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| --- |
| [Brain Mets/Palliative/Oligo/Immuno](https://bit.ly/PalliativeRoR)| [Breast](https://bit.ly/BreastRoR) | [CNS/Peds](http://bit.ly/CNSandPeds) | [Constraints](https://bit.ly/RoRConstraints) | [GI](https://bit.ly/RoRGI) | [GU](https://bit.ly/GURoR) | [Gyn](https://bit.ly/RoRGyn) | [H&N/Skin](https://bit.ly/HNRoR) | [**Heme**](https://bit.ly/RoRHeme)| [Sarcoma](https://bit.ly/RoRSarcoma) | [Thorax](https://bit.ly/RoRThorax) | [Rad Phys/Bio](https://bit.ly/RORPhysBio)  [**www.RadOncReview.org**](http://www.radoncreview.org)  For best navigation, click on the Table of Contents (ToC) to navigate and click on a subheader or header to return to the ToC. Otherwise, use the Document Outline feature or control-F to search for a clinical trial or type ASCO '20 to see what's new. Best held horizontally on mobile.  **This document is a collaborative resource. All comments, corrections, and additions are welcome! Editing tips [**[**here**](https://docs.google.com/document/d/163jAwVLz8Wnno7jttJnDIM-4kTxkSSmj9XLP1W5pPJs/edit)**].**  Patterns of recurrence data found in the Follow Up section for most disease sites. Ongoing Trials are found in Future Directions. |

See NCTN Trial Portfolios by Disease Site: [[Lymphoma](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Lymphoma_Trials.pdf)] and [[Leukemia](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Leukemia_Trials.pdf)]

**“Just as concurrent Ritux/RT reduces the transformation of early follicular lymphoma to DLBCL, so does concurrent Lenalidomide-Dex/RT decrease change from solitary plasmacytoma to Multiple Myeloma" [**[**Link here**](#vbda5uf1edhl)**]**

**See [**[**Making Every Single Gray Count**](#gq1ic3qggdvh)**] for Hematologic malignancies.**

# 

# Hematologic

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**ARRO**: [[Pediatric High Risk Classical HL](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/PediatricHighRiskClassicalHL.pdf)], [[DLBCL case](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/HeadNeckDLBCL-NGT.pdf), [contour](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/HeadNeckDLBCL-NGT-Contour.pdf)], [[Early-stage favorable classic HL](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/HodgkinsCQ.pdf)], [[Orbital MALT](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/Orbital.pdf)]

**eContour**: [[NLPHL: axillary](http://econtour.org/cases/40)], [[ES-F HL](http://econtour.org/cases/45)], [[ES-U HL](http://econtour.org/cases/39)], [[MALT: conjunctiva](http://econtour.org/cases/99)], [[MALT: lacrimal](http://econtour.org/cases/98)], [[MALT: parotid](http://econtour.org/cases/46)], [[FL: inguinal](http://econtour.org/cases/41)]

**Making Every Single Gray Count: ISRT Delineation Guidelines for Hematological Malignancies** [[Dabaja IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/31928641)].

Must read article! Excellent Mini-Atlas highlights very interesting cases. Intentionally controversial atlas, as it still recommends radiotherapy after PET D2 response, while highlighting the importance of the 5 Gy isodose line [[in relation to](#wd0qpuiowed7)] 1c of doxorubicin.

Contour the post-chemo tissue volume, take into account tumor shrinkage, respect normal structures that were never involved by lymphoma. Be a bit more generous when in doubt. Connect CTVs when nodal volumes are less than 5 cm apart.

* H&N: DLBCL treated with 3c R-CHOP, PET3 D2, ISRT to 30 Gy recommended. Salivary glands limited to 5 Gy IDL.
* NKTCL: Invasion into BOS and NPX. Treated with DeVIC concurrently with RT. 50-54 Gy delivered, exceeding tolerance of some critical structures (e.g., cochlea, optic nerve, parotid, submandibular gland). PEG tube to avoid breaks if necessary.
* Sinus: DLBCL treated with 6c R-CHOP, PET6 D2, ISRT to 30 Gy recommended. Brain, orbits limited to 5 Gy IDL.
* Orbital MZL (localized or diffuse): Boom boom.
* NLPHL of axilla: 30.6/17 ISRT. Females: Sim akimbo to limit breast dose at expense to lung. Male: arms up to spare lung.
* Stomach: DLBCL treated with 6c R-CHOP, PET6 D2, ISRT to 30 Gy recommended. NPO x6h, DIBH.
* Mesenteric: Bulky DLBCL, 6c R-CHOP, PET6 D2, ISRT to 30 Gy recommended. NPO x6h. Kidneys < 5 Gy IDL.
* Groin: IA FL, G2. 24/12. PET/CT NED elsewhere.
* MM: Limit RT field to lytic site without attempting to encompass adjacent areas without evidence of myelomatous lesions, as it is important to spare bone marrow and other critical structures. We can never predict the next site which will fail.
* Cutaneous lymphomas: Indolent B and T-cell lymphomas often respond to low doses of RT with durable remissions.

[**StatPearls: Acute Lymphocytic Leukemia (ALL)**](https://www.ncbi.nlm.nih.gov/books/NBK459149/) *Last update: 11/24/2019.*

[**StatPearls: Acute Myeloid Leukemia (AML)**](https://www.ncbi.nlm.nih.gov/books/NBK507875/) *Last update: 11/28/2019.*

[**StatPearls: Acute Promyelocytic Leukemia (APL)**](https://www.ncbi.nlm.nih.gov/books/NBK459352/) *Last update: 9/7/2019.*

[**StatPearls: ALK Negative Anaplastic Large Cell Lymphoma**](https://www.ncbi.nlm.nih.gov/books/NBK519019/)*Last update: 11/18/2019.*

[**StatPearls: Anaplastic Large Cell Lymphoma (ALCL)**](https://www.ncbi.nlm.nih.gov/books/NBK537150/) *Last update: 8/12/2019.*

[**StatPearls: Burkitt's Lymphoma**](https://www.ncbi.nlm.nih.gov/books/NBK538148/) *Last update: 6/15/2019.*

[**StatPearls: Primary CNS Lymphoma (PCNSL)**](https://www.ncbi.nlm.nih.gov/books/NBK538148/) *Last update: 6/15/2019.*

[**StatPearls: Chronic Lymphocytic Leukemia (CLL)**](https://www.ncbi.nlm.nih.gov/books/NBK470433/)*Last update: 9/7/2019.*

[**StatPearls: Chronic Myelogenous Leukemia (CML)**](https://www.ncbi.nlm.nih.gov/books/NBK531459/) *Last update: 6/19/2019.*

[**StatPearls: Follicular Lymphoma**](https://www.ncbi.nlm.nih.gov/books/NBK538206/) *Last update: 6/26/2019.*

[**StatPearls: Hairy Cell Leukemia**](https://www.ncbi.nlm.nih.gov/books/NBK499845/) *Last update: 9/9/2019.*

[**StatPearls: Hepatic Lymphoma**](https://www.ncbi.nlm.nih.gov/books/NBK539850/)*Last update: 11/12/2019.*

[**StatPearls: Hodgkin Lymphoma**](https://www.ncbi.nlm.nih.gov/books/NBK499969/) *Last update: 12/8/2019.*

[**StatPearls: Leukemia cutis**](https://www.ncbi.nlm.nih.gov/books/NBK541136/) *Last update: 11/22/2019.*

[**StatPearls: Lymphoblastic Lymphoma**](https://www.ncbi.nlm.nih.gov/books/NBK537237/) *Last update: 11/12/2019.*

[**StatPearls: Lymphoplasmacytic Lymphoma (Waldenstrom Macroglobulinemia)**](https://www.ncbi.nlm.nih.gov/books/NBK513356/) *Last update: 11/12/2019.*

**StatPearls: Lytic Bone Lesions** *Last update: 4/4/2019.*

[**StatPearls: Mantle Cell Lymphoma**](https://www.ncbi.nlm.nih.gov/books/NBK536985/)*Last update: 2/2/2019.*

[**StatPearls: Multiple Myeloma**](https://www.ncbi.nlm.nih.gov/books/NBK534764/)*Last update: 3/19/2019.*

[**StatPearls: Myeloproliferative Neoplasm**](https://www.ncbi.nlm.nih.gov/books/NBK531464/)*Last update:11/13/2019.*

[**StatPearls: Plasma Cell**](https://www.ncbi.nlm.nih.gov/books/NBK507913/)*Last update: 12/2/2019.*

[**StatPearls: Plasmablastic Lymphoma**](https://www.ncbi.nlm.nih.gov/books/NBK532975/)*Last update: 12/2/2019.*

[**StatPearls: Post Transplantation Cancer**](https://www.ncbi.nlm.nih.gov/books/NBK537256/)*Last update: 9/11/2019.*

[**StatPearls: Renal Lymphoma**](https://www.ncbi.nlm.nih.gov/books/NBK526034/)*Last update: 12/17/2019.*

[**StatPearls: T Cell Prolymphocytic Leukemia**](https://www.ncbi.nlm.nih.gov/books/NBK541000/) *Last update: 6/26/2019.*

[**StatPearls: Thyroid Lymphoma**](https://www.ncbi.nlm.nih.gov/books/NBK544282/)*Last update: 11/7/2019.*

### 

## [Splenomegaly](#_e4a3jnknxfj8)

* **Splenic irradiation for splenomegaly** [[Zaorsky CTR '17](https://www.sciencedirect.com/science/article/pii/S0305737216301414?via%3Dihub)]
* Typically in the context of MPD or CLL.
* Most common fractionation 10/10 over 2 weeks, but 5/5 may be used.
  + Palliative splenic RT for CLL: 0.25 Gy-1 Gy qday or 2-3x/w to 4 Gy-10 Gy.
* Monitor blood counts.
* Response rate 85-90%.

## [Total body irradiation (TBI)](#_e4a3jnknxfj8)

ILROG Guidelines: Total Body Irradiation [[Wong IJROBP '18](https://www.ncbi.nlm.nih.gov/pubmed/?term=29893272)].

* Goals: Ablate stem cells, residual malignant cells and reduce the likelihood of stem cell transplant rejection.
* **AAPM Report 17** [[1984](https://www.aapm.org/pubs/reports/RPT_17.pdf)]
  + **High-dose ablative** (**Myeloablative**): Eradication of stem cells in bone marrow.
    - Usually **12-15 Gy in 6-12 fractions** over 3-5 days in BID fashion.
      * 10/1 and 14/8 are myeloablative, but hyperfractionation reduces acute and chronic toxicity.
    - LDR < 20 cGy/min recommended to decrease the rate of radiation pneumonitis.
    - Commonly, the dose rate at the patient is ~5-10 cGy/min. The machine dose rate is 25x higher if pt is 5m away.
  + **Low dose non-ablative** (**Myelosuppressive**): Often in conjunction with chemotherapy.
    - Usually 2-6 Gy in 2-4 fractions. Some older patients may receive 2 Gy in 1 fraction.
* **Dose is usually prescribed to mid-depth at the level of umbilicus.**
  + 18 MV photons are typically utilized. Lower energy beams have a more shallow Dmax and more dose variation through the body. Use bolus or beam spoiler to bring surface dose to 90% of TBI dose.
  + Gantry angle to the umbilicus of pt (~85 degrees). 40x40 cm, with collimator at 45 degrees.
  + Lungs may be limited to 70% of the Rx dose.
* **Uniformity along the body axis ± 10%**.
  + Dose uniformity achieved with compensators for H&N and legs.
  + Bolus or beam spoiler of 1-2 cm thick acrylic to bring surface dose to 90% of TBI dose.
* Acute parotitis occurs in ~75% of pts within 24h following TBI.

**Mycosis Fungoides Staging**

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| T1: < 10% BSA. a/b ± plaque.  T2:  **≥ 10%** **BSA**. a/b ± plaque.  T3: **≥ 1 cm** in diameter with deep infiltration (Tumor).  T4: Gen erythroderma > 80% BSA.  N1: Dutch G1 | NCI LN 0-2.  No atypical lymphocytes | ITC.  N2: Dutch G2 | NCI LN 3, a/b ± T-cell clone.  Early involvement w MF, cerebriform nuclei > 7.5 μm.  N3: G3-4 | NCI LN 4.  Loss of LN architecture. | |  |  |  |  |  | | --- | --- | --- | --- | --- | |  | **T1** | **T2** | **T3** | **T4** | | **N0** | **IA** | **IB** | **IIB** | **IIIA**  If B1: **IIIB**  If B2\*: **IVA1** | | **N1** | **IIA** | | | **N2** | | **N3** | **IVA2** | | | | | **M1** | **IVB** | | | |   B0: a/b ± clone.  B1: **> 5%** **Sezary** a/b ± clone.  B2: ≥ 1k cell/uL w + clone. |

**B1 does not influence staging** unless T4 (IIIB)

\*B2 disease automatically at least IVA1.

## [TSEBT](#_e4a3jnknxfj8)

Total skin electron beam RT [[Zaorsky tweet](https://twitter.com/NicholasZaorsky/status/1226199181766938624?s=20)].

See Mycosis Fungoides staging above and TSEBT in the Mycosis Fungoides [[Treatment Planning](#_863hkgmxw2d)] section for more.

* Extended SSD is used, typically around 400 centimeters. A large acrylic sheet (i.e., "spoiler") is placed around 20 cm from the patient surface to further scatter the electron beam. Dual fields are used, ± 18-22 degrees above and below the midline.
* Stanford: 3.5m from e- source, 3/8" lucite scatterer/degrader. 3 fields per day (AP/RPO/LPO d1; PA/RAO/LAO d2).
  + Typically 6 MeV electrons with beam spoiler to make 4 MeV electrons.
  + Superior and inferior beams ± 18-22 degrees from midline.
    - Off axis due to x-ray background dose of 2% strongly peaked in forward direction at CAX.
  + High dose rate desirable to shorten treatment time (at least 0.25 Gy/min but up to several Gy/min).
* Generally speaking, 30-36 Gy used to be given in the past, but this was quite morbid with hypohidrosis and heat stroke upon re-irradiation to similar doses. Current trend is to use 12 Gy as it has fewer AE and is more amenable to re-irradiation.
* Boost prior to TSEBT may be warranted to decrease thickness of lesions beforehand (e.g., 8/2 "bam bam"). Even when focal boosts are used for tumors, the median duration of CR is less than one year for patients with tumors ( ≥ 1 cm).
* Prescribed dose is **12**-36 Gy, generally 4-6 Gy per week (i.e., 2-3 weeks vs. 8-10 weeks).
  + Example: 1.5-2 Gy delivered per 2d/cycle, 4 d/wk (2 cycles/wk) with one week break after 18-20 Gy.
  + Example of low dose TSEBT: Boost tumor lesions to 8/2 ("Bam bam"), then 12 Gy total skin.
* Patients with T2+ in CR to TSEBT may benefit from adjuvant therapy such as PUVA, photopheresis, or mechlorethamine.
* Consider boost to "shadowed" areas such as perineum, scalp vertex, palms/soles, inframammary folds, panniculus.
  + Consider TLD placement on "shadowed" areas to determine necessary boost required.
* Goals: To achieve dose homogeneity in coronal plane, Dmax at skin surface, and 80% IDL to 0.7-1.0 cm depth.
  + EORTC criteria: 80% IDL ≥ 4 mm deep, with 20% IDL < 20 mm from skin surface.  
    < 10% heterogeneity in air. < 15% of dose to eyes. Total dose to bone marrow should be < 0.7 Gy.
  + Internal eye shields daily if facial disease. *If there is no facial disease, then external shields are used.*

## 

## [CAR T-Cells](#_e4a3jnknxfj8)

See [[Relapsed/Refractory NHL](#_brilw0sh9mf2)] section for more.

* **CAR T Cells: Continuation in a revolution of immunotherapy** [**QS**](http://www.quadshotnews.com/2020/03/horse-before-cart.html)[[Singh Lanc Onc '20](https://www.ncbi.nlm.nih.gov/pubmed/32135120)] [RoR](https://docs.google.com/document/d/1CfbqB4YnaPB8U3r2LykLv2v3bRLJyYQV0tvX4Js2Mog/edit#heading=h.q9ptcay0swp3)
* **Adoptive cell transfer**: Removes immune cells from pt, potentially altering them to target a cancer, growing *ex vivo* and re-infusing to the patient. There are three main sources of tumor-specific immune cells: 1) TILs 2) Antigen-specific cells through adaptive immune system and 3) Antigen-specific cells which were genetically engineered.
* **Chimeric antigen receptor** (**CAR**) **T-cell therapy**

Tisagenlecleucel - Refractory B-ALL, Axicabtagene ciloleucel - approved for relapsed DLBCL.

A type of adoptive cell transfer where T cells are engineered to target tumor Ags expressed on the membrane of cancer cells. Chimeric receptors are formed by fusion of extracellular tumor specific Abs, a transmembrane and intracellular portion that stimulates T-cell activity when an Ag binds to the extracellular Ab. CAR T-cell not dependent on MHC neoantigen presentation, therefore can be effective even with MHC downregulation by the tumor.

* + Autologous stem cells are extracted from the patient and manufactured ex-vivo and then re-infused into the patient.
  + Cell killing mechanism independent of MHC I.
  + Takes 2-5 weeks. Trafficking of CAR T to tumor cells is a major issue (decreased activated T cell adhesion)
    - RT can upregulate ICAM1 and VCAM1.
    - RT enhances chemotaxis.
  + Impractical for patients with rapid progression.
  + Not always possible to generate CAR T cells in heavily pretreated patients.
  + Radiation might have a role after leukapheresis. Perhaps there may be a beneficial effect if RT is delivered during the 2-4 week process where CAR T-cells are manufactured and the patient is being lymphodepleted.
  + Generally speaking, CAR-T may be effective in around 50% of the time (at least for RR HL), so RT also may be used for consolidation after CAR-T.
* **Patterns of failure following CAR-T therapy** [[Figura ASTRO '19](https://www.eventscribe.com/2019/ASTRO/fsPopup.asp?Mode=presInfo&PresentationID=558932)]
  + Nearly all recurrences for refractory B-cell lymphomas are in the areas of previously involved disease sites by 6 months. Disease sites with high metabolic activity and lesions ≥ 2cc in cross sectional area or ≥ 20cc in metabolic volume are at increased risk of progression following CAR-T therapy. All necrotic lesions progressed at the time of failure.
* NKT cells are an alternative [[Liu Leukemia '18](https://www.ncbi.nlm.nih.gov/pubmed/28725044)] without significant side effects [[Liu NEJM '20](https://www.nejm.org/doi/full/10.1056/NEJMoa1910607)].
* **ELIANA** [[Maude NEJM '18](https://www.nejm.org/doi/pdf/10.1056/NEJMoa1709866)]: Phase 1-2a. **Tisagenlecleucel** (CAR T-cells engineered to react to CD19)
  + 75 pts. CD 19+ relapsed / refractory B-ALL. CAR T cells were engineered to react to CD19. MFU 13 mo.
  + 3 mo ORR 81% w all pts found to be negative for minimal residual dz.
    - Median remission duration NR. Persistence of tisagenlecleucel in blood seen as long as 20 mo.
  + EFS at 6 / 12 mo of 73→ 50%.
  + OS at 6 / 12 mo of 90→ 76%.
  + G3-4 73%. Cytokine release syndrome in 77%, 50% of whom rec'd tocilizumab.
  + Neurological events in 40% of pts managed with best supportive care, no cerebral edema reported.

## [Deauville PET criteria](#_e4a3jnknxfj8)

Deauville scoring for Hodgkin lymphoma in as few words as possible [[Zaorsky tweet](https://twitter.com/NicholasZaorsky/status/1226197121378004992?s=20)].

PET is not enough. Ensure lymph nodes > 1.5 cm long axis to measure < 1 cm on PET/CT.   
However, many med oncs are using Deauville / PET alone to omit radiation without attention paid to residual disease on CT.

See commentary on [[AHOD0031](#z4jtj7lkebt5)] for pediatric HL trial data on the importance of CT-based residual, not PET-alone staging.

The exact same dilemma is occurring with adults - [[Lugano](#kix.7c6l4uvk94al)] essentially ignores CT-based residual, while [[EORTC 20884](#2umqw59gv3o3)] demonstrated the importance of CT-based residual with ABVD-like chemo in advanced stage HL for adults.

* **Deauville PET criteria**
  + D1: No uptake > background
  + D2: Uptake ≤ mediastinum
  + D3: Uptake > mediastinum, but ≤ liver
  + D4: Uptake > liver. "*It's hard to be greater than liver, and it's even harder to be greater than greater than liver."*
  + D5: Uptake >> liver. *ABVD and BEACOPP are not very effective for D5.*
* Measuring response
  + D1-2 is negative, as solidified by [[HD16](#kix.cdurj53xisqs)] (Metabolic CR).
  + D3 is positive, and may receive lower doses of RT than a D4 response.
  + D4-5 positive, consider Bx for D5 (DLBCL transform? Give different chemo, repeat PET, RT to any residual disease followed by ASCT).

* **Lugano Classification of PET/CT and CT alone response criteria for HL and NHL** [[Cheson JCO '14](http://ascopubs.org/doi/full/10.1200/JCO.2013.54.8800)]  
  Strongly recommends PET/CT, while hedging on the utility of CT based residual. Best evidence suggests CT-based nodal residual should measure ≤ 1.5 cm in maximum dimension.   
  "Recent data suggest that the CT scan may play a complementary role in pts with HL who have either a positive interim or post-treatment PET-CT, with a greater reduction in [[CT-based](#ldoqc65ifmyl)] tumor mass correlating with an improved outcome. How to best use this information remains to be determined."
  + CR: PET negative (D1-3), regardless of CT residual. If CT only: target regression to **≤ 1.5 cm** in max dimension.
  + PR: ≥ 50% reduction in CT SPD (**Sum of the product and diameters** for largest 6 lesions) with at least 1 initial PET avid site still FDG avid (D 4-5), no new sites.
  + PD: D4-5 with increased uptake, any new lesion or ≥ 50% increase in SPD from nadir.
  + SD: Not any other.
  + If PET/CT is negative in the bone marrow, a BMBx is not indicated unless DLBCL.

* **International Working Group consensus on response evaluation criteria in lymphoma** [[Younes Ann Onc '17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5834038/)]:

Complete response by PET Deauville score alone without accounting for CT-residual should be considered experimental!

* + Used 2,983 individual adult and pediatric lymphoma patients with 47,828 imaging measurements.
  + Demonstrated assessment of burden can use the sum of longest diameters of a maximum of 3 target lesions.
    - A single dimension measurement of 1.5 cm more constituted involvement.
    - 1.0 - 1.4 cm should be considered indeterminate, while < 1.0 cm should be considered negative.
    - This may not apply to narrow, elongated nodes (i.e. inguinal, axillary, portocaval).
  + Complete response should be resolution of all target lesions by CT with D1-3, and negative BMBx.
    - CT criteria: Lymph nodes > 1.5 cm long axis should now measure < 1 cm.
    - PET criteria: ≥ 30% decrease in sum of longest diameters of target lesions with D1-3.
  + D1-3 alone is not sufficient, as many novel targeted agents may alter glucose uptake and/or metabolism.

## [Toxicity](#_e4a3jnknxfj8)

Cardiac Contouring Atlas (Supplement) [[Duane RTO '17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5356506/)]

* Fatigue, erythema, edema, loss of nails, alopecia, hypohidrosis [[Lloyd JAAD '13](https://www.jaad.org/article/S0190-9622(13)00547-1/fulltext)]
* Estimated risk of secondary malignancy of 0.25%.
* Can repeat TSEBT after 6-12 mo if necessary, but be wary of hypohidrosis and heat stroke.
* Newer [[ILROG guidelines](#gq1ic3qggdvh)] from 2020 essentially highlight the ease and importance of mean dose of OARs less than 5 Gy!
* The [[EORTC-LYSA analysis](#wd0qpuiowed7)] suggested one cycle of anthracyclines is equivalent to 5 Gy mean heart dose.
* TL; DR - 5 Gy isodose lines matter! Regardless of whether it is pediatric or adults, HL or NHL.

* **Consider DIBH for mediastinal RT** [[Charpentier PRO '14](https://www.practicalradonc.org/article/S1879-8500(13)00277-4/abstract)]: **FBCT vs. DIBH**.

DIBH improves MLD, Lung V20 and MHD, but leads to increased mean breast dose.

There appears to be the most benefit in reduction of mean coronary dose and mean heart dose for patients with upper mediastinal involvement, or disease no lower than 3 cm below the level of the carina.

* + 47 pts. Mostly HL. Median dose 30 Gy, mostly AP/PA.
  + MLD 11→ 9.5 Gy.
  + V20 28→ 22%.
  + Mean heart dose 14→ 12 Gy.
  + Mean breast dose 3→ 3.6 Gy. This is still below the 4 Gy MBD recommended in pediatrics!
* **Consider the "butterfly" technique for mediastinal lymphoma** [[Voong Rad Onc '14](https://ro-journal.biomedcentral.com/articles/10.1186/1748-717X-9-94)]
* **The meaningless meaning of mean heart dose in mediastinal lymphoma in the modern RT era** [QS](http://www.quadshotnews.com/2019/10/meaningless-meaning-of-mean.html)[[Hoppe PRO '20](https://www.ncbi.nlm.nih.gov/pubmed/31586483)]:
  + Modern treatments can lead to more heterogeneous dose distributions across the heart. Therefore, contour and work to avoid coronary arteries and left ventricle dose [[Loap IJROBP ‘20](https://www.ncbi.nlm.nih.gov/pubmed/32386738)]

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| [Rate ratios (RRs) for valvular heart disease (VHD) by estimated radiation dose (EQD2, Gy) to the affected heart valve compared with no radiation exposure. RRs calculated conditional on matched sets. Matching variables were gender, age at Hodgkin lymphoma (HL) diagnosis and date of HL diagnosis (Supplementary Table 1, available online). Circles are estimates for dose categories: 0 Gy, up to 30 Gy, 31–35 Gy, 36–40 Gy, and >40 Gy and are plotted at the median doses in each category, ie, 0.0, 22.9, 34.0, 38.8, and 42.2 Gy. Vertical lines are 95% confidence intervals. Curved line is the best fitting dose-response relationship (RR = 1+exp[-5.02]dose*exp[0.075*dose]), allowing for curvature (two-sided Pnonlinearity = .03, likelihood ratio test). See Supplementary Figure 2 (available online) for additional details.](https://academic.oup.com/jnci/article/107/4/djv008/894367)   * Risk for valvular heart disease and heart failure increase exponentially for mean LV and mean heart dose > 20 Gy. * Any anthracyclines is roughly correlated with at least 21 Gy mean heart dose without anthracyclines. * Experts recommend keeping dose to heart < 5 Gy (15 Gy max) or LV mean to < 2 Gy (10 Gy max). [RoR](#kix.tuzrssbb1xyc) * This sharp rise in events for mean heart dose > 20 Gy has also been demonstrated in lung cancer, but events happen much sooner in adults. For patients treated with conventionally fractionated dose-escalated RT alone, 2y cardiac events for < 10 Gy / 10-20 Gy / >20 Gy MHD of 4→ 7→ 21%! [RoR](https://docs.google.com/document/d/1oKD3L5ieCk03FWU6fCnj8aiHKRPJD-q6IpjXpQCuexw/edit#heading=h.k70amn44ux20) |

* **Risk for Valvular Heart Disease after Treatment for Hodgkin Lymphoma** [[Cutter JNCI '15](https://academic.oup.com/jnci/article/107/4/djv008/894367)]:

Greater than 20 Gy to heart valves appears to be a legitimate risk factor for late valvular disease (Figure 3).

* + 1,852 5y HL survivors diagnosed 15-41 yo between 1965 and 1995. Cases (n=89) with at least moderate valvular heart disease as first CV diagnosis following HL treatment. Control (n=200) matched on age, sex, and date.
  + Of the 89 cases, aortic (n=63) and mitral valves (n=42) were more frequently affected.
  + Risks increased exponentially with RT dose.
  + Doses to affected valve(s) of ≤ 30 Gy / 31-35 / 36-40 / > 40 Gy with HR 1.4→ 3.1→ 5.4→ 11.8.
  + 30y cumulative risks for ≤ 30 Gy / 31-35 / 36-40 / > 40 Gy of 3→ 6→ 9→ 12%.
* **Risk for heart failure in survivors of HL: effects of cardiac exposure and anthracyclines** [[van Nimwegen Blood '17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5418626/)]:

Greater than 20 Gy mean heart dose appears to exponentially increase risk for heart failure (Figure 1A).

Greater than 20 Gy to the left ventricle appears to be a legitimate risk factor for heart failure (Figure 1B).

The risk for heart failure rises sharply above 20 Gy for mean LV dose, regardless of anthracyclines (Figure 2).

* + 2,617 5y HL survivors diagnosed before at 51 between 1965 and 1995. Cases (n=91) had moderate or severe heart failure as their first cardiovascular diagnosis. Controls (n=278) were matched on age, sex, and HL diagnosis date.
    - Most patients received around 300 mg/m2 of doxorubicin.
  + Mean heart dose and mean LV dose were estimated by reconstruction of individual treatments.
  + Average mean LV dose (MLVD) of 17→ 14 Gy.
  + MLVD of ≤ 15 / 20 / 25 / 26+ Gy with HR for HF of 1.3→ 1.7→ 2.8→ 4.4.
  + Anthracycline-containing chemotherapy increased HF rate by 2.8, independently of RT dose.
  + 25y cumulative risk of HF for MLVD of ≤ 15 / 20 / 21+ Gy without anthracyclines of 4→ 6→ 13%.
  + 25y cumulative risk of HF for MLVD of ≤ 15 / 20 / 21+ Gy with anthracyclines of 11→ 16→ 33%.

**ILROG Guidelines for Pediatric HD** [[Hodgson PRO '15](https://www.sciencedirect.com/science/article/pii/S1879850014001179?via%3Dihub)]

**Italian Expert Consensus on IMRT to the Mediastinum♱** [[Filippi Rad Onc '20](https://www.ncbi.nlm.nih.gov/pubmed/32164700)]

Cardiac Contouring Atlas (Supplement) [[Duane RTO '17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5356506/)]

See the [[A note on Pediatric Hodgkin's Lymphoma](#8uj1461dcmqy)] Summary Box.

Newer [[ILROG guidelines](#gq1ic3qggdvh)] from 2020 essentially highlight the ease and importance of mean dose of OARs less than 5 Gy!

The [[EORTC-LYSA analysis](#wd0qpuiowed7)] suggested one cycle of anthracyclines is equivalent to 5 Gy mean heart dose.

TL; DR - 5 Gy isodose lines matter! Regardless of whether it is pediatric or adults, HL or NHL.

* Target original extent of disease. Effectively describes ISRT without explicitly endorsing it.
* Suggested constraints: Many dose limitations on the higher end are in the relapsed/refractory setting ቷ [[Wirth IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/32272184)].
  + Heart: Mean < 5 Gy (15 Gy♱). V15 < 10% (25-35%)ቷ, V30 < 15% (20%)ቷ. Avoid coronary arteries and LV.
    - Left ventricle < 2 Gy♱ (10 Gy)♱
  + Lung: V20 < 20% (30 - 35%♱). V5 < 35% (55 - 60%♱). Mean < 8ቷ - 10 Gy**♱** (12-13.5 Gy**♱**).
    - Ideally, limit V20 < 30%. Pneumonitis is uncommon with V24 < 30% except when used with bleomycin.
  + Whole breast < 4 Gy (15 Gy). V4 < 10% (20%). V10 < 10%. Absolute: V5 < 55-60%.
    - Breast tissue growth and development affected at 5-10 Gy.
  + Thyroid V25 < 62.5%. V5 < 93%**♱**. V20 < 82%**♱**. V25 < 63%**♱** (70%**♱**). V30 < 62%**♱**. 2.2 mL < 25 Gy**♱**.
    - Thyroid abnormalities are more common >26 Gy. *Around 65-75% risk of abnormal thyroid function.*
    - Thyroid mean >15 Gy associated with a 30% risk of thyroid insufficiency.
  + ST growth and development affected at 25-30 Gy. *Or, even at less than 25 Gy if age < 10 yo.*
    - ST growth is only affected slightly if receiving < 20 Gy and age > 10 yo.
  + Bone growth affected starting at 8 Gy.
  + Premature closure of epiphyseal plates > 20 Gy.
    - Dental abnormalities with doses of 20-40 Gy.
    - Jaw dysfunction was more severe when the pterygoid and masseter received mean ≥ 20 Gy.[Tinkle IJROBP ‘20](https://www.ncbi.nlm.nih.gov/pubmed/31987969)
    - Scoliosis at 15y for ± 24 Gy of ~35→ 70%, though severe physical and functional deformity uncommon.
  + Orbital hypoplasia with mean bony orbit dose ≥ 30 Gy.[Tinkle IJROBP ‘20](https://www.ncbi.nlm.nih.gov/pubmed/31987969)
  + FH: > 25 Gy increases risk of SCFE, and doses > 30-40 Gy increases risk of AVN.

* **ILROG Guidelines: Proton therapy for adults with mediastinal lymphoma** [[Dabaja Blood '18](https://www.ncbi.nlm.nih.gov/pubmed/30108066)]
  + Potential for great benefit in patients with mediastinal disease that spans below the origin of the left main stem coronary artery and is anterior to, posterior to, or on the left side of the heart.
  + Young female patients for whom proton therapy may reduce breast dose and risk of secondary breast cancer.
  + Heavily pretreated patients who are at higher risk of radiation-induced toxicity to bone marrow, heart, and lungs.

