Lymphoma Radiotherapy Treatment Clinical Protocol

1.0 Treatment Indications

1.1 Low Grade Non-Hodgkin's Lymphoma (NHL)

To include Follicular and MALT NHL.

Management will depend upon the extent of disease and any symptoms. Low grade NHL is characterised by an indolent course of recurrences and relapses. Disseminated disease can be palliated but not cured with systemic anti-cancer therapy (SACT). Localised disease can be treated with curative radiotherapy alone. For patients staged with PET-CT, freedom from progressive disease at median follow-up of 52 months is 74.1% for stage 1 and 49.1% for stage 2 disease, with a local control rate of 97.6% (Brady et al).

For extranodal marginal zone lymphoma of the stomach, if H.pylori positive or negative then eradication is the preferred first line treatment. Patients with persistent disease should be offered radiotherapy.

1.2 High Grade Non-Hodgkin's Lymphoma (NHL)

To include Diffuse Large B-Cell (DLBCL), Primary CNS Lymphoma, Primary Mediastinal and NK/T Cell NHL.

DLBCL is aggressive, but potentially curable. SACT is the treatment of choice in most situations. Patients with localised residual PET positive disease who are not proceeding to salvage SACT should be offered radiotherapy. Radiotherapy may be used to consolidate response to sites of bulk (defined as >7.5cm) that is PET-negative at the end of SACT. There is conflicting data and no prospective evidence for the benefit of radiotherapy in this scenario. If disease is not bulky and encompassable in a single radiotherapy plan, local irradiation may be used after 3 cycles of R-CHOP chemotherapy as combined modality treatment. Local radiotherapy may also be used to consolidate response to SACT in high risk sites (breast, bone, testis, thyroid) or for palliation.

Primary CNS lymphoma is usually DLBCL. For fit patients an approach of using high dose SACT and stem cell transplant is preferred, thus avoiding the late cognitive effects of radiotherapy (IELSG32). In patients not fit for stem cell transplant, radiotherapy can be used to consolidate the response to SACT. Radiotherapy can be considered where there is an incomplete response to primary treatment and in the palliative setting for those not fit for SACT. The volume to be treated differs from palliative whole brain radiotherapy and includes the optic nerve and upper spinal cord to the level of C2.

For patients with primary mediastinal B cell lymphoma, who achieve a complete metabolic response following SACT, there is data published in abstract form to suggest that radiotherapy can be safely omitted without compromising progression free survival. (98.5% in combined modality vs. 96.2% in the SACT arm – not statistically significant at 30-months – IELSG37 abstract). Follow up is ongoing but overall survival at 5-years was 99% in both groups. The omission of radiotherapy in this group should be discussed at local MDT and with the patient. Patients with localised disease who have positive or equivocal PET-CT after SACT should be offered radiotherapy.

NK/T cell NHL is rare in the Western world, however is relatively common in East Asia and South America. It usually involves the nasal cavity, paranasal sinuses or sometimes Waldeyer's ring. Outside of these sites the disease usually presents in advanced stages. The disease is usually locally destructive into the submucosa and radiotherapy volumes should reflect this. For localised disease a combined modality approach of SACT and then radiotherapy is usually adopted.

1.3 Classical Hodgkin's Disease (HD)

When deciding treatment modality in early stage Hodgkins Lymphoma different centres may adopt different approaches based on data from various groups/trials:
German Hodgkin Study Group (GHSG)
EORTC
UK RAPID trial for early (stage I-IIA, not stratified for favourable/unfavourable) Hodgkin's lymphoma: x3 ABVD, followed by PET-CT with no radiotherapy if PET negative. (This approach may be particularly considered in younger patients with mediastinal disease where late toxicity would be of particular concern. A slight reduction in progression free survival is accepted with no difference in overall survival seen).

GHSG and EORTC divide early stage into favourable and unfavourable using slightly different criteria.

GHSG classification:	**EORTC classification:**
Large mediastinal mass (>1/3 maximum thoracic diameter)	Large mediastinal mass (>1/3 maximum thoracic diameter)
Extra-nodal disease	Age >= 50 years
Elevated ESR (>50 without B symptoms > 30 with B symptoms)	Elevated ESR (>50 without B symptoms > 30 with B symptoms)
3 or more lymph node areas	4 or more lymph node areas

GHSG classification:

