LONDON CANCER
NORTH AND EAST

London Cancer

Guidelines for the management of Lymphoma

June 2014

1. Introduction

These guidelines are intended to direct the treatment of patients with lymphoma with radiotherapy. They have been developed from guidelines already in existence at Barts Health NHS Trust, University College London Hospitals NHS Foundation Trust, Royal Free London NHS Foundation Trust, Princess Alexander Hospital, North Middlesex Hospital and Barking, Havering and Redbridge University Hospitals NHS Trust. They should be read and used in conjunction with other guidelines covering the investigation and management of Hodgkins and Non-Hodgkins Lymphoma. They also do not remove the need to follow the Local Rules and Work Instructions that have been developed at individual radiotherapy departments

2. CANCER DEFINITION

2.1. Staging System (Ann Arbor Staging Classification for Lymphoma)

Stage I	Involvement of a single lymph node region (I); Single extra nodal site (IE)
Stage II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) Localised involvement of an extra lymphatic organ or site and its regional lymph node(s) with or without involvement of other lymph node regions on the same side of the diaphragm (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by localised involvement of extra lymphatic site (IIIE) or spleen (IIIS) or both (IIIES)
Stage IV	Diffuse involvement of one or more extra lymphatic organs with or without associated nodal involvement or distant nodal involvement. Any liver / bone marrow disease
X	Bulk disease>10cm
A	=absence of B symptoms
B	=presence of either unexplained fever>38°C; drenching night sweats; weight loss>10% in the 6 months prior to diagnosis

2.2. Histological Classification

WHO Classification (Full extent is beyond the scope of this document).

Non-Hodgkins Lymphoma (NHL)

- Low Grade / Indolent (e.g. Follicular, MALT)
- High Grade (e.g. Diffuse Large B-Cell Lymphoma; Primary Mediastinal; NK/T Cell Lymphoma)

Hodgkins Lymphoma (HD)

- Classical HD: Nodular Sclerosing; Mixed Cellularity; Lymphocyte Deplete; Lymphocyte Rich
- Lymphocyte Predominant HD (LPHD)

Early stage HD

Favourable

- Clinical Stage I/II and no risk factors

Unfavourable

- Clinical Stage I/II with one or more of the following risk factors:
  - Large mediastinal mass (>10cm)
  - Extranodal involvement
  - Elevated ESR (>30mm/h for B stage; >50mm/h for A stage)
  - 3 or more lymph node regions involved
  - B symptoms

2.3. Advanced stage HD

Favourable

- Clinical Stage III/IV with 0-3 adverse risk factors (listed below)

Unfavourable

- Clinical stage III or IV with four or more adverse risk factors
  - Albumin level of <4.0 g/dL.
  - Hemoglobin level of <10.5 g/dL.
  - Male sex.
  - Age of ≥45 years.
  - Stage IV disease.
  - White blood cell (WBC) count of ≥15,000/mm3.
  - Absolute lymphocytic count of <600/mm3 or a lymphocyte count that was <8% of the total WBC count.

3. INDICATIONS and INTENT

Radical intent

- Following short course chemotherapy
- As single modality therapy e.g. localized stage I Lymphocyte Predominant HD;
- Consolidation following chemotherapy
- Chemotherapy refractory disease

Palliative Intent

4. TIMING

- Radiotherapy to start 4 weeks from time of decision to treat. Following chemotherapy recommended starts at maximum within 3 months of completing chemotherapy (e.g. patient factors) but ideally to start 4 weeks following completion.
- Lymphoma falls into Category 2 patients

4.1. Radiotherapy Dose schedules

Classical Hodgkin Lymphoma

- Favourable Early Stage after 2 cycles ABVD
  20Gy / 10 fractions over 2 weeks
- Unfavourable Early Stage after 4 cycles ABVD
  30Gy / 15-17 fractions
- Unfavourable Early Stage after BEACOPP
  Dose may be reduced to 20Gy / 10 fractions
- 35-40Gy / 20 fractions may be considered in certain instances e.g. chemotherapy refractory disease.