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| **ISRT in Adult Lymphomas: An Overview of ILROG Guidelines** ቷ [[Wirth IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/32272184)]:  Consider administration of beta blockers and repeating PET/CT if there is extensive brown fat uptake (Fig 1b). Image in treatment position if possible, such as arms down in females to potentially minimize breast tissue in field (Fig 2c).  RT alone for early stage indolent lymphoma: Follicular lymphoma 24-30 Gy, NLPHL 30 Gy. Consider including nearby nodal beds in CTV, even if not enlarged. Several cm should be added in the craniocaudal plane. Include involved nodal compartment axially (Fig 6). Sites in proximity to sensitive structures may use minimal CTV expansion. [RoR](#3kcd1cfmy4rq)  ES-HL after limited systemic therapy: [[H10](#l3ma2fsoxgos)] confirmed efficacy of 30 Gy INRT after 3c ABVD, with results comparable to IFRT in [[RAPID]](#qdquj2bkm50) and [[H7](#_yonot9i3cnf)]. There was less of a benefit for unfavorable disease. [[HD14](#jdhro67rq5me)] investivated 30 Gy IFRT after "2+2" for unfavorable HL, while [[HD17](#kix.vjvgvzlylzh5)] is investigating the use of INRT for interim PET positive patients. For patients who remained PET positive (D3+) after 2-3c ABVD, IFRT resulted in 5y PFS of nearly 90% in both [[RAPID]](#qdquj2bkm50) and [[HD16](#kix.cdurj53xisqs)]. For PET positive (D3+) patients after 2c ABVD in [[H10](#l3ma2fsoxgos)], INRT was associated with a 5y PFS of 77% and 91% after further ABVD or escBEACOPP, respectively. CTV includes all initially involved nodes, including those that have normalized after systemic therapy (Fig 7). Widely separated initially involved sites may be treated separately. The CTV reflects the original cranio-caudal disease extent. Include initially infiltrated organ margins. Do not include initially normal nodes. For EORTC favorable HL in metabolic CR after 3-4c ABVD, 30 Gy is the standard dose (ESMO guidelines suggest 20 Gy). For GHSG favorable HL, 20 Gy is standard after 2c ABVD. For residual PET positive sites, 36-40 Gy is recommended. Potential microscopic disease in surrounding FDG negative masses (and initial sites in structural CR) may be treated to 30 Gy to reduce potential toxicity. [RoR](#3kcd1cfmy4rq)  DLBCL after limited systemic therapy: IFRT after 3-4c of R-CHOP is preferred. For patients in metabolic CR following chemo, the CTV includes locations of initially involved nodes, including sites that have normalised after systemic therapy. Include PET negative nodes when necrosis is suspected (Fig 8b). Contiguous initially equivocal nodes should be included. The CTV reflects the original cranio-caudal disease extent, and large ISRT volumes may approximate an old-fashioned mantle field (Fig 9c). Include initially infiltrated organ margins. Patients in PET CR should receive 30-36 Gy, while limited PET positive sites after 2-4c may receive 36-40 Gy. [RoR](#lwp1seqewhg3)  Unfavorable stage I-II mediastinal lymphoma (HL and PMBCL): While small volume upper mediastinal lymphomas may often be safely irradiated, a bulky mass contiguous with the lower mediastinum (Fig 9a,b) may be difficult to irradiate while respecting [[dose constraints](#kix.tuzrssbb1xyc)]. Many physicians determine an ISRT volume based on sites of initial bulk, slow response and the presence of a residual mass, which often corresponds to initially bulky sites (Fig 10). If a standard ISRT volume presents a high toxicity risk, chemo alone may be used. Single distant cardiophrenic nodes may sometimes be safely encompassed in a small separate field. PMBCL treated with DA-R-EPOCH alone appears reasonable in the setting of PET-CR. Bulky PMBCL or residual mass may predict a higher risk of relapse.  Primary extranodal lymphoma: CTV usually includes the entire organ (Fig 11) or compartment. 24-30 Gy is standard, with 24 Gy commonly used for sensitive sites such as the orbit. MZL limited to the conjunctiva only may spare the whole orbit (Fig 12) 4/2 provides durable local control in about 2/3 of patients, and is being evaluated for MZL in prospective trials. A strategy of using 4 Gy, reserving higher doses for patients not achieving CR, is very attractive. DLBCL is usually recommended 30-36 Gy after 3-6c of systemic therapy, and occasionally partial organ irradiation is warranted (e.g., breast - Fig 13). For testicular lymphoma, the CTV includes contra testes and scrotum. [RoR](#3ulp2e2jakqh)  Aggressive NHL/HL after full dose systemic therapy: DLBCL with initial bulk > 7.5 cm, rapidity / completeness of metabolic response and presence of PET negative residual mass has not been well studied with respect to patterns of failure. Volumes typically involve CT-based residual masses if a portion of the residual is avid (Fig 15-16), typically corresponding to initial bulk, as well as adjacent initially involved nodes to minimize risk of marginal relapse (Fig 14b). After PET CR, 30-36 Gy is recommended, while residual masses should receive 36-50 Gy. Advanced HL appears to have potential benefits when RT is delivered to patients with residual masses or initial bulk > 5 cm, but this is highly controversial. Many trials do not report CT-based residual. Current practices are highly selective with the use of RT in advanced HL. After escBEACOPP, RT is effective for patients with residual FDG avid masses ≥ 2.5 cm in largest diameter. After PET CR, 30 Gy is standard, while residual PET avid masses should receive 36-45 Gy.  Relapsed/Refractory: RT has an evolving role such as in the setting of CAR-T therapy as an "immunostimulant" for definitive local treatment. Sites with limited anatomical extent may see the CTV encompass all initially involved (pre-relapse) sites (Fig 17,18). 30 Gy for HL, 30-36 for DLBCL if in CR while 36-45 Gy or 40-55 Gy for residual HL [RoR](#_bib9repd1bfk) and DLBCL [RoR](#_brilw0sh9mf2), respectively.  **ILROG Guidelines: RT for Solitary Plasmacytoma and Multiple Myeloma** [[Tsang IJROBP '18](https://www.sciencedirect.com/science/article/pii/S0360301618308022?via%3Dihub)]. [RoR](#kix.54wzk8q4h2qy)   * Much lower doses are used for multiple myeloma. 40 Gy all day for SBP/SEP. * Interestingly, treating 1-2 normal vertebral bodies above and below disease are obsolete for MM.   **ILROG Guideline: Modern RT for Nodal NHL - Target Definition and Dose Guidelines** [[Illidge IJROBP '14]](https://www.sciencedirect.com/science/article/pii/S0360301614000649?via%3Dihub).  See the [[Treatment Planning](#_j718s277urks)] section in the NHL section for more information.   * RT as primary modality will require larger margins. ISRT can range from 2-5 cm. * RT alone may be used as curative intent for Stage I/II follicular lymphoma, stage IE marginal zone lymphoma, stage I/II nodular lymphocyte predominant HL, and relapsed/refractory hodgkin and non-hodgkin lymphoma. * RT alone: "CTV should incorporate GTV and include at a minimum adjacent lymph nodes in that site and a generous margin dictated by the clinical situation". * Includes recommendations on PCNSL, orbital, H&N (including thyroid), NKT cell, breast, lung, testicular, bone, abdomen/pelvis, bowel.   **ILROG Guideline: Modern RT for Extranodal Lymphomas: Field and Dose Guidelines** [[Yahalom IJROBP '15]](https://www.sciencedirect.com/science/article/pii/S0360301615000504?via%3Dihub).  See the [[Treatment Planning](#_j718s277urks)] section in the NHL section for more information.  Includes recommendations on [[PCNSL](#kix.mmiq0lal9y9s)], [[Orbital](#_u3w4jkvaw541)], [[Gastric](#_4c4268dmp1aa)], H&N (including thyroid), [[NKT cell](#_dg59kyvhbvpz)], breast, lung, [[testicular](#icfeike3n8ha)], [[bone](#q9eht5r44i91)], abdomen/pelvis, bowel.   * Indolent nodal lymphomas, stage I/II curative: 24-30 Gy. * Marginal zone lymphomas, curative intent   + Salivary: 24 Gy.   + [[Gastric](#_4c4268dmp1aa)]: 30 Gy (maybe 24 Gy?).   + [[Orbital](#_u3w4jkvaw541)]: 24 Gy (maybe 4 Gy? [[Fasola IJROBP '13](#qpinxhuxa1c6), [ILROG 2020 guidelines](#gq1ic3qggdvh)]     - This is the only site of which we are aware where [[Boom Boom](#2ir15dd82frs)] *may* be definitive therapy.   + Other sites: 24-30 Gy. * Advanced stage or palliative intent indolent B-cell NHL: 4/2. * Palliation of cutaneous T-cell lymphoma:   + 8/2 or 8/1 for localized CTCL/MF. 12 Gy for total skin.   **General treatment recommendations: Classical HL**.  ABVD is the most widely used. ABVD x4-6, BEACOPP x2 + ABVD x2 ("2+2"), Stanford V, or ABVE-PC (peds).   * **IA/IIA favorable**: **ABVD x2c → 20 Gy IFRT** [[HD 10](#x1kloo3nqbsq), [HD16](#kix.cdurj53xisqs)]. * **I-II unfavorable**: **ABVD x4c→ 30 Gy IFRT** [[HD 11](#gcj1ji1zn4vz)]. * **III-IV**: **ABVD x6c** (or BEACOPP in Europe). RT for partial response or bulky disease. * Relapsed/refractory: 2nd line chemo ± RT ± transplant. Brentuximab (Anti-CD30) and PD1 inhibitors. * [[EORTC H10](#kwrasxe9ykmw)] style: 2 or 3 disease sites may be favorable, ABVD x3c for favorable (overtreatment?), 30 Gy is delivered regardless of unfavorable or favorable (overtreatment?), and BEACOPP escalation for PET D3-4.   **ILROG Guideline: Optimal Use of Imaging in Radiation Therapy for Lymphoma** [[Mikhaeel IJROBP '19](https://www.sciencedirect.com/science/article/pii/S0360301619301919?via%3Dihub)]:   * MRI is indicated in areas such as the CNS, head (orbits, nose/paranasal sinuses, skull base) and skeletal sites. * Deauville 3 requires cautious interpretation, with consideration given to clinical context, histological type, disease stage, bulk, and estimated prognosis. In many trials using a de-escalation strategy with omission of RT, D3 was not considered a complete metabolic response. * For CT masses with partial FDG uptake, the entire mass should be included in the target volume.   **Making Every Single Gray Count: ISRT Delineation Guidelines for Hematological Malignancies** [[Dabaja IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/31928641)]. [RoR](#gq1ic3qggdvh)  Must read article! Excellent Mini-Atlas highlights very interesting cases. Intentionally controversial atlas, as it still recommends radiotherapy after PET D2 response, while highlighting the importance of the 5 Gy isodose line [[in relation to](#wd0qpuiowed7)] 1c of doxorubicin.   * Contour the post-chemo tissue volume, take into account tumor shrinkage, respect normal structures that were never involved by lymphoma. Be a bit more generous when in doubt. Connect CTVs when nodal volumes are less than 5 cm apart.   **Aggressive NHL dose considerations**   * Upfront DLBCL after chemo: 30-40 Gy. Give 30 Gy if DS 1-3. Boost to higher doses if DS4. * Upfront double-hit DLBCL: Correct dose is unknown, but may lean toward the higher end of the dose spectrum when consolidating. * Upfront PMBCL:   + Avoid RT if given DA-R-EPOCH if possible.   + After R-CHOP x6, given 30-40 Gy depending on PET response. * Relapsed/refractory DLBCL:   + DS1-3 with salvage chemo and ASCT: 30-36 Gy.   + Transplant ineligible, curative intent: 45-55 Gy.   + Palliative intent with limited life expectancy: hypofractionated schedule of 8-30 Gy. |

## [Treatment Planning](#_e4a3jnknxfj8)

See the comprehensive Summary Box above.

[INRT](#kix.xyuk3xdapvni): GTV to CTV expansion is typically 1 cm isotropic on pre- or post-chemo PET/CT.

[ISRT](#kix.7ffs0o3ikl45): GTV to CTV expansions is typically 1.5 cm in the direction of spread or 1 cm isotropic on pre-chemo PET/CT. For ISRT with radiation alone, up to 5 cm may be allowable.

**ARRO**: [[Pediatric High Risk Classical HL](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/PediatricHighRiskClassicalHL.pdf)], [[DLBCL case](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/HeadNeckDLBCL-NGT.pdf), [contour](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/HeadNeckDLBCL-NGT-Contour.pdf)], [[Early-stage favorable classic HL](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/HodgkinsCQ.pdf)], [[Orbital MALT](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/Orbital.pdf)]

**eContour**: [[NLPHL: axillary](http://econtour.org/cases/40)], [[ES-F HL](http://econtour.org/cases/45)], [[ES-U HL](http://econtour.org/cases/39)], [[MALT: conjunctiva](http://econtour.org/cases/99)], [[MALT: lacrimal](http://econtour.org/cases/98)], [[MALT: parotid](http://econtour.org/cases/46)], [[FL: inguinal](http://econtour.org/cases/41)]

**ISRT in Adult Lymphomas: An Overview of ILROG Guidelines**[[Wirth IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/32272184)] [RoR](#8tnt1mw76a6)

**Making Every Single Gray Count: ISRT Delineation Guidelines for Hematological Malignancies** [[Dabaja IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/31928641)]. [RoR](#gq1ic3qggdvh)

ILROG Guideline: Optimal Use of Imaging in Radiation Therapy for Lymphoma [[Mikhaeel IJROBP '19](https://www.sciencedirect.com/science/article/pii/S0360301619301919?via%3Dihub)]. [RoR](#1lhns44qzpfr)

ILROG Guidelines: Lymphoblastic lymphoma [[Dabaja IJROBP '18](https://www.ncbi.nlm.nih.gov/pubmed/30238900)].

ILROG Guidelines: Proton therapy for adults with mediastinal lymphoma [[Dabaja Blood '18](https://www.ncbi.nlm.nih.gov/pubmed/30108066)]. [RoR](#2kr447951kf)

ILROG Guidelines: RT for Solitary Plasmacytoma and Multiple Myeloma [[Tsang IJROBP '18](https://www.sciencedirect.com/science/article/pii/S0360301618308022?via%3Dihub)]. [RoR](#kix.54wzk8q4h2qy)

ILROG Guidelines: Role of RT in Patients With Relapsed/Refractory DLBCL [[Ng IJROBP '18]](https://www.sciencedirect.com/science/article/pii/S0360301617341871?via%3Dihub). [RoR](#_brilw0sh9mf2)

ILROG Guidelines: The Role of RT in Relapsed/Refractory Hodgkin Lymphoma [[Constine IJROBP '18](https://www.ncbi.nlm.nih.gov/pubmed/29722655)]. [RoR](#_bib9repd1bfk)

ILROG Guidelines: Radiation in CNS Leukemia [[Pinnix IJROBP '18](https://www.redjournal.org/article/S0360-3016(18)30920-9/fulltext)]. [RoR](#_dix8o3c34tab)

ILROG Guidelines: Total Body Irradiation [[Wong IJROBP '18](https://www.ncbi.nlm.nih.gov/pubmed/?term=29893272)]. [RoR](#_935p2ycajfok)

ILROG Guidelines for Pediatric HD [[Hodgson PRO '15](https://www.sciencedirect.com/science/article/pii/S1879850014001179?via%3Dihub)]. [RoR](#kix.tuzrssbb1xyc)

ILROG Guideline: Modern RT for Extranodal NHL - Field and Dose Guidelines [[Yahalom IJROBP '15]](https://www.sciencedirect.com/science/article/pii/S0360301615000504?via%3Dihub). [RoR](#3ulp2e2jakqh), [PCNSL](#kix.mmiq0lal9y9s)

ILROG Guideline: Modern RT for Primary Cutaneous Lymphomas: Field and Dose Guidelines [[Specht IJROBP '15](https://www.sciencedirect.com/science/article/pii/S0360301615000279?via%3Dihub)]. [RoR](#_buun9ubd3cdd)

ILROG Guideline: Modern RT for Nodal NHL - Target Definition and Dose Guidelines [[Illidge IJROBP '14]](https://www.sciencedirect.com/science/article/pii/S0360301614000649?via%3Dihub). [RoR](#lwp1seqewhg3)

ILROG Guideline: Modern RT for Hodgkin Lymphoma Field and Dose Guidelines [[Specht IJROBP '14]](https://www.sciencedirect.com/science/article/pii/S0360301613005348?via%3Dihub). [RoR](#3kcd1cfmy4rq)

* **INRT**: Relies on ideal pre-chemo imaging, requires PET/CT to be in treatment position (e.g. arms up).

INRT is really only utilized in Europe, as the same person who orders the scan (Med Onc) is also the Rad Onc. They'll get the scans in a treatment position (e.g., arms up if in mediastinum). INRT definition varies between groups.

* + EORTC: Pre/Post PET. 1 cm PTV margin.
  + GHSG: Post PET. 1-3 cm PTV margin, depending on the site.

* **ISRT**: Pre-chemo tumor volumes, accounting for uncertainties in imaging and changes in anatomy with chemo.

ISRT is required for patients who were worked up in a different position then their ultimate radiotherapy position (e.g., USA).

* + These volumes are slightly larger than INRT, while smaller than IFRT.
  + CTV = All initially involved sites expanded manually with 1.5 cm margin CC in direction of potential spread.
    - If GTV was defined, it is expanded by 1 cm isotropic margin.
    - May limit fields inferiorly in the heart.
* PTV = 3 mm for head and neck, 1.5 cm CC and 1 cm axial in mediastinum (0.8 cm isotropic if 4D), 1 cm elsewhere.
  + May also use DIBH and decrease PTV margins. Beware: failures for residual in front / just below the heart in patients with initial anterior mediastinal involvement are not uncommon.

### [Outdated fields](#_d5y4iwywaoda)

* **IFRT**: Treats involved lymphoid region defined by Rye classifications, field borders based on bony anatomy.
  + Axilla: Upper border C5-6, Lower border to the lower tip of scapula or 2 cm below lowest axillary node, Medial border to ipsi cervical TP, lateral flash axilla.
* **RFRT**: Includes immediately adjacent LN regions.
* **Mantle**: Comprehensive nodal field including major nodal regions above diaphragm.
  + Isocenter midway between superior and inferior edges, usually near/slightly below suprasternal notch.
  + Sup: Midpoint of chin, along mandible, 2-3 cm above tip of mastoid.
  + Inf: near diaphragm, ~4 cm above xiphoid.
  + Inf axilla: 4th costochondral junction. Include ~1 cm of lung in the lower axilla and 2-4 cm of lung in the upper axilla.
  + Lat axilla: Junction of lateral margin of pectoralis with deltoid. Exclude humeral heads.
* Modified/mini mantle: Mediastinal, bilateral hila, SCV. Excludes axilla and neck/occiput unless bulky. From larynx to T10-12.
* Waldeyer's ring: Lateral fields matched to lower neck field.
* pAO ± spleen:
  + Top of T11 (at least 2 cm above pre-chemo volume) to bottom of L4 (at least 2 cm below pre chemo volume).
  + Lat: edge of transverse processes or 2 cm lat to post-chemo volume.
  + 1.5 cm margin on post-chemo splenic volumes
  + Contour kidneys and consider drawing blocks.
* **Inverted Y**: pAO, iliac, spleen, inguinofemoral nodes.
  + Pretreatment renal scan may be helpful in certain cases.
  + 1.5 cm margin on post-chemo splenic volumes to account for respiratory motion.
* **TNI** (Circa 1978): **Mantle followed by inverted Y** and spleen (usu after 2-3w break between mantle and inverted Y).
* **STNI**: Mantle plus pAO and spleen. Excludes pelvic LNs.
* Mediastinal IFRT: Mediastinal, bilateral hila, bilateral SCV (even if not involved).
  + Sup: C5-6 interspace (top of larynx if SCV involved).
  + Inf: 5 cm below carina or 2 cm below inferior extent of pre-chemo disease, whichever is lower.
  + Lat: 1.5 cm margin on post-chemo volume.
  + Hilar: 1 cm margin unless initially involved, then 1.5 cm margin.

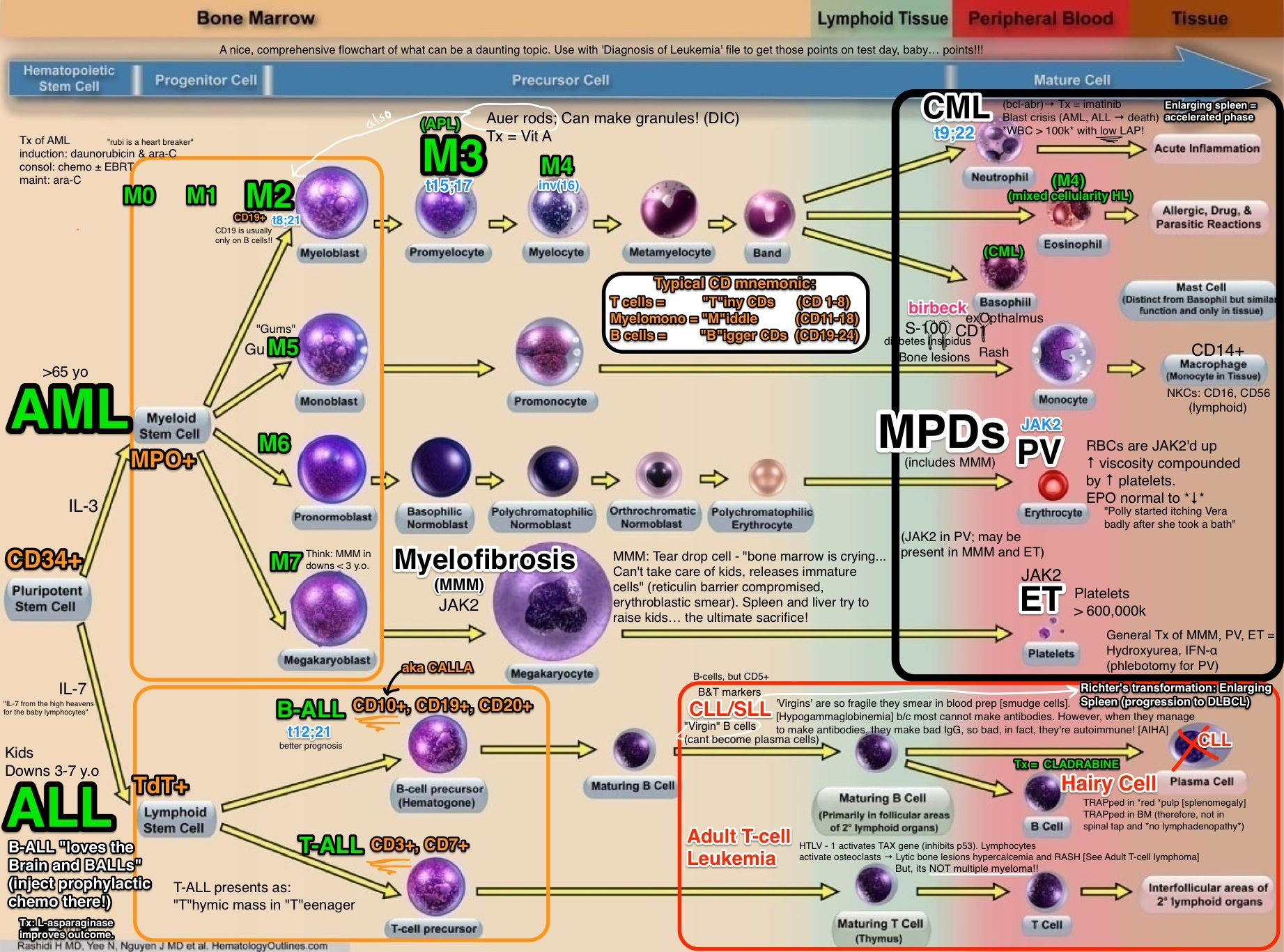
# [B-ALL and T-ALL](#_e4a3jnknxfj8)

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| **B-ALL Risk Groups**   * **Low risk** (27%): Standard risk + low-risk cytogenetics (e.g. hyperdiploid with DNA index ≥ 1.16) * **Standard risk** (32%): Minimal residual disease after treatment, Hyperdiploid, Favorable age (1-10y), WBC < 50k.   + No low-risk cytogenetics (hyperploid 51-67 chromosomes, **t12;21** (ETV6-RUNX1), trisomies of ch17, 10, 4).   + Minimum residual disease: Quantify very low levels of leukemia, such as 1 in 1000-10,000 cells. This is done by flow cytometry, PCR for leukemia-specific IgH or TCR gene rearrangements. * **High risk** (37%): **≥ 50k WBC**, < 1y or ≥ 10y, CNS3 or testicular disease, or BCR-ABL1, steroid pre-treatment. * **Very-high-risk** (4%): Hypodiploidy, KMT2Ar, TCF3-PBX1. IKZF1 deletion is not universally accepted.   + Extreme hypodiploidy (< 44 chromosomes or DNA index below 0.81). * **Favorable risk features**: High hyperdiploidy (51-67 chromosomes), ch 4/10/17 trisomy, t12;21 (ETV6-RUNX1). * **Unfavorable risk features**: Hypodiploidy (< 44 chromosomes), KMT2Ar, t17;19 (TCF3-HLF), iAMP21, ± IKZF1 del.   **Classification of CNS status**   * **CNS1** = **Negative tap**. * **CNS2** = < 5 WBC/mm3 with blasts. * **CNS3** = ≥ 5 WBC/mm3 with blasts, or signs of CNS involvement   **Use of Radiation in ALL**   * **All CNS3 patients receive WBRT 18/10**-11 (1.6-1.8 Gy). * WBRT fields should include the posterior half of the globe, with inferior border C2. * **Isolated CNS relapse should receive 18 Gy**, with timing depending on the treatment protocol. * **TBI is given for select high-risk patients receiving HSCT**, in patients who require cranial RT and TBI. Cranial RT should be given as a boost before or after TBI. TBI dose 13-14 Gy at 1.5-2 Gy per fraction. * Consider scrotal irradiation 24/12 for clinical evidence of persistent testicular disease after induction.   **ILROG Guidelines: Radiation in CNS Leukemia** [[Pinnix IJROBP '18](https://www.redjournal.org/article/S0360-3016(18)30920-9/fulltext)]  "All patients with ALL should receive CNS prophylaxis. Although the presence of CNS-3 involvement at the time of dx is uncommon (~3-7%), more than half will eventually develop CNS leukemia in the absence of CNS-directed therapy. CNS-directed therapy may include cranial RT, IT chemotherapy (e.g. MTX, cytarabine, corticosteroids), and/or systemic chemotherapy (e.g. HD-MTX, cytarabine, pegaspargase). Cranial RT is often avoided in favor of IT chemotherapy and systemic therapy when possible due to concern for late effects." - NCCN 2019 |

See NCTN Trial Portfolios by Disease Site: [[Leukemia](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Leukemia_Trials.pdf)]

Childhood Acute Lymphoblastic Leukemia [[Marcus COG Powerpoint](http://qarc.org/COG/AcuteLymphoblasticLeukemia_.pdf)] [RoR](https://docs.google.com/document/d/17O0LOemBhckXGuuPBCh6u8vqBfc6lg88r46B8YctMXU/edit#heading=h.gzbeagzdfcb6)

* In Peds, ALL >> AML [[Slide 8](http://qarc.org/COG/AcuteLymphoblasticLeukemia_.pdf)].
* Down syndrome is associated with increased risk of ALL. ~2% occurs by age 5, while ~3% by age 30.
  + Down syndrome children with B-ALL have increased relapse and toxicities [[Rabin ASCO '20](https://meetinglibrary.asco.org/record/185872/abstract)].
* High risk is classified by > 50k WBC, but only 17% present with > 50k WBC at diagnosis.
* DIC is much more common in AML than ALL (i.e., myeloblasts / promyelocytes).
* Tumor lysis syndrome: High uric acid, high potassium and high phosphate (low calcium) may result in renal failure due to precipitation of uric acid. Check for G6PD in case rasburicase needs to be used. It is prevented with IV fluids (no potassium) and allopurinol or rasburicase.
* Workup: CBD/diff, DIC screen, clot to blood bank, tumor lysis labs (electrolytes, BUN/Cr, Ca, Mg, Phos, uric acid, G6PD), CXR.
* Childhood ALL outcomes: Vastly improved since the 1950s (EFS 8%) and even 1980s (EFS 70%). 4y EFS in the 2010s is 85% with 4y OS 92% [[Slide 26](http://qarc.org/COG/AcuteLymphoblasticLeukemia_.pdf)]. Outcomes have improved despite most drugs used today being available in the 70s and 80s, and improved outcomes are attributed to better supportive care, risk-adaptive therapy, and recognizing the CNS is a sanctuary site.
* Childhood ALL treatment [[Slide 39](http://qarc.org/COG/AcuteLymphoblasticLeukemia_.pdf)]: 2-3 years of chemo. Remission induction with inpatient chemo x1 mo (CR is achieved in >95% of patients). Intensification/Consolidation for 6-9 mo, typically outpatient (intensity varies by risk group). Continuation/Maintenance. CNS-directed therapy is typically intrathecal chemotherapy. Cranial RT for 10-20%. Stem cell transplant is only for relapsed/refractory disease.
* CNS-Directed therapy: Previously, all kiddos got cranial RT. Younger age increases susceptibility, as brain growth occurs until around age 10. Per QUANTEC, “Cognitive dysfunction in children is largely seen for whole brain doses of ≥ 18 Gy”. IQ decline can occur five or more years later. [RoR](https://docs.google.com/document/d/17O0LOemBhckXGuuPBCh6u8vqBfc6lg88r46B8YctMXU/edit#heading=h.t9bpc6jib8hn) In recent years, intensification of systemic therapy and intrathecal chemo is effective for standard risk and most high risk patients. Cranial RT is protocol specific. Prophylactic RT dose is commonly 12/8, while dose for CNS3 disease is typically 18/10.



## [B-ALL](#_dix8o3c34tab)

* Majority of pediatric leukemias are B-cell in origin (85%).
* WBRT
  + CNS1: No RT.
  + CNS2: May or may not have RT (typically 12/8 - 150 cGy), depending on the risk group and protocol.
  + CNS3: Typically favor 18/10 Gy (180 cGy).
* Note: WBC is not specified for very high risk, but WBC > 50k is high risk.
* Just like WBRT ppx is becoming less common, so is testicular ppx with RT.
* **AALL02P2** [[Barredo Peds Blood Cancer '18](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6136835/)]: Isolated testicular relapse. **Chemo ± Testicular RT** (if testicle enlarged/bx+).

Testicular RT is only necessary for patients who have persistent testicular enlargement. If biopsy positive, then testicular RT should be offered. Note: Short term follow up.

* + 40 pts. Isolated testicular relapse ≥ 18 months after first remission.
    - Induction Dexamethasone / VCR / daunorubicin and IT triple therapy was preceded by one dose of HD-MTX (5 g/m2). Following induction, 25 of 26 pts who had persistent testicular enlargement underwent biopsy. Eleven had biopsy proven disease and received bilateral testicular radiation (24/12).
  + 5y EFS ~65%.
  + 5y OS ~73%.

## [T-ALL](#_dix8o3c34tab)

* Associated with anterior mediastinal mass. Male predominance.
* WBRT
  + T-ALL differs from B-ALL as some consider T-ALL high risk, regardless of CNS risk group.
  + CNS1,2 (if intermediate risk): 12/8 (150 cGy).
  + CNS3: 18/10 (180 cGy).
* For testicular involvement after induction chemotherapy, deliver 24/12.
* Anaplastic large cell lymphoma in Peds, all CD30+, > 90% ALK rearrangement.
* Some institutions treat T cell ALL as high risk ALL.
* Several groups have associated an early thymocyte precursor (ETP) phenotype with an unusually poor outcome.
  + ETP is ~15% of T-ALL.
  + Generally speaking, T-ALL with ETP takes longer to get in remission, but with intensified chemotherapy, once in remission, they end up doing comparably to non-ETP T-ALL.

## IQ Decline with RT

* **WBRT and decline in intelligence - the influence of dose and age on IQ** [[Silber JCO '92](https://ascopubs.org/doi/pdf/10.1200/JCO.1992.10.9.1390)]:

Tiptoes under the 20 Gy line (18/10 common). No one gives above 20 Gy WBRT in young kiddos anymore.

Younger kiddos have more neurological decline than kiddos above the age of 8y.

* + 48 pts: 24 pts ALL, 24 pts PNET.
    - WBRT 18 Gy (n=14), 24 Gy (n=17), 32-40 Gy (n=17).
  + IQ decline for 24 / 36 Gy WBRT 8→ 12 points decline vs. 18 Gy WBRT.
  + IQ decline for 10y at time of RT is 12 points less than a 3y at time of RT for equivalent doses.
  + This model accounts for half of the total variation in IQ score.
* **ALL: 24 vs. 18 Gy ppx WBRT** [[Halberg IJROBP '92](https://www.redjournal.org/article/0360-3016(92)90976-O/abstract)]: **WBRT 18 Gy** (n=16) **vs. 24 Gy** (n=19).  
  Tiptoes under the 20 Gy line (18/10 common). No one gives above 20 Gy WBRT in young kiddos anymore.

These results indicate a mild, but diffuse information processing deficit in children who rec'd 24 Gy, but not in children who received 18 Gy. Reducing the cranial RT from 24 to 18 Gy reduced neurotoxicity to acceptable levels.

