in studies or trial protocols. Particularly Di Brina et al., a planning study comparing the rotational IMRT and 3DCRT has identified that a reduction of the dose delivered to the bone could be achieved with rotational IMRT.[22] Four studies provide only protocol recommendations on the basis of a previously published clinical trial protocol for a ph2 study of IMRT and IGRT in STSE.[31].

Quality assessment of the studies

MINORS scores are presented in Table 2 and in detail in Table 6 in appendix. The mean MINORS score was 10.3, ranging from 5 to 14, with a maximum score of 16. In general, studies were good at prospectively identifying their aims, defining endpoints and collating data. However, unbiased assessment of the endpoints was not undertaken in any of the studies and loss to follow-up often exceeded 5%.

Discussion

Radiation-induced toxicities are commonly associated with a threshold dose to specific normal tissue structures.[12] The outlining of normal tissue structures and use of dose and volume thresholds, known as, dose-volume constraints, allows for stringent RT beam optimisation and planning. This will strive to achieving the optimal therapeutic index, which is maximising dose to the target volume versus minimising dose to the neighbouring normal tissue. The probability of developing grade 2 + temporary acute and permanent long-term toxicities has been reduced in previous studies for other tumours sites.[15,49,50,13] Our results highlight a wealth of literature reporting radiotherapy toxicities for STSE. As expected grade 2 + toxicities were higher in the adjuvant setting, which may be explained by higher doses and larger volumes of normal tissue treated. The clinical target volume (CTV) outlining in the adjuvant setting includes the reconstructed gross tumour volume (GTV) and an axial margin of 1.5 to 2 cm and 4 to 5 cm longitudinally and in some clinical scenarios it can include the whole longitudinal extension of the scar plus 1 to 2 cm. The neo-adjuvant CTV incorporates

Table 5
Dose-volume constraints or recommendations found in the literature. (Abbreviations: 2-Dimensional radiotherapy (2DRT), 3-Dimensional Conformal Radiotherapy (3DCRT), Intensity modulated radiotherapy (IMRT)).

Author	Technique	Planning outcomes and/or dose volume constraints reported
Di Brina, L. et al[22]	Rotational IMRT & 3DCRT	Planning outcomes reported in the study comparing 3DCRT and IMRT (VMAT). Bone doses reported achieved: D1cm (Gy) - all patients 60.6 ± 0.9; 3DCRT 66.9 ± 0.5 vs VMAT 57.3 ± 1.2 (p < 0.001); D5ccm (Gy) - all patients 58.8 ± 1.0; 3DCRT 66.1 ± 0.6 vs VMAT 55.0 ± 1.3 (p < 0.001); D10ccm (Gy) - all patients 57.5 ± 1.1; 3DCRT 65.4 ± 0.8 vs VMAT 53.3 ± 1.4 (p < 0.001); Dmax (point dose) (Gy) - all patients 63.5 ± 0.8; 3DCRT 67.7 ± 0.5 vs VMAT 61.3 ± 1.2 (p < 0.001)
Devisetty, K. et al.[25]	not specified	Maximum doses reported from patients who developed severe toxicities
Stewart A. et al.[27]	IMRT & 3DCRT	Planning recommendations; Femur:1) if 0–50% bone circumference within PTV aim to a) 100% bone cortex under 52 Gy or b) 50% of cortex of bone must not receive over 45 Gy in 2 Gy per fraction or equivalent; 2) if 50–99% bone circumference within PTV aim to spare 1/3 of bone circumference if it is at least 1 cm from the PTV; 3) if 100% bone circumference within PTV aim for central sparing of cortex/bone marrow; Joint: <50% of any joint within the field; Contralateral leg: No beams entering or exiting through contralateral leg if possible; Genitalia: Exclude where possible; Max. dose to testes 6 Gy; Max. dose to ovaries 8 Gy; Skin corridor: Aim for 0 Gy; Soft tissue outside PTV: Less than 55 Gy in 2 Gy per fraction; Neurovascular bundle: 56 Gy in 2 Gy per fraction
Kalbasi A. et al.[29]	IMRT	Planning recommendations as part of clinical trial protocol; Skin V12Gy $\leq$ 50%;2cm longitudinal strip of skin V12Gy $\leq$ 10%; Long bones (femur, humerus) V30Gy $\leq$ 50% Femoral or humeral head V30Gy $\leq$ 5 cc, Dmax $\leq$ 33 Gy
O'Sullivan, B.[31]	IMRT	Planning recommendations as part of clinical trial protocol; Bone mean dose < 37 Gy; Maximum bone dose < 59 Gy; The percentage of bone receiving $\geq$ 40 Gy < 64%; musculature/ tissue dose < 20 Gy Maximum 21 Gy
Pak D. et al.[33]	3DCRT & 2DRT	A dosimetric comparison was done in as much as a single subtrochanteric fracture case. Mean dose of 62.0 Gy, a V30 = 42.8 cc, V45 = 42.8 cc, and V60 = 42.8 cc at the subtrochanteric region for the fracture patient were substantially outside the upper limits of the 95% confidence intervals calculated for the nonfracture patients All fracture sites had mean doses greater than 40 Gy
Dickie, C. et al.[16]	3DCRT	Bone fractures modelled; The risk of radiation-induced fracture is reduced if femur V40 < 64%. Fracture incidence was lower when the mean dose to bone was < 37 Gy or maximum dose anywhere along the length of bone was < 59 Gy.
Lawless, A. et al.[45]	IMRT	A dosimetric study applying previously dose-volume constraints for femur: mean < 37 Gy and max dose < 59 Gy
Casey, D et al.[46]	IMRT	A dosimetric study testing the application of previous dose-volume constraints for femur: Dmean < 37 Gy, V40Gy < 64%, and Dmax < 59 Gy

the GTV and an added margin of 1.5 to 2 cm axially and longitudinal margin of 3 to 4 cm[5,51].

