East of England Radiotherapy Network:

Sarcoma Protocol V4.0

Contents

1.0 Indications and patient population

This protocol covers treatment in the following situations:

a. Curative pre-operative radiotherapy for soft tissue sarcoma (STS) of the limb or trunk

b. Curative post-operative radiotherapy for soft tissue sarcoma (STS) of the limb or trunk

c. Definitive curative radiotherapy for soft tissue sarcoma (STS) of the limb or trunk

d. Palliative radiotherapy for soft tissue sarcoma (STS) of the limb or trunk

1.1 Curative treatment eligibility

1.1a Inclusions

- Any soft tissue sarcoma with any of the following features:
    - Grade 2 or 3
    - In the deep muscle compartment
    - >5cm in size
- Any grade tumour with marginal excision (<1mm), where further surgery not possible or will likely to be morbid or cause a functional defect.

1.1b Exclusions

- Where a corridor of normal tissue cannot be avoided, patients may need to consider amputation instead of risk chronic lymphoedema
- Not suitable for immobilisation required to deliver radiotherapy

1.1c Essential Pre-Radiotherapy investigations for curative patients

- All new diagnoses of STS of limb and trunk should be discussed at a sarcoma MDT with local imaging (MRI/CT), staging for metastatic disease (usually CT chest +/- abdomen and pelvis), and biopsy result.
- All new patients should have baseline blood tests including renal function if intravenous contrast required
- For post-operative patients, a pre-operative MRI for use for radiotherapy planning should ideally be no more than 4 weeks prior to surgery
- Sperm-banking should be offered to patients receiving any dose to the testes
- Ovary cryopreservation should be considered for young women receiving pelvic RT

2.0 Localisation

It is important to discuss in detail with radiographers/planning before proceeding, ideally at pre-planning meeting, and individualised for each patient.

Localisation	Options	Notes
Position	Dependent on location	Supine/ prone (to be decided prior to CT scan)
Arm/ leg/ head/ thorax position	Upper trunk	Arms above head
	Abdomen/ pelvis	Arms by sides or folded across chest
Immobilisation and supports	Upper trunk	Wingboard
	Abdomen/ pelvis	Head rest, knee, and ankle support
	Limb	Consider personalised immobilisation (vac bag / orfit)
Organ pre-requisites	N/A	
Contrast	Pre-op patients	IV contrast if required
	Other	If appropriate
Radiopaque markers	Wire lump / scar	
Bolus	If a clinical decision is made to include the skin, then use of physical bolus may be considered, although bolus should be used with caution because of the increased skin dose and reaction.	
Other imaging	Pre-op MRI	CT if no MRI available
	PET	If clinically appropriate
CT acquisition	3DCT	Slice thickness – 2-3mm. Scanning limits – individualised for each patient.
	4DCT for chest wall and abdominal wall sarcoma may be required.	
Medications	Individualised	
Histology and op note (if available)	Check tumour size, margins	

3.0 Dose prescription & chemotherapy

Intent	Comment	Dose (Gy)/#	#/ week	Planning technique/ further comment
a. Curative pre-operative radiotherapy for soft tissue sarcoma of the limb or trunk		50/25	5	
b. Curative post-operative radiotherapy for soft tissue sarcoma of the limb or trunk	Clear surgical margins (R0)	60/30; larger volume to 52.2Gy/ 30 with simultaneous integrated boost (SIB) to 60Gy	5	IMRT planned
	Positive surgical margins (R1)	66/33; larger volume 53.5Gy/33 with SIB to 60Gy	5	IMRT planned
	Phase 1	50/25	5	3D Conformal radiotherapy/ IMRT
	Phase 2	10/5	5	
	Elderly pts/ poor performance status	55/20	5	3D Conformal radiotherapy/ IMRT
	Hypo-fractionated radiotherapy	36/6	1	
	Dose per # may be reduced by 1.8Gy on an individualised patient basis	50.4/28	5	Where spinal cord, brachial or lumbar plexus or significant amounts of bowel are within PTV.
		59.4/33	5	