* + 37 pts received WBRT, 12 pts with Wilms tumor in the control group. MFU 6y.
  + Children treated with 18 Gy were equivalent to controls who did not receive WBRT.
  + Children who rec'd 18 Gy scored ~12 points higher than 24 Gy.
  + 2/12 controls, 2/16 low dose and 7/19 high dose WBRT pts had IQ < 90.
  + Eight of the nine irradiated pts with deficits were irradiated before age 5.
* **There is no difference for 18 Gy vs. 24 Gy WBRT in children > 6y (controversial)** [[Fuss SuO '00](https://link.springer.com/article/10.1007/PL00002327)]: Meta.  
  The collected data suggest that whole brain irradiation doses of 18 and 24 Gy have no major impact on intellectual outcome in children older than age 6, but may cause impairment in younger children. Doses > 24 Gy comprise a substantial risk for FSIQ decline, even in older children.
  + 36 publications with 1,938 children.
  + FSIQ < 85 (below normal) were found at > 24 Gy and > 36 Gy doses in children < 3y and > 6y.
  + For children < 6y, IQ appears to be adversely affected regardless of if 18 or 24 Gy.
  + There appears to be no major impact in WBRT 18-24 Gy for children above 6 years of age.
  + All patients experience IQ decline for doses above 24 Gy.

**Follow up**

* Early relapse: Less than 3 years from initial diagnosis OR less than 18 mo if isolated extramedullary relapse.
* Late relapse: Greater than or equal to 3 years from initial diagnosis OR ≥ 18 mo if isolated extramedullary relapse.
* Year 1 (q1-2 mo): PE (includes testicular exam where applicable), CBC/diff, LFTs until normal.
* Year 2 (q3-6 mo): PE (includes testicular exam where applicable), CBC/diff.
* Year 3+ (q6-12 mo): PE (includes testicular exam where applicable), CBC/diff.
* Monitoring late effects: TTE, neuropsychological testing as clinically indicated, monitor for healthy weight and encourage a healthy lifestyle given an increased risk of obesity, referral to survivorship clinic.
* Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers: [www.survivorshipguidelines.org](http://www.survivorshipguidelines.org).

# [Hodgkin Lymphoma](#_e4a3jnknxfj8)

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| **Staging**  **I**: 1 region or extralymphatic site.  **II**: 2 or more regions on the same side of the diaphragm.  **III**: Both sides of the diaphragm ( ± spleen). *Stage IV requires extranodal sites.*  **IV**: diffuse or disseminated involvement of 1+ extralymphatic organ, isolated extralymphatic organ involvement in conjunction with disease in distant sites, or any liver/bone involvement, or nodular involvement of lungs.   * B = B symptoms. * E = Extralymphatic (E.g., bone marrow, liver and lung) * **Bulky mediastinal = >10 cm** (NCCN) or 33% transthoracic width. * **Bulky non-mediastinal = 6 cm** (controversial - utilized by COG).   *MSKCC/DFCI and ASTRO refresher says > 7 cm.*   * X staging classification for bulk is now gone. | **Rye classification**: [[Zaorsky tweet](https://twitter.com/NicholasZaorsky/status/1226197813765251073?s=20)].  Most commonly cervical chains/mediastinum, with 90% of pts having contiguous nodes.  Waldeyer's ring and spleen are considered lymphatic but extranodal regions for staging purposes.   1. Waldeyer's Ring - pharyngeal tonsil (adenoids), palatine tonsils, lingual tonsil (BOT) 2. Cervical/SCV/occipital/ preauricular 3. Infraclav 4. Axillary/pectoral 5. Epitrochlear/brachial 6. Mediastinal 7. Hilar (unilat) 8. Para-aortic 9. Spleen 10. Mesenteric 11. Iliac 12. Inguinofemoral 13. Popliteal |

See NCTN Trial Portfolios by Disease Site: [[Lymphoma](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Lymphoma_Trials.pdf)]

Hodgkin lymphoma node group sites for Ann Arbor, GHSG, EORTC, NCIC, and NCCN [[Zaorsky tweet](https://twitter.com/NicholasZaorsky/status/1226197813765251073?s=20)].

Deauville scoring for Hodgkin lymphoma in as few words as possible [[Zaorsky tweet](https://twitter.com/NicholasZaorsky/status/1226197121378004992?s=20)].

**eContour**: [[NLPHL (axillary)](http://econtour.org/cases/40)], [[Early stage favorable HL](http://econtour.org/cases/45)], [[Early stage unfavorable HL](http://econtour.org/cases/39)]

**ARRO**: [[Pediatric High Risk Classical Hodgkin Lymphoma](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/PediatricHighRiskClassicalHL.pdf)], [[Early-stage favorable classic hodgkin lymphoma](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/HodgkinsCQ.pdf)].

ILROG Guideline: Modern RT for Hodgkin Lymphoma Field and Dose Guidelines [[Specht IJROBP '14]](https://www.sciencedirect.com/science/article/pii/S0360301613005348?via%3Dihub). [RoR](#3kcd1cfmy4rq)

**Childrens Oncology Group (COG) risk stratification**: Most kiddos are IR [[AHOD 0031](#kix.stbtgkiiae8k)]. Does NOT use IPS!

* **LR**: IA/IIA non-bulky.
* **IR**: I/IIA bulky, I-IIAE, I-IIB, and IIIA and IVA. *Bulky early stage or advanced without B-symptoms.*
* **HR**: IIIB/IVB. *Higher likelihood of systemic disease with B-symptoms, such as occult subdiaphragmatic disease.*

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| Making Every Single Gray Count: ISRT Delineation Guidelines for Hematological Malignancies [[Dabaja IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/31928641)]. [RoR](#gq1ic3qggdvh)  **There are [**[**many problems with Lugano**](#kix.7c6l4uvk94al)**] PET-guided response which pays no attention to CT-based residual!**  Newer [[ILROG guidelines](#gq1ic3qggdvh)] from 2020 essentially highlight the ease and importance of mean dose of OARs less than 5 Gy!  The [[EORTC-LYSA analysis](#wd0qpuiowed7)] suggested one cycles of anthracyclines is equivalent to 5 Gy mean heart dose  TL; DR - 5 Gy isodose lines matter! Regardless of whether it is pediatric or adults, HL or NHL.  **ILROG Guideline: Modern RT for Hodgkin Lymphoma Field and Dose Guidelines** [[Specht IJROBP '14]](https://www.sciencedirect.com/science/article/pii/S0360301613005348?via%3Dihub).  Newer [[ILROG guidelines](#gq1ic3qggdvh)] from 2020 essentially highlight the ease and importance of mean dose of OARs less than 5 Gy!   * RT Alone (NLPHL): "In most clinical situations that require RT as the primary modality, the GTV should be readily visualized during simulation. In this situation, the clinical target volume (CTV) should be more generous because microscopic or subclinical disease is more likely to be present without chemotherapy. The absence of effective systemic therapy in such cases should also influence dose decisions." * Give 20 Gy for F [[HD 10](#x1kloo3nqbsq)], early stage treated with ABVD. U gets 30 Gy [[HD 11](#gcj1ji1zn4vz)]. Stanford always gets 30 Gy. * In 1978, total nodal irradiation was used and a dose of 30-44 Gy was employed. * In 2019, ISRT is utilized and doses are around 20-30 Gy.   **Early Stage Hodgkin's Lymphoma Summary** [[Rad Onc Tables](https://docs.google.com/spreadsheets/d/1iLceAGho4aPbyA9f0L0tOs-lE8_uIYyJaM_NxEJu51M/edit?pli=1#gid=1155879573&range=K4)]   * STNI was a historical standard, but it eventually lost out once ABVD chemo was developed as there was a suggestion of OS benefit when utilizing ABVD alone (poorly designed, janky unrelated deaths on STNI arms) [[Canadian HD 6](#iur05s7jdz4q)]. As a result, RT use had declined over time. * Multiple trials since demonstrated RT can be safely reduced to IFRT when chemo given [[H 7, H 8, E2496, HD 8](#390k1s7ys52j)] * [[HD 10](#x1kloo3nqbsq)] for favorable HL establishes 2c ABVD→ 20 Gy is similar to historical standard of ABVD x4 and IFRT of 30 Gy * [[HD 11](#gcj1ji1zn4vz)] for unfavorable HL establishes ABVD x4c→ 30 Gy or BEACOPP x4c→ 20 Gy as standard. * HD 10 was not in the PET era. PET-era trials showed PFS benefit in setting of RER PET2- on [HD 16](#dm0qmwagug32) or PET3- on [RAPID](#qdquj2bkm50). * [[HD 17](#b0y23yw1oxh)] now looking at reducing fields to INRT. The US uses a similar concept called ISRT. INRT/ISRT is now standard field size based on observational data.   **General treatment recommendations: Classical HL**.  ABVD is the most widely used. ABVD x4-6, BEACOPP x2 + ABVD x2 ("2+2"), Stanford V, or ABVE-PC (peds).   * **IA/IIA favorable** (PFS10 ≥ 87%): **ABVD x2c→ 20 Gy ISRT** [[HD 10](#x1kloo3nqbsq), [HD 16](#kix.cdurj53xisqs)] or **ABVD x3c→ 30 Gy** [[H 10](#kwrasxe9ykmw), [RAPID]](#qdquj2bkm50)   Chemo-alone approaches: Expect lower PFS, even with D1-2 response at PET2 [[H10](#kwrasxe9ykmw)] or PET3 [[RAPID]](#qdquj2bkm50).   * + PET2 D1-2 gets additional ABVD x2c [[H 10](#kwrasxe9ykmw)].   + PET3 D1-2 requires no more ABVD [[RAPID]](#qdquj2bkm50). * **I-II unfavorable** (PFS10 ≥ 84%): **ABVD x4c→ 30 Gy ISRT** [[HD 11](#gcj1ji1zn4vz), [H 10](#kwrasxe9ykmw)] or **"2+2"→ 30 Gy ISRT** [[HD 14](#jdhro67rq5me)]   Chemo-alone approaches: Expect lower PFS, double digits if bulky. Consider 6c ABVD for bulky.   * + PET2 D1-2 gets additional ABVD x4c [[H 10](#kwrasxe9ykmw)].   + PET3 D1-2 requires no more ABVD [[RAPID]](#qdquj2bkm50).   + PET2 D1-3 gets additional ABVD or AVD x4c (Bleomycin is poorly tolerated if > 60y) [[RATHL](#r3jf9bc5p6a4)]. * **III-IV**: **ABVD x6c** (or BEACOPP x4-6c in Europe).   It is reasonable for patients to be referred for consideration of consolidative RT with CT-based residual > 1.5 cm and partial response (i.e., < 50% reduction in bulky disease > 5 cm - [[HD 12](#txff7c8x1v47)]), PETF D3+ > 2.5 cm [[HD 18](#kix.3ymc4q9jg3po)] or even all initially bulky disease > 5-10 cm, but the evidence here is less clear [[FIL 0607](#kix.5r5qjr1l0h26), [FIL 0801](#9bbu5145xuho)]. Only [[HD 12](#txff7c8x1v47)] mandated RT for < 50% reduction of bulky disease or > 1.5 cm CT-based residual of bulky lesions. The FIL studies allowed ABVD x6c but only have 3-5 years of follow up, so the role of initially bulky disease in advanced HL is less clear than for persistently avid disease at the end of chemotherapy.   * + 6c-8c ABVD. Usually, 6c ABVD is given and preferred to 8c ABVD. BEACOPP is uncommonly given in US.   + EORTC-style will deliver "2+2" for PET2 D3-4. * Relapsed/refractory: 2nd line chemo ± RT ± transplant. Brentuximab (Anti-CD30) and PD1 inhibitors. * If not chemo candidate, STLI indicated: Mantle + spleen + PA (only include pelvis if initially involved).   + 30 Gy to STLI, 6 Gy boost to initial involved sites.   + Recall: OS advantage w CCRT over STLI in EORTC H8F.   **General treatment recommendations: NLPHL**.   * IA/IIA favorable: No chemo! R0 excisional biopsy may be observed, but ISRT to **30**-36 Gy preferred. * I-II unfavorable: Chemo→ ISRT ± rituximab. * IIIA-IVA: Chemo→ ± ISRT ± rituximab, local RT for palliation, or Rituximab alone. * IIIB-IVB: Chemo→ ± ISRT ± rituximab.   + Chemo = R-CHOP, R-ABVD or R-CVP. * Recall: NLPHL is CD20+, classical HL is not. * ISRT with **generous margins** (due to microscopic or subclinical dz more likely to be present without chemo - CTV w **2-5 cm CC** and modified for normal tissue boundaries) or IFRT. May observe if completely excised.   **Does the Transition to ISRT Matter in Terms of Late Toxicity?** [Zhou IJROBP '16]: (**1970-1986**) **vs.** (**2002-2012**).   * 50 HL survivors from CCSS vs. 191 HL survivors from AHOD0031 and AHOD0831. * Mean female breast dose 18→ 4 Gy. This is around an 85% reduction! * Mean heart dose 32→ 12 Gy. This is a decrease by around 20 Gy!   **Chemo only in early-stage Hodgkin lymphoma: More relapses but "same" (or possibly worse) OS** [[Yahalom CHMR '14](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4180027/)]  The [[EORTC-LYSA analysis](#wd0qpuiowed7)] suggested one cycle of anthracyclines is equivalent to 5 Gy mean heart dose.  Newer [[ILROG guidelines](#gq1ic3qggdvh)] from 2020 essentially highlight the ease and importance of mean dose of OARs less than 5 Gy!  "Recently a trend to treat patients with more chemotherapy alone has been promoted by some claiming that chemotherapy alone is good enough, and the overall survival is similar. These arguments need to be carefully examined, and the risk of more chemotherapy upfront and salvage considered. The suggestion that interim PET will identify patients that can have similar results with chemotherapy alone has recently been questioned by the results of both European and UK studies. It is the subject of this critical review."   * There has been decreased utilization of IFRT, suggested OS detriment [[SEER Koshy IJROBP '12](https://www.ncbi.nlm.nih.gov/pubmed/22251881), [NCDB Parikh RTO '16](https://www.ncbi.nlm.nih.gov/pubmed/26522061)] SMN rate at 15y appears to be equivalent with or without RT at 15%. * Reasons for the "same" OS in spite of better FFTF: Effective salvage, long survival with active disease, death from other causes.   + Effective salvage includes high dose chemo with SCT, which can be potentially devastating.   + Long survival may be attributable to single agent vinblastine or palliative RT.   + Many studies are only reported with MFU from 3-7 years, typically lacking funding to revisit and determine cause of death later on.   + Death from other causes on the [[Canadian HD 6 study](#19ud936o0afr)] (ABVD vs. STNI ± ABVD) include Alzheimers disease, accidental drowning, and suicide. These events were only noted in the ABVD + STNI arms. When these "other" deaths are removed, the OS difference becomes no longer significant. * [GHSG HD 10](#x1kloo3nqbsq) set standard of care as 2c ABVD→ 20 Gy as similar to historical standard of ABVD x4 and IFRT of 30 Gy.   This is the favored treatment for ESHD, but many med oncs try to omit with more chemo instead.   * + [EORTC H 10](#kwrasxe9ykmw), [GHSG HD 16](#kix.cdurj53xisqs), and [RAPID](#qdquj2bkm50) trial demonstrated decreased PFS if RT is omitted in the PET era. * When ABVD is offered as an alternative to ABVD + RT, around 2-3x of dose is required (See [HD 6](#iur05s7jdz4q), [H 10](#kwrasxe9ykmw)).   + ABVD alone may be associated with increased deaths from myocardial infarction, as well as significant bleomycin induced lung injury.   + There appears to be a 5% mortality with ABVD x4c [[Böll JCO '13](https://www.ncbi.nlm.nih.gov/pubmed/23509310)] * Chemo alone fails approximately 10% more patients than CMT.   + Salvage regimens include ICE, brentuximab vedotin, larger fields, and higher dose of RT to relapse/refractory sites followed by high dose chemo and SCT. The concern for toxicity is quite high after these regimens.   + This leads to loss of fertility and disruption of young life plans for careers and building a family. Even if the risk of relapse is only 10% when omitting RT, is it justified with these risks? * The paradigm to omit RT was in the era of 40 Gy mantle fields or total lymphoid irradiation, which indiscriminately irradiated the breasts, lungs, and heart. |

* 10% of all lymphomas.
* 9k cases per year, 1k deaths.
* Bimodal: 15-35 and >50.
* First degree relatives have 5x risk for HL.
* Homogeneous enhancing nodes (also thyroid) H&N likely necrotic.
* Early stage favorable: 95% cure rate. Advanced stage: 80-90% cure rate, PFS 90%.
* Hodgkin's lymphoma comprises 6% of childhood cancers. M/F ratio 2.5:1 for children < 5y, while 1:1 for children 15-19y.
  + Most common in 10-19 years, rare among children < 4y.
  + Bimodal distribution: Early peak in mid to late 20s, second peak after 50 years.
  + Siblings with 2-5x increased risk, if same-sex 9 fold risk.
  + **EBV found in 60% of childhood cases** - 75% if under 10 compared to 20% of other children.
* **Adverse factors**:   
  See the [["B4-HEE 50"](#wh92t3r32ayx)] rules for early stage hodgkin's disease and [["SHAM-LAW"](#xidr2ay05j0t)] IPS-7 for advanced hodgkin's disease.

Compared to [[IPI](#_2niu9tol7b6g)] for non-hodgkin's lymphoma.

* + Adults: Stage IV, Hgb < 10.5, Age ≥ 45y matter most. Male, Lymphocytes, Albumin, WBC matter less.

Of all labs, Hemoglobin matters most.

Not included in IPS: bulky disease, B-symptoms, histology, number of sites, BMBx, ESR, plt, Alk phos, LDH.

* + Children: Most are [intermediate risk] (e.g. bulky early stage/advanced without B sx). Does NOT use the IPS score!
    - Stage IV, bulky mass ( > 6 cm in peds), fever, albumin level.

## [Histology](#_h06kfryq1p0p)

See the [[Pediatric Hodgkin Lymphoma](#_n8a2lxdnbrk4)] section for more.

* **Classic** (95%): Four subtypes. Reed-sternberg cells (although usually <1 % of all cells). **CD15/30+**.
  + **NS** (70%): **Adolescents and young adults**. **Mediastinum is the most common**.
    - Overall most common, but **less common in children** (< 50%) **than adolescents/adults** (75%).
  + **MC** (20%): Males. **Young children < 10y**. Associated with **EBV**, **AIDS**.
    - Mixed cellularity is more **common in children** (20%) than adolescents/adults (9%).
    - Mediastinal mass in ~75% of AYA, while ~35% of young children. This suggests greater prevalence of mixed-cellularity and lymphocyte-predominant histology vs. nodular sclerosing.
  + **LR** (15%): **Good prognosis**. Usually early stage.
    - LR is relatively more common in children < 10y (13%).
  + **LD** (≤5%): **Worse prognosis**. **Older**. Associated with **AIDS**.
    - LD subtype is rare in children.
* 30m EFS for NS / MC / LR / LD of 89→ 86→ 97→ 55%.
* 30m OS for NS / MC / LR / LD of 97→ 94→ 97→ 87%.

### [NLPHL](#_h06kfryq1p0p)

Treatment: Observation if single node and completely resected. AV-PC x3c for > 1 LN or stage II. Relapse after R0 may be salvaged with AV-PC ± RT as per stage II disease. For adults, RT alone is quite reasonable.

* **LP** (5%): Usu presents with unilateral high cervical LAD. "Popcorn". **CD20/45+**. Best prognosis. 30m EFS/OS ~95%.  
  NLPHL may be treated by chemotherapy followed by surgery. Radiation alone is used less so than previously.

NLPHL is essentially the only subset of lymphomas - hodgkins or NHL - which may be curable by excision alone!

ILROG Guideline: Modern RT for Hodgkin Lymphoma Field and Dose Guidelines [[Specht IJROBP '14]](https://www.sciencedirect.com/science/article/pii/S0360301613005348?via%3Dihub). [RoR](#3kcd1cfmy4rq)

* + Only 5% of HL. Pathology review! Around 50% may be reclassified as classical HL.
* ~75% present with stage I-II.
* Frequency of 5-10% in the pediatric population, with a higher frequency in children < 10y.
* Rarely involves a mediastinal mass.
* Rituximab is ok, but not very durable with at least 25% relapse.
* 30 Gy IFRT with generous **margins** as subclinical dz more likely present w chemo. CTV + 2-**5 cm** CC modified for normal tissue boundaries. May observe if R0.
* Universal expression of CD20, natural history includes frequent **late relapses** (>5y).
  + Late recurrences are common up to 10 years. *Classical HL usually relapse in the first 2-3 years.*
* Have a high propensity to **transform to DLBCL**: Transformation at 10 / 20y of 7→ 30% [[Al-Mansour JCO '10]](http://ascopubs.org/doi/full/10.1200/JCO.2009.24.9516).
  + Greatest risk of developing subsequent NHL of all HL.
* **Resection alone** [[Mauz-Körholz Cancer '07](https://www.ncbi.nlm.nih.gov/pubmed/17526010)]: Retro. **Surgery alone**.

Surgery may be curative. As a general principle, all lymphomas typically occur "in the neighborhood", so local control of initial disease is important.

* + 58 children. CD20+. 50 boys, 8 girls. Median age 11y. 54 Stage IA. 2 Stage IIA. 2 Stage IIIA. MFU nearly 4y.
  + 4y OS 100%. 4y PFS 57%.
  + 51 of 58 patients achieved CR after surgery. In the CR group, overall PFS 67%.
  + All seven patients who had residual disease after initial surgery all developed recurrences.
  + Among 18 patients who had LR, 11 patients had local recurrences and 7 patients recurred in stage IIA.
  + Only one patient with stage III disease presented with DLBCL at 10 years of follow up.
* **COG AHOD03P1** [[Appel JCO '16](https://www.ncbi.nlm.nih.gov/pubmed/27185849)]: **Surgery for single node, AV-PC x3c if > 1 LN or stage II. RT if no CR**.
  + 178 patients. R0 of a single node (n=52, of whom 9 received AV-PC at relapse). AV-PC at diagnosis (n=126).
  + 11 patients had less than CR and received IFRT.
  + 5y EFS 86%. 5y OS 100%.
  + 5y EFS after surgery alone and observation of 77%.
  + 5y EFS after AV-PC with or without RT of 89%.
* **GHSG HD4 and HD12 [**[Eichenauer JCO '15](http://ascopubs.org/doi/abs/10.1200/jco.2014.60.4363)]: Retro. **Rituximab vs. EFRT vs. IFRT**   
  Rituximab is ok for ES-NLPHL, but not very durable with at least 25% relapse.

IFRT alone has the best PFS and similar OS to CMT or EFRT, therefore IFRT alone is recommended.

* + 256 pts. IA NLPHL.
  + Rituximab 4y PFS / OS of 81→ 100%.
  + CMT 8y PFS / OS of 89→ 99%.
  + EFRT 8y PFS / OS of 84→ 96%.
  + IFRT 8y PFS / OS of 92→ 99%.
  + SMN 6.6%.
* **GHSG HD7 to HD15** [[Eichenauer JCO '19](https://www.ncbi.nlm.nih.gov/pubmed/31626571)]:  
  10y OS is in excess of 90% for early stage NLPHL.

Only a minority of deaths in patients with NLPHL are due to underlying lymphoma, whereas SMN and nonmalignant conditions possibly related to chemo or RT cause most deaths.

* + 471 pts. Median age 39y. 1993-2009. MFU 9y.
  + 10y PFS 75%. 10y PFS for ES / IS / AS of 80→ 72→ 70%.
  + 10y OS 92%. 10y OS for ES / IS / AS of 93→ 96→ 87%.
  + SMN in 10% (n=48). SMN accounted for around half of deaths (n=20).
  + Deaths in 9% (n=43), but minority NLPHL related (n=10). Possible AE leading to death (n=13).

## 

## [Chemotherapy](#_h06kfryq1p0p)

* \*Lifetime max dose of **adriamycin** = **450** **mg**.\*
* The [[EORTC-LYSA analysis](#wd0qpuiowed7)] suggested one cycle of anthracyclines is equivalent to 5 Gy mean heart dose.
* Newer [[ILROG guidelines](#gq1ic3qggdvh)] from 2020 essentially highlight the ease and importance of mean dose of OARs less than 5 Gy!
* Typically, omission of radiotherapy requires around twice as many anthracyclines. Why omit RT when we would increase long term cardiac toxicity less than doubling anthracyclines so long as mean heart dose is less than 5 Gy? [[Yahalom](#xy8jnck1g2gu)].
* **MOPP**: Mechlorethamine (mustard- leukemia), Vincristine (neuropathy), Procarbazine (leukopenia), Prednisone.
* **ABVD**: Decreased sterility and SMN vs. MOPP.
  + Adriamycin 25, Bleomycin 10, Vinblastine 6, Dacarbazine 375 (**sterility**, **N/V**, immunosuppression).
    - GHSG 13: Can't take the D from ABVD without substantial loss of efficacy, nor the B either.
  + One cycle is 4w, doses q2w.
* **ABVE-PC is the most** common in Pediatric Hodgkin's Lymphoma.

See the [[Pediatric Hodgkin Lymphoma](#_n8a2lxdnbrk4)] section for more.  
33% can obtain CR with ABVE-PC.

* + Adriamycin, Bleomycin, Vincristine, Etoposide, Prednisone, Cyclophosphamide
    - Alkylators such as cyclophosphamide may lead to sterility, though less than vinblastine and dacarbazine.
    - Requires inpatient admissions.
  + Compare to ABVD, which uses Vinblastine and Dacarbazine - sterility, N/V, immunosuppression.
    - Generally speaking, outpatient.
* **Stanford V**: Decreased bleomycin, doxorubicin toxicity vs. ABVD. No dacarbazine.   
  Keep in mind that Stanford uses 75% less bleomycin dose and 50% less adriamycin dose.
  + **RT is always given** - 30-36 Gy to initial bulky mediastinal sites and splenic nodules ≥ 5 cm.
  + MOPE-ABV: Mechlorethamine, Vincristine, Prednisone, Etoposide, Doxorubicin, Bleo, Vinblastine.
* **BEACOPP**: Eight cycles total. RT given for disease > 5 cm.
  + Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Oncovin, Procarbazine, Prednisone.
* **EPOCH**: DA-EPOCH is adjusted based on neutropenia and thrombocytopenia.
* Brentuximab: Anti-CD30 antibody.

**Workup**:

* B symptoms (33%): Fever, > 10% weight loss in ≤ 6 mo, drenching night sweats.
  + Higher likelihood of systemic disease, such as occult subdiaphragmatic disease.
  + Mediastinal mass in ~75% of adolescents and young adults, while ~35% of young children. This suggests greater prevalence of mixed-cellularity and lymphocyte-predominant histology in young children than nodular sclerosing (most common presentation for nodular sclerosing is a mediastinal mass).
* Pruritus.
* Excisional LN biopsy. Core OK, not FNA as does not show LN architecture.
* **BMBx** for cytopenias if present (per NCCN) or **B-sx**, **stage III-IV**, bulky or recurrent disease.
  + Bone marrow biopsy becomes controversial when staged with PET/CT.
* PET/CT: Only 15-20% will have stage IV disease.
* Deauville scoring for Hodgkin lymphoma in as few words as possible [[Zaorsky tweet](https://twitter.com/NicholasZaorsky/status/1226197121378004992?s=20)].
* Labs: Albumin, pregnancy test, HIV, HBV, HCV.
* Counseling: Fertility, smoking cessation, psychosocial (NCCN).
* Other:
  + Fertility: 2 Gy permanent, 0.5 Gy transient for sperm. 8-10 Gy permanent for oocytes.
  + Dental eval.
  + PFTs if ABVD or BEACOPP given (Bleomycin).
  + MUGA before ABVD.
  + Vaccines if splenic RT.
    - In the pre-PET era, ~30% of early stage, favorable HL w occult splenic involvement [[Carde JCO '93](http://ascopubs.org/doi/pdf/10.1200/JCO.1993.11.11.2258)].

## [Unfavorable risk factors for stage I-II HL](#_h06kfryq1p0p)

Hodgkin lymphoma node group sites for Ann Arbor, GHSG, EORTC, NCIC, and NCCN [[Zaorsky tweet](https://twitter.com/NicholasZaorsky/status/1226197813765251073?s=20)].

"B4-HEE-50". All use 4+ nodal sites except GHSG.

Bulky mediastinal = >10 cm (NCCN) or 33% transthoracic width.

Bulky non-mediastinal = 6 cm (controversial - utilized by COG). MSKCC study and ASTRO refresher say > 7 cm.

See the [["B4-HEE 50"](#wh92t3r32ayx)] rules for early stage hodgkin's disease and [["SHAM-LAW"](#xidr2ay05j0t)] IPS-7 for advanced hodgkin's disease.

Compare to [[IPI](#_2niu9tol7b6g)] for non-hodgkin's lymphoma, where labs (besides LDH) don't matter and the age cutoff is 60y. However, FLIPI uses hemoglobin < 12 as a cutoff (not 10.5 as in IPS-7).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **RF** | **GHSG** | **EORTC** | **NCIC** | **NCCN** |
| B | ESR for **B symptoms** | **>50** if A or >30 if B | >50 if A or >30 if B | >50 or any B sx | >50 or any B sx |
| 4 | **# nodal sites** | 3+ | **4+** | **4+** | **4+** |
| H | **Histo** | - | - | **MC or LD** | - |
| E | **Extranodal lesions** | **Any** | - | - | - |
| E | **ESR** for B symptoms | **>50** if A or >30 if B | >50 if A or >30 if B | >50 or any B sx | >50 or any B sx |
| 50 | **Age** | - | ≥ **50y** | ≥ 40y | - |
|  | **Mediastinum** | MMR > 0.33 | MMR > 0.35 | MMR > 0.33 or >10 cm | MMR > 0.33 |
|  | **Bulky** | - | - | - | **>10 cm** |
|  | **Notes** | Lumps together ICL/Subpec w axilla. | Lumps ICL/Subpec w cervical/SCL. |  |  |

MMR = Max width of mass and max width of intrathoracic diameter. EORTC: MTR - intrathoracic diameter at T5-6 vertebral level.

* Both GHSG and EORTC have only 5 LN regions, combining mediastinum and bilateral hila as a single region.
* **GHSG**: Only one with **3+** nodal sites as opposed to 4+. *"3-BEE" for unfavorable factors.*
* **EORTC** age ≥ 50y, while NCIC age ≥ 40y. *Recall: IPS-7 with age of 45y (average of the two).*
* **NCIC**: Also includes MC or LD histology.
* **NCCN**: Only one to include bulky as >10 cm. *NCIC uses bulky mediastinum as 10 cm.*
* Stanford: B symptoms, large mediastinal mass (>5 cm).
* Many times, pts w bulky dz or B sx can be included in advanced stage protocols.
  + E.g. E2496 had ⅓ pts with stage I/II bulky mediastinal adenopathy.
* Density of macrophages as measured by CD-68+ cells was found to be a prognostic factor, although this was confirmed within the E2496 study, the 23 gene expression panel proved to be a better determinant of prognosis.
* [[COG](#kix.ltndftsjgktg)] prognostic score now simplified on 4 factors: Stage IV, large mediastinal mass, fever, albumin level. *NOT IPS.*

### [Advanced disease: IPS-7](#_hp06zw8euzx2)

Compare to [[IPI](#_2niu9tol7b6g)] for NHL, which utilizes less labs and has an age cutoff of 60.

* **Germany** [[Hasenclever NEJM '98](https://www.nejm.org/doi/full/10.1056/NEJM199811193392104)]: Defines IPS-7 as risk stratification for advanced disease.

**"SHAM LAW": Stage, Hgb < 10.5, Age > 45y, Male, Lymphocytes < 600 or 8%, Albumin < 4, WBC > 15**.

IPS-7 devised using pts mainly from the 1980s treated with chemo ± RT.

Not included in IPS: bulky dz, B sx, histology, number of sites, bone marrow, ESR, platelets, Alk phos, LDH, comorbidities.

* + 7784 pts. Advanced HL. Data from 25 centers used to create a prognostic score.
  + 5y FFP for 0 / 1 / 2 / 3 / 4 / 5+ of 84→ 77→ 67→ 60→ 51→ 42%.
  + Each factor can reduce OS by 8%/y.
  + **5y FFP** for **0** / **4+** / 7 factors of **80**→ **50**→ 40%.*Add 10% to these values for the modern era.*
* Modern era: 5y FFP from 88% to 62%.
  + Good Risk IPS (0-1 factors): 5y FFP ~90%.
  + Fair Risk IPS (2-3 factors):
  + Poor Risk (4-7 factors): 5y FFP 60%. If PET2(+), consider switching to BEACOPPesc [[Gallamini JCO '18](#g7p2t89nw73t)].
* **IPS-3**: “SHA” Stage IV, Hgb < **10.5**, Age ≥ **45y**.   
  One point per factor. Labs (except Hgb) don't matter.
  + 5y PFS for 0 / 3 factors of 83→ 63%.
  + 5y OS for 0 / 3 factors of 95→ 52%.
* **First PET2 trial** [[Gallamini JCO '07](http://ascopubs.org/doi/full/10.1200/JCO.2007.11.6525?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed)]: ABVD x2, no treatment change allowed on the basis of PET2 results.  
  For II-IVB disease, IPS was lost as prognostic value in the setting of PET adapted therapy.   
   IPS did not pan out on MVA, but PET-2 did.
  + **260 II-IVB pts**. 70 pts IIA w poor prognostic factors. All but 11 rec'd ABVD + RT for bulky/residual.
  + 2y PFS of 12.8→ 95% if PET negative.

|  |
| --- |
| **General Principles of Pediatric Hodgkin's Lymphoma**   * Requires B symptoms to be high risk (e.g., advanced stage, but IIIB or IVB). * Most patients are intermediate risk by [[COG]](#kix.ltndftsjgktg) risk stratification. Know [[AHOD 0031](#kix.stbtgkiiae8k)] cold. * Most adolescents are Nodular Sclerosing (mediastinal mass). See [[histology](#_dic5bcvuxhcr)] section for more. * Mixed cellularity is more common in kiddos, less common in adolescents. * ABVE-PC [[chemotherapy](#_drunoo6fhvas)] is utilized. Less sterility! Uses Vincristine (not blast), omits Dacarbazine - risk of sterility. * Most relapses are in the neighborhood of original involvement, *not* at new sites. |

## [Pediatric Hodgkin Lymphoma](#_h06kfryq1p0p)

See the Summary Box above.