LPHD

- Early stage, sole therapy
  30-35Gy / 15-20 fractions (dependent on bulk and site)

Non-Hodgkin Lymphoma

- High grade Lymphoma
  30Gy / 15-17 fractions
- NK/ T cell Lymphoma requires higher doses of at least 50Gy in 2Gy/fraction
- Primary CNS Lymphoma - Post chemotherapy 35-40Gy in 1.8-2Gy/fraction with boosting of residual volume to total of 45-50Gy
- Low grade Lymphoma (e.g. Follicular Lymphoma)
  24-30 Gy / 12-15 fractions

Examples of Palliative Schedules:

- 20-30Gy / 5-10 fractions
- 12Gy / 4 fractions
- 8Gy / single fraction
- 4Gy / 2 fractions

5. ESSENTIAL INVESTIGATIONS AND INFORMATION REQUIRED PRIOR TO DECISION TO TREAT FOR EBRT

The following investigations should have been performed with results available before planning commences:

- Clinical history
- Baseline clinical examination and Performance Status
- Histology
- FBC, U+E's, biochemical profile, LDH
- Bone marrow evaluation
- Results of staging investigations: CT and or FDG PET-CT. In some instances MRI may be of value e.g. Primary CNS lymphoma; disease in head and neck region
- For patients receiving radiotherapy after chemotherapy, PET-CT / CT scans before and after treatment are used to determine the involved sites and residual disease. PET-CT pre and post chemotherapy is advised for ISRT (Involved Site Radiotherapy).

6. INFORMATION FOR PATIENTS

Patients should be given an appropriate patient information leaflet about their treatment and have access to a lymphoma nurse clinical nurse specialist or other specialist practitioner.

7. CONSENT

All patients must have given written informed consent before radiotherapy planning commences. Consent is to be taken by a practitioner who is familiar with lymphoma radiotherapy planning and administration.

8. TRIALS

- IELSG 32
  Randomised Phase2 trial of primary chemotherapy with high dose Methotrexate and high dose Cytarabine with or without Thiopeta and with or without rituximab followed by brain radiotherapy vs High dose chemotherapy supported by Autologous stem cell transplant for immune-competent patients with newly diagnosed primary CNS Lymphoma
- UK Haplo v1.0
  A UK multi-centre phase 2 trial of haplo-identical stem cell transplantation in patients with haematological malignancies
- RIC UCBT
  Transplantation of umbilical cord blood from unrelated donors in patients with haematological diseases using a reduced intensity conditioning regimen

9. RADIOTHERAPY TREATMENT PLANNING:

9.1. POSITION / IMMOBILISATION

- Patients to be planned and treated in the supine position.
- Chin up position for neck and SCF sites. For head sites clinician to indicate appropriate neck position.
- Appropriate immobilization for the site being treated is required. In head and neck regions this should include a customized immobilization shell.

9.2. IMAGE ACQUISITION

- Patients are 3D-planned using data from a CT planning scan.
- Contiguous slices with slice thickness of no more than 3mm taken through the region of interest.
- i.v. contrast is recommended to improve identification of nodal chains unless there are specific contra-indications. With common treatment planning systems, dosimetric calculations should not be influenced, except in sites such as mediastinum and para-aortic region where blood, volume is relatively large. Pre and post i.v. contrast planning CT scans are then required. It is recommended that each centre carry out a dosimetric analysis of the effects of contrast on the treatment planning calculations for individual anatomical sites.

9.3. VOLUME DELINEATION AND NOMENCLATURE

Lymph node region atlases for CT planning have been published for major regions in the head and neck; trunk and pelvis and these should be referred to when outlining nodal regions.

Involved Field Radiotherapy (IFRT) has been the standard with equivalence to wide field radiotherapy when used in combination with chemotherapy.

Involve Site Radiotherapy (ISRT) has been utilized in recent paediatric Hodgkin Lymphoma protocols and in the recent 18-30 trial as a step to further reduce the radiation volume treated and hence probability of late effects. Validation from large datasets is awaited from the current clinical trials.

Hoskin et al, (2013) recommended the adoption of ISRT for patients receiving combined modality treatment as long as appropriate pre-chemotherapy imaging is available. In this instance, FDG PET-CT would be advisable. If imaging is not available or radiotherapy is being used as sole therapy, IFRT should be used instead. Use of ISRT remains at clinician discretion with the patient fully counselled.