Intent	Comment	Dose (Gy)/#	#/ week	Planning technique/ further comment
	to minimum 45Gy.			
c. Definitive curative radiotherapy for soft tissue sarcoma of the limb or trunk		66/33	5	
		50/20	5	
	Hypo-fractionated radiotherapy	36/6	1	
d. Palliative radiotherapy for soft tissue sarcoma of the limb or trunk N.B Higher does as per curative intent may be appropriate in some palliative circumstances or patients, but this will be decided by the clinician on an individual basis.		40/15	5	3D conformal or V Sim
	Where clinically significant amounts of bowel are within the PTV	36/20	5	3D conformal
		30/10	5	3D conformal or V Sim
	Where clinically significant amounts of bowel are within the PTV	27/15	5	3D conformal
		20/5	5	V Sim
		8/1	1	V Sim

4.0 Target volumes

- Use standard nomenclature as per AAPM 263
- https://www.aapm.org/pubs/reports/RPT_263.pdf

4.1 Curative radiotherapy

4.1.1 GTV

a. Preoperative RT

- The GTV is defined and delineated as the tumour as visualised on the diagnostic contrast-enhanced T1-weighted MRI scans.

b. Post-operative RT

- For patients who have undergone surgery, there is by definition no GTV. The pre-operative GTV should therefore be reconstructed on the planning CT to enable the accurate delineation of the CTV.
- Information from the pre-operative diagnostic MRI, operation report, and histopathology report is used to reconstruct the GTV, considering any altered anatomy after surgery, and possible growth of the GTV between imaging and surgery. The post-operative seroma should not be used as a surrogate for the GTV, but instead should be included in the CTV

4.1.2 CTV

a. Preoperative radiotherapy:

- The CTV is created by adding a 2 cm margin to the GTV radially taking intact skin, bone and fascia barriers into account, adding 0.5cm margin over bone or fascial boundaries. A more generous 3 cm margin is used for histologies known to be associated with high local recurrence rates (myxofibrosarcoma, malignant peripheral nerve sheath tumour, MPNST).

- In the longitudinal direction, a margin of 3 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 3cm margin.

- The CTV includes any suspicious areas of oedema visualised on T2 MRI sequences, based on clinical judgement, which may require a larger margin more than 3cm.

- Care should be taken as not to taper the CTV longitudinally so as not to taper the volume axially into a cone, this is best done by creating the CTV by freehand rather than using an expansion algorithm. The CTV should be cylinder shaped rather than spindle shaped.

b i. Post-operative radiotherapy: 3DCRT:

Radiotherapy is delivered in a 2-phase shrinking field technique.

- CTV phase 1 - CTV1 = GTV + 5 cm superiorly and inferiorly, and 2cm axially (3cm for myxofibrosarcoma and MPNST). If the GTV abuts bone or fascia, then the GTV to CTV margin should be 5mm over these barriers. The CTV should contain the scar, seroma, surgical clips, and biopsy and drain sites, but should remain within the skin surface unless a clinical decision is made to include the skin, where bolus may be considered. In some cases it may not be feasible to include the full length of the scar if it extends the volume significantly, particularly if it includes treating 2 joints. The longitudinal margins may need to be longer than 5cm in order to encompass the entire seroma, which should ideally be included. Care should be taken as not to taper the CTV longitudinally so as not to taper the volume, this is best done by creating the CTV by freehand. The CTV should be cylinder shaped rather than spindle shaped. For non-limb sites, CTV = GTV + 2-3cm, depending on site and achievability, decided on an individual patient basis.

- CTV phase 2 - CTV2 = GTV + 2cm superiorly and inferiorly, and 2cm axially. For non-limb sites, aim to achieve a volume reduction if feasible to spare normal tissues, although frequently this is not possible.