Early Stage HD (Favourable): Stage I/II with no risk factors

Early Stage HD (Unfavourable): Stage I/IIA with one or more risk factors

Advanced Stage HD: IIB with risk factors OR Stage III/IV

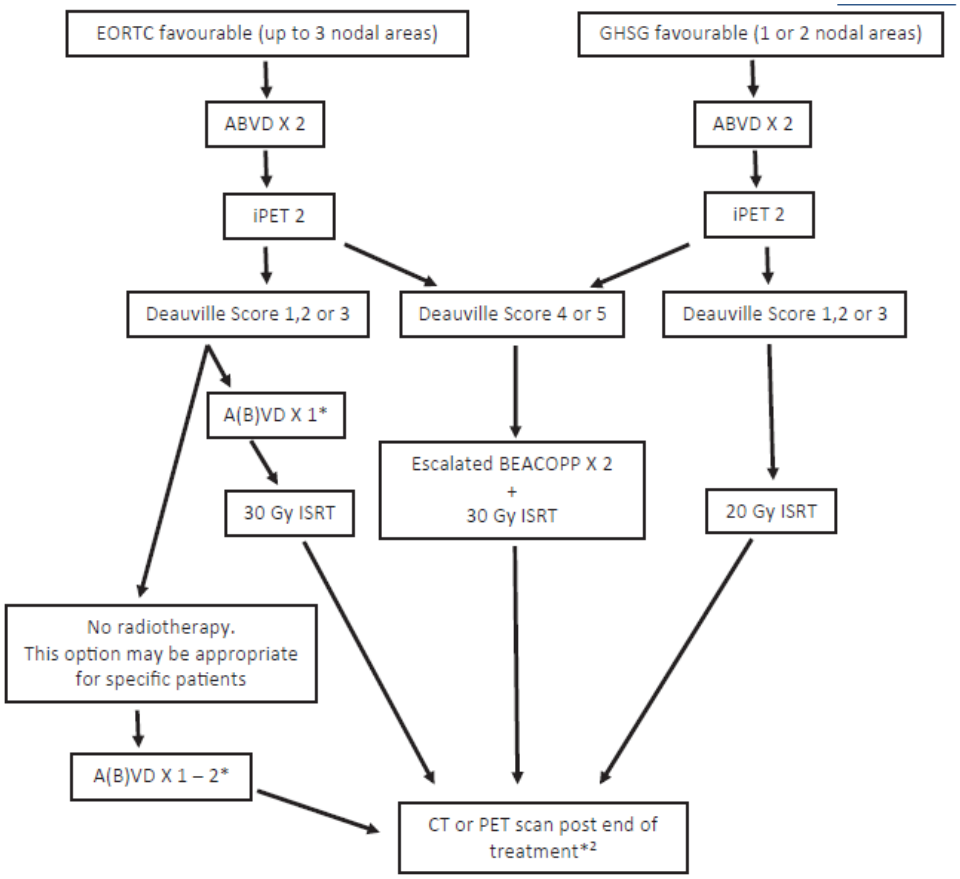
EORTC classification:

Limited stage HD: stage I-II without risk factors
Intermediate stage HD: I – II with risk factors

Advanced stage HD: Stage III-IV

Flow chart for managing early stage favourable patients

Taken from Guidelines for the first-line management of classical Hodgkin lymphoma – a British society of Haematology guideline

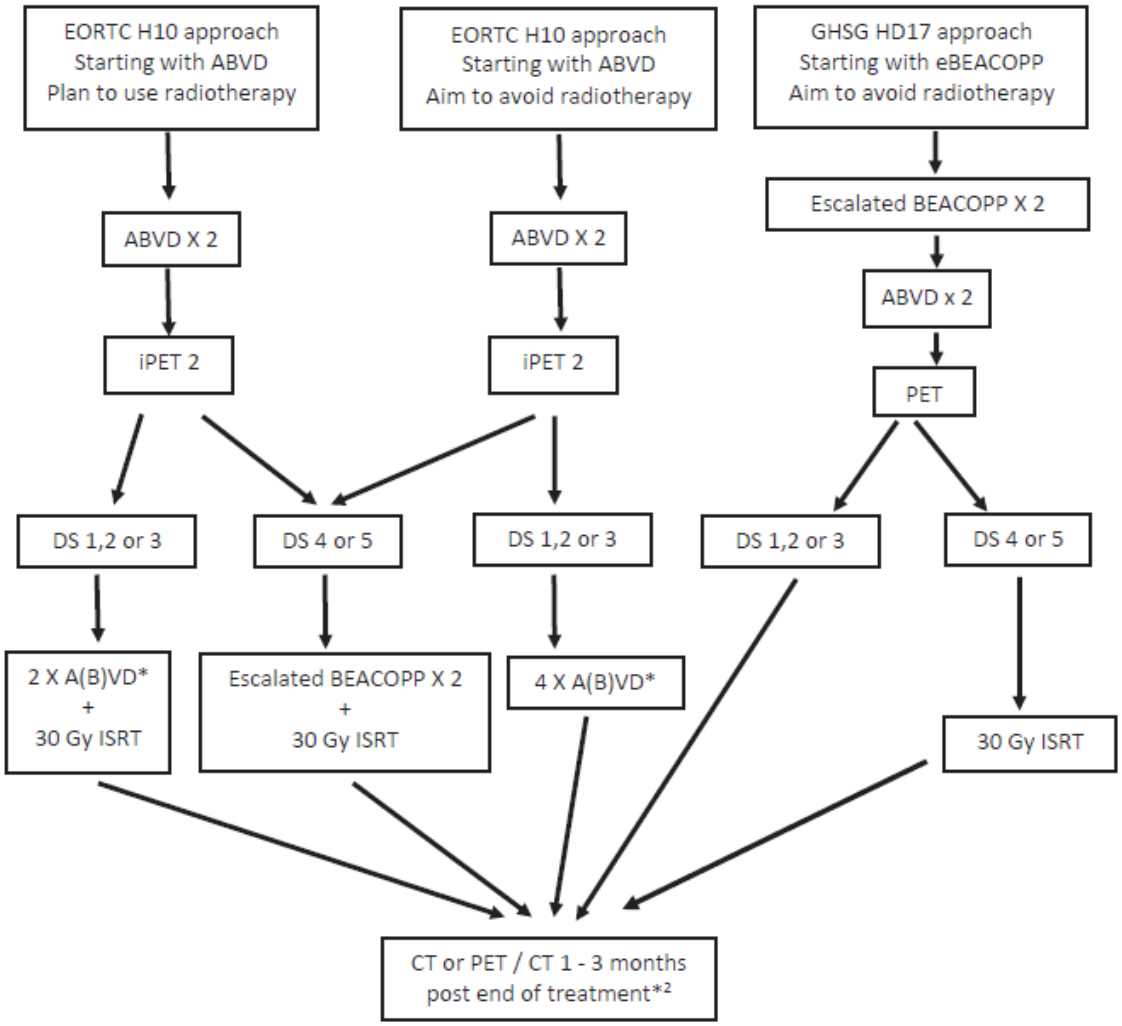


* For patients who achieve iPET2 DS1-3 post ABVD x 2, it is increasingly common to remove bleomycin from the subsequent cycles of ABVD as an extrapolation from the RATHL trial data.