ARRO: [[Pediatric High Risk Classical Hodgkin Lymphoma](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/PediatricHighRiskClassicalHL.pdf)]

[Childhood Hodgkin Intnl P[rognostic Score (CHIPS)](#kix.ltndftsjgktg)]: Stage IV, fever, alb < 3.5, bulky mass > 6 cm in longest transverse direction.

Compare to [["B4-HEE 50"](#wh92t3r32ayx)] rules for early stage adult HL and [["SHAM-LAW"](#xidr2ay05j0t)] IPS-7 for advanced HL.

Compare to [[IPI](#_2niu9tol7b6g)] for NHL, where labs (besides LDH) don't matter. Only FLIPI-2 "β-MASH" uses size.

Low risk: I/IIA non bulky [[AHOD 0431](#mfjw1ota4ypy)].

Intermediate risk: Bulky early stage or advanced HL without B-symptoms [[AHOD 0031](#kix.stbtgkiiae8k)]. *Most common! Know this trial cold.*

High risk: Advanced HL with B symptoms [[AHOD 1331](#2xdpcsg6zsoq)].

Declining use of RT in NHL and HL for pediatrics (Figs 1 and 2) [[Jairam IJROBP '13](https://www.redjournal.org/article/S0360-3016(12)03657-7/abstract)]

See [[NLPHL](#_n4jcucusmmt)] section. Generally speaking, surgery for 1 LN is preferred. ABVE-PC x3c if > 1 LN or stage II. RT for salvage.

Pediatric Hodgkin Lymphoma [[Lo and Hodgson COG Powerpoint](http://qarc.org/COG/HodgkinLymphoma.pdf)]

### [Low Risk Peds](#_n8a2lxdnbrk4)

IA/IIA non-bulky (< 6 cm in longest transverse diameter).

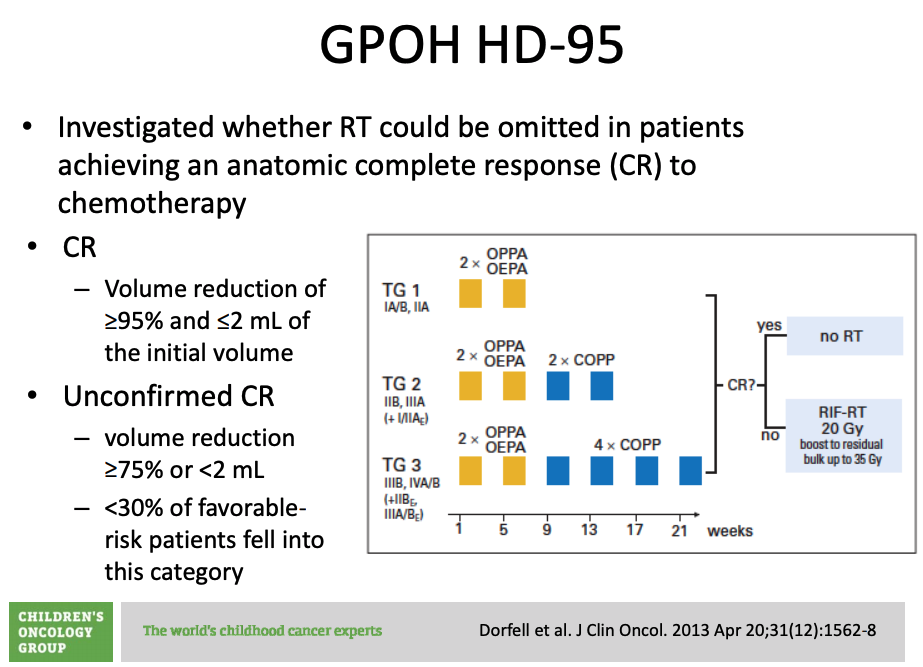
Dose reduced RT after VAMP chemotherapy from 25.5 Gy to PR or 15 Gy to CR [[Slides 18-20](http://qarc.org/COG/HodgkinLymphoma.pdf)]

There is no single standard treatment for favorable risk pediatric HL. Acceptable options include Chemo x2-4c (OEPA, VAMP, COPP-ABV, AV-PC). Response-based, low dose ISRT to 15-25.5 Gy [[Slide 32](http://qarc.org/COG/HodgkinLymphoma.pdf)].

* **CCG 5942** [[Wolden JCO ‘12](https://www.ncbi.nlm.nih.gov/pubmed/22649136)]: **COPP/ABV** x4/6c or intensified chemo**→ ± 21/12 IFRT if CR** (60%).   
  IFRT improves EFS without OS improvement in low risk HL, although 31% were bulky.

This is the trial that realized 10 cm to define bulky in peds was too large! New criteria = 6 cm.

* + 826 pts, 498 achieved CR. 1995-1998. Low risk HL: IA/IIA, but includes 31% bulky. MFU 8y.
    - Bulk = 1/3 thoracic diameter or > 10 cm nodal aggregate.
    - CR requires a 70% decrease in XS area along with change from positive to negative gallium.
  + 10y EFS 84%. 10y OS 93%.
  + In per protocol analysis, 10y EFS 83→ 91%. 10y OS ~96%.
  + Risk factors for worse EFS were bulky, B symptoms, or nodular sclerosing.

[](http://qarc.org/COG/HodgkinLymphoma.pdf)

* **GPOH HD-95** (1995-2001) [[Dörffel JCO '13](https://www.ncbi.nlm.nih.gov/pubmed/23509321)]: **OP/EPA-COPP x2-6c→ if CR, ± 20 Gy RT** (+10-15 Gy if large residual).

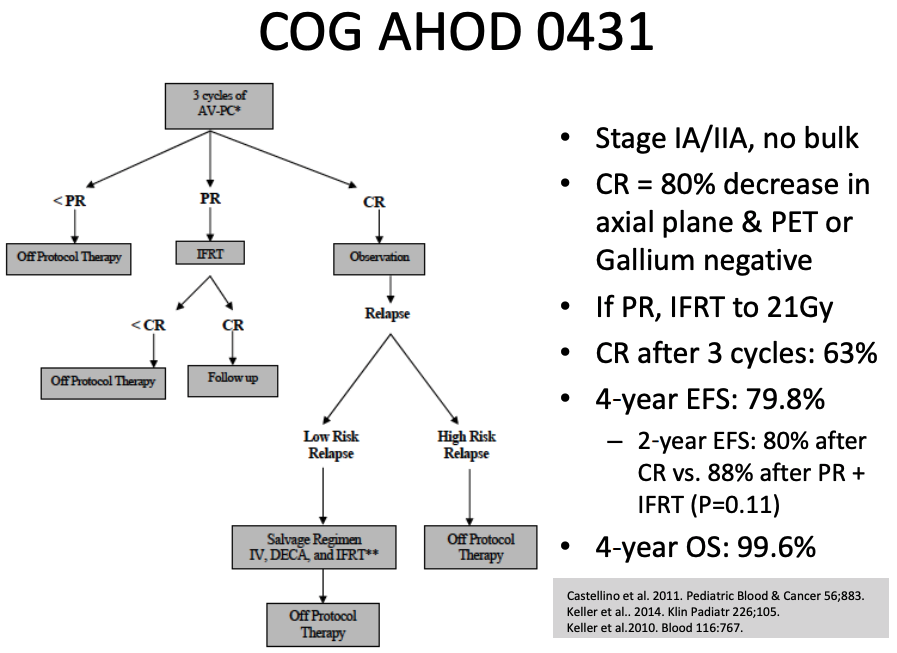
Patients with significant volume reduction (< 30% of favorable risk) may omit radiotherapy without detriment in PFS.

Procarbazine was replaced by etoposide in boys to decrease gonadotoxicity, resulting in 5y DFS for girls / boys of 93→ 86%. Therefore, in [[GPOH-HD-2002](#mohjdkasfnwi)], a procarbazine-free regimen was used, but with escalated etoposide and IV dacarbazine [[Slide 35](http://qarc.org/COG/HodgkinLymphoma.pdf)].

* + 925 patients. The stage IA/B, IIA cohorts were able to omit radiotherapy successfully.
    - CR: Volume reduction of ≥ 95% and ≤ 2 mL of initial volume
    - uCR: Volume reduction ≥ 75% or < 2 mL. < 30% of favorable risk patients fell into this category.
  + 10y PFS for stage IA/B and IIA cohort (received no COPP) of ~97→ 92% (p=0.21).
  + 10y PFS for stage IIB, IIIA and extranodal I/IIAE (received 2c COPP) of 69→ 91%.
  + 10y PFS for stage IIIB, IVA/B and extranodal IIB-IIIA/B (received 4c COPP) of ~82→ 89% (p=0.26).
* **Euronet-PHL-C1** [[Körholz '12](https://www.skion.nl/workspace/uploads/euronet-phl-c1_workingcopy_inkl_amendm06_mw_2012-11-14_0.pdf), [Mauz-Körholz JCO '15](https://www.ncbi.nlm.nih.gov/pubmed/26304892)]: **OEPA x2c→ if CR, no RT. If PR/SD, RT**.

Patients in the TG1 risk group with ESR ≥ 30 or bulky disease ≥ 200 mL will receive additional COPP ± RT.

* + Includes group TG1 (Stage IA/B, IIA), and similar additional COPP for TG 2-3 per HD-95. RT 19.8 Gy IFRT.
    - CR or uCR: Volume reduction ≥ 75% and residual volume < 5 mL OR residual < 100 mL.
  + 2y EFS for ± ESR ≥ 30 mm/h and/or a bulk volume ≥ 200 cc of 77→ 93%.

[](http://qarc.org/COG/HodgkinLymphoma.pdf)

* **AHOD 0431** [[Keller Cancer ‘18](https://www.ncbi.nlm.nih.gov/pubmed/29738613)]: **AVPC x3c→ Eval for CR** (PET1, PET3). **If PR, 21/14 IFRT**.  
  No RT after PET3(-) demonstrated high rates of relapse. The study was amended to be PET1(-) for no RT in Dec 2008.  
  CR requires 80% decrease in XS area and PET3 D1-2. No residual extra mediastinal nodal mass > 2 cm, with the exception of the mediastinal mass which could be larger than 2 cm provided it was 80% decrease in XS area.
  + Nonrandomized. 278 pts < 21y. Low risk cHL: Stage IA/IIA, non-bulky. MFU 6.5y.  
    Bulky (not enrolled) = 1/3 thoracic diameter or **> 6 cm** in longest transverse diameter on axial CT.
    - Treatment strategy was evaluated by determining the proportion that received minimal chemo alone, the proportion that had a first or second remission without the receipt of high dose chemo/stem cell rescue or higher dose IFRT (> 21 Gy), and overall survival.
    - Low risk relapse after CR: IV/DECA + 21/14 IFRT.
    - High risk relapse after CR: off protocol.
  + 4y minimal chemo and no RT in 49%, 89% were in remission without receiving HDC/SCR or > 21 Gy RT.
  + CR3 64%, PET1 D1-2 50%. PET1(+) patients are more likely Stage II, ESR > 20, and elevated CRP at presentation.
    - 4y EFS for ± PET3 of 72→ 80%.
    - 4y EFS for ± PET1 of 68→ 88%.
    - 4y EFS for ± PET1 who achieved CR3 without RT of 60→ 85%.
  + 4y OS 99.6%.
  + 4y EFS for NS / MC of 76→ 95%.

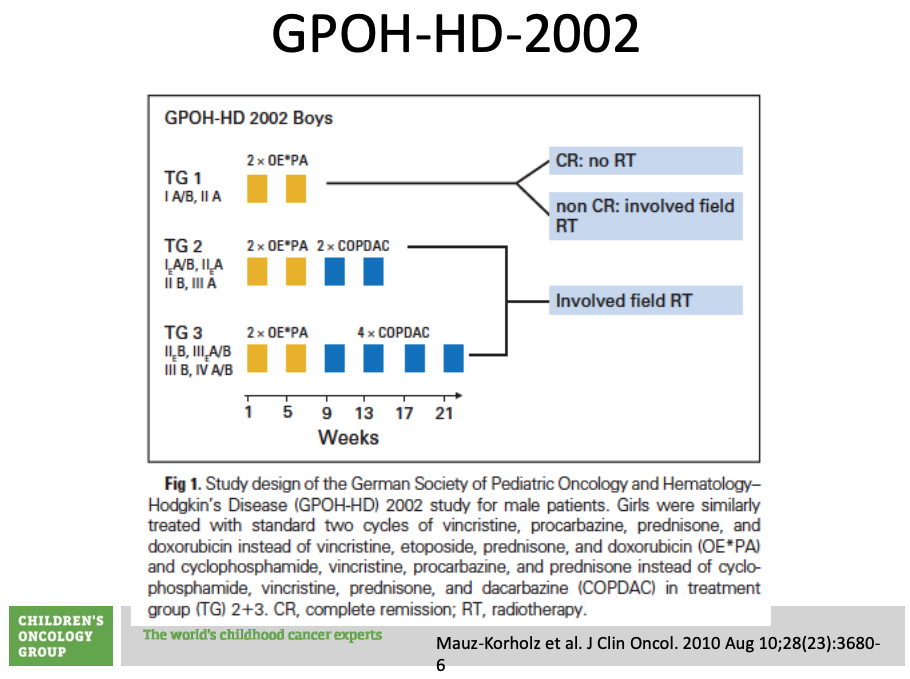
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### [Intermediate Risk Peds](#_n8a2lxdnbrk4)

I/IIA bulky, I-IIAE, I-IIB, and IIIA and IVA. Bulky (> 6 cm longest transverse diameter) early stage or advanced stage without B-sx.

The most common risk group in kiddos! Most relapses are in the neighborhood of original involvement, not at new sites.

Dose intensive chemo (OEPA/COPP, ABVE-PC) x3-6c plus ISRT to 15-25.5 Gy. Consider omitting RT after ABVE-PC x4c in patients who achieve RER and CR, but not in patients with initial thoracic bulk or anemia. [RoR](#kix.stbtgkiiae8k)

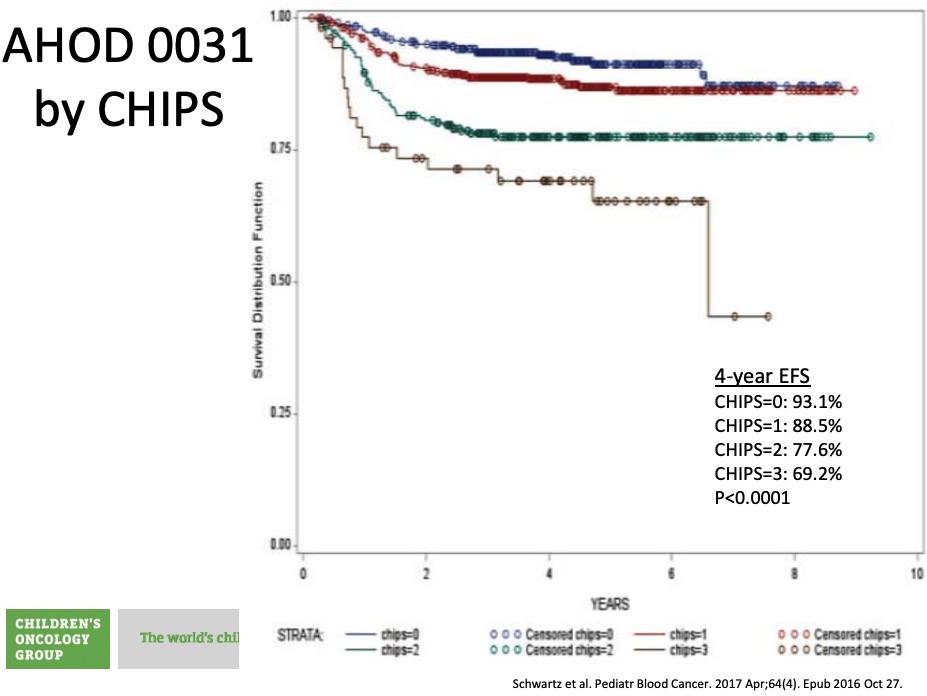
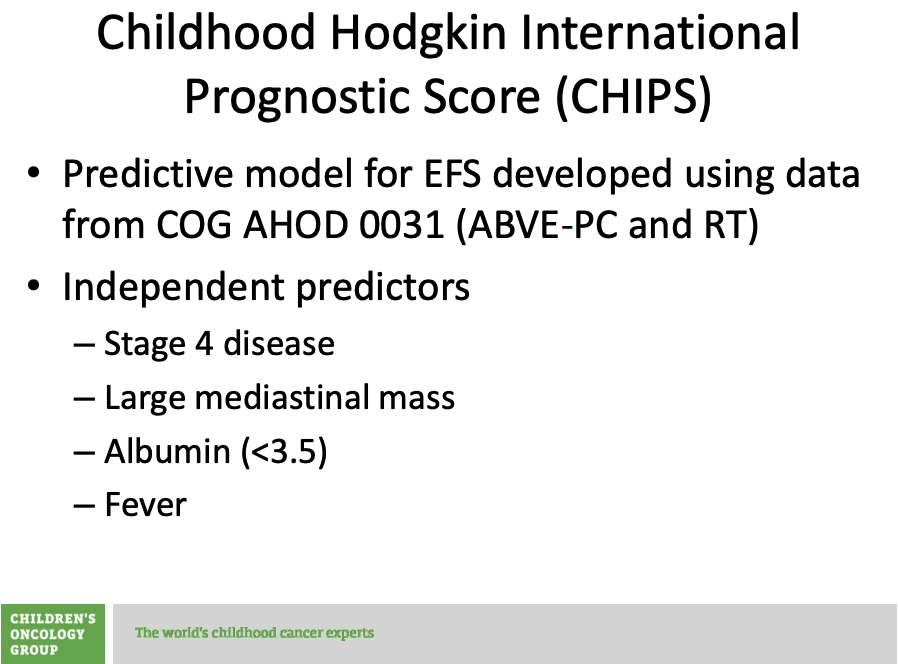
[](http://qarc.org/COG/HodgkinLymphoma.pdf)

* **GPOH-HD-2002** (2002-2005) [[Mauz-Korholz JCO '10](https://www.ncbi.nlm.nih.gov/pubmed/20625128)]: All IR patients received RT: 19.8 Gy (+10-15 Gy if large residual).

The TG-1 group omitted RT successfully, confirming results of GPOH-HD-95.

In [[GPOH-HD-95](#7qk3joakzq1e)], Procarbazine was replaced by etoposide in boys to decrease gonadotoxicity, resulting in 5y DFS for girls / boys of 93→ 86%. Therefore, in GPOH-HD-2002, a procarbazine-free regimen was used, but with escalated etoposide and IV dacarbazine [[Slide 35](http://qarc.org/COG/HodgkinLymphoma.pdf)].

* 573 patients. Girls received OPPA or COPP (contains procarbazine). MFU 5y.
  + Nodal involvement if largest diameter > 2 cm, questionable if largest diameter 1-2 cm.
  + CR: Volume reduction of ≥ 95% and ≤ 2 mL of initial volume
  + uCR: Volume reduction ≥ 75% or < 2 mL.
  + RT: Standard 19.8 Gy. If < 75% volume reduction, boost to 30 Gy administered, while residual masses greater than 100 mL received 35 Gy. Stage IV lung disease was only irradiated only if lung nodules were still detectable after 2c of chemo. Lung and liver RT varied from 12-15 Gy in 1.0-1.2 Gy fractions.
* 5y EFS for TG 1 ~92%. *This confirms results of GPOH-HD-95,*
* 5y EFS for TG 2-3 for girls / boys of ~85→ 90% (p=0.12).

[](http://qarc.org/COG/HodgkinLymphoma.pdf)

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| **AHOD 0031: If only adult Hodgkins was this easy!** *You will get a million questions on this trial.*  See the details on this trial below. See [[general principles](#8uj1461dcmqy)] of Pediatric Hodgkin Lymphoma.  PET assessment of response was used to confirm and supplement anatomic RER and CR status, not replace CT. In essence, residual disease mattered most. Yet, many med oncs select for omission of radiation alone based on PET-only response...  The exact same dilemma is occurring with adults - [[Lugano](#kix.7c6l4uvk94al)] essentially ignores CT-based residual, while [[EORTC 20884](#2umqw59gv3o3)] demonstrated the importance of CT-based residual with ABVD-like chemo in advanced stage HL for adults.  **Key definitions to know cold:**   * CT2 (to define RER): Decrease in cross-sectional area by 60%.  * CT/PET4 (to define CR): Decrease in cross-sectional area by 80% or return to normal size for all target lesions, no residual extra mediastinal nodal mass >2 cm, no dz in non-measurable sites AND negative gallium or PET. PET alone cannot define CR, CT response is also mandated (e.g. nodes < 1 cm, < 2 cm if extra-mediastinal). |

* **AHOD 0031** (2002-2009) [[Friedman '14](https://www.ncbi.nlm.nih.gov/pubmed/25311218), [Dharmarajan ‘15](https://www.ncbi.nlm.nih.gov/pubmed/25542311), [Charpentier ‘16](https://www.ncbi.nlm.nih.gov/pubmed/27869096)]: **ABVE-PC**→ **CT2** (RER/SER)→ **CT4** (CR).

See the summary box above for the definition of RER and SER.

**RER** (≥ 60% ↓ in XS area)→ **CT4, if CR→ ± 21/14 IFRT** (1.5 Gy). If < CR, IFRT delivered. If CR, IFRT omitted.

**SER** (< 60% ↓ in XS area)**→ IFRT ± more intensive chemo**. *Around 20% of SERs fail by 4y - is 21 Gy enough??*

It appears to be reasonable to omit RT based on CT2-based rapid early response in those who develop CR.

Relapses rarely occur solely in new sites (6%), occurring equally in both bulky (~75%) and non-bulky (~75%) sites. In irradiated patients, relapses rarely occur solely out of field. Should we really only be treating bulky disease? Is 21/14 Gy enough? Now, the dose ranges from 15-25 Gy. Utilize INRT, which typically has 2 cm margins.

RT significantly improved EFS in patients with anemia and large mediastinal mass, even if achieving RER/CR.

* + 1712 pts. 2002-2010. Stage IB, IAE, IIB, IIAE, IIIA, IVA.
    - Bulky = 1/3 thoracic diameter at diaphragm on PA CXR or > 6 cm in longest diameter on axial CT.
    - Around 80% were RER. Of these, just over half were CR.
    - PET alone cannot define [[CR](#n2uokm5flfjl)], CT response mandated (e.g. nodes < 1 cm, < 2 cm if extra-mediastinal).
    - RT: 21/14 (1.5 Gy) AP/PA.
  + 4y EFS for ± IFRT in RER-CR PET negative subgroup of ~87%.
  + 4y EFS for ± IFRT in RER-CR PET positive or equivocal subgroup of ~84→ 88% (p=0.11).
  + 4y EFS for patients with anemia and bulky IB / IIB of 78→ 89%.
  + 4y EFS for SER / RER of 77→ 87%.
  + 4y OS for SER / RER of 95→ 99%.
  + 4y EFS for IFRT ± more intensive chemo in SER of ~75→ 79% (p=0.11).
  + 4y EFS for IFRT ± more intensive chemo in SER PET positive or equivocal subgroup of 55→ 71%.
  + 4y EFS for RER-CR with anemia and stage I/II HL with bulk ± 21 Gy IFRT of 66→ 86%.

### [High Risk Peds](#_n8a2lxdnbrk4)

Stage IIIB/IVB. Higher likelihood of systemic disease with B-symptoms, such as occult subdiaphragmatic disease.

Typically includes bulky lymphadenopathy, hilar lymphadenopathy, ≥ 3 nodal regions, and ENE to contiguous structures.

Dose intensive chemo (OEPA/COPP, ABVE-PC) x4-6c plus ISRT to 15-25.5 Gy. All initial bulk, SER (non-bulky) and post-chemotherapy residual disease should receive RT.

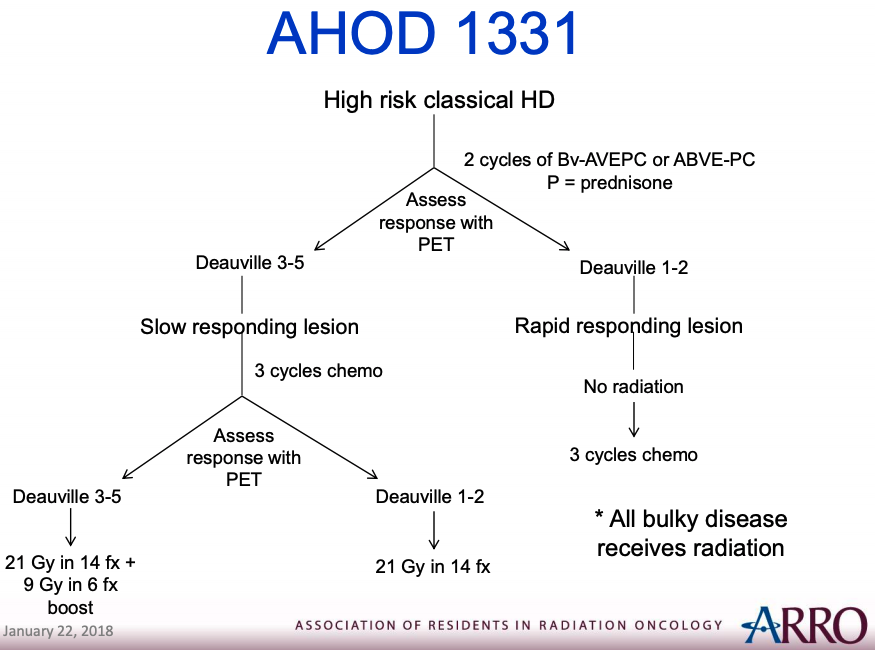
* **AHOD 0831** (2009-2012) [[Kelly BJH '19](https://doi.org/10.1111/bjh.16014)]:**ABVE-PC**→ **PET2** (RER/SER)→ **PET4** (CR). PET negative if D1-2.

See the summary box above for the definition of RER and SER.

**RER** (≥ 60% ↓ in XS area)→ **PET4, if CR→ ± 21/14 IFRT** (1.5 Gy). If < CR, IFRT delivered. If CR, IFRT omitted.

**SER** (< 60% ↓ in XS area)**→ IFRT ± more intensive chemo**. *Around 20% of SERs fail by 4y - is 21 Gy enough??*

* + 164 pts. Stage IIIB/IVB. Primary endpoint: "Second event" free survival, goal 95%. Bulk in 84%. MFU 4.5y.
    - RT for RER: Initial bulk (large mediastinal mass, nodal aggregate > 6 cm, and macroscopic splenic nodules).
    - RT for SER: Initial bulk, slow responding non-bulky disease, residual > 2.5 cm at end of chemo.
    - 75% of patients received RT on this study! Around half and half RER and SER.
    - Goal to achieve 95% EFS which was not met (bar set too high, like LR). [RoR](#mfjw1ota4ypy)
  + 5y 1st EFS of 79%. 4y 2nd EFS of 90%.
  + 5y 1st EFS for SER / RER of 73→ 84%. 4y 2nd EFS for SER / RER of 89→ 95%.
  + 4y OS 96%.
  + 3y 1st EFS for PET1 D1-2 / PET2 D1-2 / PET2 D3+ of ~93→ 81→ 74% (p=0.07).
  + 3y 1st EFS for PET2 D1-2 / PET2 D3+ of ~84→ 74% (p=0.06).
  + 12 SER patients had persistent PET+ lesions at the end of chemo, 8/12 with clinical evidence of active disease.
  + Persistent PET+ at the end of chemo were especially high risk for relapse and/or early progression.

[](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/PediatricHighRiskClassicalHL.pdf)

* **AHOD 1331 [**[NCT02166463](https://clinicaltrials.gov/ct2/show/NCT02166463)**]**: **ABVE-PC vs. AVE-PC-Brentuximab** x5c.

ARRO: [[Pediatric High Risk Classical Hodgkin Lymphoma](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/ARROcase/Content_Pieces/PediatricHighRiskClassicalHL.pdf)].

PET2 RER→ No RT.

PET2 SER than CR→ 21 Gy ISRT.

PET2 SER then PR→ 21 Gy ISRT + 9 Gy boost.

* + Stage IIB, IIIB, IVA, IVB. RT to all bulky mediastinal lesions.
    - Bulky = 1/3 thoracic diameter at diaphragm on PA CXR or > 6 cm in longest diameter on axial CT.
    - All initially bulky disease receives RT, but RER may omit RT.
  + No formal RT questions, but clearly different than established standards. Don't treat off study!
  + Only pts with bulky mediastinal dz or SER will receive RT. May allow pts to avoid receiving RT.
    - One measure was going to be Radiation free survival!

### Relapsed/Refractory Peds

Interestingly, these patients could avoid RT all together prior to salvage therapy on trials below. AHOD00P1 did not deliver radiotherapy, however, AHOD0121 includes to option of hyperfractionated IFRT, 21/14 (1.5 Gy) BID to all involved site that had not been previously trated to maximum tissue tolerance.

* **COG AHOD00P1** [[Trippett Peds Blood Ca '15](https://www.ncbi.nlm.nih.gov/pubmed/25308760)]: Phase II Pilot. **Ifosphamide/Vinorelbine x2c. If CR/PR: Additional CTX**.
  + 66 patients. Biopsy proven relapsed/refractory HL. Age < 30y.
  + ORR 72%. Most patients underwent ASCT.
  + 5y EFS 57%. 5y OS 74%.
* **COG AHOD0121** [[NCT00070187](https://clinicaltrials.gov/ct2/show/NCT00070187)]: Phase II/III. **BEAM + ASCT ± Cyclosporine, IFN-៵, and IL-2**.
  + Patients who completed salvage induction therapy and had not received full tissue tolerance from prior RT *may* received IFRT 21/14 (1.5 Gy) BID for 7 days.
  + We are *very* curious to see how many of the 24 patients who were enrolled A) ever received radiotherapy as a part of treatment and B) received it on AHOD0121.

## 

## [Early stage Hodgkin's Disease](#_h06kfryq1p0p)

Historic trials that established CMT as standard of care:

In the 1960s and 1970s, > 80% actuarial 10 to 15y FFR and < 10% mortality from HL.

Modern outcomes: Early stage favorable: 95% cure rate. Early stage unfavorable: 80% cure rate, PFS 90%.

* **Adding chemo to RT improves PFS**:
  + [**GHSG HD7** [Engert JCO '07]](http://ascopubs.org/doi/full/10.1200/JCO.2006.07.0482): EFRT ± neoadjuvant ABVD x2. 7y FFTF 67→ 88%. ~OS.
  + **SWOG 9133** [[Press JCO '01]](https://ascopubs.org/doi/abs/10.1200/jco.2001.19.22.4238): 3y FFS 81→ 94% with STNI.
  + **Stanford G4**: Abbreviated Stanford 8 week chemo→ 30 Gy IFRT with 94% 10y FFP and OS.  
    Keep in mind Stanford uses 75% less bleomycin dose at 50% less adriamycin dose.
    - Stage I-II non-bulky HL. 42% and 33% were unfavorable by GHSG and EORTC, respectively.
  + See EORTC studies below.

### [Smaller RT fields may be used when chemo is utilized](#_3asre3sir10o)

* [**EORTC H7F** [Noordijk JCO '06]](https://www.ncbi.nlm.nih.gov/pubmed/16754934): **STNI vs. EBVP x6c→ IFRT**. All RT 36-40 Gy.

This trial utilized EBVP chemotherapy, which is inferior to MOPP-ABV chemotherapy. This is precisely why there was only an EFS benefit on H7F while there was an OS benefit on H8F.

* + 333 pts. Prognostic score 1-5.
    - EBVP = Epirubicin, bleomycin, vinblastine, and prednisone
  + 10y EFS 78→ 88%. 10y OS ~98%.
* **EORTC H7U** [[Noordijk JCO '06]](https://www.ncbi.nlm.nih.gov/pubmed/16754934): EBVP x6c→ IFRT 36-40 Gy vs. MOPP/ABV hybrid x6c→ IFRT 36-40 Gy.   
  Chemo intensification trial. Defined MOPP/ABV as superior to EBVP, which was used in H8F.

Not a "smaller RT field" trial, but included in this section to group with H7F.

* + 389 pts. Prognostic score >8.
  + 10y EFS 68→ 88%, 10y OS 79→ 87%.
* [**EORTC H8F** [Fermé NEJM '07]](https://www.nejm.org/doi/10.1056/NEJMoa064601?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov): **STNI vs. MOPP-ABV x3→ IFRT**.   
  STNI is inferior to MOPP-ABV→ IFRT with an OS detriment (better chemo than H7F).
  + 996 pts.
  + 10y OS 92→ 97%. 5y EFS 74→ 98%.
* [**EORTC H8U**](https://www.nejm.org/doi/10.1056/NEJMoa064601?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov) [[Fermé NEJM '07]](https://www.nejm.org/doi/10.1056/NEJMoa064601?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov): 3 arms: **MOPP-ABV x4→ STNI vs. MOPP-ABV x6/4→IFRT** 36-40 Gy.   
  IFRT with MOPP-ABV x4c of chemotherapy is equivalent to STNI. IFRT is preferred.
  + 542 pts.
  + 5y EFS ~86%, 10y OS ~86%.
  + Reference arm x6c with IFRT as defined by H7U.
* **Stanford V:** advanced Hodgkin's only treated initial bulk, large mediastinal masses, and/or macroscopic splenic dz.
  + **E2496** [[Li JCO '13](https://www.ncbi.nlm.nih.gov/pubmed/23182987)]: **Stanford V/36 Gy to all bulky sites vs. ABVD x6-8c/36 Gy to initial mediastinal bulk only**.