- A normal tissue corridor of un-irradiated tissue should be maintained for limb tumours to prevent lymphoedema, which should be as large as feasible and no less than 1cm width.

b ii. Post-operative radiotherapy: IMRT:

- 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 is used for histologies 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. 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

- If the GTV abuts bone or fascia, then the GTV to CTV margin should be 5mm over these barriers. The CTV should contain the scar, seroma, surgical clips, biopsy and drain sites but should remain within the skin surface unless a clinical decision is made to include the skin, where bolus may be considered. In some cases, it may not be feasible to include the full length of the scar if it extends the volume significantly,

particularly if it includes treating 2 joints. The longitudinal margins may need to be longer than 5cm to encompass the entire seroma, which should ideally be included.

- Care should be taken as not to taper the CTV longitudinally so as not to taper the volume, this is best done by creating the CTV by freehand. The CTV should be cylinder shaped rather than spindle shaped.

4.2 Curative PTV delineation

- The PTV is created by adding a margin of 0.7cm to the CTV isotropically in all directions for limb sarcomas. A larger PTV margin of 1cm may be required for STS involving the chest or abdominal trunk wall.

- For post-operative IMRT the CTV_6000 and CTV_5200 should not overlap longitudinally but should end on adjacent slices. To create PTV_6000 and PTV_5220, CTV_6000 and CTV_5220 should be expanded isotropically by 0.7cm. With this isotropic expansion, the PTV_6000 and PTV_5220 will overlap longitudinally. PTV_6000 takes priority over PTV_5220 for planning.

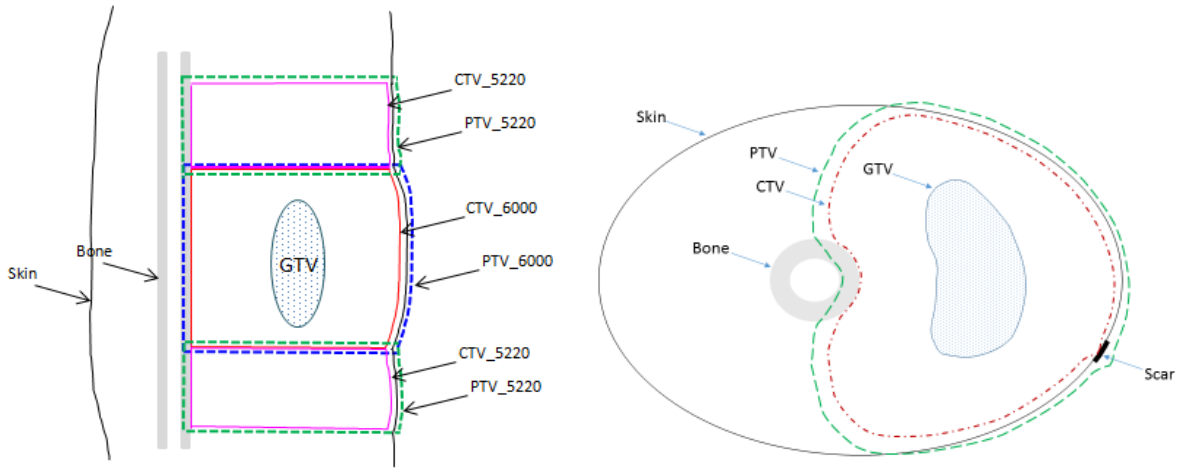

Figure 1. Schematic description of target definition for postoperative radiotherapy boost (Haas R.L.M. et al 2012)

4.3 Palliative radiotherapy

For simple treatments, contour GTV and add margin to PTV of 10mm axially and 10-20mm sup-inf. Consider formal contouring as previous for 3D conformal treatment.