*2 End of treatment imaging is usually CT scan for patients who achieve iPET DS1-3 and PET scan for patients with iPET DS4-5. PET should be planned for 3 months post radiotherapy if no clinical concerns for progressive disease. CT is usually planned for at least 4 weeks post completion of treatment.

Flow chart for managing early stage unfavourable patients

Taken from Guidelines for the first-line management of classical Hodgkin lymphoma – a British society of Haematology guideline



* For patients who achieve iPET2 DS1-3 post ABVD x 2, it is increasingly common to remove bleomycin from the subsequent cycles of ABVD as an extrapolation from the RATHL trial data.

*2 End of treatment imaging is usually CT scan for patients who achieve iPET DS1-3 and PET-CT for patients with iPET DS4-5. PET-CT should be planned for 3 months post radiotherapy if no clinical concerns for progressive disease. CT is usually planned for at least 4 weeks post completion of treatment.

- A RATHL trial approach could be used in patients with stage IIA with adverse features or IIB.

PET positive residual disease

- Radiotherapy can be considered to sites of PET positive residual disease after SACT in advanced disease (including any contiguous PET negative residuum).

1.4 Nodular lymphocyte predominant Hodgkins Disease (NLPHD)

For early stage (I/II) - radical radiotherapy alone is used.
For advanced stage (III/IV) – radiotherapy can be considered as consolidation after SACT.

1.5 Primary cutaneous lymphoma

This includes primary cutaneous T cell lymphomas (75-80%), with mycosis fungoides being the most common type and cutaneous B cell lymphomas (20-25%).

For primary cutaneous lymphomas treated with radiotherapy this is usually done using electrons or superficial Kv. Sometimes photons are required for deeper lesions or those on a curved surface.

Cutaneous T cell lymphomas include: mycosis fungoides, primary cutaneous anaplastic large cell lymphoma (PCALCL), subcutaneous panniculitis-like T-cell lymphoma (SPLTCL), primary cutaneous gamma delta T-cell lymphoma and primary cutaneous NK/T-cell lymphoma, nasal type.

In mycosis fungoides radiotherapy can be used depending on the extent of skin involvement. Radiotherapy is highly effective in treating skin lesions and may be given in the form of TSET (total skin electron therapy) or local treatment

For the other types of T cell lymphoma listed above localised disease is usually treated with radiotherapy alone.

Cutaneous B cell lymphomas include: primary cutaneous follicle center lymphoma (PCFLC), primary cutaneous marginal zone lymphoma (PCMZL), and primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL- leg type).

Localised indolent primary cutaneous lymphomas are treated with primary radiotherapy.

For localised high grade primary cutaneous lymphomas e.g. primary cutaneous diffuse large B-cell lymphoma, leg type, SACT in combination with radiotherapy is used.

2.0 Referral Criteria

The following are required before treatment planning can commence:

- Full clinical examination plus clinical history
- Histology
- FBC, U+E's, bone profile, LDH, ESR
- Bone marrow evaluation: no longer indicated for HD and DLBCL if PET-CT done
- Staging investigations: CT and/or FDG PET-CT, occasionally MRI is also of value for certain sites
- Endoscopy for GI lymphomas should be considered
- Slit lamp examination for primary CNS and other ocular lymphomas

3.0 Timing of Radiotherapy

If combined modality treatment is to be given, then radiotherapy will ideally start within 4 weeks of completion of SACT, and at a maximum of 3 months of completion of SACT if there are factors that cause a delay.

4.0 Pre-Treatment Scanning / Patient Preparation

The volume may be localised clinically for electron treatment / superficial, or using a planning CT scan with IV contrast if clinically appropriate. The International Lymphoma Radiation Oncology Group (ILROG) guidelines state ideally imaging studies such as PET-CT should be obtained in the treatment position using the planned immobilisation devices. In practice, this is currently not possible in most UK centres. However, where possible PET-CT scans should be fused electronically with planning scans and the planning scan should replicate the initial PET-CT position as far as possible (particularly arm position for mediastinal and axillary treatment).

In cases where respiratory movement is likely to affect the treated volumes, for example mediastinal or upper abdominal radiotherapy, consider using motion management, for example using deep inspiratory breath hold or 4DCT.

In cases of skin treatments requiring a CT scan or in cases where a mass has been resected and a scar remains, it is useful to wire the extent of the skin disease or the scar in order to visualise the area on CT scan.

For mediastinal radiotherapy, scanning with arms down at a 15 degree incline has been shown to reduce the breast and heart dose compared to scanning with arms up and should be considered, especially for young female patients (Debaja BS et al and Benassi M et al).

5.0 Target Definition

All pre and post-treatment diagnostic images are required to assist with radiotherapy planning if radiotherapy is to follow SACT treatment. Lymph node region atlases (RTOG or equivalent) should be referred to as required to assist in the outlining of nodal regions.

5.1 Involved Field Radiotherapy

Involved field radiotherapy (IFRT) has equivalence to extended field radiotherapy when used in combination with SACT. Involved node radiotherapy (INRT) has been shown to be equivalent to IFRT (Campbell, B et al) and so IFRT is now only used in patients where all disease has been excised and there was no pre-excision cross sectional imaging. In UK practice involved site radiotherapy (ISRT) is more often used in preference to INRT due to differences in set up position between diagnostic pre-SACT imaging and radiotherapy imaging.