GTV – Gross tumour volume

CTV – Clinical Target volume

<u>IFRT – CTV definition</u>

- Involved field CTV (IF-CTV) will include the anatomical nodal region affected by lymphoma defined by the clinician as that which should be treated by radiotherapy.
- IF-CTV will be outlined to include the involved nodal region, the margins of any tumour mass (primary or residual) in all dimensions, & the contigual nodal regions.
- For patients who have had prior chemotherapy, the post chemotherapy volume is used in all directions except cranio-caudal direction where the pre-chemotherapy volume is used
- There may be instances where it will be desirable to modify the IF–CTV to limit toxicity. This will be performed under the clinician's discretion taking into account site of involvement.

Involved nodal regions are described with summary 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 includes bilateral hilar nodes; Inferior border (INF) to bottom of T10
SCF	includes ipsilateral neck. If mediastinum involved pre-chemo extend INF 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 = where external iliac becomes most superficial; INF border to Sartorius muscle
Para-aortics	bottom T10 to aortic bifurcation

ISRT – CTV definition:
CTV for Involved Site radiotherapy (IS-CTV) includes all initially involved sites.

Pre-chemotherapy imaging is used to define the superior and inferior extent of the original disease. This is expanded cranio-caudally by 1.5cm in the direction of lymphatic spread to form the superior and inferior levels of the IS-CTV.

In transverse plane, the IS-CTV includes the nodal chain (or organ) and any residual disease. It is not necessary to encompass entire nodal regions (or adjacent ones either).

CTV is modified by hand to not extend into air, muscle planes or bones unless evidence of direct invasion.

CTV delineation of Extra-nodal Sites:

Maxillary antrum	CTV = whole ipsilateral antrum. If disease extends beyond it CTV = pre-chemotherapy GTV + 10mm
Waldeyer's ring (WR)	Conventionally lymphoma in any part would be treated with inclusion of all sites of the WR in the radiotherapy field and risks a dry mouth. Following the principles for nodal lymphoma the following is considered: CTV = pre-chemo GTV + 10mm, except 15mm cranio-caudally. If multiple contiguous sites affected, follow margins above. If other areas within the WR also suspicious, treat the whole ring.
Orbit	C*onjunctival* tumours: electrons or superficial X-rays with corneal shielding. Some form of eye fixation recommended. CTV = GTV+5mm. GTV=whole conjunctiva also option as difference in volume minimal. *Lachrymal gland*: CTV = entire gland, no margin. *Orbit*: Most will be marginal zone or diffuse large B-cell lymphomas. CTV=whole orbit, constrained to bone. Particularly localised tumours may have a partial orbit treated.
Brain	*High Grade lymphoma.* Phase 1 CTV = whole brain from frontal, parietal and occipital lobes down to the C1-C2 junction. The IELSG PCNSL trial treats whole brain post-chemotherapy to 36Gy and boosting the phase 2 residual volume with 1-2cm margin to 45Gy. *Low grade lymphoma* localised irradiation may be used. CTV = GTV+10 mm expansion constrained to bony and lobular anatomy. Shield the eye after 30Gy. Palliative elderly patients consider 30Gy / 15 fractions
Parotid	CTV = entire ipsilateral gland. Extra-capsular spread pre-chemotherapy: GTV = pre-chemotherapy volume; CTV = GTV+10 mm expansion
Bone	Conventionally whole bone irradiated after chemotherapy but not necessary in many cases. MRI is used to define pre-chemotherapy volume = GTV. CTV = 15 mm cranio-caudally along the bone marrow cavity and 10 mm in all other directions.
Skin	*Low grade lymphoma*: GTV=pre-chemotherapy volume. CTV=GTV with a 10 mm expansion.

	Complete excision biopsy will not require radiotherapy. If positive excision margin, treat as above with the scar as GTV. Localised low grades may be treated using superficial techniques. *Diffuse large B-cell lymphoma*: more aggressive on leg than upper body. Outlining is same as for low-grade lymphoma but to a different dose. *T-Cell lymphoma*: Outlining is same as for low-grade lymphoma but to a different dose. *Mycosis Fungoides*: referral for TSEBT to be considered *Palliative treatment*: residual disease post-chemotherapy=GTV. CTV=same as for low grades. For multiple sites radiotherapy will be given to up to 4 sites.
Stomach	CTV = whole stomach. Patient preparation recommended e.g. fasting from midnight the day before. Treat earlier rather than later in the day.
Testis	CTV= whole sac. Electrons to be used wherever possible setting the testis in wax block for irradiation
Lung	Most will be MALT lymphoma. GTV=pre-chemotherapy volume. CTV=GTV+10mm expansion.
Breast	CTV = whole breast. Small, low-grade lesion may be treated with partial breast irradiation CTV = GTV + 10mm, constrained to tissue planes.
Other organs	e.g. thyroid, prostate and bladder CTV outlining is as for parotid.