ABVD RT differs from Stanford V as RT only given to bulky mediastinum, while on Stanford V RT given to nodal sites ≥ 5 cm and macroscopic splenic disease if present.   
There was no difference between ORR.

* + - 794 patients, ~33% bulky disease [[Advani JCO '15](https://www.ncbi.nlm.nih.gov/pubmed/25897153)]. MFU 6.5y.
    - 5y FFS ~73%. 5y OS ~88%.
    - In field relapses in < 10% of patients in each arm.
* **Meta** [[Herbst Haematologica '10](https://www.ncbi.nlm.nih.gov/pubmed/19951972)]: **Chemo ± IFRT**.  
  Conclusion: IFRT increases DFS and OS. This was in the pre-PET era.
  + 1,245 patients from 5 RCTs. 1980-2009.Only included trials with six cycles of chemo in both arms, randomized after a good response to chemo and at least 80% of pts with stage I-II disease.
  + HR for tumor control and OS ~0.40 with CMT vs. chemo.

### [EFRT: Increased secondary malignancies for unfavorable patients](#_3asre3sir10o)

* [**GHSG HD7** [Engert JCO '07,](http://ascopubs.org/doi/full/10.1200/JCO.2006.07.0482) [Sasse JCO '17](https://www.ncbi.nlm.nih.gov/pubmed/28418763)]: **± ABVD x2→ EFRT 30-40 Gy**.

Like [[HD 10](#x1kloo3nqbsq)] which was for early stage, there were no differences in second neoplasias at long term follow up.

* + 650 favorable pts. MFU 10y.
  + 7y FFTF 67→ 88% with ABVD. 7y OS ~93%.
  + 15y PFS 52→ 73%. No difference in OS.
  + 15% secondary malignancies in each arm at long term follow up!
  + Second neoplasia without prior progression or relapse of HL ~12%.
* [**GHSG HD8** [Engert JCO '03](http://ascopubs.org/doi/abs/10.1200/JCO.2003.03.023?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed), [Sasse JCO '17](https://www.ncbi.nlm.nih.gov/pubmed/28418763)]: (**COPP, ABVD**) **x2→ 30 Gy EFRT vs. IFRT**. 10 Gy to bulky in both arms.   
  IFRT is noninferior to EFRT. No differences in OS or second neoplasias seen in the long term.

Subset analysis demonstrated > 60y is an important prognostic factor.

* + ~1,000 unfavorable Stage I and II pts. MFU 12.7y.
  + Elderly did worse w EFRT in 5y FFTF and OS.
  + ~15% secondary malignancies in each arm at long term follow up.
  + Second neoplasia without prior progression or relapse of HL of 14→ 9%.
  + Deaths due to SMN of 5.3→ 3.4% is higher in EFRT in part explained by increased AML cases.   
    Long term follow up demonstrated deaths due to second neoplasia ~5.5%.

### [Reduced IFRT dose for early stage](#_3asre3sir10o)

* Of note, of those that failed in 20 Gy arms, 50% of failures were in field (normally, never in field failures).
  + 20 Gy may not be adequate after CR to chemo.
  + This is in line with [[AHOD 0031](#z4jtj7lkebt5)] for pediatrics... Is 21/14 Gy enough? NCCN says up to 25 Gy is allowed.

* **GHSG HD10** [[Engert NEJM '10](https://www.nejm.org/doi/10.1056/NEJMoa1000067?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov), [Sasse JCO '17](https://www.ncbi.nlm.nih.gov/pubmed/28418763)] : Non-inferiority. 2x2 design, **ABVD x2/4c→ IFRT 30/20 Gy**.2c ABVD and 20 Gy for favorable early stage HL is similar to the historical standard of ABVD x4 and IFRT of 30 Gy.

**2c ABVD and 20 Gy is the favored treatment for early stage HL**. Still, many med oncs try to omit with more chemo.

This trial was not in the PET era.

PET-era trials showed PFS detriment when omitting RT in the setting of RER PET2- on [[HD16](#kix.cdurj53xisqs)] or PET3- on [[RAPID](#qdquj2bkm50)].

* + 1470 pts. Early stage, **favorable**. Only 7.5% B sx. No PET imaging on this study! MFU 8.2y.  
    Recall: GHSG utilizes two or less nodal sites.
  + 5y PFS ~91-94%. 5y OS ~97%,
  + 10y PFS ~87%, 10y OS ~94%.
  + More dysphagia 2→ 3% and mucositis 0.7→ 3.4% with 30 Gy.
  + No difference in secondary malignancy at 10 years.

* **GHSG HD11** [[Eich JCO '17,](http://ascopubs.org/doi/abs/10.1200/JCO.2010.29.8018?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed) [Sasse JCO '17](https://www.ncbi.nlm.nih.gov/pubmed/28418763)]: Non-inferiority. 2x2: **ABVD x4/6 vs. BEACOPP x4→ IFRT 20-30 Gy**.

Superiority of BEACOPP over ABVD was not observed in these early stage unfavorable patients.

For unfavorable HL, utilize ABVD x4c→ 30 Gy or BEACOPP x4c→ 20 Gy.

No differences in OS or second neoplasias seen in the long term.

* + ~1400 early stage **unfavorable** pts. MFU 8.8y.
  + 5y FFTF improved in the 20 Gy BEACOPP arm.
  + 10y PFS for 20 / 30 Gy after BEACOPP of ~84%.
  + 10y PFS for 20 / 30 Gy after ABVD 76→ 84%. *Do not use 20 Gy after ABVD x4c.*
  + G3+ for ABVD / BEACOPP of 52→ 74%.
  + G3+ for 20 / 30 Gy of 6→ 12%.
  + No difference at secondary malignancy at 10y.
* See [[**EORTC H9F**](#6y73o0ydd5mx)**]** below, which was also an omission of RT trial.

* **EORTC H9U** [[Fermé EJC '17]](https://www.sciencedirect.com/science/article/pii/S0959804917309565?via%3Dihub): **ABVD x4/6c vs. BEACOPP x4c→ IFRT 30 Gy** all arms, 6 Gy boost for PR.

BEACOPP is more toxic; used as rationale in the USA for continued ABVD over BEACOPP in ES-U.

* + 808 early stage unfavorable HL (age ≥ 50, 4-5 sites, bulky, ESR ≥ 50 no B-sx; ESR ≥ 30 w B-sx).
  + 4y EFS ~90%, 4y OS ~95%.
* **ABVD in older patients** [[Böll JCO '13](https://www.ncbi.nlm.nih.gov/pubmed/23509310)]:  
  In pts ≥ 60y, ABVD x4c is associated with substantial dose reduction, treatment delay, toxicity and treatment-related death.
  + 117 patients from the age of 60-75 on [[HD 10](#x1kloo3nqbsq)] and [[HD 11](#gcj1ji1zn4vz)]. MFU 7.6y.
  + Treatment related mortality 5%.
  + 5y PFS 75%.

### [Omitting RT reduces PFS](#_3asre3sir10o)

* **NCIC HD6** [[Meyer NEJM '12](https://www.nejm.org/doi/full/10.1056/NEJMoa1111961)]: **35/20**. **F**: **ABVD x4-6 vs. STNI**. **U**: **ABVD x4-6c vs. ABVD x2→ STNI**.

Major finding: EFRT with decreased OS related to death from other causes, negating any benefit of lymphoma control.

"This trial is an excellent example of how small number of events, unrelated causes of death, and incomplete analysis of morbidity may distort the results, conclusion and interpretation of the study" [[Yahalom '14](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4180027/)]

The dose of ABVD is doubled or tripled in the setting of omission! Yikes.

STLI has been long abandoned, and also includes the spleen.

* + 405 patients. Non-bulky stage I-IIA HL. Designed at the same time as E2496. MFU 11y.
  + 12y OS 97→ 84%.
    - Favorable: ~12y OS and EFS.   
      Mortality events for favorable patients (STNI alone) had no long-term mortality, and minimal morbidity.
    - Unfavorable: 12y FFP 86→ 94% but 12y OS 92→ 81% due to more non-cancer deaths.

Mortality events for less favorable group 11→ 23 patients.   
Death from other causes on the Canadian HD 6 study include Alzheimers disease, accidental drowning, and suicide. These events were only noted in the ABVD + STNI arms. When these "other" deaths are removed, the OS difference becomes no longer significant.

* + 12y PFS 87→ 92%.

* **EORTC H9F** [[Noordijk JCO '16](http://ascopubs.org/doi/abs/10.1200/jco.2005.23.16_suppl.6505), [Thomas IJROBP '18](https://www.sciencedirect.com/science/article/pii/S0360301617339846?via%3Dihub)]: **EBVP x6→ Obs vs. 20 vs. 36 Gy IFRT** if CR after chemo.  
  Cannot omit radiation! No RT arm stopped due to failure rate >20%. 20 Gy appears to be equivalent to 36 Gy.
  + 783 pts. IA-IIB. No risk factors allowed (e.g. ≥ 50y, 4-5 nodal areas, MTR > 0.35, ESR 50/30). 80% CR. MFU 7.5y.
  + Obs 4y EFS 70%, closed early.
  + 5y EFS for either RT ~85%. 5y OS ~98%.

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| **PET Guided Therapy for Early Stage Hodgkin Lymphoma: Are we Positive about a Negative Interim Scan?** [[Bakst IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/32142868)]: Excellent review article which discusses results of [[RAPID](#qdquj2bkm50)] (failed to meet non-inferiority), [[H10F](#kwrasxe9ykmw)] (failed to meet non-inferiority) and [[HD16](#kix.cdurj53xisqs)]. ABVD x2c with 20 Gy ISRT should be standard of care for early stage HL per [[HD 10](#x1kloo3nqbsq)].  Deauville scoring for Hodgkin lymphoma in as few words as possible [[Zaorsky tweet](https://twitter.com/NicholasZaorsky/status/1226197121378004992?s=20)].  **Meta** [Vargo ASTRO '19]: **Chemo alone ± RT**.   * PET-negative randomized studies. * Radiotherapy improves PFS for both favorable and unfavorable disease. |

### [PET: Omitting RT reduces PFS](#_3asre3sir10o)

See the Summary Box above.

Remembering which studies had PET: EORTC H10 vs. GHSG HD15. "Germans needed drivers learning permit"

Deauville scoring for Hodgkin lymphoma in as few words as possible [[Zaorsky tweet](https://twitter.com/NicholasZaorsky/status/1226197121378004992?s=20)].

Set PET with FDG threshold of 40% of SUVmax.

Around 80% will be PET2-, although residual CT mass > 1.3 cm should be accounted for.

* **First PET2 trial** [[Gallamini JCO '07](http://ascopubs.org/doi/full/10.1200/JCO.2007.11.6525?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed)]: ABVD x2, no treatment change allowed on the basis of PET2 results.
  + **260 II-IVB pts**. 70 pts IIA w poor prognostic factors. All but 11 rec'd ABVD + RT for bulky/residual.
  + 2y PFS of 12.8→ 95% if PET negative. IPS did not pan out on MVA, but PET-2 did.
  + For II-IVB disease, IPS was lost as a prognostic value.
* **Picardi** [[Leuk and Lymph '07](https://www.tandfonline.com/doi/full/10.1080/10428190701559140)]: VEBEP→ PET(-) w residual CT mass >1.3 cm randomized to **Obs vs. IFRT 32 Gy**.   
  All chemo alone failures in initial site and contiguous nodal regions.
  + 260 bulky (≥ 5 cm) pts. 88% PET2-, though 60% PET2- w residual CT mass > 1.3 cm.
  + 65% stage I-II. MFU over 3y.
    - RT: Mostly Mantle field, or T field, Y field or pAO.
  + 3y EFS 86→ 96%.
  + Original site/IFRT failures of 14→ 4%.
  + Among 70 PET- pts without residual mass who rec'd chemo alone, 10 pts lost to f/u and 3y EFS 88%.

* **EORTC LYSA GELA H10 F/U** [[Raemaekers JCO '14](https://ascopubs.org/doi/full/10.1200/JCO.2013.51.9298), [André JCO '17](https://www.ncbi.nlm.nih.gov/pubmed/28291393)]:

**All arms: ABVD→ PET2**. **In experimental arms, all PET2(+) were escalated to BEACOPPesc x2→ 30 Gy INRT**.

**Favorable, PET2(-)**: **ABVD x3c**→ **30 Gy** **INRT** (3c total) **vs. ABVD x2→ ABVD x2** (4c total).

**Unfavorable, PET2(-)**: **ABVD x4c**→  **30 Gy INRT** (4c total) **vs. ABVD x2→ ABVD x4** (6c total).

See PET-Guided Therapy for Early-stage HL: Are we positive about a negative interim scan? [[Bakst IJROBP '20](#on80n14yxoeb)].

Noninferior, designed to demonstrate up to a 10% difference in FFTF in order to show omission of RT is acceptable.

Interim analysis demonstrated dropping RT leads to more early progressions. Study amended to give RT moving forward.

For both F and U groups, noninferiority of ABVD only could not be demonstrated. Risk of relapse was increased when INRT was omitted, especially in the favorable group.

Note: Favorable patients were likely over-treated on this trial, as ABVD x2c→ 20 Gy is standard per [[HD 10](#x1kloo3nqbsq)].

* + 1,925 I-II U/F pts. 2006-2011. All patients got PET2 (even control arm). MFU 4.5y.
    - PET2 negative = D1-2. **D3+ considered positive**.
    - RT: CTV for CRu = CC pre-chemo initial tumor mass, accounting for tumor shrinkage in axial direction. After 30 Gy, an additional 6 Gy boost to residual disease was allowed.
    - This is INRT as in Europe, the Rad Onc is the Med Onc. So, they get the PET/CT in treatment position.
  + PET2(-) achieved for U / F of 79→ 89%.
  + Interim analysis: 1y PFS for PET2(-) of 100→ 95% and 97→ 95% for F/U patients, respectively.  
    *There appears to be a clear detriment in omitting RT for favorable patients with D3+.*
  + For PET2(-) responders (81%):
    - 5y PFS for favorable disease of 99→ 87%.
    - 5y PFS for unfavorable disease of 92→ 90%.
  + For PET2(+) responders (19%): 5y PFS for intensification to BEACOPP x2→ 30 Gy INRT of 77→ 91%.
  + In the ABVD arm, relapses predominantly within involved nodes within two years of treatment. Of 30 relapses that occurred, 83% involved an initial site of disease and 735 occurred exclusively in sites of initial involvement.

* **UK RAPID** [[Radford NEJM '15](https://www.nejm.org/doi/10.1056/NEJMoa1408648?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov), [Barrington RTO '19](https://www.ncbi.nlm.nih.gov/pubmed/31112475)]: **ABVD x3→ ± 30 Gy IFRT if PET3-**; PET3(+) ABVD x1→ 30 Gy.  
  See PET-Guided Therapy for Early-stage HL: Are we positive about a negative interim scan? [[Bakst IJROBP '20](#on80n14yxoeb)].

Noninferior, designed to demonstrate up to a 7% difference in FFTF in order to show omission of RT is acceptable.

Statistically negative, did not demonstrate non inferiority for NFT. Per protocol, there is a clear benefit for RT in PET3(-) pts.

Recall: 2c ABVD and 20 Gy is similar to the historical standard of ABVD x4 and IFRT of 30 Gy on [[HD 10](#x1kloo3nqbsq)], which only included favorable patients. There were around 40% unfavorable patients on RAPID, and all received ABVD x3→ 30 Gy.

Why try to omit RT if it leads to low toxicity?

* + 602 pts. CS IA-IIA. 62% favorable by EORTC. Excluded B-symptoms and mediastinum. MFU 5y.
    - PET3 negative = D1-2. **D3+ considered positive**.
  + PET3 negative (PET-CR) in 75%.
    - PET D5 was the best predictor of prognosis. PET D1-4, EORTC, or GHSG classifications not predictive.
  + 26 patients assigned to the RT group did not receive it (12%), including 5 deaths prior to initiation of RT.
  + ITT 3y PFS ~91→ 95% (p=0.16). 3y OS ~97→ 99.5% (p=0.21).
  + Per protocol 3y PFS 91→ 97%.
* **Cochrane Meta** [[Blank '17](https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007110.pub3/full)]: 3 RCTs for 1500 pts demonstrated PFS inferior in PET-adapted arms that omitted RT.
  + Sensitivity analysis without trials with potential high risk of bias showed chemo + RT associated with improved OS compared to chemo alone.

* **GHSG HD16** [[Fuchs JCO '19](https://ascopubs.org/doi/abs/10.1200/JCO.19.00964)]: **ABVD x2→ Control: IFRT 20 Gy** vs. **PET2(-) Obs**.PET2(+) IFRT 20 Gy.   
  See PET-Guided Therapy for Early-stage HL: Are we positive about a negative interim scan? [[Bakst IJROBP '20](#on80n14yxoeb)].

2c ABVD and 20 Gy IFRT is the widely accepted standard of care for early stage favorable HL per [[HD 10](#x1kloo3nqbsq)], but many med oncs try to omit radiation based on PET/CT response. There is a detriment in PFS when omitting radiation for PET2(-).

Most failures are "in the neighborhood" of the original sites of disease.

Utilizing D3+ as a PET(+) cutoff still demonstrates benefit with IFRT, though the difference is more pronounced with D4+.  
TBL [QS](http://www.quadshotnews.com/2019/09/progress-isnt-free.html): Among patients meeting GHSD-favorable criteria for Hodgkin lymphoma and a negative PET after 2 cycles of ABVD, the omission of radiation results in a significant decrease in disease control.

* + 1150 patients. 2009-2015. 18-75y. Early stage favorable HL per [[GHSG](#f587rygg5092)] (resembling [HD 10](#x1kloo3nqbsq)). MFU 4y.
    - PET2 negative = D1-2. **D3+ considered positive**.
  + PET2(-)/CR in around half.
  + 5y PFS for D1-2 of 93→ 86%. 5y OS ~98%.
  + 5y PFS for D1-2 / D3-4 receiving RT of 93→ 88%.
  + 5y PFS for D1-3 / D4 receiving RT of 93→ 81%. *The difference becomes more pronounced in D4 patients.*
  + 5y IFF 2→ 9%. *Failures "in the neighborhood" of original sites appear to be driving the difference in PFS.*
  + 5y OFF ~4%.
  + G3 toxicity 3.4%.

**Chemo escalation to BEACOPP**:

* The potential benefit for BEACOPP in early stage unfavorable was not teased out until the PET era. Prior to the PET era, there appears to be no OS benefit with "2+2" for early stage unfavorable [[HD 14](#jdhro67rq5me)] or BEACOPP over ABVD [[EORTC H 9U](#nsxxvfpr9e9q), [GHSG HD 11](#gcj1ji1zn4vz)]. In the PET era, however, unfavorable early stage disease which is PET2(+) after ABVD appears to benefit after switching to BEACOPP [[EORTC H 10](#kwrasxe9ykmw)]. Switching to BEACOPP after PET2(+) also appears to be favorable for advanced disease [SWOG, [GITIL/FIL](#kix.5r5qjr1l0h26)].
  + On EORTC H 10: 5y PFS for PET2+ intensification to BEACOPP x2 + 30 Gy INRT of 77→ 91%.
* BEACOPP is not commonly used in the United States due to G3+ toxicity of at least 85%.

* **GHSG HD14** [[Tresckow JCO '12]](http://ascopubs.org/doi/abs/10.1200/JCO.2011.38.5807?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): **ABVD x 4c vs. BEACOPP x2c/ABVD x2c ("2+2")**. **All got 30 Gy IFRT**.  
  GHSG now uses "2+2" with 30 Gy IFRT for unfavorable early-stage HL, but 7y follow up demonstrated no difference in overall survival with "2+2" over ABVD x4c. The "2+2" regimen is not commonly given in the US due to toxicity and added complexity. Newer study [[HD17](#kix.vjvgvzlylzh5)] is looking into "2+2" ± 30 Gy IFRT for PET4(-), similarly to HD 10 and HD 16.
  + ~1500 early stage (I-II) unfavorable pts. MFU 3.6y.
  + CR ~95%.
  + 5y FFTF 88→ 95%, 5y PFS 89→ 95%. 5y OS ~97%.
    - Subgroup: bulky mediastinal mass and elevated ESR can predict higher relapse rate.
  + BEACOPPesc with higher myelosuppression, 0.52% death rate.
  + Use GnRH during chemo to augment probability of subsequent preggers.
  + G3+ 51→ 87%
  + SMN ~2.0%.
* See also [[HD9](#v6n132huby0q)], [[S0816](#n9ux2mops4hc)], [[RATHL](#r3jf9bc5p6a4)], [[GITIL/FIL 0607](#kix.5r5qjr1l0h26)].

[**Immunotherapy**](#_h06kfryq1p0p)

* **GHSG NIVAHL** (2017-2018) [[Bröckelmann JAMA Onc ‘20](https://www.ncbi.nlm.nih.gov/pubmed/32352505)]: Phase II. **Concurrent vs. Sequential N-AVD**→ **30 Gy ISRT**.

Both strategies combining Nivo and AVD are feasible and resulted in high remission rates.

Protocol available in Supplementary material.

* + 109 patients. Unfavorable ES-HL. Only 30% bulky or extranodal. MFU 13 mo.
    - Nivo-AVD x4c vs. Nivo x4 doses→ N-AVD x2c→ AVD x2c. All received 30 Gy ISRT.
    - This trial mandated RT to ≥ 3 non-bulky, non-extranodal sites!
  + Interim ORR after N-AVD x2c / Nivo x4c of 100→ 96% with CR in 87→ 51%.
  + 1y PFS of 100→ 98%.

## [Advanced Hodgkin's Disease](#_h06kfryq1p0p)

* Bone marrow biopsy becomes controversial when staged with PET/CT.
* Stage IIB/IIBX HL are included in many advanced stage protocols.
* Stage III: Both sides of diaphragm ( ± spleen - IIIS). Stage IV requires extranodal sites.
* Stage IV: diffuse or disseminated involvement of 1+ extralymphatic organ ± lymphatic involvement, isolated extralymphatic organ involvement + distant lymphatic, or any liver/bone involvement, or nodular involvement of lungs.
* Consolidative RT after chemo appears to improve PFS for pts with bulky disease or poor chemo responders.
  + The role of RT in advanced stage is controversial because most early studies utilized MOPP or MOPP hybrids, relatively large RT fields, and limited response-assessment.
  + Commonly, many centers treat with chemo alone (esp if not bulky) and RT is only employed with PR.
* BEACOPP has unarguably better PFS compared to ABVD, but equivalent OS. Source: [GHSG HD14 [Tresckow JCO '12]](http://ascopubs.org/doi/abs/10.1200/JCO.2011.38.5807?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed).
* **GHSG Meta for advanced-stage Hodgkin's lymphoma** [[Skoetz Lancet Onc '12](https://www.sciencedirect.com/science/article/abs/pii/S1470204513703413)]:

This is the first time PFS differences translated into OS differences in advanced stage HL.

However, around 70% of patients with advanced stage Hodgkin's lymphoma can be cured with ABVD alone.

* + 14 eligible trials. 11 different regimens and nearly 10,000 patients identified. MFU 6y.
  + 5y OS advantage for BEACOPPesc over ABVD of 10%.

|  |
| --- |
| **The EORTC 20884 conundrum and patterns of practice in the United States**: CR as defined in the EORTC advanced HL trial below mandates the entire disappearance of measurable lesions on CT. Today, many med oncs utilizing ABVD instead of BEACOPP try to omit RT based on PET avidity, regardless of CT-based residual, which is contrary to [[international guidelines](#kix.j96zbvd82uvx)]. Further, [[HD 12](#txff7c8x1v47)] demonstrated a 7% PFS benefit for patients who received radiation for patients with initial bulk > 5 cm or CT-based residual > 1.5 cm. Per [[HD 18](#kix.3ymc4q9jg3po)], patients with PET2 residual > 2.5 cm should receive a PET at completion of therapy. In all groups, 30 Gy of RT was recommended for residual FDG uptake (i.e., D3+) after completion of chemotherapy.  This conundrum rings especially true when virtually only BEACOPP has been utilized on RCTs for omission of RT in advanced stage hodgkin lymphomas (See [[HD 12](#txff7c8x1v47)], [[HD 15](#koawh8v4c3md)], [[HD 18](#kix.3ymc4q9jg3po)] - potential exception [[FIL 0801](#9bbu5145xuho)] which suggests a role of RT for initially bulky masses > 5 cm after ABVD x6c, but does not comment on size of residual at the time of RT). The 1y NPV of 94% after a negative PET in the context of CR with CT-based residual as per [[HD 15](#koawh8v4c3md)] does not apply in the context of ABVD, which is widely utilized in the United States. It is reasonable for patients to be referred for consideration of consolidative RT with CT-based residual > 1.5 cm and partial response (i.e., < 50% reduction in bulky disease > 5 cm - [[HD 12](#txff7c8x1v47)]), PETF D3+ > 2.5 cm [[HD 18](#kix.3ymc4q9jg3po)] or even all initially bulky disease > 5-10 cm, but the evidence here is less clear [[FIL 0607](#kix.5r5qjr1l0h26), [FIL 0801](#9bbu5145xuho)]. Only [[HD 12](#txff7c8x1v47)] mandated RT for < 50% reduction of bulky disease or > 1.5 cm CT-based residual of bulky lesions. The FIL studies allowed ABVD x6c but only have 3-5 years of follow up, so the role of initially bulky disease in advanced HL is less clear than for persistently avid disease at the end of chemotherapy. |

* **EORTC 20884** [[Aleman NEJM '03]](https://www.ncbi.nlm.nih.gov/pubmed/12802025?dopt=Abstract): **MOPP-ABV x6-8c ± IFRT 24 Gy** if CR (60%).   
  No EFS benefit to consolidative RT if CT-based CR obtained after chemo (CR = entire disappearance of measurable lesions).

Subgroup of PR patients have similar EFS as CR subgroup, suggesting a role for consolidative RT in PR.

Today, many med oncs try to omit RT based on PET avidity, regardless of CT-based residual. This is contrary to international guidelines, which mandates attention is paid to CT based residual.

* + 421 advanced stage pts. 60% CR, 25% PR, < 1% SD, 2% PD. MFU 6.5y.
    - CR: 24 Gy to pre chemo nodal, 16-24 Gy to pre chemo extranodal areas.
    - PR: 30 Gy to pre chemo nodal, 18-24 Gy to pre chemo extranodal areas. Boost 4-10 Gy when necessary.
    - Bulky defined as mass ≥ 10 cm or bulky mediastinum (0.35 MTR at T5-6).
    - CR is defined as the disappearance of all measurable disease.
  + For CR (60%): 5y EFS ~84→ 79% (p=0.35), 5y OS 91→ 85%.
  + Subset of 227 pts who did not achieve PR after chemo who were treated with IFRT noted equivalent 8y EFS/OS (79% / 87%) as CR patients, suggesting a potential role for IFRT after PR.
  + Higher AML/MDS without RFS or OS benefit with IFRT.
* **Tata Memorial** [[Laskar JCO '04]](http://ascopubs.org/doi/full/10.1200/JCO.2004.01.021): **ABVD x6c ± IFRT 21 Gy** if CR (71%) with 10 Gy boost to bulky.
  + 179 pts (71%) with CR. ~50% <15y. ~50% stage I-II.
  + 8y EFS 76→ 88%, 8y OS 89→ 100%.
    - RT benefit associated with bulky disease, advanced stage, B-sx, younger age.
    - CR is defined as the disappearance of all measurable disease.
  + Critique: ~60% with MC-HL (worse prognosis than NS, most common in Western hemisphere). 15% EFRT (11% inverted T, 4% mantle) due to extensive pre-chemo disease. ~50% < 15y and ~50% stage I-II; both of these cohorts have better prognosis with CMT, so consolidative RT should be standard for these patients.

* **GHSG HD9** [[Engert JCO '09,](http://ascopubs.org/doi/abs/10.1200/JCO.2008.19.8820?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed) [von Tresckow '18](https://www.thelancet.com/pdfs/journals/lanhae/PIIS2352-3026(18)30140-6.pdf)]: **8c COPP-ABVD vs. BEACOPP vs. BEACOPPesc**. 70% got RT.

BEACOPPesc appears to be standard of care, although not compared to standard ABVD.

* + 1196 IIB-IV pts. MFU 10y.
  + 10y FFR 64→ 70→ 82%. 10y OS 75→ 80→ 86% a/w AML/MDS of 0.4→ 2.2→ 3.4%.
  + 15y PFS of 57→ 67→ 75%.
  + 15y OS 72→ 75→ 81%.
  + 15y second primary malignancies 7→ 13→ 11%.
  + Keep in mind this was not compared to standard ABVD.

* **GHSG HD12** [[Borchmann JCO '11,](http://ascopubs.org/doi/abs/10.1200/JCO.2010.33.9549?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed) [von Tresckow '18](https://www.thelancet.com/pdfs/journals/lanhae/PIIS2352-3026(18)30140-6.pdf)]: 2x2. **8c BEACOPPesc vs. 4c/4c base ± 30 Gy** to initial >5 cm/PR.  
  Do not omit RT for residual disease, but RT may be omitted in CT-based CR even with initially bulky disease.

Non-inferiority of 4+4 was shown in long term follow up.

* + 1670 IIBX-III/IV pts. MFU 12y.
    - RT: Non-bulky (< 5 cm) and residual disease < 1.5 cm got no RT.
    - Patients with bulky disease having < 50% reduction in size got RT regardless of treatment arm. As a result, 11% of pts not assigned to undergo RT received it.
    - CR is defined as the disappearance of all measurable disease.
  + 5y FFTF for no RT / RT of ~87→ 90.4% (p=0.08) w subset demonstrating ~6% FFTF benefit in pts receiving RT w CT-based residual dz, while pts with CT-based CR did not have FFTF benefit with RT.
  + 5y OS ~91%.
  + 10y PFS for BEACOPPesc / "4+4" of 83→ 81%. 10y OS for BEACOPPesc / "4+4" of ~87%.
  + 10y PFS for residual disease ± RT of 83→ 90%.
  + 10y second primary malignancies for BEACOPPesc / "4+4" of 9→ 6%.
  + Disease progression 1.1→ 3.3% without improvement of treatment related deaths 3.4→ 2.4%.

* **GHSG HD15** [[Engert Lancet '12](https://www.sciencedirect.com/science/article/pii/S014067361161940)]: **BEACOPP-14 x8c vs. BEACOPPesc x6-8c ± 30 Gy RT if PET PR.**   
  This is the first large PET RCT! Until [[HD 18](#bb61bt2imnn3)], this was the only trial to incorporate PET-guided RT in advanced stage HL.

Unfortunately, all of the PET de-escalation data for advanced disease only exists in the context of BEACOPP.

Overall survival detriment with 8c vs 6c of BEACOPP attributable to treatment related deaths and SMN.

Patients who have PET(+) residual disease after chemotherapy are at high risk of progression or relapse.

* + 2182 advanced stage pts. BEACOPP-14 x8c vs. BEACOPPesc x6-8c ± 30 Gy RT if PET PR. MFU 8y.
    - RT: 30 Gy to **> 2.5 cm** residual PET positive masses (**This trial was before Deauville**). 75% PETF(-).

This reduced the overall percentage of pts receiving RT from 70% in HD 9 to 11% in HD 15.

12 month NPV for PET of 94.1% even with CT-based residual mass present .

* + 4y PFS for PET +/- of 86→ 93%, irrespective of tumor size.
  + 5y OS for BEACOPPesc 8c / 6c of 92→ 95%.
  + BEACOPP-14 without AML or MDS based on a MFU of 3y. This is a short follow up.
  + BEACOPP-14 statistically noninferior to 8c BEACOPPesc.

* + PET(+) > 2.5 cm (n=739) with ± 40% relative reduction with 1y progression of 5→ 23% [[Kobe JCO '14](https://www.ncbi.nlm.nih.gov/pubmed/24799482)].

* **SWOG 0816** [[Press JCO '16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4966513/), [Ha Leuk Lymph '20](https://pubmed.ncbi.nlm.nih.gov/32452714/)]: **ABVD x2c→** ABVD x4c, **PET2+ switched to escBEACOPP x6c**.

No RT given despite 20% > 10 cm. The Ha paper simulated RT use as per HD15 criteria of PET + residual disease ≥ 2.5 cm.  
For advanced disease, more likely to fail at new sites when chemo alone is used, but patients with new sites of failure likely had a component of residual disease at the original sites as well.

* + 336 HIV- stage **III-IV**. 50% IPS 0-2, 50% IPS 3-7. 18% PET2+, 82% PET2-. PET3 at EOT.
    - 20% > 10 cm, 60% B symptoms.
    - PET2(+): Of the 60 pts, 11 declined to switch to eBEACOPP.
    - PET2(-): Continue ABVD up to 6 cycles.
  + 2y OS 98%, 2y PFS 79%. 2y PFS for PET2(+) of 64%. *This is very high!*
  + In those who switched over, 55% achieved CR, 40% PR, 5% SD.
  + G4-5 toxicity w BEACOPP of 37→ 86%. *1 tx related death in PET2- arm, 2 on PET2+ arm.*
  + Relapse in original site / new site / both of 32→ 53→ 6%.
  + Median baseline size of lesions that recurred at the original site of 3.5 cm. Only ~25% were >5 cm and only two (9.5%) were >10 cm at the initial presentation.
  + Potential impact of consolidative RT: A secondary analysis of SWOG 0816 [[Ha Leuk Lymph '20](https://pubmed.ncbi.nlm.nih.gov/32452714/)]
    - Among 49 PET3+ S0816 patients, RT would have raised the 2y PFS from 31% to 50-58% using three residual disease cutoffs (1.5, 2.0, 2.5 cm) and assuming 80-90% in-field control rates.