The involved field CTV will include the anatomical nodal region affected by lymphoma defined by the clinician. The CTV will be outlined to include the involved nodal region, the margins of any tumour mass (primary or residual) in all dimensions and the contigual nodal regions.

For patients who have had chemotherapy the post-chemotherapy volume is used in all directions to delineate CTV with the exception of the cranio-caudal direction where the pre-chemotherapy volume is used. In some instances it will be desirable to modify the CTV to limit toxicity. This is undertaken at the clinician's discretion, taking into account site of involvement.

Involved nodal regions are described as follows:

Neck	Ipsilateral neck (mastoid – suprasternal notch) including supraclavicular fossa (SCF)
Mediastinum	Lower neck (from top of thyroid cartilage), bilateral SCF to 5cm below lower extent of disease
Mediastinum + Hilum	As for mediastinum but to include bilateral hilar nodes; inferior border at bottom of T10
SCF	Includes ipsilateral neck.; if mediastinum is involved pre-chemo then inferior border is extended as per mediastinum node region
Axilla	Includes ipsilateral lower neck, SCF and infra-clavicular fossa (ICF) (top of thyroid cartilage to axillary fold)
Inguinal	Ipsilateral femoral, inguinal and external iliac node region; from bifurcation of common iliacs to sartorius muscle (at approx. inferior border of lesser trochanter)
External Iliac	

	Ipsilateral inguinal, external iliac, internal iliac, obturator and common iliac node regions (from aortic bifurcation to inferior border of superior pubic ramus)
Femoral	Ipsilateral femoral and inguinal nodes; sup border is at point where the external iliac becomes most superficial; inferior border to Sartorius muscle
Para-aortics	Inferior border of T10 to aortic bifurcation

5.2 Involved site Radiotherapy: nodal

Involved site radiotherapy (ISRT) reduces the radiation volume to be treated and hence the probability of late effects compared to IFRT. It is recommended where appropriate pre-chemotherapy imaging is available, with FDG PET-CT being advisable. There has been a move towards ISRT and away from IFRT where possible.

GTV - where definitive radiotherapy is the primary treatment GTV is the visible tumour. In cases where treatment is given post SACT any residual tumour should be outlined as the post chemotherapy GTV. A pre chemotherapy GTV should be reconstructed using pre SACT imaging. If the residual mass is partially PET FDG avid then the entire mass should be encompassed in the GTV, sometimes a radiotherapy boost is then considered to the PET avid part.

CTV – In combined modality for early stage disease the CTV will include all initially involved sites. Pre-chemotherapy imaging is used to define the superior and inferior extent of the original disease and is expanded cranio-caudally by 1-1.5cm in the direction of lymphatic spread to form the superior and inferior levels of the CTV. This margin is to allow for uncertainties in image registration, changes in patient positioning and shape. This is distinct from involved node radiotherapy (INRT) where this margin for uncertainty is not included.

In the transverse plane the CTV includes the nodal chain (or organ) and any residual disease with a margin at the clinician's discretion (for example 1cm). It is not necessary to encompass entire nodal regions or adjacent nodal regions. If there was equivocal nodal disease i.e. nodes with equivocal FDG avidity then these should be included in the CTV where possible, particularly in cases where radiotherapy is the definitive treatment.

Where radiotherapy is being used as the primary treatment modality i.e. in low grade NHL or NLPHL, the CTV should be more generous (at least 1.5cm cranio-caudally) to reflect the fact that microscopic disease is more likely to be present. Lymph nodes in the vicinity should also be encompassed as they will not be sterilised by chemotherapy if there was microscopic disease present.

If separate nodal volumes are involved they can be encompassed in the same CTV however if > 5cm apart it may minimise toxicity to treat as two separate fields.

CTV is modified to avoid extension into air, muscle planes or bones unless there is evidence of direct invasion.

5.3 Involved site radiotherapy: delineation of extra-nodal sites

Maxillary Antrum and paranasal sinuses	CTV = whole ipsilateral antrum/ sinus If disease extends beyond this then CTV = pre-chemotherapy GTV + 1.0cm
NK/T cell lymphoma	*Nasal cavity tumours* Stage IE (unilateral nasal cavity) CTV = bilateral nasal cavity, ipsilateral maxillary sinus, bilateral anterior ethmoid sinuses and hard palate. Stage II (bilateral nasal cavity) CTV = bilateral nasal cavity, bilateral maxillary sinus, bilateral anterior ethmoid sinuses and hard palate +/- nasopharynx if the tumour is in the posterior aspect of the nasal cavity +/- posterior ethmoid sinuses if anterior ethmoid sinus involvement +/- nodal regions if involved (prophylactic nodal irradiation not required)
	Waldeyer's ring CTV = Entire WR, adjacent organs or structures with disease extension, and cervical lymph nodes (irrespective of gross involvement of cervical lymph nodes).
Waldeyer's Ring (WR)	If multiple contiguous sites are affected: CTV = pre-chemotherapy GTV + 1.5cm cranio-caudally and 1.0cm in all other directions If other areas within the WR are suspicious or there is uncertainty about the GTV then the whole ring (soft palate to vallecula) is treated. Neck nodes are treated only if involved.
Orbit	*Conjunctival and eyelid tumours*: GTV = whole conjunctiva to the fornices; CTV = GTV + 0.5cm Treat with electrons with bolus. If any concern about extension outside of the conjunctiva the entire globe should be treated with IMRT.
	Retrobulbar, lacrimal gland and deep conjunctival tumours: CTV = whole orbit, constrained to bone For primary intra-ocular lymphoma include optic nerves to level of chiasm.
Brain	CTV = whole brain down to the C1-C2 junction. The posterior globe and orbit should be included, and if there