PTV – Planning target volume

CTV is expanded in 3D to create the PTV to account for organ motion and set-up error. These are to be defined individually for each disease site and treatment centre. For guidance typical margins are as follows.

- Head and Neck: 5 – 10mm
- Mediastinum: 10mm transversely and 15mm cranio-caudally
- All other sites: 10mm

Organs at Risk:

Organs at risk (OARs) depend upon the area to be treated. Tolerance doses must be defined for OARs

DVH constraints for OAR

OAR	Limiting Dose / Volume
Brain stem	If whole organ irradiated, Dmax < 54Gy to any part of the volume. If partial volume $D_{1\text{-}10cm3}$ < or = 59Gy
Breast	Minimise volume inside PTV, particularly in young women < or = 30 years. Mean dose< or = 2Gy
Cochlea	Mean dose < or = 45Gy
Coronary artery	Minimise volume inside treatment field and keep doses as low as possible without compromising on PTV coverage
Heart	Mean dose < 26Gy; D100 < 30Gy. V30 <46%; V33 <60%; V38 <33%; V42 < 20%
Kidney	Single kidney irradiated: V15 65-70% Both kidneys irradiated: V15 20-25% for each kidney; mean dose < 18 Gy Partial kidney irradiation (all constraints are for combined kidneys): mean doses < 18Gy, V28 <20%; V23 <30%; V20 <32%; V12 <55%. If mean dose to one kidney>18Gy, V6 for remaining kidney <30%
Lens	Maximum dose of 6Gy to any part of the volume, unless compromising PTV coverage
Liver	Mean dose < 32Gy; V40 of 30-35% D100 of 20Gy, D66 of 28Gy, D33 of 38Gy
Lung (whole)	V20 < or = 30%. Mean lung dose (MLD) < or = 20Gy

Oesophagus	Mean dose < 34 Gy, V35 < 50%
Optic Chiasm	Maximum dose of 55Gy to any part of the volume
Optic nerve	Maximum dose of 55Gy to any part of the volume
Ovary	Maximum dose of 10Gy to any part of the volume outside the PTV. If inside the PTV discuss individual case with clinician
Parotid	Bilateral irradiation: mean dose <25 Gy Unilateral irradiation: mean dose <20Gy to the contra-lateral parotid
Small bowel	For individual loops V15 < 120cm3 For whole peritoneal cavity V45 <195cm3
Spinal cord	Dependent on length of field. D max < or =50Gy to any part of the volume. For neck + mediastinum field D max < or = 42Gy
Testis	Maximum dose of 2Gy to any part of the volume
Thyroid	D100<45 Gy

9.4. PLANNING / TECHNIQUE

3D planning using CT data
Consider 4D imaging or deep inspiratory breath-hold technique for disease sites significantly affected by respiratory motion.

9.5. TREATMENT TECHNIQUE

Conformal plan with field arrangements devised according to treatment site.
A parallel-opposed field arrangement often remains the preferred beam arrangement.
IMRT may be found beneficial for head and neck sites e.g. NK-Tcell lymphoma of nasopharynx.
Inspiratory breath-hold techniques and image guided radiotherapy may offer advantage in certain scenarios and to be considered.

9.6. TREATMENT VERIFICATION

Linac Verification
Image guided verification desirable particularly for sites adjacent to critical dose limiting OAR and in the re-treatment setting.

9.7. ON TREATMENT REVIEW DEFINITION AND SCHEDULE GAP CATEGORY FOR MANAGEMENT OF UNSCHEDULED INTERRUPTIONS

Weekly review for assessment and documentation of toxicity
Toxicity - according to site and extent of OAR exposure.
All toxicities to be explained to the patient at time consent obtained.
In addition, irradiation of lymph node sites may lead to lymphedema.