* **RATHL** [[Johnson NEJM '16](https://www.nejm.org/doi/full/10.1056/NEJMoa1510093)]: **PET→ ABVD x2c. 1) PET2(-): ABVD vs. AVD x4c**. **2) PET2(+): BEACOPP\***.

Although non inferiority margin was negative, omission of bleomycin favored due to decreased pulmonary toxicity.

Only 3% of patients in this study received radiation therapy. This is likely why the 3y PFS is less than 90%.

Around 15-20% of patients who are PET2 negative will relapse after ABVD! Recommend accounting for CT residual.

* + 1119 patients. Advanced HL, although over 40% stage II patients. MFU 3.5y.
    - \*BEACOPP regimens varied:
      * BEACOPP-14 x4c→ PET3. If PET3(-), BEACOPP-14 x2c.
      * eBEACOPP x3c→ PET3. If PET3(-), eBEACOPP x1c.
      * All PET3(+) patients received radiation or salvage regimen.
    - RT "at discretion" or delivered in patients in PET2(+) cohort who had positive findings on the 3rd PET/CT.
    - **PET2(+) = D4+**.
  + For PET2(-) (omission of Bleo), 3y PFS 86→ 84% and 3y OS ~97%. *There is less pulmonary toxicity with AVD.*
  + For PET2(+), 3y PFS 67%. 3y OS 88%.
    - 75% of patients had negative findings on the final PET/CT scan (\*before final eBEACOPP/BEACOPP-14).
  + G3+ toxicity ≥ 60%.

* **GHSG HD18** [[Borchmann Lancet '18](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)32134-7/fulltext)]: **eBEACOPP x2c→ PET2**. **PET2(-)**: **2c vs. 6c**/8c. **PET2(+)**: **6c ± Ritux**.

PET2 Deauville 1-3 patients have a high negative predictive value and may benefit from only 4c of eBEACOPP.

PET2 Deauville 4 patients need escalation of therapy and should be considered for at least 6c of eBEACOPP.

Radiation is considered for CT residual of ≥ 2.5 cm at PET2, and RT was delivered for PET final with ≥ 2.5 cm of CT-based residual with residual avidity. Around 33% of PET2+ patients received radiotherapy. The problem with utilizing additional cycles of BEACOPP in lieu of RT is the high rates of toxicity on this trial.

* + 1945 patients. Advanced stage, although 14% stage II. MFU 5.5y.
    - If nodal CT residual ≥ 2.5 cm at PET2, then PET repeated after chemo completion.
    - In all groups, 30 Gy RT recommended for residual ≥ 2.5 cm with FDG uptake at the end of therapy.
    - After completion of chemotherapy, 33% of PET2+ and 3% of PET2- cohorts received RT.
    - **PET2(+) = D3+**.
  + For PET2(-), 5y PFS ~91%. 4c of BEACOPPesc had roughly half the toxicity of 6-8c of BEACOPPesc.
  + For PET2(+), 5y PFS ~89%. Interim futility analysis demonstrated no benefit of adding rituximab.
    - 3y PFS for D3 / D4 of 96→ 88%.
  + G3+ toxicity 95%!

* **GITIL/FIL 0607** [[Gallamini JCO '18](http://ascopubs.org/doi/full/10.1200/JCO.2017.75.2543?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed)]: **ABVD x2c→ PET2+ switched to escBEACOPP** ± rituximab.  
  Consolidative RT for disease ≥ 5 cm in the setting of PET2(-), PET6(-) appears to have no benefit.

There is a potential for a nearly 10% 3y PFS benefit for size >10 cm (20% of all on trial).

BEACOPP appears to be a poor salvage option for Deauville 5.

* + 782 pts. **IIB-IVB**. 150 PET2+ (19%), 630 (81%) PET2-.
    - RT: Pts ≥ 5 cm at dx (60%) and CR on PET2- were randomly assigned to ± 30 Gy RT.
    - PET2(+) (**D4+**): escBEACOPP x4c→ BEACOPP x4c ± rituximab.
    - PET2(-) (**D1-3**): Continue ABVD up to 6 cycles.
  + 3y PFS for PET2 positive / negative of 60→ 87%.
  + 3y PFS for PET2+ switched to escBEACOPP ± rituximab ~60%.
  + 3y PFS for PET2- and PET6- with ≥ 5 cm mass at dx ± RT of ~95%. *Doesn't break down > 1.5 - 2.5 cm residual.*
  + 3y PFS for PET2- and PET6- with ≥ 10 cm mass at dx ± RT of ~86→ 94% (p=0.34).
  + 3y OS for PET2 positive / negative of 89→ 99%.
  + 3y PFS for deauville 5 / 4 of 35→ 73%. *Only 6% of the study population was D5, and BEACOPP sucks for that.*
  + G3-4 neutropenia for ABVDx 6c / 2c / BEACOPP 41→ 30→ 76%.
  + Death for PET2 - / + of 2→ 11%.

* **FIL 0801** [[Ricardi RTO '19](https://www.thegreenjournal.com/article/S0167-8140(19)30922-3/abstract)]: **ABVD x 6c→ PET6(-) ± RT to original bulk > 5 cm**.

Conclusion: Advanced stage HL patients after achieving complete metabolic response after ABVD x6c may benefit from the addition of consolidation RT to bulky lesions at baseline, regardless of the maximum diameter of the mass, with a PFS benefit ranging from 7-10% at 3 and 5 years.

* + 512 advanced stage HL. 354 had PET6(-), of whom 33% (n=116) were initially bulky.
  + Notably, 9 patients enrolled on the RT arm did not receive consolidative RT (physicians decision), with 5 of them relapsing during follow up.
  + Per protocol 5y PFS of ~82→ 90% (p=0.24). This did not reach statistical significance mainly because of the limited sample and number of events (13 vs. 5, respectively).
  + Did not comment on the size of the CT-based residual at RT (e.g., > 1.5 cm or > 2.5 cm).

* **ECHELON-1** [[Connors NEJM '18](https://www.nejm.org/doi/full/10.1056/NEJMoa1708984)]: **ABVD vs. A+AVD**.   
  A+AVD is superior to ABVD. For advanced stage HL, there is a trend to omit RT based on PET-based residual alone, not accounting for CT-based residual. This is a good example of an alternative chemotherapy regimen which is ridiculously expensive.  
  ABVD x6c costs $4,000, while ABV + BV x6c costs $300,000.
  + 1334 patients. Stage III-IV HL. MFU 2y.
    - A = Brentuximab Vidotin (Anti-CD-30).
  + 2y PFS 77→ 82%.
  + Hospitalization 28→ 37%.
  + G2+ peripheral neuropathy 9→ 20%. Pulmonary toxicity 3→ 1%.
* In the context of BEACOPPesc, RT is only required in PET-avid residual masses >2.5 cm.
* In context of ABVD, clinical data suggests RT to initially bulky to 25.2 Gy and residual disease to 30.6 Gy.
* In context of Stanford V, IFRT to 36 Gy should be given to all sites initially ≥ 5 cm and macroscopic splenic disease.

## 

## [Relapse or Refractory](#_h06kfryq1p0p) HL

Relapsed/refractory: 2nd line chemo ± RT ± transplant. Brentuximab (Anti-CD30) and PD1 inhibitors.

ILROG Guideline: Modern RT for Nodal NHL - Target Definition and Dose Guidelines [[Illidge IJROBP '14]](https://www.sciencedirect.com/science/article/pii/S0360301614000649?via%3Dihub). [RoR](#lwp1seqewhg3)

ILROG Guidelines: The Role of RT in Relapsed or Refractory Hodgkin Lymphoma [[Constine IJROBP '18](https://www.ncbi.nlm.nih.gov/pubmed/29722655)]

* For patients who were not irradiated, recurrences are rarely in new sites.
* Relapse in 5% early stage, 35% advanced stage. Around 10% of pts will have disease that is refractory to initial therapy.
* Gold standard = conventional chemo or high-dose chemo with autologous SCT.
  + Around 50% are salvageable with transplant. But not all respond to chemo and go to transplant, so overall only 1/3 of ppl are salvaged. This is a higher rate than patients with NHL.
* The majority of relapses occur within 3y of treatment.
* There is dogma that RT cannot manage chemo failures.
  + However, Josten's paper demonstrated 77% achieved CR w RT for relapse, with 5y FFTF 28% and 5y OS 51%.
* Belief that RT can improve FFR and potentially OS.
* Adverse prognostic features: Initial remission < 1y, stage III/IV at relapse, anemia.
* Indications for RT in first relapse:
  + Cytoreduction 36-45 Gy after salvage chemo or ASCT.
  + Consolidation 30-36 Gy after ASCT or salvage chemo.
* **ALLG HDNHL04/TROG 03.03** [[Wirth IJROBP '19](https://www.ncbi.nlm.nih.gov/pubmed/30553941)]: Prospective. **Peri-transplant RT** to disease sites at registration.  
  Radiation in the up-front setting has an important role in decreasing relapses.
  + 55 NHL (n=22) and HL (n=23) pts.
    - RT: 30 Gy IFRT. Delivered post-transplant. CR 30 Gy, while PD 36-40 Gy for HL and 40-50 Gy for NHL.
    - All relapsed/refractory sites treated. Contiguous equivocal sites included when safe to cover.
  + Original sites that were unirradiated have a 15-35% incidence of relapse in original sites.
  + Original sites that were irradiated have a 4-7% incidence of relapse in original sites.
* Following successful ASCT, give brentuximab (cat 1).
  + AETHERA [[Moskowitz Lancet '15]](https://www.ncbi.nlm.nih.gov/pubmed/25796459): **± Brentuximab** after ASCT for relapsed or refractory HL.
    - 329 pts. PFS 24→ 43 mo. ~OS.
    - NCCN recommends 1y of maintenance brentuximab following ASCT for refractory HL.
* KEYNOTE 087 [[Chen JCO '17](http://ascopubs.org/doi/full/10.1200/JCO.2016.72.1316)]: Single arm phase II. Relapsed/refractory HL.
  + 210 pts. CR 22%, ≥ PR 69%. 31 pts had response ≥ 6 mo.
* **KEYNOTE-204** [[Kuruvilla ASCO '20](https://meetinglibrary.asco.org/record/186007/abstract)]: Phase III. **Brentuximab-vedotin** (BV) **vs. Pembro**.

Another victory for Pembro in the HL realm. Does it blow anyone else's mind that these pts could have received hundreds of thousands of dollars worth of systemic therapy without ever having seen RT? Don't even get us started on [[ECHELON-1](#zgtm6b5xf2vm)] for stage III-IV HL. ABVD x6c costs $4,000, while ABV + BV costs $300,000 for a measly 5% PFS benefit at 2 years. What PFS benefit does RT add? Likely 5-10%, for a fraction of the cost of these agents. We suggest RT should be employed more often in the up-front and refractory setting, even for advanced disease. Initial bulk > 7 cm, and more importantly residual disease > 1.5-2.5 cm, should be taken into account regardless of PET response. [RoR](#2umqw59gv3o3)

* + 300 patients. Relapsed/refractory auto-SCT or ineligible for auto-SCT. Prior BV allowed (n=15). MFU 2y.
  + Median time of treatment 146→ 305 days.
  + MPFS 8→ 13 mo.
  + 12 mo PFS 35→ 54%.
  + ORR 54→ 66%. CR ~25%.
  + Median DOR 14→ 21 mo.
* **General treatment recommendations: Refractory/Relapsed HL.**

Deauville scoring for Hodgkin lymphoma in as few words as possible [[Zaorsky tweet](https://twitter.com/NicholasZaorsky/status/1226197121378004992?s=20)].

* + Second-line systemic therapy (ICE: Ifosfamide, carboplatin, etoposide)→ PET/CT.
  + If Deauville 1-3, high dose therapy + ASCT→ brentuximab x1y.
  + Deauville 4: ± ISRT with ASCT.
  + Deauville 5: No ASCT, give ISRT. Consider biopsy.
  + Recent ILROG guidelines to give 36-40 Gy pretransplant only to PET+ persistent disease.

## 

## [Toxicity](#_h06kfryq1p0p)

* 44 Gy associated with late toxicity.
* For the first 15 years, the greatest risk is from HD. Afterwards, the sequelae of tx dominates [Hudson JCO 16:3592-3600. '98].
* Acute: N/V, fatigue
* Subacute: Lhermitte's, pericarditis, pneumonitis (treat with slow prednisone taper over 2-3 mo, 1mg/kg).
* Late:
  + CHD as the first CVE increased by 7.4% for each 1 Gy increase to MHD [[1]](http://ascopubs.org/doi/abs/10.1200/JCO.2015.63.4444?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed).
    - MHD 20 Gy at 2.5 increase for CHD. Median interval of 19 years.
  + Hypothyroidism with > 45 Gy and within 5 years of treatment [[1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2677922/)]. Get annual TSH.
  + Decreased immunity (spleen)
  + Pulmonary toxicity
  + Infertility
* **Secondary malignancy**:
  + RR of 40 Gy 6.5, RR < 30 Gy 1.5.
  + Stanford regimen [[O'brien JCO '10](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4872329/)]: 15-25 INRT or inverted Y ± 10 Gy boost. Treated 1970-1990. SMN 17%: Breast, thyroid, sarcoma, leukemia (solid tumor RR 2x).
    - 17% risk at 20 years... Roughly 1% risk of SMN per year.
  + SMN [[Schaapveld NEJM '15](https://www.nejm.org/doi/10.1056/NEJMoa1505949)]: 3905 pts with ≥ 5y survival since tx between 1965 and 2000. MFU 20y.
    - Standardized incidence ratio (SIR) of 4.6 (1055 SMN in 908 pts).
    - Secondary AML dec due to less use of alkylating agents (AML RR 22x).
    - Secondary solid cancer risk was overall unchanged in most recent study period (1989-2000).
* Breast cancer risk varies by target volumes: Mantle→ mediastinal fields reduce incidence of secondary breast cancer
  + Median time to breast cancer 18 years, screening detects earlier stage disease [[Elkin JCO '11]](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3138631/).
  + 30y incidence of BrCa 14% in women dx with HL < 35y of age [[Sud JCO '17](http://ascopubs.org/doi/full/10.1200/JCO.2016.70.9709)].
    - Risk of all secondary rancers 1.3x higher if first degree relative with cancer, or for lung/CRC/breast risk of 3.3→ 2.1→ 1.8x difference. *Greatest risk for lung* [[Sud JCO '17](http://ascopubs.org/doi/full/10.1200/JCO.2016.70.9709)].
* **Neurocognitive deficits** in adult survivors of childhood HL [[Krull JCO '12](http://ascopubs.org/doi/full/10.1200/JCO.2012.48.2315)]: Lower sustained attention, short term memory, long-term memory, naming speed, and cognitive fluency. MRI demonstrated leukoencephalopathy in 53% of survivors and 37% had evidence of CV injury.

* **EORTC-LYSA Analysis of CVD after treatment for HL** [[Maraldo Lanc Heme '15](https://www.ncbi.nlm.nih.gov/pubmed/26686259)]:

There is an additive risk of cardiovascular disease with mediastinal RT and anthracyclines.

**One cycle of anthracycline is considered equivalent to 5 Gy mean heart dose**.

* + 1,919 patients treated from 1964-2004 completed the questionnaire. Median age at dx 30y. MFU 9y.
  + 1,238 first CV events were recorded in 703 patients: IHD (20%), CHF (12%), arrhythmia (16%), VHD (11%).
  + Mean heart dose per 1 Gy increases HR 1.015. This means 5 Gy heart increase is equivalent to 1c for anthracycline.
  + Dose of anthracycline per 50 mg/m2 increase in cumulative dose HR 1.077.

## [Treatment Planning](#_h06kfryq1p0p)

See INRT or ISRT in the [[General Treatment Planning](#_d5y4iwywaoda)] section. As of 2020, IFRT is effectively dead.

ISRT in Adult Lymphomas: An Overview of ILROG Guidelines[[Wirth IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/32272184)] [RoR](#8tnt1mw76a6)

Must-Read article from 2020: ILROG's [[Making Every Single Gray Count](#gq1ic3qggdvh)].

* RT doses have decreased over time, and become more focal (e.g. ISRT) [[Zhou IJROBP '19](#tc5njehmui33)].
* Supine, PET/CT sim with contrast, fuse pre-chemo PET. Oral contrast for A/P.
* Initiate RT around 3-4 weeks after completion of chemotherapy.
* If treating both sides of diaphragm (this pretty much never happens - med onc will given a million chemo regimens to avoid RT in advanced disease), traditionally needed to stage treatment with two week break in between to spare marrow/toxicities.
* Consider DIBH for mediastinal RT to decrease heart dose at the slight expense of breast dose [[Charpentier PRO '14](#kix.ywvjqqniy44m)].
* See INRT and ISRT in the General Heme [[Treatment Planning](#_d5y4iwywaoda)] section.
* See IFRT and RFRT in the [[old-school](#_kcw4xomlfoa)] section.
* See [[ILROG Guidelines](#as6ily3q2cfk)] for Pediatric Hodgkin's disease.
* **RT alone** (e.g., [[NLPHL](#a6rb8owckjee)]).
  + Involved regions: 30-36 Gy (30-35 Gy for NLPHL)
  + Uninvolved regions: 25-30 Gy
  + If RT alone, use large 3-5 cm margins (e.g. NLPHL when RT alone is primary modality).
    - NLPHL: CTV = GTV + minimum adjacent lymph nodes in that site + generous margin.
* **NCCN**

Caution: Newer [[ILROG guidelines](#gq1ic3qggdvh)] from 2020 recommend adjuvant RT after Deauville 2 responses! Why give more anthracyclines to avoid RT (typically twice as much) and obtain PET D3 response when we can easily keep the mean heart dose less than 5 Gy with RT? [[EORTC-LYSA analysis](#wd0qpuiowed7)].

Recall 21/14 was used in [[AHOD 0031](#kix.stbtgkiiae8k)]. However, there was a 20% rate of failure for [SER]. We should be considering doses higher than 21/14 in patients with CT residual - not just a "negative" PET/CT - after chemotherapy. NCCN says 15-25 Gy is ok for intermediate risk pediatric hodgkin's lymphoma.

* + Non-bulky ES-F dz w/ABVD: 20-30 Gy. Favor ABVD x2c → 20 Gy if PET2(-)/D1-2 per [[H10](#l3ma2fsoxgos)].
  + Non-bulky ES-F dz w/Stanford V: 30 Gy. Stanford is always 30 Gy.
  + Non bulky ES-U dz: 30 Gy.
  + Bulky disease: 30-36 Gy.
  + PET Deauville 3-4 post-chemo: 30-45 Gy
  + PET Deauville 5: Re-biopsy, consider up to 55 Gy if RT alone for DLBCL:
    - CR to salvage: 30-40 Gy.
    - PR to salvage: 40-50 Gy.
    - RT alone: 40-55 Gy.
* Residual lymphoma after chemo to 36-40 Gy.
  + If < CR, dose 30 Gy with boost to 36-40 Gy. Give 30 Gy to pre chemo + 1.5 cm cropped, then postchemo GTV.

## 

## [Follow up](#_h06kfryq1p0p)

* Breast screening q1y 8-10y after treatment or age 40.
* Lipid screen q3y.
* Greatest risk of hypoT within 5y of treatment, still could occur 20 years out.
  + TSH annual.
* H&P, CBC, ESR.
* CT N/C/A/P 6,12,24 mo.
* Do not routinely do PET.
* Baseline echo, stress test at 10 years.
* Carotid ultrasound if neck treatment.

## [Future Directions](#_h06kfryq1p0p)

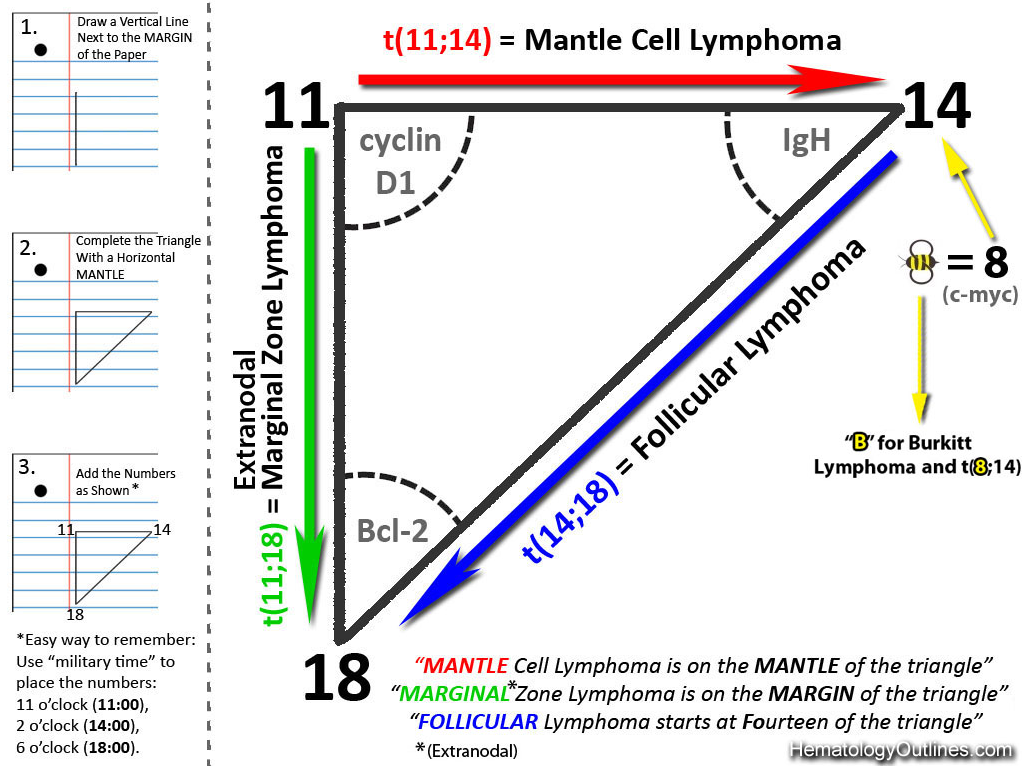
See NCTN Trial Portfolios by Disease Site: [[Lymphoma](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Lymphoma_Trials.pdf)]

S1826 can avoid radiotherapy all together depending on the investigator.

* **S1826** [[NCT03907488](https://clinicaltrials.gov/ct2/show/NCT03907488)]: Phase III. **Nivo/AVD vs. Brentuximab Vedotin/AVD**.
  + Newly diagnosed, untreated stage III/IV Hodgkin Lymphoma for patients ≥ 12y old.
  + AVD: Doxorubicin, Vinblastine, Dacarbazine.
  + Investigators must declare intent for radiotherapy, even if PET6 is positive, RT may still be avoided.
* **E4412** [[NCT01896999](https://clinicaltrials.gov/ct2/show/NCT01896999)]: Phase I/II. **Combination of Ipilimumab, Nivolumab and Brentuximab Vedotin**.
  + Relapsed or refractory Hodgkin Lymphoma.
* **Summary of HD 16, 17, 18**:  
  Powerpoint with initial results of HD 16-18 [[Borchmann GHSG '18](https://oncologypro.esmo.org/content/download/176395/3227371/version/1/file/2018-Preceptorship-Lymphoma-1st-Line-Peter-Borchmann.pdf)].
  + [[HD 16](#kix.cdurj53xisqs)]: early stage favorable, tried ABVD x2c and observation if PET2(-). *PFS detriment when omitting RT.*
  + [[HD 17](#kix.vjvgvzlylzh5)]: early stage favorable, tried "2+2" and omission of RT if PET4(-). *Awaiting results.*
  + [[HD 18](#kix.3ymc4q9jg3po)]: advanced stage, tried BEACOPPesc x4c-8c ± Rituximab. Consider RT for CT-based residual ≥ 2.5 cm.

* **GHSG HD17** [[NCT01356680](https://clinicaltrials.gov/ct2/show/NCT01356680)]: BEACOPP/ABVD **"2+2"**→ **Control: IFRT 30 Gy** vs. **PET4(-) Obs**. PET4(+) INRT 30 Gy
  + Early stage, unfavorable (resembling [H10U](#penhg2fsn5t2)).
* **GHSG HD21** [[NCT02661503](https://clinicaltrials.gov/ct2/show/NCT02661503)]: Advanced stage HL. Radiation utilized for CT residual ≥ 2.5 cm!
  + eBEACOPP x2c. PET2(-): x2c. PET2(+): x4c.
  + BrECADD x2c. PET2(-): x2c. PET2(+): x4c.
* Future directions: Account for CT residual > 2.5 cm!!

# [Non-Hodgkin Lymphoma](#_e4a3jnknxfj8)



B symptoms were eliminated from the staging of NHL.

CHOP was approved in 1993.

Rituximab was approved in 1997.

See NCTN Trial Portfolios by Disease Site: [[Lymphoma](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Lymphoma_Trials.pdf)]

Radiotherapy for NHL [[Imber and Yahalom Cancer J '20](https://pubmed.ncbi.nlm.nih.gov/32496455/)]

[**StatPearls: Burkitt's Lymphoma**](https://www.ncbi.nlm.nih.gov/books/NBK538148/) *Last update: 6/15/2019.*

[**StatPearls: Follicular Lymphoma**](https://www.ncbi.nlm.nih.gov/books/NBK538206/) *Last update: 6/26/2019.*

[**StatPearls: Mantle Cell Lymphoma**](https://www.ncbi.nlm.nih.gov/books/NBK536985/)*Last update: 2/2/2019.*

**eContour**: [[MALT (conjunctiva)](http://econtour.org/cases/99)], [[MALT (lacrimal gland)](http://econtour.org/cases/98)], [[MALT (parotid)](http://econtour.org/cases/46)], [[Follicular (inguinal)](http://econtour.org/cases/41)]

**ARRO**: [[DLBCL case](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/HeadNeckDLBCL-NGT.pdf), [contour](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/HeadNeckDLBCL-NGT-Contour.pdf)], [[Orbital MALT](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/Orbital.pdf)]

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| Making Every Single Gray Count: ISRT Delineation Guidelines for Hematological Malignancies [[Dabaja IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/31928641)]. [RoR](#gq1ic3qggdvh)  **There are [**[**many problems with Lugano**](#kix.7c6l4uvk94al)**] PET-guided response which pays no attention to CT-based residual!**  **ASCO Guideline:** [**Hepatitis B Virus Screening for Pts with Cancer Before Therapy PCO Update**](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/supportive-care-and-treatment-related-issues#/9811) *May 11, 2015*   * **Test for HBV if anti-CD20** (e.g. Rituximab) **or SCT planned**. Also screen if risk factors for HBV. * Screening should include HBsAg and anti-HBc (core Ab)   + Reactivation can occur if both surface Ag and core Ab positive, or only core Ab positive.     - If only core Ab positive, may choose to monitor w HBV DNA and ALT levels.   + Either anti-HBc or anti-HBc IgG (not IgM) should be used.   + Start antiviral tx for surface Ag and core Ab positive, if only core Ab positive then treatment may be administered if soon to start cancer tx associated with high risk for HBV reactivation, or monitor HBV DNA and ALT.   **ILROG Guideline: Modern RT for Nodal NHL - Target Definition and Dose Guidelines** [[Illidge IJROBP '14]](https://www.sciencedirect.com/science/article/pii/S0360301614000649?via%3Dihub). [RoR](#lwp1seqewhg3)  **ILROG Guideline: Modern RT for Extranodal NHL - Field and Dose Guidelines** [[Yahalom IJROBP '15]](https://www.sciencedirect.com/science/article/pii/S0360301615000504?via%3Dihub). [RoR](#3ulp2e2jakqh), [PCNSL](#kix.mmiq0lal9y9s)  **ILROG Guideline: Modern RT for Primary Cutaneous Lymphomas: Field and Dose Guidelines** [[Specht IJROBP '15](https://www.sciencedirect.com/science/article/pii/S0360301615000279?via%3Dihub)]. [RoR](#_buun9ubd3cdd)  **ILROG Guidelines: Role of RT in Patients With Relapsed/Refractory DLBCL** [[Ng IJROBP '18]](https://www.sciencedirect.com/science/article/pii/S0360301617341871?via%3Dihub). [RoR](#_brilw0sh9mf2)  **ISRT in Adult Lymphomas: An Overview of ILROG Guidelines**[[Wirth IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/32272184)] [RoR](#8tnt1mw76a6)  **Newer [**[**ILROG guidelines**](#gq1ic3qggdvh)**] from 2020 essentially highlight the ease and importance of mean dose of OARs less than 5 Gy!**  TL; DR - 5 Gy isodose lines matter! Regardless of whether it is pediatric or adults, HL or NHL.  **Radiotherapy for NHL** [[Imber and Yahalom Cancer J '20](https://pubmed.ncbi.nlm.nih.gov/32496455/)]   * RT use for DLBCL from 2000 / 2012 declined from 47→ 32%. * **LS-Aggressive NHL**: [[SWOG 8736](#q7zy3uortpgx)] established the role of CMT in the pre-rituximab era, where non bulky stage I-IIE received 8c CHOP vs. 3c CHOP→ CRT to 40-55 Gy. Initial studies demonstrated superior outcomes and less toxicity with CMT, but persistent and delayed relapses resulted in equivalent outcomes in the long-term update. [[SWOG 0014](#59m21epibzi1)] established 3c R-CHOP followed by IFRT as standard of care for LS-DLBCL with 1+ IPI risk factor. Modern guideline-recommended doses have decreased to 30 Gy, and ISRT is now utilized.   + **Favorable LS-DLBCL**: [[LYSA 02-03](#ptyy03dwjkpi)] demonstrated RT to salvage partial response in non-bulky LS-DLBCL or PET4 regression > 50% but persistent positive PET or IPI of 1 or more received IFRT, which highlights the ongoing need for risk-adapted CMT. [[FLYER](#v15wcyq666sd)] demonstrated R-CHOP x4c→ R x2c alone to be standard of care for favorable nonbulky DLBCL. However, RT should be considered for residual disease, extranodal (e.g. skeletal, primary gastric, or thyroid DLBCL), non-chemo candidates, or complete metabolic response is in doubt.   + Bulky disease: See [[RICOVER-noRTh](#amzolllp07ku)] (patients > 60y), [[UNFOLDER](#kix.jygmd2npyuiv)] (patients 18-60).   + Extranodal disease: Irradiated in [[UNFOLDER](#kix.jygmd2npyuiv)], while contralateral scrotal irradiation to 30.6 Gy is well-established.   + Geriatric patients: RT may truncate the number of R-CHOP cycles. * **Advanced aggressive NHL**: The role of interim PET remains unclear. However, patients with initially bulky disease (≥ 7.5 cm) and PET6- scans may receive chemo alone [[OPTIMAL > 60](#6enjiip2ylxf)]. However, special attention should be paid to CT-based residual. * **Relapsed/Refractory aggressive NHL**: See Table 3 for early evidence supporting RT prior to CART infusion.   **DLBCL**  Although studies cited below delivered 36-50 Gy, 30 Gy may be reasonable per [[Lowry RTO '11](#kix.k3nodad2fzof)]  IPI 0, Limited stage, < 7.5 cm   * R-CHOP x4c if PET3 D1-3 [[SWOG 1001](#ggy7hqxhpbxx)] or PET4 D1-2 [[Lysa 02-03](#ptyy03dwjkpi)]; R-CHOP x4c→ R x2c [[FLYER](#v15wcyq666sd)].   + R-CHOP x3c + ISRT also acceptable [[SWOG 8736](#q7zy3uortpgx)].   IPI > 0, Limited stage, < 7.5 cm   * R-CHOP x6c if PET4 D1-2 [[Lysa 02-03](#ptyy03dwjkpi)] or x4c if PET3 D1-3 [[SWOG 1001](#ggy7hqxhpbxx)].   + R-CHOP x3c + ISRT also acceptable [[SWOG 8736](#q7zy3uortpgx)].   Bulky disease > 7.5 cm   * R-CHOP x6c→ R x2c + 36 Gy to CT-based residual [[RICOVER-60-noRT](#amzolllp07ku)].   Bony involvement   * RT is recommended for all DLBCL with initial bony involvement [[Held JCO '13](#q9eht5r44i91)].   Advanced disease: R-CHOP x6c with RT for bulk, skeletal involvement, inadequate response to initial therapy.  **Aggressive NHL dose considerations**   * Upfront DLBCL after chemo: 30-40 Gy. Give 30 Gy if DS 1-3. Boost to higher doses if DS4. * Upfront double-hit DLBCL: Correct dose is unknown, but may lean toward the higher end of the dose spectrum when consolidating. * Upfront PMBCL:   + Avoid RT if given DA-R-EPOCH if possible.   + After R-CHOP x6, given 30-40 Gy depending on PET response. * Relapsed/refractory DLBCL:   + Localized disease, Bulky > 5 cm [[PARMA](#uj222yfr8s81)], incomplete response to salvage chemo or ASCT, skeletal involvement, critical sites where LC is important.   + Cytoreduction prior to ASCT: 40-50 Gy or higher if refractory.   + DS1-3 with salvage chemo and ASCT: 30-36 Gy. Residual avidity: 40-50 Gy.   + Transplant ineligible, curative intent: 45-55 Gy.   + Palliative intent with limited life expectancy: hypofractionated schedule of 8-30 Gy. |

* In 2017, 72k cases per year, 20k deaths. M:F 1.26:1.Incidence has doubled since 1970.
* Discontinuous spread is more common than Hodgkin's disease.Around 90% contiguous volumes w HL.
* Approximately 33% of NHL will present in an extranodal site.
* **Causative conditions**: Immunodeficiency, autoimmune, environmental (pesticides, solvents), Viral: EBV (NKT/Burkitt), HTLV-1, HHV-8, HCV (DLBCL and splenic MZL), H pylori (gastric MALT), C. psittaci (orbital MALT), RT with weak association, alkylating agents, previous CLL/Hairy cell (Richter's transformation to DLBCL in 5-10%).
* Anaplastic large cell lymphoma (ALCL) of childhood: CD30+ 100%, most have rearrangement of ALK gene.
* **Bulky = 7 cm**.
  + DLBCL 6-10 cm or 7.5 cm per [[UNFOLDER](#kix.jygmd2npyuiv)] study.
  + Hodgkin's lymphoma 10 cm, 7 cm per MSKCC/DFCI, or 6 cm for children's HL per AHOD 0031.
  + Follicular lymphoma 6 cm per [[FLIPI-2](#m710n950valy)].
* **Grouping**
  + **Old grouping**: **Low/Intermediate/High grade** by NCI in the 1970s[[Lancet '82](https://www.sciencedirect.com/science/article/pii/S0140673682904548?via%3Dihub)]
    - Low: G1-2 follicular, CLL/SLL, MALT.
    - Int: G3 follicular, mantle cell, GZL, DLBCL, T/NK cell, PTL, ALCL.
    - High: Burkitt's, lymphoblastic, double hit DLBCL.
    - Miscellaneous: MF, Histiocytic, Extramedullary plasmacytoma

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| **New grouping (WHO 2016 Classification):** **Aggressive vs. Indolent** [[Blood '16](http://www.bloodjournal.org/content/127/20/2375?sso-checked=true)] 70 distinct entities WHO 2016 does not attempt to differentiate into aggressive or indolent due to variable clinical behavior.   * **Think of DLBCL and G3 Follicular vs. "the rest"**. * Burkitt's, lymphoblastic and double-hit DLBCL worse. |

* **B-cell vs. T-cell and NK cell**:
  + B cell (85%): DLBCL 33% > follicular 20% > MALT = B-cell CLL 5-10% > mantle cell 5%.
  + T cell (15%): T/NK cell, PTCL 6% > MF < 1% < ALCL 2%. *T cell uncommon, but aggressive.*

## [Low grade](#_oqhi8xeg79db)

G1-2 follicular, **CLL**/SLL, **MALT**.