IMRT studies reported lower rates of grade 2 + toxicities than 3DCRT. Although this is noted, 3DCRT remains the standard RT technique and in certain circumstances may provide better outcomes than IMRT, thus studying both techniques is relevant to clinical practice, particularly as the low-dose bath associated with IMRT is larger than in 3DCRT. Importantly, as techniques evolve with the time, 3DCRT studies tend to be older than IMRT studies. Therefore, such reduced toxicities may not be attributable to the treatment technique applied, but can be influenced by other factors such as IGRT and other complex planning techniques that are nowadays available, as well as lead-time bias. Surgical techniques were not considered in this review and we acknowledge that there are changes in the techniques from the oldest to the more recent reviewed papers, 2000 and 2022.

This review identifies the lack of delineation guidelines on normal tissues for STSE. In fact only 7 out of 30 studies reporting toxicity described outlining of normal tissue structures. The main normal tissue outlines reported in these studies were for bone, however bone fractures are amongst the lowest incidence of reported toxicity. The outlining of normal tissue corridor, joints, skin and subcutaneous tissue and neurovascular bundle were reported in 3, 1, 1, 2, respectively.[17,27,32,31] Upon review of the definitions there is no clear guidance on how to define these structures. The normal tissue corridor is historically defined as a longitudinal strip of normal tissue outside of the PTV that should be spared to reduce the risk of lymphoedema. Lymphoedema occurs as a consequence of damage to the lymphatic drainage system caused by radiation. Proteins and lipids accumulate in the interstitial space and tissues and undergo architectural changes, including adipose tissue deposition and fibrosis.[52] Interestingly, this corridor does not relate an anatomical structure to the pathophysiology of lymphoedema. The assumption is that it may represent a volume of lymphatic tissue corridor. For instance, the outlining of the main lymphatic vessels, vein and arteries collecting the lymph drainage or even some of the muscle compartments is not mandated. RT plans are therefore optimised to minimise or avoid radiation dose to a pre-defined normal tissue corridor, which does not correspond to an anatomical structure. As shown on Table 3 grade2 + lymphoedema or subcutaneous incidence cannot be ignored; by outlining the main vessels and/ or muscle compartments there may be a potential to optimise RT plans based on these which may translate into a the reduction of these toxicities. Although two studies stated that the neurovascular bundle was outlined, the anatomical definition in these studies was unclear. [27,32].

This contrasts with other tumour sites, where specific normal tissue structures defined as OARs have been defined. For example, pharyngeal constrictor muscles have been defined as OARs in for head and neck cancer to prevent dysphagia.[50] The definition of joint volumes is also unclear, particularly regarding what anatomical regions should be included or used as outlining surrogates.

QUANTEC is possibly the largest consensus guidance for normal tissue dose-volume constraints.[12] However, apart from bony structures, dose-volume constraints relevant for STSE were not included in this paper. Dickie and colleagues[16] have proposed evidence-based dose-volume constraints which should be used for the femur to avoid long-term femoral fractures. They demonstrated that treated bones should not receive a mean dose higher than 40 Gy and the volume of bone receiving 40 Gy should not exceed 64% to reduce radiotherapy-related fractures. This translated to a 4% incidence reduction of bone fractures at 5 years.[16] This has so far been the only paper reporting long-bones dose-volume constraints and has been used worldwide as identified in our results. These dose-volume constraints may not be applied to smaller bones as for example patella or metatarsal bones, for which the incidence of fractures was either smaller or non-existent. The use of such constraints is even more important in the presence of risk factors associated with bone fractures: periosteal stripping, RT dose, size of the tumour, gender, age and reduced bone density.

Additionally, it is essential to define additional normal tissue constraints to help reduce lymphoedema and fibrosis, which can significantly impact on function and quality of life. This review identifies a need for similar work to be conducted with other structures to understand the relationships between the irradiation of the normal tissues such as the neurovascular bundle, muscle compartments, joints and the development of long-term lymphedema, fibrosis or joint arthrosis. Similarly it is challenging to translate dose-volume constraints used in a 3DCRT planning era to a mainly fixed field and rotational IMRT driven modern ages.

This systematic review highlights a long overdue unmet need to standardise the outlining of the normal tissues at risk of toxicity as well as the use of normal tissue constraints in RT planning for STSE. STSE are rare and it is challenging to accrue large sample sizes. Another challenge for this work to be undertaken is variability in tumour location, size as well as accounting for surgical technique. Current work to correlate response, dose constraints, toxicities and functional outcomes is prospectively being undertaken as part of a prospective recruiting study at our institution.

Conflicts of interest

The authors declare that thre are noconflicts of interest.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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