5.0 Organs at risk

- Aim for the use of standard nomenclature as per Global Harmonization Group consensus guidelines: https://www.thegreenjournal.com/action/showPdf?pii=S0167-8140%2820%2930294-2
    - Organ at risk (OAR) dose constraints are divided into mandatory and optimal. This is to reflect that dose constraints for some OARs will not be achievable without compromising PTV coverage, e.g., when PTV is abutting or overlapping bone. 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. The dose to the contralateral limb should be reported for all cases.

OAR	Dose Constraints	Comment
Mandatory		
Normal tissue Corridor[1]	V_{20Gy} <50%	If possible, part of the circumference of the limb should be treated to a lower dose. A longitudinal strip of skin and soft tissue should be contoured according to the judgment of the treating clinical oncologist, to allow sparing of lymphatic drainage. This will be used to optimise the IMRT plan. The dose distribution should be reviewed on each axial slice. The structure should be volume 2cm above and below PTV.
Brachial Plexus	Mean dose < 60 Gy Max dose (D0.1cc) < 65Gy	It is recommended that the brachial plexus is outlined using the RTOG brachial plexus atlas for guidance.
Optimal		
Bone in treatment field	V_{50Gy} ≤ 50%	Bone in the treatment field is defined as the whole cross-section of the bone on the same CT slices as PTV.
Whole bone	Mean dose ≤ 40Gy V_{40Gy} ≤ 64%	The whole bone adjacent to the tumour should be outlined as OAR.
Femoral head & neck	Mean dose ≤ 40Gy	From the top of the femoral head to inferior aspect of the lesser trochanter
Joint	V_{50Gy} ≤ 50%	If possible, the dose to the adjacent joint should be limited as much as possible, which may be difficult if the joint is in the PTV. Outlining the joint may be difficult because lack of clear definition of what needs to be included but the purpose of this would be to keep the dose to the joint as low as possible.
Contralateral limb		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 should be reported as follows: • Dose to $1cm^3$, $2cm^3$, $5cm^3$

OAR	Dose Constraints	Comment
		• Mean dose along the length of PTV +2cm superiorly and inferiorly.
Genitalia		Should be volumed as an organ at risk and avoided as much as possible. For males, the genitalia should be moved away from the treatment area, and sperm banking should be offered if any dose is delivered to the testes.

1. The 'normal tissue corridor' is intended to be an avoidance structure to limit radiation dose to the proportion of the limb (in axial section) outside of the treatment target volumes, with an aim to prevent circumferential irradiation to a significant dose and therefore minimise the risk of lymphoedema as a late toxicity. There are no established absolute definitions of how this is defined and it should be constructed pragmatically for each individual patient treatment, and finalised collaboratively between the physician and the dosimetry team for the purpose of achieving the clinical goal.

5.1 Constraints

	Pre-operative radiotherapy	Post-operative radiotherapy	
	Dose to PlanPTV_5000	Dose to PlanPTV_6000/ PlanPTV_6600	Dose to PlanPTV5220/ 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

6.0 Planning process/ technique

- IMRT/ VMAT/ Heliac Arc Therapy for curative treatments.
- Conformal for high-dose palliative or if possible, for curative treatments while still achieving optimal dose-distribution constraints.

7.0 Peer Review/ Contour QA

All curative volumes to be prospectively peer reviewed where possible – but no pre-op treatment to be delayed (to be peer reviewed retrospectively).

A description of the contouring (planning note) and of the peer review process including changes made should be saved in the patient record.

The peer review process and outcomes should be audited.

Local MDT/ pre-planning discussion prior to patient CT appointment recommended.