* **CLL/SLL**: 10-15% undergo Richter's transformation from SLL/CLL to DLBCL (enlarging spleen). MS 5-8 mo.
* See [[**MALT lymphoma**](#r4u8w3ltw8om)]section below.

### 

### [Follicular Lymphoma](#_tnvttp8r1v6b)

More likely advanced stage (80%), MS 5-7y. **t(14;18)**.

See [[FLIPI](#se1sppvzwblx)] or [[FLIPI-2](#m710n950valy)] for prognostication.

See [[Palliative RT for indolent lymphoma](#_eis4ebue02bk)], [[Indolent lymphoma: Curative RT](#_6xbiotie083x)], and [[Indolent lymphoma: Rituxan ± RT](#_6dcw107fl4k5)].

* Stage I-II 20%, Stage III/IV 80% (Stage III / IV of 20→ 60%).
* Histologic grades: 1 follicular small cleaved, 2 follicular mixed, 3 follicular large.
  + Grading based on % large cells or centroblasts/HPF.
  + G1 = 1-24% large cells or up to 5 centroblasts per HPF.
  + G2 = 25-50% large cells or 6-15 centroblasts per HPF.
  + G3A = > 50% large cells or > 15 centroblasts per HPF, centrocytes still present.
  + G3A = > 50% large cells or > 15 centroblasts per HPF, sheets of centroblasts. *Treat as DLBCL.*
* Watchful waiting for G1-2, stage I/II FL is appropriate [[Advani JCO '04](#1tteydwaz07k)], as ~50% of patients will avoid treatment at 15y. However, the rate of transformation to DLBCL can be as much as 20% (decreased to < 5% with RT [[Ruella](#oufz0rscwg32)]).
* Around 10-20% of early stage untreated (or Boom-boom) pts will transform to DLBCL [[Advani JCO '04](#1tteydwaz07k), [Haas JCO '03](#eapuffyqp109)].
* 5y PFS in [[PET/CT-ISRT era](#cexo7o7pardd)] for stage I / II follicular lymphoma of 74→ 49%.

Upstaging of FL occurs in 10-60% of patients with PET/CT. Prior to PET era,

* + Mostly distant failures. 25% DM (90% of all relapses). < 2.5% in field or marginal recurrences.
  + This high rate of failure with RT alone is why [[RT + induction Rituximab](#one00eoxa2hm)] makes a lot of sense for early stage FL.
* Although RT is the only curative modality, less than a quarter of patients will receive radiation up front. There is a preference towards watchful waiting or rituximab alone. NCCN now favors Rituximab monotherapy over RT, even for bulky disease.
* Advanced stage is considered incurable. Systemic therapy (GELF criteria) for symptoms, threatened end-organ function or cytopenias, bulky disease ≥ 7 cm, large disease burden. If symptomatic, palliative boom boom recommended.

## [Intermediate grade](#_oqhi8xeg79db)

**G3** follicular, mantle cell, GZL, DLBCL (e.g. GCB, **PMBCL**), T/NK cell, PTL, ALCL.

* **Grade 3 follicular**: Large cell follicular. Treated like DLBCL.
* **Mantle cell**: Commonly presents with spleen, BM, and GI involvement (EGD to r/o lymphomatous polyposis).
  + Associated with poor px, MS 3y. **t(11;14)**(q13;q32) translocation with overexpression of CCD1.
  + Stage I/II (rare): IFRT alone (30 Gy) + 2-3 cm margin.
  + Stage IIX/III/IV: (HyperCVAD alternating with HD-MTX + ARA-C) + Rituxan→ HD CTX + ASCR.
* See [[**Primary T-cell lymphoma**](#lycr0wjsgr1n)]in the CTCL section.
* See [[**Anaplastic large cell lymphoma**](#ox16tk8auwwq)] in the CTCL section.
* **Grey Zone Lymphoma** (GZL)
  + Very rare. Relatively new entity per latest WHO classification. Similar to [[PMBCL](#_i2b87da19gbv)], but in **young males** [[1](http://www.cancernetwork.com/oncology-journal/management-primary-mediastinal-b-cell-lymphoma-and-gray-zone-lymphoma)].
  + Features intermediate between DLBCL and classical Hodgkin lymphoma.
  + Commonly presents at an early stage with B symptoms and mediastinal involvement.
  + A high proportion are EBV positive.
  + None of the patients that received initial ABVD-like regimens achieved a CR.
  + Higher response rate in pts that received initial CHOP-like regimens, although the sample sizes are small.
  + Just like PMBCL, R-CHOP x 6 or **DA-EPOCH-R** x6c ± ISRT 30 Gy.
    - 5y EFS 66%, 5y OS 75%.
  + Due to rarity, we need more patients to determine optimal management.

### [PMBCL](#_pxlt9ck8u0wu)

* Thought to originate from thymic B cells. Most common in **young females** [[1](http://www.cancernetwork.com/oncology-journal/management-primary-mediastinal-b-cell-lymphoma-and-gray-zone-lymphoma)].
* Around 2/3 present with mass >10 cm, and around 1/3 present with SVC syndrome.
* Different clinical-pathologic entities (almost always positive for PD1/PDL1), younger age, role of RT controversial, if PET neg and non-bulky, can consider obs.
  + **Pembrolizumab in Relapsed/Refractory PMBCL** [[Armand JCO '19](https://www.ncbi.nlm.nih.gov/pubmed/31609651)]: **Pembrolizumab** up to 2y.   
    Pembro is associated with high ORR, durable activity, and manageable safety profile for rrPMBCL.
    - ORR 48% with 33% CR on KEYNOTE 013. MFU 2.5y.
    - ORR 45% with 13% CR on KEYNOTE 170. MFU 1y. Pembro 200 q3w up to 2y.
    - Median duration of response was not reached in either study.
    - Treatment-related AE in ~23%.
    - Among 42 pts, magnitude of 9p24 gene abnormality is associated with PD-L1 expression and PFS.
* May consider **DA-EPOCH-R alone** x6c [[Dunleavy NEJM '13](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4568999/)] although R-CHOP + RT remains standard of care.
  + 5y EFS 93%, 5y OS 97%, CR 96%.
  + Omission of RT if D1-3 after DA-EPOCH-R.
* Other tx: R-CHOP x6c + RT or R-CHOP x4c→ ICE x3c ± RT.
  + R-CHOP vs. R-EPOCH (no RT): PFS 66→ 83%, OS 76→ 94%.
* Addition of R to CHOP x6c appears to also benefit PMBCL to the same degree as in DLBCL [[MInT](#yuv9qplkh22y)].
* **IESLG-26** [[Martelli JCO '14](https://www.ncbi.nlm.nih.gov/pubmed/24799481), [Ceriani IJROBP '17](https://www.ncbi.nlm.nih.gov/pubmed/27839910)]: Prospective. **R + anthracycline based chemo→ PETF ± RT** (82%)

Although there is a low CMR, greater than 90% of pts are projected to be alive and progression free at 5y.

All D1-3 patients had no progression at 5y. There were no relapses in D4 after RT and anthracycline based chemo, suggesting adjuvant therapy is not needed.

* + 125 pts with 88 pts having PET results. PMBCL. MFU 5y.
    - Responses: D1-2 47%. D3 23%. D4 21%. D5 9%.
    - On secondary analysis of pts with PET results available (n=88), D1-3 defined as CR.

CR (D1-3) for ± RT of 74→ 89%. PETF performed after all therapy was completed.

* + - RT 30-42 Gy, commenced within 8w of last dose of chemo
  + After RT, 11% had persistent D4-5.
  + 5y PFS for D4-5 / D1-3 of 68→ 99%, 5y OS 83→ 100%.
  + For ± D1-2, 5y PFS 92→ 98% and 5y OS 91→ 100%.
  + All D5 patients had progression in the field and died.
* **NIH** [[Dunleavy NEJM '13](https://www.nejm.org/doi/full/10.1056/NEJMoa1214561)]: Phase II. **DA-R-EPOCH** alone.  
  DA-EPOCH-R results in excellent outcomes, suggesting routine RT may not be needed.
  + 51 PMBCL pts. Median 30y. Median tumor 11 cm. 30% Stage IV. MFU 5y.
    - Pts with reduction of mass ≥ 20% between 4-6c received 8c.
    - Pts with reduction of mss < 20% between 4-6c discontinued after 6c.
  + 5y EFS 93%. 5y OS 97%.
  + This study quites a 100% NPV and 17% PPV for PET, but only performs a biopsy (n=3/18).
  + At 10-14y follow-up, 2 pts (4%) relapsed and were disease free with salvage RT.

### [NKT cell lymphoma](#_pxlt9ck8u0wu)

Locally aggressive, extranodal. Strong association with **EBV**.

ILROG Guideline: Modern RT for Extranodal NHL - Field and Dose Guidelines [[Yahalom IJROBP '15]](https://www.sciencedirect.com/science/article/pii/S0360301615000504?via%3Dihub). [RoR](#3ulp2e2jakqh), [PCNSL](#kix.mmiq0lal9y9s)

* Most commonly nasal cavity or paranasal sinuses, also may occur in waldeyer's ring.
* Give 50 Gy to gross disease, nasal cavity and paranasal sinuses if CCRT, > 50 Gy if RT alone.
  + Unilateral nasal cavity: Cover bilateral NC, ipsi maxillary sinus, bilateral ethmoids, hard palate.
  + Bilateral nasal cavity: As above but bilateral maxillary sinus.
  + Posterior nasal aperture: Include entire NPX.
  + Extension into anterior ethmoid sinus: Cover posterior ethmoid sinuses.
  + Cover involved lymph node levels if stage IIE.
* Stage IE/IIE: Early/up-front RT is key.
  + Concurrent RT 50 Gy + DeVIC x3c. Dex, VP-16 (etoposide), ifos, carbo.
  + Or cis-RT (40-52.8 Gy)→ VIPD chemo. VIPD = VP-16, ifosfamide, cisplatin, and dexamethasone.
  + Unfit for chemo = RT alone ≥ 50 Gy + 10 Gy boost.
* **Japan** [[Yamaguchi JCO '17](http://ascopubs.org/doi/10.1200/JCO.2016.68.1619)]: Retro.  
  RT concurrently with DeVIC leads to favorable outcomes.
  + 358 pts from 31 institutes. 2000-2013. Nasal NKT cell lymphoma. 72% localized. MFU 5.5y.
    - RT DeVIC was utilized in 66% of localized cases.
    - L-asparaginase most commonly used for advanced, only 30%.
  + 5y OS for localized / advanced of 68→ 24%.
  + 5y OS for RT-DeVIC of 72%, 5y PFS 61%.
  + IL-2 is a prognostic factor for worse OS and PFS.
* **JCOG 0211** [[Yamaguchi JCO '09](https://www.ncbi.nlm.nih.gov/pubmed/19805668), ['12](http://ascopubs.org/doi/full/10.1200/JCO.2012.45.6541)]: Phase I/II. **50 Gy RT-DeVIC**.   
  RT concurrent with DeVIC has excellent local control and low toxicity.
  + 33 pts. Nasal NKT cell lymphoma, Stage I-IIE. MFU 5y.
    - CTV = GTV + 2 cm and entire NC and paranasal sinuses. Stage IIE disease also included cervical lymph nodes.
    - DeVIC chemo: Dex, VP-16 (etoposide), ifos, carbo x3c.
  + 2y OS for historical RT alone control / JCOG0211 of 45→ 78%.
  + 5y OS for historical RT alone control / JCOG0211 of 40→ 70%
  + CR 77%, ORR 81%.
  + Acute G3 mucositis 30%. Late G1-2 of the eye in 33%.
  + 5y PTV control rate 94% (Only 2 in field failures).
* **Korea** [[Kim JCO '09](https://www.ncbi.nlm.nih.gov/pubmed/19884539)]: Phase II. **40/20 + concurrent VIPD**.
  + 30 pts. Nasal NKT cell lymphoma, Stage I-IIE. 2006-2007.
    - RT 40/25 to mass plus margin, nodes optional.
    - Concurrent CDDP 30 + adjuvant etoposide, ifosfamide, cisplatin, Dex q3w x3c.
  + After CCRT, CR 83%, ORR 80%.
  + 3y OS 83%. 3y PFS 85%.

## [High grade](#_oqhi8xeg79db)

See [[DLBCL in the Pre-rituxan era](#_uiplve43ogrb)], [[DLBCL in the Rituxan era](#_ltbtdniqvsh4)], [[PET adapted therapy](#_876zy8ls1q7k)] and [[Relapse or Refractory NHL](#_brilw0sh9mf2)].

Burkitt's, lymphoblastic, **double hit** DLBCL.

* **Burkitts**: 4:1 M:F. t(8;14) b-myc→ IgH.
* **DLBCL**: MC NHL accounting for 33% of NHL.
  + Only 30-40% present as stage I-II. Extranodal disease is common.
  + GCB vs. ABC vs. PMBCL:
    - **GCB** does best. 5y OS 64%.
    - **PMBCL**: Great prognosis. Check PDL1 mutation to differentiate if secondary (+ = PMBCL).
    - **ABC**: Older. Worse. Males. Activation of NFκB - 5y OS 34%.
  + **"Double hit"** with **MYC** breakpoint and another break at **BCL-2** and/or **BCL-6**.
    - FISH analysis important for "double hit" MYC breakpoint at 8q24, and another break at BCL2.
      * Present in 2-12% of DLBCL, associated with higher proliferative index and poor outcome.
  + R-EPOCH appears to have no PFS or OS benefit and increased toxicity over R-CHOP [[CALGB 50303](#wd0qpuiowed7)].

### [Testicular Lymphoma](#_yo7zrvnuvmmp)

* Primary testicular lymphomas are around 0.6% of all lymphomas.
* Around 80% are DLBCL. Common in men >60y.
* Stage I-II 70% of the time.
  + Only 50% received RT from 1980-2005.
* Scrotal relapse without RT at 3 / 15y of 15→ 42%.
* **IELSG-10** [[Vitolo JCO '11](https://www.ncbi.nlm.nih.gov/pubmed/21646602)]: Phase II. **R-CHOP21 x6-8c + IT-MTX and 30 Gy RT to contralateral testes**.
  + 53 pts. Untreated stage I-II primary testicular lymphoma. MFU 5.5y.
    - RT: 30 Gy to contralateral testes, 30-36 Gy for regional lymph nodes.
  + No patients relapsed in the scrotum.
* Treatment fields
  + Usually single electron field. Frog Leg position. Penis taped to abdomen. Scrotum supported by and immobilized with bolus underneath and on the sides. Electron energy is based on measured thickness. Bolus may be placed anteriorly.
  + Non-coplanar parallel opposed photons with better dose uniformity. Utilize 1 cm bolus with a shelf of styrofoam between legs. May use three bags of water 2/3 full with dilute contrast. Place one bag on top of styrofoam and each laterally to scrotum. Bolus on top to flatten bags. Measure water in each bag to keep consistent. No air in bags.
  + Treatment is the entire scrotum, not just contralateral testes.

## [Staging/Workup](#_oqhi8xeg79db)

* No B symptoms used in NHL staging.
* E staging: Sites that are extranodal, but not extralymphatic (not E): Waldeyer's ring, thymus, spleen.
  + Extralymphatic: Bone, liver, lung.
* PCR for T-cell receptor gene rearrangements and IgH amplified.
* FISH for double and triple hit lymphoma: MYC, BCL2, BCL6.
* B-cell markers: CD19-22, **Pax5**, **CD79a**.
* T-cell markers: CD2-7, CD43, CD45R0.
* H&P, attention to duration/onset, B-sx, immunosuppression, HIV. Waxing/waning nodes suggest indolent/low grade.
* PE: KPS, comprehensive nodal exam, waldeyer's ring, organomegaly, nasopharyngolaryngoscopy prn.
* Labs: CBC,CMP, LFT, ESR, LDH, albumin, β2 microglobulin (FLIPI-2), **HBV** (Surface Ag and core Ab), HCV, HIV, pregnancy test, LP in select cases if high risk.
* Excisional biopsy. Core OK, not FNA as it does not show lymph node architecture.
* CT N/C/A/P or PET/CT. More than 20% of CT-stage I-II pts are upstaged with PET/CT [[Cheson JCO '16](http://ascopubs.org/doi/full/10.1200/JCO.2010.32.5225?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed)].
* Bilateral bone marrow biopsy.
* **LP**: Testicular, paranasal sinus, ≥ 2 extranodal sites with an elevated LDH (If 4-6 IPI risk factors including kidney/adrenal), HIV associated lymphoma, double expressor lymphoma (MYC > 40% and BCL2 > 50%).
  + LP with 4-8c of IT MTX for DLBCL for CNS ppx:
    - Paranasal sinus
    - Testicular
    - Epidural
    - Bone marrow with large cell lymphoma
    - HIV lymphoma
    - ≥ 2 extranodal sites with increased LDH
    - 4-6 NCCN risk factors for CNS disease: IPI (APLES) + K (Kidney/adrenal gland involvement).
      * Low 0-1, Int 2-3, High 4-6.
* MUM1: Lymphocyte-specific transcriptional factor, a member of the interferon regulatory factor (IRF) family, known to play a role in the regulation of gene expression in response to interferons and other cytokines.
* Peripheral smear for CLL:
  + SLL: LAD or splenomegaly w peripheral B-cells < 5 x 109 per liter.
  + CLL: monoclonal B-cells > 5 x 109 per liter.
* Fertility counseling

## [I**PI**: International prognostic index](#_oqhi8xeg79db)

Compare to [["B4-HEE 50"](#wh92t3r32ayx)] rules for early stage hodgkin's disease and [["SHAM-LAW"](#xidr2ay05j0t)] IPS-7 for advanced hodgkin's disease. Besides LDH, labs matter more for hodgkin's lymphoma than for non-hodgkin's lymphoma, and the age cutoff is younger (e.g. 45y).

Follicular lymphoma, however, does include Hgb < 12 (as opposed to IPS-7 hgb of < 10.5) and also β2 microglobulin.

* Only for intermediate and high grade NHL.
* IPI remains prognostic but does not account for genetics.

* **IPI** [[NEJM '93]](https://www.nejm.org/doi/10.1056/NEJM199309303291402?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov): **"APLES"** Age > **60**, ECOG PS ≥ **2**, LDH > ULN, >1 Extranodal group, Stages III-IV to estimate 5y OS.

Highest risk group has 5y OS around 25%, which is essentially doubled with the addition of rituximab [[R-IPI](#ersue7c57sk5)].

* + 1,274 pts. Aggressive nodal NHL, Stage I-II. If > 60y, see [[Age adjusted IPI](#ovbko4wdhxb1)] below.
  + 5y OS ranges from 75-25% for 0-1 or 4+ risk factors, respectively.
  + To obtain outcomes in the Rituximab era, add about 20% to each 5y OS.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| [**IPI**](https://www.nejm.org/doi/10.1056/NEJM199309303291402?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov)APLES | 5y OS\* | [**R-IPI**](http://www.bloodjournal.org/content/109/5/1857.long?sso-checked=true)APLES | [4y OS](http://www.bloodjournal.org/content/109/5/1857.long?sso-checked=true) | [**FLIPI**](http://www.bloodjournal.org/content/104/5/1258.long?sso-checked=true)NoLASH | 5y OS | **FLIPI-2** β-MASH | 5y OS |
| **0-1** | 75% | **0** | 95% | **0-1** | 90% | 0 | 98% |
| **2** | 50% | **1-2** | 80% | **2** | 80% | 1-2 | 88% |
| **3** | 40% | **3-5** | 55% | **3-5** | 55% | 3-5 | 77% |
| **4-5** | 25% |

\*Add ~20% to 75/50/25 above for addition of Rituximab (R-IPI).

* **R-IPI** [[Sehn Blood '07]](http://www.bloodjournal.org/content/109/5/1857.long?sso-checked=true): **"APLES"** Age > **60**, ECOG PS ≥ **2**, LDH > ULN, >1 Extranodal group, Stages III-IV.

Highest risk group has 5y OS > 50% illustrating improvement in outcomes with R-CHOP!  
This nomogram is from a single institution and is not externally validated (See NCCN R-IPI below).

* + 365 pts. DLBCL patients treated with R-CHOP.
  + Very good (0 factors): 4y PFS 94%, 4y OS 94%.
  + Good (1-2 factors): 4y PFS 80%, 4y OS 79%.
  + Poor (3-5 factors): 4y PFS 53%, 4y OS 55%.
* **NCCN R-IPI** [[Zhou '14](http://www.bloodjournal.org/content/123/6/837.long)]: **"APLES"** Age > 40/**60**/75, ECOG PS ≥ **2**, LDH 1/3, Extranodal, Stages III-IV.  
  Unlike R-IPI, this has been validated in an external cohort. Age is the best predictor, followed by LDH.
  + 1,650 pts treated in the Rituxan era.
    - Age 40-60: 1 point, Age 60-75: 2 points, age > 75: 3 points.
    - ECOG PS 2+: 1 point.
    - LDH 1-3: 1 point, LDH > 3: 2 points.
    - Extranodal: 1 point.
    - Ann arbor Stage III-IV: 1 point.
  + 5y OS for 0-1 / 2-3 / 4-5 / 6+ points of 96→ 82→ 64→ 33%.
  + 5y PFS for 0-1 / 2-3 / 4-5 / 6+ points of 91→ 74→ 51→ 30%.

* **Age-adjusted IPI** [[Shipp NEJM '93]](https://www.nejm.org/doi/10.1056/NEJM199309303291402?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov): **"PLS"** ECOG PS ≥ 2, LDH > ULN, Stages III-IV.
  + Used for patients under the age of 60.

* **Stage-adjusted IPI** [SWOG 8736 [Miller NEJM '98](https://www.nejm.org/doi/10.1056/NEJM199807023390104?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov), [Stephens JCO '16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5012710/)]: For stage I or II: Age > 60, PS 2, LDH, Stage II/IIE.
  + Low risk 0 or 1, otherwise high.
* E-IPI: Elderly IPI proposed. Used from E4494 data set, where the median age was 70y. However, R-IPI did not identify a good risk group, minimizing utility in > 60 yo.

* **FLIPI** [[Solal-Céligny Blood '04]](http://www.bloodjournal.org/content/104/5/1258.long?sso-checked=true): **"No LASH"** ≥ 5 Nodal sites, LDH > ULN, **Age > 60y**, Stages III-IV,  **Hgb < 12** g/dL.

See the [[Follicular Lymphoma](#_emzdxvpgn0rs)] section for more.

* + 4,167 pts with FL. Pre-Rituxan era! Use FLIPI-2 instead.
  + See table above for 5y OS, which ranges from 90-50% for 0 and 3+ risk factors, respectively.

* **FLIPI-2** [[Frederico JCO '09]](http://ascopubs.org/doi/abs/10.1200/JCO.2008.21.3991): **"β-MASH"** β-2 micro > ULN, BM involved, **Age > 60**, nodal Size > 6cm long axis, **Hgb < 12**  
  Notably, the FLIPI-2 does not include grade, PET/CT CR, or stage II disease, which influences OS [[1](https://onlinelibrary.wiley.com/doi/full/10.1002/cncr.25117),[2](https://onlinelibrary.wiley.com/doi/full/10.1002/hon.2437_10)].

Doesn't include LDH, number of nodal sites, or stage (but Marrow matters).

* + 2,035 newly diagnosed FL patients.
  + 5y OS for LR (0) / IR (1-2) / HR (3-5) of 98→ 88→ 77%; 5y PFS 80→ 50→ 20%.
  + See table above for 5y OS, which ranges from 100-80% for 0 and 3+ risk factors, respectively.
* **MIPI** for advanced-stage mantle cell lymphoma. "APLL"
  + Age (50-59 or ≥ 70=1, 60-69=2), PS ≥ 2=2, LDH (>0.67 ULN=1, >1=2, ≥ 1.5=3), Leukocytes (>6.7 =1, >10 = 2, ≥ 15 = 3).
  + 5y OS: LR (0-3) 70%, IR (4-5) 45%, HR (6-11) 10%.
* **INT E4494**: Median age 70. Rituxan improves RFS and OS to CHOP alone.

## [Chemotherapy / Systemic therapy](#_oqhi8xeg79db)

* **Rituxan** 325 mg/m2
* **CHOP** q3w: Cyclophosphamide 750mm2, Adriamycin 50mm2, Vincristine 1.4 mg/m2, prednisone 100 mg d1-5.
  + \*Lifetime max dose of adriamycin = 450 mg.
  + There is a suggestion of every cycle of adriamycin being equivalent to 5 Gy mean heart dose [[EORTC LYSA](#wd0qpuiowed7)].
* **Hyper CVAD**: Two alternating courses:
  + Course 1: Cyclo, Vincristine, Adria, Dex.
  + Course 2: **MTX**, **cytarabine**.
* **EPOCH**: CHOP + Etoposide.
  + Consider DA-EPOCH for PMBCL, although R-CHOP ± RT still first line.

* **CALGB 50303** [[Bartlett JCO '19](https://ascopubs.org/doi/10.1200/JCO.18.01994)]: **R-EPOCH vs. R-CHOP x6c**.  
  No benefit with R-EPOCH, increased toxicity.
  + 491 pts. DLBCL. 2005-2013. Stage II-IV. 75% stage III-IV, 50% stage IV. MFU 5y.
    - CNS ppx with IT MTX for pts w multiple extranodal sites, and elevated LDH or marrow invlmt.
  + 5y PFS ~78%. 2y OS ~86%.
  + PMBCL and double-hit DLBCL populations were small.
  + G3+ toxicity 98→ 78%.
* **Adoptive cell transfer**: Removes immune cells from pt, potentially altering them to target a cancer, growing *ex vivo* and re-infusing to the patient. There are three main sources of tumor-specific immune cells: 1) TILs 2) Ag-specific cells through adaptive immune systems and 3) Ag-specific cells which were genetically engineered.
* See the [[CAR T-Cells](#_q9ptcay0swp3)] section for more information on how to treat relapse/refractory NHL.

## [Palliative RT for indolent lymphoma](#_oqhi8xeg79db)

See the [[Low Grade Lymphoma](#_tnvttp8r1v6b)] section.

* **Low dose IFRT for indolent lymphomas** [[Haas JCO '03]](http://ascopubs.org/doi/full/10.1200/JCO.2003.09.542): Retro. **4/2 or 4/1**.   
  Boom boom has 60% CR, 2-4y TTLP depending on CR or PR to therapy.

Short course RT for palliation of stage III-IV follicular lymphoma has favorable outcomes.

* + 109 indolent pts w 304 symptomatic, recurrent sites. 90% G1-2 FL. ~50% bulky (≥ 5 cm). Failed systemic.
    - RT with 1.5 cm margins.
  + ORR 92%, 61% CR and 31% PR.In the retreatment setting this becomes 98% response with 70% CR, 30% PR.
    - Retreatment with low dose IFRT with selection bias as only offered to those who responded initially.

Compared to chemo: For recurrence, typically have to switch chemo instead of trying again.

Only the first chemo course w superior PFS. Suggests Boom boom to be given after first line chemo.

* + - Response reached in most all pts at the time of first follow up at 4-6 weeks. Patients note responses within 10d.
  + Median TTP 14 mo, median TTLP 25 mo.   
    More likely to develop new lesions elsewhere than fail locally (unless PR, then equivalent risk).
    - For CR, TTP 25 mo and TTLP 42 mo.
    - For PR, TTP and TTLP are equivalent at 10 mo, as more likely to fail locally with PR.
    - For transformation to DLBCL, median TTP only 3 mo regardless of if CR or not.
  + Probability of no progression at 1/2/3/5y of 40→ 33→ 25→ 10%.
  + Nearly 10% of patients transformed to DLBCL.
* 24/12 appears to be reasonable for indolent lymphoma [[Lowry RTO '11](#kix.k3nodad2fzof)], but 20% fail at five years (although Rituximab was not used in this study). Therefore, NCCN recommends 24-30 Gy for indolent lymphomas.

* **UK FORT** [[Hoskin Lancet '14]](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(14)70036-1/fulltext): Prospective, noninferiority. **4/2 vs. 24/12 for follicular or MZL**.Boom boom has 50% CR, 30% PR. Boom boom is not non-inferior to 24 Gy.  
  Around one quarter will fail locally in 2 years with boom boom.

Due to slow accrual, the trial opened up eligibility to both definitive and palliative patients.

* + 548 pts w 614 sites. 85% FL, 15% MAZL. 60% stage I-II. 50% with either previous RT or chemo. MFU 2y.
    - Around 20% of pts rec'd systemic chemo before local progression.
  + ORR 81→ 91%, CR 49→ 68%, PR 30→ 20%.
  + Shorter TTP with 4 Gy (HR 3.42). ~OS.
  + 26 mo LF 25→ 8%.
  + Acute G3-4 1→ 3% (only 4 and 8 pts, respectively), acute G1-2 25→ 57%.
  + Late G3-4 ~1%, late G1-2 23→ 37%.

## 

## [**Indolent lymphoma: Curative RT**](#_oqhi8xeg79db)

See the [[Low Grade Lymphoma](#_tnvttp8r1v6b)] and [[Orbital lymphoma](#_u3w4jkvaw541)] sections.

Radiation is the only curative modality for early follicular lymphoma.

Less than 25% of patients with early stage FL patients received upfront RT.

[[Watchful waiting](#1tteydwaz07k)] or rituximab monotherapy are increasingly recommended despite the fact up to 20% will transform to DLBCL.

* **NCDB analysis** [[Vargo Cancer '15](https://www.ncbi.nlm.nih.gov/pubmed/26042364)]: **Chemo ± RT**.

The use of RT is associated with an OS improvement of over 10%! Upfront RT best.   
MVA w propensity score matching demonstrated upfront RT to be independently associated with improved OS [HR 0.54].

Observation never has cured anyone, and chemotherapy alone is not curative.

RT remains the backbone of curative treatment.

* + 35,961 pts. Stage I-II G1-2 follicular lymphoma. 1998-2012. Stage I in 60%.
  + **RT use from 1999 to 2012 declined from 37→ 24%**. Rituximab was approved in 1997.
  + 5y OS 74→ 86% and 10y OS 54→ 68% w addition of RT.
* The use of RT is lowest in patients under the age of 45 and over the age of 75. Patients with the lowest burden of comorbidities stand to benefit the most from curative treatment.

* **UK multicenter** [Lowry [RTO '11]](https://www.sciencedirect.com/science/article/pii/S0167814011002052?via%3Dihub): **40-45 Gy vs. 24/12 (indolent) vs. 30/15 (aggressive).**There is no difference in ORR, LF, PFS or OS with reduced dose RT.

[[Boom Boom](#2ir15dd82frs)] is a useful alternative for indolent palliation, with only 25% local failure at 2 years.

This is a huge reason why 24-30 Gy is standard of care for indolent lymphomas, favoring the latter for aggressive lymphomas

* + 1,001 pts: 361 indolent sites (Follicular/MZL), 640 aggressive sites (DLBCL). RT alone, chemo→ RT, or palliation. Any stage receiving local therapy for definitive or curative treatment. 82% DLBCL, 67% Stage I-II. 10% rec'd Ritux
  + Indolent 5y LC ~77%. *This sub-optimal LC rate for indolent lymphomas suggests 24 Gy may not be adequate (although Rituximab was not well utilized). Therefore, NCCN recommends 24-30 Gy for indolent lymphomas.*
  + Aggressive 5y LC ~83% with 5y OS 66%
* **BC Outcome of curative RT for localized FL in pre-PET/CT era** [[Campbell Cancer '10](https://onlinelibrary.wiley.com/doi/full/10.1002/cncr.25117), [Lo ASTRO '19](https://www.eventscribe.com/2019/ASTRO/fsPopup.asp?Mode=presInfo&PresentationID=558925)]:  
  Nearly half of patients had distant metastasis. This is why PET/CT staging is crucial in the modern era.