	is ocular involvement the entire globe should be included bilaterally.
Parotid	CTV = entire ipsilateral gland
Bone	Pre-chemotherapy volume = GTV CTV = GTV + at least 1.5cm cranio-caudally along the bone marrow cavity and 1.0cm in all other directions within bone (assuming no extracortical extension).
Skin	*Low grade lymphoma*: GTV = extent of visible and palpable disease CTV = GTV + 1.0 – 3.0cm margin (deep margin should be the same but taking into account barriers to spread i.e.bone/muscle)
	High grade lymphoma: GTV = pre-chemotherapy volume CTV = GTV + at least 1.0 – 2.0cm margin
	Mycosis Fungoides: CTV = GTV + 1.0-2.0cm margin (>2.0cm margin if unifocal lesion and treatment is radical) Referral for total skin electron treatment may be considered
Stomach	CTV = whole stomach (from GOJ to beyond duodenal bulb) + include any involved or suspicious nodes Patient preparation is recommended e.g. fasting overnight or for at least 4hrs prior to treatment daily with antiemetics. Consider small volumes (<50mls) of oral contrast and motion management
Testis	CTV= scrotal sac Consider baseline 9am testosterone pre-treatment and sperm banking
Lung	CTV = pre-chemotherapy GTV + 0.5-1.0cm (If extension into lung from mediastinal disease which has regressed following chemotherapy considering not treating or treating to a lower dose to minimise toxicity).
Breast	CTV = whole breast A well-defined lesion may be treated with partial breast irradiation to reduce morbidity with CTV = GTV + 1.0cm, constrained to tissue planes
Other Organs	e.g. thyroid, prostate and bladder: CTV outlining is as for parotid. For other organs more rarely involved please refer to ILROG guidelines.

5.4 PTV

PTV may vary according to treatment site, immobilisation device, frequency of imaging and departmental margins.
Certain sites e.g. spleen and stomach can be affected significantly by respiration in the superior and inferior directions. Examples of PTV margins used:

Head & Neck PTV = CTV + 3-5mm margin

Mediastinum PTV = CTV + 10mm transverse margin and 15mm cranio-caudal margin*

Stomach PTV = CTV 20-30mm isotropic margin *

All Other Sites PTV = CTV + 5-10mm isotropic margin

*If deep-inspiration breathe hold or other breathing control technique is used this margin may be reduced.

6.0 Beam Arrangement

A VMAT treatment plan should be used for most radical cases, and palliative cases where this will improve the toxicity profile. However simpler planning techniques such as parallel opposed fields or 3D conformal plans can give a better organ at risk profile and may be preferred to VMAT in certain situations.

For mediastinal treatments where there is concern about low dose bath to lungs or breast tissue, butterfly VMAT (BVMAT) technique should be considered.

A direct electron field defined by clinical mark-up may be the most appropriate beam arrangement for treatment to certain regions e.g. skin lesions, testis. Bolus will be used where appropriate.

Some localised low grade skin lesions may be treated with superficial radiotherapy.

7.0 Dose and Fractionation

Indication	Dose
Early stage favourable Hodgkin's lymphoma	20Gy in 10#
Early stage unfavourable Hodgkin's lymphoma (including nodular lymphocyte predominant Hodgkin's) and advanced Hodgkin's lymphoma consolidation or primary treatment in those not suitable for SACT	30Gy in 15#
Chemorefractory Hodgkin's lymphoma	30-40Gy in 15-20#
High-grade non-Hodgkin's lymphoma - combined modality: 3-RCHOP + RT - consolidation to bulk - high risk site after response to SACT - or primary treatment in those not suitable for SACT	30-36Gy in 15-18#
Chemorefractory high grade NHL	Consider boost of 36-40Gy in 18-20# (unless concerns about frailty or OAR constraints in which case 30Gy is adequate)
Radical treatment of early stage low-grade non-Hodgkin's lymphoma	24Gy in 12# (consider 4Gy 2# especially for orbital/salivary gland disease*).
NK/T cell NHL	45-50Gy in 25# interdigitated with or after SACT. Consider 5-10Gy boost if no chemo used and RT is primary treatment.
Primary CNS NHL: - Consolidation dose after complete response to chemo - WBRT after incomplete response to chemo salvage or primary treatment - Palliative WBRT	23.4Gy 13# 36Gy 20# 30Gy 10#/ 20Gy 5#
Primary cutaneous lymphoma	Low grade: PCMZL + PCFCL 24Gy 12# Consider 4Gy 2# Mycosis fungoides: 8Gy 1#, 8Gy 2#, 12Gy 3#

Indication	Dose
	High grade: PCDLBCL-leg type, primary cutaneous T cell lymphoma (not MF): 30Gy 15# after chemotherapy Up to 40 in 20# if RT primary treatment/ refractory disease
Palliative treatment of low-grade non-Hodgkin's lymphoma	4Gy in 2#
Palliative treatment of high-grade lymphoma (or low-grade lymphoma that does not respond to 4 Gy in 2 fractions)	20 or 25Gy in 5#, 30Gy in 10#, 8Gy single fraction
As bridging prior to CAR-T cell therapy	20Gy in 5# and 30Gy 10# are the most commonly used fractionations in the UK for emergency bridging. 25Gy in 5# (covid fractionation) is also another option. Doses of up to 40Gy in 2Gy/fraction can also be considered for elective bridging.