<u>Acute Toxicities:</u>

Head and Neck	sore throat
	Dysphagia
Mediastinum	Pneumonitis
Skin	Erythema
	Hair loss
Abdomen and pelvis	Nausea
	Loose stools
	Cystitis

<u>Late Toxicities</u>

Neck	hypothyroidism
Mediastinum	Pulmonary fibrosis
	Cardiac effects – ischaemic heart disease; heart valve toxicity; pericarditis; pericardial effusion;

Pelvic	Infertility
	Early menopause
	Late bowel and bladder toxicity
Second malignancy	Breast cancer in young women

Follow up

- OPA 4-6 weeks following completion of radiotherapy

10.REFERENCES

1. AJCC Cancer Staging Handbook. TNM Classification of Malignant Tumours (6th Edn). 2002
2. Jaffe ES, Harris NL, Stein H, et al.: World Health Organisation Classification of tumours. Pathology and Genetics of tumoursof Haematopoeitic and Lymphoid tissues. 2001 ARC Press, Lyon, France
3. Jost LM, Stahel RA; ESMO Guidelines Task Force.: ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of Hodgkin's disease. Ann Oncol 16 (Suppl 1): i54-5, 2005.
4. Hasenclever D, Diehl V: A prognostic score for advanced Hodgkin's disease. International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 339 (21): 1506-14, 1998
5. Gregoire V. Proposal for the delineation of the nodal CTV in node positive-operative neck. Radiother Oncol. 79(1):15-20, 2006
6. Taylor A, et al. Mapping pelvic Lymph nodes: guidelines for delineation in intensity modulated radiotherapy. Int J Radiat Oncol Biol Phys, 63(5):1604-12, 2005
7. Yahalom J, Mauch P. The involved field is back: Issues in delineating the radiation field in Hodgkin's disease. Ann Oncol 2002; 13(Suppl 1):79-83.
8. Hoskin PJ, Diez P, Williams M,et al.: Recommendations for the Use of Radiotherapy in Nodal Lymphoma. Clinical Oncology 25(1):49-58, 2013
9. Specht L, Yahalom J, Illidge T et al.: Modern Radiation Therapy for Hodgkin's Lymphoma: Field and Dose Guidelines from the International Lymphoma Radiation Oncology Group (ILROG). Int J Radiat Oncol Biol Phys. Epub ahead of print. 2013 Jun 18
10. Engert A, Plutschow A, Eich HT, et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. N Engl J Med 2010; 363:640-652.
11. Eich HT, Diehl V, Gorgen H, et al. Intensified chemotherapy and dose reduced involved-field radiotherapy in patients with early unfavourable Hodgkin's lymphoma: Final analysis of the German Hodgkin Study Group HD11 trial. J Clin Oncol 2010;28:4199-4206.
12. Chen RC, Chin MS, Ng AK,et al., Early-stage, lymphocyte-predominant Hodgkin's lymphoma: patient outcomes from a large, single-institution series with long follow-up. J Clin Oncol. 2010 Jan 1;28(1):136-41.
13. Josting A, Nogova L, Franklin J, et al. Salvage radiotherapy in patients with relapsed and refractory Hodgkin's lymphoma: A retrospective analysis from the German Hodgkin Lymphoma Study Group. J Clin Oncol 2005; 23:1522-1529.
14. Goda JS, Massey C, Kuruvilla J, et al. Role of salvage radiation therapy for patients with relapsed or refractory Hodgkin lymphoma who failed autologous stem cell transplant. Int J Radiat Oncol Biol Phys 2012; 84:e329-e335.
15. Miller TP, Dahlberg S, Cassady J, et al. Chemotherapy alone compared with chemotherapy and radiotherapy for localized intermediate and high grade non-Hodgkin's lymphoma. NEJM 1997:339, 21-6.
16. Lowry L, Smith P, Qian W, et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase 3 trial. Radiother Oncol. 2011 Jul;100(1):86-92.
17. National Cancer Research Network Trials Portfolio at www.ncrn.org.uk
18. Ferreri AJ, Verona C, Politi LS et al,. Consolidation radiotherapy in primary central nervous system lymphomas: impact on outcome of different fields and doses in patients in complete remission after upfront chemotherapy. Int J Radiat Oncol Biol Phys. 2011 May 1;80(1):169-75.