8.0 Target verification

Modality	Frequency	Match point	Additional information
kV planar/ MV planar/ CBCT	Minimum Daily KV	Bone match	Consider weekly CBCT

9.0 Side effects

9.1 Possible early or short-term side effects		
Expected (50% - 100%)		**Initial management (if appropriate)**
Skin soreness and irritation		RTOG • Grade 1: Faint or dull erythema; mild tightness and itching of the skin may occur. • Grade 2a: Tender or bright erythema; skin may feel tighter/itchy/sore. Moisturiser: patient to use preferred centre moisturiser (aloe vera gel, E45 etc.) on intact skin- must be sodium lauryl sulphate free. Steroid creams: topical treatment may be required but should not be used on broken skin or if signs of infection are present.
Hair loss in the treatment area		
Tiredness		
Bowel symptoms	Diarrhoea	WHO toxicity grade • Grade 1: Increase of 2-3 stools per a day over pre-treatment. • Grade 2: Increase of 4-6 stools per day, or nocturnal stools with moderate cramping. • Grade 3: Increase of 7-9 stools per a day, or incontinence or severe cramping. • Grade 4: Increase of >10 stools per day, or bloody diarrhoea or need for parenteral support. Dietary advice: advise to avoid high fibre, high fat foods, spices, caffeine, alcohol, fruit juices and lactulose containing products if appropriate. Recommend adequate oral hydration and consider smaller frequent meals. Anti-diarrhoeals: Commence 4mg of Loperamide then 2mg after each stool (max 16mg in 24 hours). If persistent then can add in codeine phosphate 60mg four times a day. Octreotide may be considered in an inpatient setting.
	Frequency	

9.1 Possible early or short-term side effects		
	Urgency	Infection screening: send stool cultures. Consider for admission and assess need for IV fluids and nutritional support. May require CT imaging to exclude colitis.
	Mucus/ wind	
	Pain	
Common (10-50%)		**Initial management (if appropriate)**
Urinary symptoms	Frequency	RTOG acute urinary toxicity grade: • Grade 1: urination or nocturia frequency twice pre-treatment habit. • Grade 2: urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasms may be reported. • Grade 3: urination with nocturia hourly or more frequently; with dysuria, pelvic pain and bladder spasm. Gross haematuria with/without clots may be reported. • Grade 4; haematuria requiring transfusion and acute bladder obstruction. Dietary advice: encourage good oral hydration. Antispasmodics: consider antispasmodics for bladder spasms. Analgesia: consider oral analgesia for dysuria. Infection screening: check urine dip +/- MSU, consider antibiotics if appropriate.
	Cystitis	

Skin breakdown in the treatment area	RTOG: • Grade 2b: Patchy moist desquamation; yellow/pale green exudate may be visible on the surface. Soreness and oedema are evident. • Grade 3: Confluent moist desquamation; more pronounced areas of broken skin, yellow/pale green exudate are visible. Soreness and oedema are evident. • Grade 4: Ulceration of the skin; haemorrhage and or necrosis of the skin are evident. Flamazine if necessary. Analgesia: review oral analgesia regime. Infection screening: take a swab if there are signs of infection and arrange antibiotic treatment if infection is indicated. Consider for admission or regular wound care review.
Wound breakdown	
Swelling of limb	
Less Common (Less than 10%)	**Initial management if appropriate**
Nausea and/ or vomiting	CTCAE 4.03 grading for nausea: • Grade 1: loss of appetite without alteration in eating habits. • Grade 2: oral intake decreased without significant weight loss, dehydration or malnutrition. • Grade 3: Inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition or hospitalisation. Anti-emetics: 5HT3 antagonists are particularly effective in radiation induced nausea and vomiting. Regular antiemetics are more effective than PRN doses. Consider prophylaxis with a 5-HT3 receptor antagonist (ondansetron 8mg orally or intravenously or granisetron 2mg orally or 1mg IV as a single dose) at least 30 minutes prior to radiotherapy session if required. Consider for admission and assess need for IV fluids and nutritional support.

Tenesmus	
Bleeding from rectum/ blood in stool	
Rare (Less than 1%)	**Initial management (if appropriate)**
Urinary retention	May require urinary catheter.