*For localised low grade NHL curative treatment with 4Gy 2# can be considered over 24Gy 12# particularly for sensitive organs e.g. eyes where it is beneficial to use a lower radiation dose and thus reduce toxicity. This approach requires careful monitor with surveillance scan 3-6 months after radiotherapy delivery. If there is an incomplete response at this point then a further 20Gy 10# should be given.

For certain patients in whom late toxicity is of less concern (particularly elderly, those with chemo-refractory disease or those for which disease is not close to critical structures), hypofractionated regimens such as those recommended in the ILROG covid-19 guidelines can be considered. For example; 4Gy 1#, 30Gy 10# or 36Gy 12#.

It is beyond the scope of these guidelines to talk about re-irradiation in detail, but it should be noted that because of the lower doses of radiation used in haematological malignancies it may be feasible to re-irradiate some patients in a relevant clinical situation after careful review of organ at risk tolerances.

8.0 Dose to organs at risk

Radiotherapy doses for lymphoma are relatively low and the majority of patients will survive in the long term, doses to organs at risk should be kept as low as reasonably achievable (ALARA). Planning constraints should be agreed on a case by case basis. At the consultants discretion these can be exceeded.

Organ at risk	**Optimal constraint**	**Acceptable constraint**	**If Necessary**
Lungs	Mean<8Gy V20<20% V5<35%	Mean< 12Gy V20<28% V5<45%	Mean<15Gy V20<35% V5<55%
Heart and left ventricle	Mean< 5Gy V15< 10%	Mean<10Gy V15<25% V30<15%	Mean>18Gy V15<35% V30<20%
Breast	V4<10% Mean<4Gy	V4<20% Mean<15Gy	V4>20% Mean>15Gy
Salivary gland	Mean<10Gy	Mean<24Gy	
Lacrimal glands	V20<80%		
Kidney*	Mean<8Gy V10<30% V20<15%	V20<25%	
Thyroid	V25<62.5% Mean <15Gy	Mean< 25%	
Ovary**	Mean<6Gy (aim <0.5Gy if aiming for fertility preservation)		
Testicle***	Mean<6Gy (aim for <0.5Gy if aiming for fertility preservation)		
Liver	Mean <15Gy V20<30% V30<20%		
Stomach	Dmax<45Gy		
Spleen	Mean<10Gy		
Pancreas	Minimise volume to >36Gy		
Small bowel	V15<120cc Dmax<45Gy		

For spinal cord and bladder aim to keep the dose a low as reasonably achievable but no specific constraint.

* Consider evaluation of differential renal function where kidney constraint can not be achieved.

** Women who are of child bearing age should all be offered a fertility preservation referral where radiotherapy is planned to the pelvis regardless of the expected dose to the ovaries given the potential mobility of the ovaries in the pelvis.
*** Men who have not completed their family and where the testes are expected to receive >0.5Gy should be offered sperm banking.

9.0 Bridging radiotherapy

Prior to CAR-T cell therapy

Bridging therapy is now used in the interval between T-cell harvest and lymphodepleting SACT prior to CAR-T infusion. In approximately 30% of patients, radiotherapy rather than SACT is used as the bridging therapy. This is given with the aim of controlling symptoms and the disease. The most common dose fractionations used currently in the UK are 20Gy 5# or 30Gy 10#. However higher doses of 30-40Gy can be considered especially where time permits when elective bridging rather than emergency bridging is being used. Alternatively, 25Gy in 5# (ILROG Covid-19 fractionation) can be considered. Radiotherapy to a number of sites concurrently in the body can be considered instead of using SACT.

Prior or after stem cell transplant

Patients who achieve a complete metabolic response prior to stem cell transplant have better outcomes than those who do not. Studies have shown higher rates of local relapse in patients not undergoing pre stem cell transplant radiotherapy. Radiotherapy can play an important part in this if the disease is localised, if there is a site of bulk >5cm or persistent PET avid disease after salvage SACT.

Radiotherapy can also be used for local control in critical situations e.g. spinal cord compression. In some situations, radiotherapy is used after stem cell transplant if there is persistent PET avid disease or for local control.

10.0 Proton beam therapy

The UK has two national proton beam therapy (PBT) centres; The Christie NHS Foundation Trust (Manchester) and University College London Hospital (UCLH) NHS Foundation Trust. Referral to these centres should be considered for certain patients, particularly young patients with mediastinal disease requiring radiotherapy. The current eligibility criteria can be viewed on the NHS England website and is as follows:

- Age up to about 25 years of age
- A children's principal treatment centre or teenagers and young adults MDT confirms that PBT is an option
- Adequate performance status and medically fit
- Clear indication for radiotherapy and defined as curable
- No metastatic disease
- Dosimetric advantage to offering PBT

Referral can be made via the national PBT referral portal.

There is currently no recommendation for adults above 25 years to be routinely considered for PBT. The NHS England clinical commissioning group found no convincing evidence that demonstrated superiority of PBT over current treatment. There may be isolated cases where the clinician feels strongly that PBT would be of benefit and referral for PBT can still be considered in these cases.

11.0 Follow Up

Clinical review by the Clinical Oncologist is usually 4 to 6 weeks following completion of radiotherapy treatment. Often a PET-CT 3 months following radiotherapy is recommended.

Young female patients (age <35 years) who have had radiotherapy to their chest for Hodgkin's Disease or NHL have been shown to be at an increased risk of breast cancer and should commence breast screening at 8 years after treatment or at age 25, whichever is later. Patients should be identified at radiotherapy planning and registered prospectively with BARD (Breast screening After Radiotherapy Dataset).

If the thyroid has been irradiated either as the site of disease or adjacent neck, then thyroid function should be checked post treatment

Plasmacytoma and multiple myeloma

1.0 Treatment indications

Both solitary plasmacytoma (SP) and multiple myeloma (MM) are plasma cell malignancies.

SP can be subdivided into solitary bone plasmacytomas (SBP) and solitary extramedullary plasmacytomas (SEP - soft tissue plasmacytomas) which occur most commonly within the head and neck region. SP comprise 5-6% of plasma cell malignancies and are usually treated radically with radiotherapy with curative intent. Local control after radical radiotherapy is excellent (85-90%), although risk of transformation to MM is also high; 65-84% at 10 years for SBP and 10-30% at 10 years for SEP.

Radiotherapy is usually only used palliatively in multiple myeloma except for the use of total body irradiation for allogeneic stem cell transplantation. Patients should be carefully selected for radiotherapy to ensure the patient's marrow function is preserved as much as possible. Certain situations such as, pathological fracture in a long bone, wedge fracture in the spine without soft tissue extension or malignant spinal cord compression require consideration of surgical intervention in the first instance. If palliative radiotherapy is to be delivered after surgical intervention this should be delivered approximately 4-6 weeks after to allow adequate healing to take place.

2.0 Referral criteria

All patients with plasma cell malignancies should have had a bone marrow aspiration and trephine, urinary Bence Jones protein and blood testing for full blood count, calcium, bone profile, renal function, serum electrophoresis, plasma viscosity, serum free light chains and immunoglobulins.

- SP are usually treated radically. Patients must have full body imaging (PET-CT on MRI) to exclude additional sites of disease. Both PET-CT and MRI may be useful depending on the location of the SP for radiotherapy planning purposes.
- Multiple Myeloma is usually treated palliatively with radiotherapy being used for pain control for either bone or soft tissue lesions either as primary treatment or after surgery.

3.0 Pre-treatment scanning/ patient preparation

For radical treatment the patient is localized in an appropriate immoblisation device depending on the site being treated. In patient requiring rib irradiation, consideration can be given to using DIBH or 4DCT to reduce treatment margins.

For palliative treatment usually no specific immobilization is required.

For MM patients, consideration should be given to their current systemic treatment and whether this needs to be interrupted during the radiotherapy course. There is little evidence or guidance about the concurrent use of novel agents and radiotherapy, however bortezomib is known to increase gastrointestinal toxicity in

combination with abdominal radiotherapy and patients should be carefully monitored if these are to be given concurrently.

4.0 Target definition

Solitary plasmacytoma

The Oncologist will, with the aid of diagnostic imaging and clinical information, define the volume to be treated. Diagnostic imaging should be fused with the planning scan where feasible. Constraints for all relevant organs at risk in the locality should be stated explicitly.

GTV - out-lined with the aid of fused imaging PET-CT/MRI.

CTV – GTV + margin (as per IDRIS trial protocol*) or up to 2cm. This margin should be edited off barriers to spread.

- *See IDRIS trial protocol for details about outlining SBP in cases with soft tissue extension, cortical breaches/fracture and availability of MRI or not. The trial protocol also provides details about the specifics of outlining in the extremities, vertebrae and ribs. Summary included in appendix.

For SEP in the head and neck region nodal irradiation is not routinely required.

PTV – CTV + margin as per anatomical site (see lymphoma section 5.4 for example PTV expansions).

Organs at risk - These will depend on the site being treated.

Corridor – strip of normal tissue which includes subcutaneous tissue. The volume should have a diameter of >=2cm and extend 3cm above and below the PTV.

Multiple myeloma

Radiotherapy is used palliatively and as such a v-sim suffices for the vast majority of treatment.

5.0 Beam arrangement

A VMAT treatment plan should be used for most radical cases, however simpler planning techniques such as parallel opposed fields or 3D conformal plans can give a better organ at risk profile and may be preferred to VMAT in certain situations.

For palliative treatments patients are treated using a v-sim plan.

6.0 Dose and fractionation

Solitary plasmacytoma

- 45Gy in 25# is the standard recommended dose as used in the IDRIS trial
- 50.4Gy in 28# could be considered for large lesions > 5cm
- 40Gy in 20# may be sufficient for cases where the lesion has been completely excised

Multiple myeloma

Most treatments are for pain control and a single 8Gy fraction has been found to be as effective as fractionated courses for bone lesions and is preferred for convenience. Large volumes or lesions with significant soft tissue component may be treated with 20Gy in 5# (for example extensive pelvic irradiation). Rarely, patients may have multiple soft tissue plasmacytomas without bone marrow infiltration and higher doses may be utilised to give durable local control (20Gy in 5#, 30Gy in 10# or 36Gy in 12#) as such individuals may live a long time and experience local recurrence in treated sites.

7.0 Dose to organs at risk

It is important to aim for the doses to the organs at risk to be As Low As Reasonably Achievable (ALARA principle). The tolerances listed below are taken from the IDRIS trial protocol.