9.2 Possible late or long – term side effects

Expected (50% - 100%)		**Initial management (if appropriate)**
Skin colour changes/ telangiectasia		
Fibrosis		Refer to Physiotherapy: CUH - R.E.A.C.T. react@addenbrookes.nhs.uk
Bowel symptoms	Diarrhoea Frequency Urgency	WHO toxicity grade • Grade 1: Increase of 2-3 stools per a day over pre-treatment. • Grade 2: Increase of 4-6 stools per day, or nocturnal stools with moderate cramping. • Grade 3: Increase of 7-9 stools per a day, or incontinence or severe cramping. • Grade 4: Increase of >10 stools per day, or bloody diarrhoea or need for parenteral support. Dietary advice: advise to avoid high fibre, high fat foods, spices, caffeine, alcohol, fruit juices and lactulose containing products if appropriate. Recommend adequate oral hydration and consider smaller frequent meals.

		Anti-diarrhoeals: Commence 4mg of Loperamide then 2mg after each stool (max 16mg in 24 hours). If persistent then can add in codeine phosphate 60mg four times a day. Octreotide may be considered in an inpatient setting. Infection screening: send stool cultures. Consider for admission and assess need for IV fluids and nutritional support. May require CT imaging to exclude colitis.
Common (10 – 50%)		**Initial management (if appropriate)**
Urinary symptoms	Frequency Urgency Cystitis Incomplete emptying/ reduced bladder capacity	RTOG acute urinary toxicity grade • Grade 1: urination or nocturia frequency twice pre-treatment habit. • Grade 2: urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasms may be reported. • Grade 3: urination with nocturia hourly or more frequently; with dysuria, pelvic pain and bladder spasm. Gross haematuria with/without clots may be reported. • Grade 4; haematuria requiring transfusion and acute bladder obstruction. Dietary advice: encourage good oral hydration. Antispasmodics: consider antispasmodics for bladder spasms. Analgesia: consider oral analgesia for dysuria. Infection screening: check urine dip +/- MSU, consider antibiotics if appropriate.
Permanent hair loss in treatment area		
Less common (Less than 10%)		**Initial management (if appropriate)**
More prone to bone fractures in the radiotherapy treatment area		
Bowel/ bladder damage	Perforation Fistula	

	Bowel adhesions/ obstructions	
Infertility		
Male: change in sexual experience	Inability to ejaculate	
	Dry ejaculate	
	Erectile dysfunction	
Female: Early menopause		
Female: change in sexual experience	Narrowing of vagina	Refer to Physiotherapy: CUH - R.E.A.C.T. react@addenbrookes.nhs.uk. NB may be seen/managed by CUH Women's & Men's Physiotherapy Team.
	Dryness of vagina	
Lymphoedema of the limb		Refer to Lymphoedema Services where available. https://www.arhc.org.uk/professionals/refer-to-us/. For patients over 18 and registered with a Cambridgeshire GP: • For Central Referrals call: 01223 675800 • Email for Arthur Rank Hospice services, based in Cambridge: nee.arthurrank@nhs.net • Email for Alan Hudson Day Treatment Centre services, based in Wisbech: nee.alanhudson@nhs.net
Poor wound healing		
Rare (Less than 1%)		**Initial management (if appropriate)**
A different cancer in the treatment area		
Neuropathy		

10.0 References

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11.0 Members of the protocol drafting committee

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12.0 Amendment History

A record of changes in this document

Date	Updated version number	Previous version number	Page Number/ Section (updated version)	Details
5.10.20	V1.0			New Document
5.11.21	V1.1	V1.0	P4/ 5	Clarification provided on doses/#
20.4.21	V1.2	V1.1	P10	Normal tissue corridor detail added
10.11.21	V2.0	V1.2		New version issued: palliative dose/ fractionation guidance updated; side effect information updated.
05.01.23	V3.0	V2.0	4.0	OAR nomenclature updated to GHG consensus guidance as per Network Oversight Group request.
12.02.24	V4.0	V3.0	Pg9	Correction to table under heading 'joint'.
				ICRU 83 reporting guidelines added