Organ at risk	Dose-volume constraint
Bowel bag	V45<=195cc
Breast	Minimise volume inside PTV – particularly in young women <=30 years. Where possible Dmean <=2Gy
Cochlear	Dmean <=45Gy
Corridor	V20<=50%
Femoral heads	Dmean <=40Gy
Heart	D100<=30Gy V33<=66% V38<=33% V42<=20%
Kidney	V15<=25% Dmean<=18Gy If Dmean to one kidney >18Gy then V6 for the other kidney <=30%
Lens	Dmax<=6Gy
Liver	Dmean <=32Gy D100<=25Gy D66 <=28Gy D33<=38Gy
Lung	V20<=30% Dmean <=20Gy
Oesophagus	Dmean <34Gy V35 <50%
Ovary	Dmax <10Gy (aim <0.5Gy if aiming for fertility preservation)

Organ at risk	Dose-volume constraint
Parotid	Dmean <=20Gy
Spinal canal	Dmax <=50Gy D1cc<=48Gy
Stomach	D100<45Gy
Testis	Dmax<=2Gy (aim <0.5Gy if aiming for fertility preservation)
Thyroid	D100<=45Gy

8.0 Follow up

Clinical review by the Clinical Oncologist is usually 4 to 6 weeks following completion of radical radiotherapy treatment. Often a PET-CT 3 months following radiotherapy is recommended.

Appendix

Outlining Guidelines for plasmacytoma - referenced to IDRIS protocol (v2.3)

If diagnostic MRI is available
CTV_4500 = MRI-defined **GTV_4500 + 15 mm**

Constrain to the outer wall of the bone unless there is soft tissue extension – in such cases constrain to the outer cortex beyond 15 mm from the edge of the soft tissue.

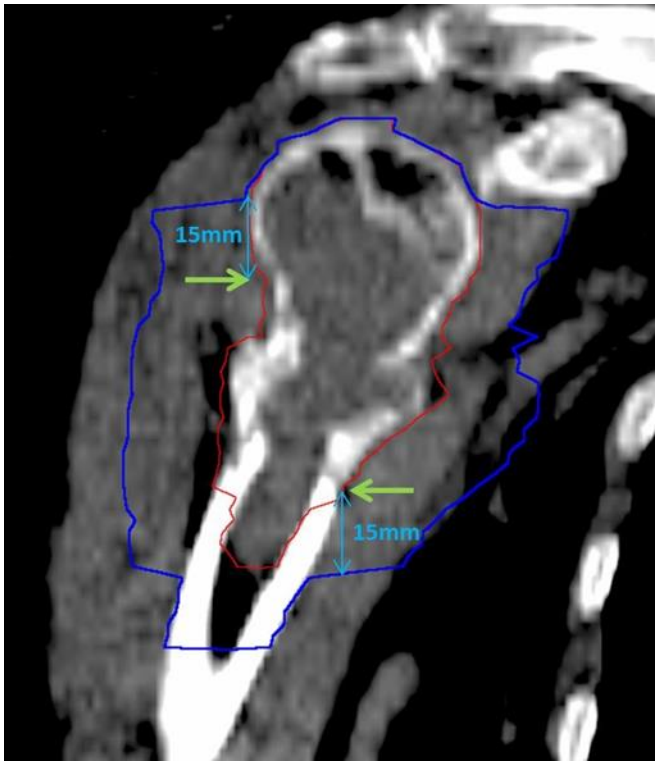
If diagnostic MRI is not available
CTV_4500 = CT-defined **GTV_4500 + 20 mm**

Constrained to the outer wall of the bone unless there is soft tissue extension – in such cases constrain to the outer cortex beyond 20 mm from the edge of the soft tissue.

Lateralised cortical breaches/fractures of the outer cortex of the bone
Include these in GTV_4500, as there is risk of subclinical spread.

If the cortical breaches occur in several places (≥ 2 quadrants) around the circumference of the bone, GTV_4500 includes the whole bone (to include the full circumference of the cortex) on those slices.

CTV_4500 = GTV_4500 + 15 mm (or 20 mm if no MRI). Then constrain to the outer cortex from 15 mm from the most superior and inferior cortical breaches (cranio-caudally).



Red = GTV_45000. Green arrows show cranio-caudal extend of cortical breaches. CTV constrained to outer cortex 15mm beyond these breaches

CTV_4500 should be cropped to skin if it extends outside the patient. Consider bolus.

CTV_4500 should be edited to exclude uninvolved organs/structures, e.g. kidneys, aorta, oesophagus, lungs, spinal canal, and respect anatomical boundaries such as the diaphragm

Specific sites:

Vertebrae:
CTV_4500 includes the whole vertebra and any soft tissue extension.

No soft tissue extension (the tumour is contained within the cortex)

CTV_4500 = the whole vertebra. This will include the Gross Tumour Volume (GTV_4500).

With soft tissue extension

CTV_exp = GTV_4500 + 15 mm in all directions. Edited to exclude uninvolved anatomical boundaries.
CTV_vert = whole vertebra (including GTV_4500), and name it CTV_vert. Edit out the spinal canal if uninvolved.
CTV_4500 = CTV_exp + CTV_vert.

If any part of the vertebra has been resected and there was any soft tissue involvement, using diagnostic imaging and operative notes, include this

area in CTV_vert. If there was no involvement of the surrounding tissue only the remaining vertebra needs outlining.

Ribs:

CTV_4500 = MRI-defined GTV_4500 + 15 mm (constrained to the outer wall of the bone unless there is soft tissue extension).

Modified to anatomical boundaries, e.g. exclude the lungs or vertebrae.
Adjacent, uninvolved ribs may be included in the volume to simplify delineation.

Extremities:

CTV_4500 = MRI-defined GTV_4500 + 15 mm (constrained to the outer wall of the bone unless there is soft tissue extension).

If the macroscopic disease on MR is contained within the medulla and does not invade the cortex, the cortex should not be included in GTV_4500.

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Checked by:	SW RTN Project Lymphoma Cancer Task and Finish Group
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