Disease recurrence uncommon after 10y and rare after 15y.

At 15y, 44% of patients remained disease-free, confirming a cure is possible.

Reduction of RT fields to ISRT did not appear to impact relapse risk in the long term.

* + 237 stage I-II FL pts. Stage IA 76%. Grade 3A 12%. 5-10 cm 30%. 1986-06. **IRRT vs. INRT**. MFU 7→ 13y.
    - RT alone, ≥ 20 Gy. Around 1/3 were 30/10, while 1/3 were 35/20.
    - IRRT: Involved nodal groups + ≥ 1 adjacent uninvolved groups.
    - INRT: Involved nodal groups + **≤ 5 cm margins**.
  + PFS at 5y / 10y / 15y of 66→ 49→ 44%.
  + OS at 5y / 10y / 15y of 85→ 66→ 57%.
    - 10y OS for IRRT/INRT of 71→ 59%, but no DSS or PFS differences.
    - RF for PFS: lymph nodes ≥ 5 cm and male gender.
    - RF for OS: Age > 60y, elevated LDH, lymph nodes ≥ 5 cm, male grade 3A tumors.
    - Of the 124 first relapses, 9% occurred beyond 10y and 2% occurred beyond 15y.
    - First failures distant in 45%, IFF component in 6%.
  + Median TTP 34 mo. 98 pts (41%) developed recurrent FL or transformed lymphoma.
  + Distant relapse without IFF in 35% of pts at 7y, while 45% at 13y.
  + After INRT, only 1% develop regional-only recurrence.

|  |
| --- |
| **Treatment of early stage FL in the PET-CT era**   * **Clinical pearl**: **Upstaging of Follicular Lymphoma occurs in 10-60% of pts with PET/CT**. * Still, around one quarter of patients will fail distantly. This is why [[RT + induction Rituximab](#one00eoxa2hm)] makes a lot of sense. * **Solution: RT + Rituximab!** There is 100% CR with Rituximab with RT, while only 80% with Rituximab alone.   + Rituximab + RT decreases the rate of transformation by nearly 10 fold according to [[Ruella](#one00eoxa2hm)] (~20→ 2%). |

* **ILROG Outcome of curative RT for localized FL in PET-CT era** [[Brady Heme Onc '17](https://onlinelibrary.wiley.com/doi/full/10.1002/hon.2437_10), [Blood '19](https://www.ncbi.nlm.nih.gov/pubmed/30446493)]: Retro.

25% of patients will develop distant mets. This is why [[RT with induction Rituximab](#one00eoxa2hm)] makes a whole lot of sense.

There is a suggestion of ~10% improvement in OS as compared to the pre-PET/CT era!

* + 512 pts. Stage I-II FL, G1-3a. 80% stage I. Median FLIPI . RT dose ≥ 24 Gy, no prior Rx. Median 30 Gy. MFU 4y.
  + PET CMR (D1-3) of 86%.Only 50% had post-tx PET/CT. CMR is a complete metabolic response.
  + 5y LC 97.5%. < 2.5% in field or marginal recurrences. 25% relapsed distantly (90% of all relapses).
  + 5y FFP 69%, 5y OS 96%.
  + 5y PFS for stage I / II of 74→ 49%. RF for PFS: Stage II disease and lack of CMR.
* **Durable CR for Stage III FL in the PET-CT era** [[MacManus Cancers '20](https://www.ncbi.nlm.nih.gov/pubmed/32316464)]: **Wide-field RT (WFRT) 24-30 Gy**.

This data is highly suggestive of Rituximab + RT being curative treatment, with none of the 11 patients who received peri-radiation Rituximab experiencing relapse.

* + 33 pts. 1999-2017. 15 patients received planned systemic therapy (Rituximab up to 4 cycles in 11). Most < 5 cm (non-bulky). Half of patients had 4-5 involved Ann Arbor sites. Most received 30 Gy. MFU 9y.
  + 10y OS 100%. 10y FFP 75%. None of the 11 patients who received rituximab relapsed or experienced transformation.
  + PETF CMR (D1-2) in 100%.
  + All secondary malignancies occurred outside RT fields.

## [Indolent lymphoma: Rituxan ± RT](#_oqhi8xeg79db)

See the [[Low Grade Lymphoma](#_tnvttp8r1v6b)] section.

Radiation is the only curative modality for early follicular lymphoma.

Less than 25% of patients with early stage FL patients received upfront RT.

[[Watchful waiting](#1tteydwaz07k)] or rituximab monotherapy are increasingly recommended despite the fact up to 20% will transform to DLBCL.

* **PRIMA** [[Salles Lancet '11](https://www.sciencedirect.com/science/article/pii/S0140673610621757?via%3Dihub), ['17](http://www.bloodjournal.org/content/130/Suppl_1/486), ['19](https://www.ncbi.nlm.nih.gov/pubmed/31339826)]: Induction therapy (one of three regimens) **± Rituximab maintenance** x2y.  
  Watchful waiting is not recommended for patients with high tumor burden.

Maintenance Rituximab improves PFS, but the PRIMA study does not report the proportion of patients with bulky disease.   
RT with Rituximab has 100% CR and should be entertained, as can decrease [[transformation to DLBCL](#oufz0rscwg32)] to < 5%.

* + 1,217 FL pts with **high tumor burden**. 1,019 pts achieved a CR or PR. MFU 9y.
    - Req'd high tumor burden at least 1+ of: Bulky dz > 7 cm, 3 separate nodes 3 cm or more, symptomatic splenic enlargement, organ compression by tumor, pleural or peritoneal effusion, raised serum concentrations of LDH or β-2 microglobulin, or presence of B-symptoms.
    - Does not tease out how many patients were bulky.
  + 3y PFS 58→ 75%. 6y PFS 42→ 59%. MPFS 4→ 10y.
  + 2y CR or unconfirmed CR 52→ 72%.
  + No difference in OS. 10y OS ~80%.
  + G3-4 17→ 24%.
  + 8.5% transformed to DLBCL in 10 years. Compared to 2% at 10 years with Rituxan + RT [[Ruella](#oufz0rscwg32)].

* **Stage I-II low grade FL** [[Advani Stanford JCO '04]](http://ascopubs.org/doi/abs/10.1200/JCO.2004.10.086?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): Retro. **Watchful waiting**.

Transformation to DLBCL of 20% if observed. Around 50% of patients will not require treatment by 15 years.

* + 43 stage I-II, G1-2 pts (not large cleaved cells). 75% stage II. Minimum f/u 1y.
  + Freedom from treatment at 5/10/15y of 76→ 56→ 48%.
    - At MFU of 6y, > 50% of pts had not yet rec'd treatment.
  + Reasons for no initial therapy: "large field required", xerostomia, prior irradiation, patient/physician preference.
  + Median time to tx 22 mo.
  + OS at 10/20y of 85→ 22%.
  + 20% of pts (9 overall) transformed to DLBCL. *5 pts on watchful waiting, 4 pts who rec'd chemo or RT.*
* **Faulty Rituximab alone study** [[Ardeshna Lanc Onc '14](https://www.sciencedirect.com/science/article/pii/S1470204514700270)]: **Watchful waiting vs. Rituximab ± maintenance**.

There is a high rate of transformation to DLBCL for rituximab alone or watchful waiting!

For some reason, NCCN still recommends Rituximab alone above RT for bulky disease > 7 cm, even though this trial did not include bulky and was not compared to the only curative modality (i.e. RT).

* + 379 G1-3a. Only 20% Grade I-II. < 7 cm (**non-bulky**), up to 4 sites with nodes > 3 cm, LDH wnl. MFU 4y.
    - Rituxan 375 q1w x4c induction ± maintenance Rituxan 375 q2m x2y.
  + Time to start a new tx at 3y for WW / Rituxan / Rituxan + maintenance of 63→ 30→ 24%.

There appears to be little to no benefit of maintenance Rituximab over induction alone.

* + 3y PFS for WW / Rituxan / Rituxan + maintenance of 36→ 60→ 82%.
  + CR 5→ 44→ 77%. Compare to 50% CR for Boom Boom, or 100% CR with RT + Rituximab.
  + 10% transformed to DLBCL at 4y (short follow up). Trend to greater than 10% in WW arm.
* **Rituximab + RT** [[Janikova L&L '15]](https://www.tandfonline.com/doi/full/10.3109/10428194.2014.990010): Prospective **Rituxan vs. RT ± Rituxan**. Retro chemo/WW arms.  
  Concludes that rituximab alone is reasonable, but very short follow up.

Complete response after Rituximab alone appears to be around 80%, while complete response with RT + Rituximab is 100%.  
RT + Rituxan arm with worse prognosis: more grade 3A, more bulky ( ≥ 5 cm), more FLIPI IR.

* + 93 pts. Stage I-II. 14 R alone, 65 RT, and 14 RT + R pts. MFU 5y without Ritux, 2.5y if Rituxan.
  + Retro: 91 chemo + immuno, 60 chemo alone, 36 chemo + RT + R, 32 chemo + RT, 23 WW.
    - Rituxan 375 q1w x4-8c induction.
    - IFRT from 24-45 Gy, including up to one neighboring nodal group.
  + CR 86→ 92→ 100%.
  + MPFS 4.9y→ 3.3y→ NR. How can MPFS be 4.9y for R alone, when MFU 2.5 years?
  + From 2008 onwards, equivalent or more patients received Rituxan alone than RT! :(

* **TROG 99.03** [[MacManus JCO '18](https://www.ncbi.nlm.nih.gov/pubmed/29975623)]: **30 Gy IFRT ±** (R)-**CVP** x6c.  
  Only 40% of patients on this study received Rituximab!!

Results in this subgroup were markedly better, suggesting OS benefit when adding Rituximab to RT (see Fig 4).

This study used CVP/(R) chemotherapy, which has high rates of toxicity. [[Rituximab + RT](https://docs.google.com/document/d/1gKy2Hpx7FxInjOpKIBkTFJWpqhJ3I-gSXz9eRwq-NSY#bookmark=id.one00eoxa2hm)] is likely more tolerable.

* + 150 pts. Stage I-II FL, G1-2. 75% stage I. 50% PET/CT staged. 2000-2012. MFU 10y.
    - Cyclophosphamide 1000 d1, Vincristine 1.4 d1, Prednisolone 50 d1-5, Rituximab 375 d1 x6c.
  + 10y PFS 41→ 59%.
  + For the 40% of pts receiving Rituximab with CVP, there was a drastic improvement in PFS over CVP alone (Fig 4).
  + 10y OS ~90%. No subset analysis was performed on the subgroup of patients receiving R-CVP with IFRT.
  + 10% transformation to DLBCL.
  + Toxicity not negligible: ~40% G3 neuropathy and 1 case of G4 neuropathy. *Perhaps Ritux + RT is more tolerable.*

* **Italian** [[Ruella IJROBP '16](https://www.sciencedirect.com/science/article/pii/S0360301615268575?via%3Dihub)]: Prospective. **Single arm IFRT ± induction Ritux**.  
  Complete response to Rituximab appears to be 80%, compared to nearly 100% for Rituximab + RT.

Less DLBCL transformation with RT + Ritux.

Similarly to concurrent [[Lenalidomide-Dex/RT](#vbda5uf1edhl)] for solitary plasmacytoma, Rituximab/RT is effective for ES-FL.

* + 94 stage I-II FL pts. 1985-2011 at 5 Italian institutions. 80% stage I. MFU 11y.
    - Rituximab 375 q1w x4c.
    - RT: Rit-RT (43 pts) median **31 Gy**, RT alone (51 pts) median 40 Gy. Appears to be no benefit > 36 Gy.
  + **CR 86**→ **98%** (**77% CR after Rituximab induction**).
  + 10y PFS/OS 57/88%.
  + 10y PFS 51→ 65%.

* + **10y DLBCL transformation 18→ 2%**.
  + BM molecular analysis demonstrating PCR positive at dx strongly associated with relapse risk on MVA.
* **Italian** [[Cencini L&L '18](https://www.tandfonline.com/doi/full/10.1080/10428194.2017.1387909?scroll=top&needAccess=true)]: Retro. **Single arm IFRT** (24 Gy) **+ Rituxan**.  
  Complete response after Rituximab + RT appears to be 100%.
  + 41 stage I-II FL pts. 2007-2014 at 2 Italian institutions. 17% G3a. 80% stage I. 1 pt ≥ 7 cm. 66% PET/CT staged.
    - Rituximab 375 q1w either induction or adjuvant to IFRT (20-44 Gy, median **24 Gy**).
  + **CR 100%!** Only 3 pts relapsed within 4y.
  + 5y PFS 90%.

## [**DLBCL in the Pre-rituxan era**](#_oqhi8xeg79db)

See the [[High Grade NHL](#_yo7zrvnuvmmp)] section.

SWOG 8736, ECOG 1484 and GELAs were chemo ± RT trials.

Isolated local relapse is around 40-60% with chemo alone.

* **SWOG 8736** [[Miller NEJM '98](https://www.nejm.org/doi/10.1056/NEJM199807023390104?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov), [Stephens JCO '16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5012710/)]: **8c CHOP alone vs 3c** **CHOP + IFRT** 40 Gy (50 Gy for PR).   
  Adding RT to chemo improves PFS and OS compared to chemo alone at 5y, although OS benefit is lost at long-term F/U.

At about 7y, the curves cross and become NS. Most failures were outside the RT field. Does this suggest suboptimal chemo?

[[SWOG 0014](#59m21epibzi1)] established 3c R-CHOP followed by IFRT as standard of care for LS-DLBCL with 1+ IPI risk factor. Modern guideline-recommended doses have decreased to 30 Gy, and ISRT is now utilized.

See also [[LYSA 02-03](#ptyy03dwjkpi)] for the role of RT in the Rituximab/PET era.

* + 401 pts. Stage I bulky (66%), non-bulky (33%) stage II/IIE. MFU 18y.
  + 5y OS 72→ 82% and 5y PFS 64→ 77% improvements wash out at 7, 10 and 12y. 15y PFS ~40%.
  + Problem: Need age adjusted IPI! More OOF failures for IPI ≥ 2.
    - Post-hoc: IPI 0-1 did well with RT.
  + There appears to be no in-field relapse with RT arm, compared to 7% in field relapse on GELA 93-4.
  + Excessive late OOF failures occur in the CHOP x3c / IFRT arm.
  + CHOP had more heart failure and inability to complete treatment.

* **ECOG 1484** [[Horning JCO '04]](http://ascopubs.org/doi/abs/10.1200/JCO.2004.06.088?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): 8c **CHOP ± IFRT** 30 Gy with CR (40 Gy for all if PR).Relapse less likely at original site with RT, along with less distant metastases. PFS may be a surrogate for OS [[Shi '18](https://www.ncbi.nlm.nih.gov/pubmed/29975624)].

Around half will relapse "in the neighborhood" with chemotherapy alone.

* + 352 pts. 66% stage II. 50% extranodal. 31% >10 cm. > 80% DLBCL.
    - Less favorable disease than SWOG. More pts in RT had bulky disease (7→ 26%).
  + CR in ~70%. In PR subgroup (all received RT), only 30% achieved CR after RT.
  + In CR patients, 6y DFS 56→ 73%, but no OS difference (not powered for it).
  + Any LR 48→ 17%. Distant relapse 82→ 52%.
  + In PR patients, 6y FFS 63%.
* **GELA Studies**: IPI 0. 2/3 Stage I. Around half extranodal. ~10% bulky. ~20% IFF.   
  Most patients are stage I in the GELA studies, with very few bulky patients.
  + [GELA 93-1 [Reyes NEJM '05]](https://www.nejm.org/doi/10.1056/NEJMoa042040?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dwww.ncbi.nlm.nih.gov): 3c **CHOP + 40 Gy** **vs. ACVBP** 3c→ MTX, etoposide, ifosfamide, cytarabine.  
    "Young and determined" trial. This regimen was not adopted due to concern for toxicity.

This compared CHOP + 40 Gy to a super aggressive chemo regimen in a low risk population.

* + - 647 pts. ≤ 60y, stage I-II. IPI 0 NHL.
    - 5y OS 81→ 90%, 5y EFS 74→ 82% with super aggressive chemo regimen.
    - ~20% in field relapse.

* + GELA 93-4 (Elderly) [[Bonnet JCO '07]](http://ascopubs.org/doi/abs/10.1200/JCO.2006.07.0722?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): 4c **CHOP ± 40 Gy IFRT**.   
    There is no EFS benefit with the addition of RT to CHOP chemotherapy, although LR cut in half.

More DM in RT arm likely due to increased local control. Rituxan likely would have cut down on DM.

In field recurrence was 7%, indicating possible poor quality of RT given 0% IFF on [[SWOG 8736](#q7zy3uortpgx), [Lysa-Goelems](#ptyy03dwjkpi)].

RT started > 5 weeks after completion of chemo in over half of patients. 12% on RT arm did not receive it.

This elderly group had age-adjusted IPI of 0 and normal LDH, a very homogeneous and low risk population.

This trial was stopped early due to no difference in EFS, along with the release of Rituxan.

* + - 576 pts. Age > 60y, stage I-II, IPI 0 NHL. MFU 7y.
      * RT: Only half of patients started before week 7.
    - ~90% response. 5y EFS ~63%, 5y OS ~70%. Lower EFS than other studies.
    - Around 25% of patients had relapses. Of these, isolated LR 47→ 21% and isolated DM 37→ 66%.
    - Any relapse 29→ 22%. Any local relapse 18→ 7%. Any distant metastasis 15→ 17%.
    - There was a 7% in-field relapse rate (compared to 0% in-field relapse with SWOG 8736).

## [DLBCL in the Rituxan era](#_oqhi8xeg79db)

See the [[High Grade NHL](#_yo7zrvnuvmmp)] section.

No prospective studies of RT in the rituxan era until 2017/2018: [Lysa/Goelams](#ptyy03dwjkpi), [UNFOLDER](#t12b3grm655b).

* **NCDB** [[Vargo JCO '15](http://ascopubs.org/doi/abs/10.1200/jco.2015.61.7654)]: **Chemo ± RT**.  
  RT adds nearly 10% to OS at 10y! Despite this, utilization of RT in LS-DLBCL continues to decline.
  + 59k pts. Stage I-II DLBCL. 1998-2012. 46% stage II, 42% extranodal, 58% > 60y.
  + 5y OS 75→ 82%, 10y OS 55→ 64%.
  + Use of RT in 2000 / 2012 of 47→ 32%.

* **MInT** [[Pfreundschuh Lancet Onc '06,](https://www.sciencedirect.com/science/article/pii/S1470204506706647?via%3Dihub) ['11](https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(11)70235-2/fulltext), [Rieger Ann Onc '11](https://www.ncbi.nlm.nih.gov/pubmed/20724576)[]](https://www.sciencedirect.com/science/article/pii/S1470204506706647?via%3Dihub): **CHOP**-like **± R** x6c. RT given in 70%.   
  Does not directly answer the question as for the role of RT in bulky disease. However, initial bulk (defined at 5-10 cm) portends to poorer prognosis with greater risk of relapse risk even after adjusting for rituximab!
  + 824 pts. Age-adjusted IPI 0-1. Stage II-IV or bulky (50%) stage I DLBCL. 87 pts with PMBCL. MFU 6y.
    - IFRT 30-40 Gy given to initial bulky disease, selectively to primary extranodal disease.
    - Bulky: 5 cm for British, 7 cm from Spanish/Polish, 7.5 cm from Danish/Swedish (40% >7.5 cm).
  + 6y EFS 56→ 74%, 6y OS 80→ 90%.
    - R-CHOP is effective for patients with IPI=1 and without bulk: 3y EFS 74→ 90% without bulk.
  + PMBCL: uCR 54→ 80%, PD 24→ 2.5%. 3y EFS of 52→ 78%. 3y OS ~78→ 89% (p=0.16).
  + DLBCL: uCR 72→ 87%. PD 24→ 10%. 3y EFS of 61→ 81%. 3y OS 85→ 93%.
  + MVA demonstrated EFS was affected by treatment group, presence of bulky disease, and age-adjusted IPI, while OS was affected by treatment group and presence of bulky disease only.

* **SWOG 0014** [[Persky JCO '08](https://www.ncbi.nlm.nih.gov/pubmed/18413640)]: **R-CHOP x3c→ 40-46 Gy IFRT**.
  + 60 pts. LS-DLBCL w 1+ RF per stage-modified IPI (For stage I or II: Age > 60, PS 2, LDH, Stage II/IIE). MFU 5y.
  + 4y PFS for SWOG 8736 / 0014 of ~78→ 88%.
  + 4y OS for SWOG 8736 / 0014 of ~88→ 92%.   
    Potential explanation for no difference vs. SWOG 8736: GCB was in 3/4 of patients which are already good players.
  + PFS at 2 / 4y of 93→ 88%.
  + OS at 2 / 4y of 95→ 92%.
* **MDACC** [[Phan JCO '10]](http://ascopubs.org/doi/abs/10.1200/JCO.2009.27.3441?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed): Retro. Most w ≥ 6c **R-CHOP ± RT**.   
  OS and PFS benefit across all stages.
  + 469 pts with DLBCL. 2001-2007. Stage I-II (40%), Stage III-IV (60%). Bulk > 5 cm (44%). MFU 3y.
    - IFRT: 30-39.6 IFRT in 30% after CR to chemo.
    - uCR: CT by PET/CT with residual mass on diagnostic CT.
  + 5y PFS 59→ 82% and 5y OS 68→ 91%.
  + uCR in 43 patients (9%). Patients who received consolidative RT for residual CT based mass which was PET negative had similar OS (95%) and PFS (61%) to those who achieved CR by both modalities.
  + Matched pair analysis of patients who received 6-8c R-CHOP with stage I or II disease or all stages indicated RT improved OS and PFS compared with no RT.
  + For patients who received PET/CT CR with no CT-based residual, univariate analysis demonstrated the role of RT was still significant in addition to stage, triple negative vs triple positive status, and IPI score.

* **RICOVER-60** [[Pfreundschuh Lanc Onc '08](https://www.sciencedirect.com/science/article/pii/S1470204508700020?via%3Dihub)]: **CHOP-14** x6 vs. 8c **± R**. Gave 36 Gy if bulky ( > 7.5 cm) or extralymphatic.   
  In elderly early-stage NHL, R-CHOP is superior to CHOP. There is no benefit to more than 6 cycles.

Amended to not allow RT initially after the superior arm was identified, but failed [[RICOVER-no RT](#amzolllp07ku)].

* + 1,222 pts. **Older** 61-80y with > 7.5 cm bulk (38%) **any stage**, or stage III/IV (51%).
    - RT pre-planned to 36 Gy if >7.5 cm and extralymphatic involvement. ~50% of bulky rec'd RT.
    - Added no-RT arm: No RT arm more often Stage III-IV, extralymphatic, higher IPI but less bulky.
  + CR (including unconfirmed) 76%. For bulky, ~60% CR.
  + 3y EFS 47→ 66%, 3y OS 68→ 78%.No benefit with more than 6c of chemo even for PR after 4c.

* + **RICOVER-no RT** [[Held JCO '14](https://ascopubs.org/doi/full/10.1200/JCO.2013.51.4505)]: CHOP-14 x6c **± 36 Gy to bulky**, not to all sites.  
    Tried to omit RT from bulky disease, but failed!

Conclusion: Rituximab adds OS benefit to CHOP; per protocol RT to bulky dz adds OS benefit.

However, the benefit for bulky disease in CR is unclear.

* + - 164 patients. Tried to avoid RT to bulky disease using the best chemo arm of RICOVER-60.
      * Best arm: 6 cycles of R-CHOP-14 with 2 cycles of adjuvant rituximab.
      * 23% of patients with bulky disease received unplanned RT in RICOVER-no RT arm.
    - Bulky ITT analysis of CR-uCR patients with relapse of 22→ 4%.
    - Post-hoc bulky CR-uCR subgroup: 3y EFS ~75→ 84% (p=0.43), 3y OS ~79→ 87% (p=0.84).
    - Post-hoc per protocol bulky subgroup: 3y EFS 54→ 80%, 3y PFS 62→ 88%, 3y OS 65→ 90%.

* **UNFOLDER** [[Pfreundschuh ASCO '18]](http://abstracts.asco.org/214/AbstView_214_226965.html): 2x2. **R-CHOP-21 vs. R-CHOP-14** x6c **± 39.6 Gy ISRT** to B and E sites.  
  No-RT arms dropped due to inferior EFS for >7.5 cm or extralymphatic.

The addition of RT does help even in prolonged courses of R-CHOP.

There is no difference in q14 vs. q21 R-CHOP.

* + 467 pts. 2:1 RT to chemo alone. **Younger** 18-60 (med age 60). **Early stage**. aaIPI 0 ≥ 7.5 cm or aaIPI 1. MFU 5.5y.
    - Measuring response: PET or CT acceptable (< 50% XS reduction).
    - Looks for CR 2-6w after the last R-CHOP. If PR or uCR after 6c of chemo, re-scan in 4 weeks.
    - RT could be avoided w CR, but **no-RT arms dropped** due to inferior EFS for >7.5 cm or extralymphatic.
  + 3y EFS 68→ 84% largely due to a high rate of PR (11→ 2%), triggering additional tx (e.g. RT) as an EFS event.
    - 3y PFS ~81→ 89% (p=0.22). 3y OS ~93%.
  + No benefit of q2w R-CHOP, with equivalent EFS, PFS, and OS.
* A promising Mexico National Center study demonstrating a significant OS benefit in consolidative RT for CT-based CR after RCHOP x6c in patients 18-60 with initially bulky disease > 10 cm was unfortunately redacted in December 2019 [[Avilès Heme '19](https://www.tandfonline.com/doi/abs/10.1080/10245332.2018.1423880)].

* **DSHNHL Skeletal Meta** [[Held JCO '13](https://www.ncbi.nlm.nih.gov/pubmed/24062391)]: Retro. **± RT to skeletal involvement**.

ILROG Guideline: Modern RT for Extranodal NHL - Field and Dose Guidelines [[Yahalom IJROBP '15]](https://www.sciencedirect.com/science/article/pii/S0360301615000504?via%3Dihub). [RoR](#3ulp2e2jakqh), [PCNSL](#kix.mmiq0lal9y9s)  
The addition of RT to disease with skeletal involvement results in an EFS benefit and trend to OS benefit in pts with bony dz.

* + 292 pts from 9 GHSG trials. Post-hoc of 161 pts with skeletal involvement in MInT and RICOVER-60.
  + Addition of RT improved 3y EFS 36→ 75% and 3y OS ~71→ 86% (p=0.06).
  + Benefit retained in stage III/IV, ECOG >1, Age > 60y, bulky, and extranodal >1. Ritixumab did not benefit.

* **Dose-reduced consolidation** [[Kelsey IJROBP '19](https://www.ncbi.nlm.nih.gov/pubmed/30858144)]: Phase II. **R-CHOP** **PET4+ CR→ 20 Gy ISRT**.

Reduced dose consolidation is feasible after complete response by PET/CT.

* + 62 pts. DLBCL NOS and primary mediastinal DLBCL in CR on PET after ≥ 4c of Rituxan/anthracycline chemo.
    - 2010-2016. Bulky disease ≥ 7.5 cm in 40%, > 10 cm in 33%. Stage I-II in 80%. MFU 4y.
    - In the 20% of patients with advanced disease, RT tried to encompass all original sites of disease.
    - CR defined as D1-3.
  + OOF in 6 patients, IFF in 1 patient.
  + 5y FFLR 98%. 5y PFS 83%. 5y OS 90%.
* Standard of care: 3-4c of R-CHOP plus RT for patients with limited-stage DLBCL with an IPI score of 0 or 1. May need to add 6c induction with bulky and/or aggressive pathology features.

## [PET adapted therapy](#_oqhi8xeg79db)

See the [[High Grade NHL](#_yo7zrvnuvmmp)] section.

* PETX influencing treatment? Too soon to tell. One study demonstrated non-avid lesions > 2 cm benefit from RT.

* **Lysa/Goelams 02-03** [[Lamy Blood '17](http://www.bloodjournal.org/content/131/2/174)]: **R-CHOP** x4-6c **± 40 Gy IFRT**. PET0, PET4, and EOT.   
  R-CHOP alone is non-inferior to R-CHOP + RT in non-bulky LS-DLBCL or D1-2 on PET4. However, to say these arms are equivalent is misleading as all patients with PET4 regression > 50% but persistent positive PET or IPI of 1 or more received IFRT, which highlights the ongoing need for risk-adapted CMT [[Imber and Yahalom Cancer J '20](https://pubmed.ncbi.nlm.nih.gov/32496455/)].

It is already known that low risk patients do very well. Would RT have benefitted higher risk patients?

RT was given for all PET4 PR regardless of randomization.

There were no in field failures on the RT arm, while around half of failures were local in chemo-alone arm.

See [[SWOG 8736](#q7zy3uortpgx)] for the role of RT prior to the pre-Rituximab era. *Recall: Superiority of RT washed out at 7y on that study, so more follow up is needed on Lysa/Goelams to determine if omission of RT is reasonable in this very low risk population.*

* + 301 pts. **Non-bulky** (< 7 cm), **LS-DLBCL**. Mostly IPI 1-2. 40% extranodal. MFU 5y.
    - Chemo: Two additional cycles given for 1+ stage adjusted IPI factor (e.g., age > 60, PS2, LDH, Stage II) or PET4 PR (regression > 50% but persistent positive PET).
    - PET4 negative: D1-2. **D3+ considered positive**.
  + CR 88%, PR 12%. Overall response: ~95%.
  + 5y EFS ~89→ 92% (p=0.18). 5y OS ~91%.
    - Equivalent EFS or OS, but RT recommended for all pts with PET4 PR regardless of randomization. These pts achieved similar results to PET4 CR, suggesting role of RT in pts who only achieve PR to chemo.
  + Relapses ~5%. MTT relapse 21 mo. In the RT arm, there were no relapses in the initial tumor site.

* **OPTIMAL > 60** [[Pfreundschuh ASCO '17](http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.7506)]: 2x2. **R-CHOP vs. R-CHLIP** (liposomal vincristine).

There is a clear trend to 5% decreased PFS with the omission of RT to bulky disease which is PET(-) after chemo, and potential OS detriment. This difference was deemed non-inferior, indicating RT can be spared in PET(-) bulky disease, resulting in a 40% relative reduction in RT use as compared to RICOVER-60, which irradiated all initially bulky disease.

Small number of patients.

Also see [[RICOVER-noRTh](#amzolllp07ku)] (patients > 60y), [[UNFOLDER](#kix.jygmd2npyuiv)] (patients 18-60) which demonstrated EFS detriment with omission of RT to CT-based residual of initially bulky disease.

* + 166 pts with bulk ≥ 7.5 cm, 50% PET6+. **Older** 61-80y. 70% stage III/IV. **PET assessment** (unlike RICOVER-60).
    - RT for PET6+ bulky ≥ 7.5 cm (n=80) to 39.6 Gy (78% actually received RT, n=62).
    - No RT for PET6- bulky ≥ 7.5 cm.
    - PET6(+) in 48% of bulky, 78% of these received RT. *Compared to ~60% RT on RICOVER-60.*
  + 4y PFS for PET6(+) no RT / PET6(+) RT / PET6(-) no RT of 35→ 70→ 80%.
  + 2y PFS for bulky OPTIMAL > 60 / RICOVER-60 of 79→ 75%.
  + 2y OS for bulky OPTIMAL > 60 / RICOVER-60 of 88→ 78%.

* **SWOG 1001** [[Persky Blood '19](https://ashpublications.org/blood/article/134/Supplement_1/349/426082/PET-Directed-Therapy-for-Patients-with-Limited)]: Phase II. **R-CHOP x3c→ PET3. D1-3: R-CHOP x1c. D4-5: 36 Gy ± 9 Gy→ Y-90**.

This trial establishes R-CHOP x4c alone as the new standard approach to limited stage disease in the majority of patients.

* + 134 pts. < 10 cm DLBCL. Median age 62. 55% Stage I. 69% stage adjusted IPI 0-1. MFU 4.5y.
    - Mediastinal, HIV associated, testicular, CNS and indolent lymphoma excluded.
  + PET3 D4-5 in 11%. Of these, 67% were converted from PR to CR after IFRT-Zevalin.
  + 5y PFS for PET3 ± ~87%.

* **FLYER** (2005-2016) [[Poeschel Lancet '19](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)33008-9/fulltext)]: **R-CHOP x4c**→ (**R-CHOP vs. Rituximab**) **x2c**.

This trial established R-CHOP x4c followed by Rituximab x 2c (over 6c of R-CHOP) to be standard for LS-DLBCL in younger patients than SWOG 1001.

* + 592 favorable LS-DLBCL aged 18-60y. Non-bulky (< 7.5 cm). No RT unless testicular involvement. MFU 5.5y.
  + 3y PFS ~95%.
* Residual mass > 2 cm with PET- is associated with worse DFS and OS after chemo alone.

## 

## [Relapse](#_oqhi8xeg79db)d or Refractory NHL

See the [[CAR T-Cells](#_q9ptcay0swp3)] section and the [[High Grade NHL](#_yo7zrvnuvmmp)] section for more.

In contrast to relapse/refractory HL, only around half of patients are eligible for transplant and only around half of patients have chemosensitive disease, so around one quarter of patients make it to transplant.

ILROG Guideline: Modern RT for Nodal NHL - Target Definition and Dose Guidelines [[Illidge IJROBP '14]](https://www.sciencedirect.com/science/article/pii/S0360301614000649?via%3Dihub). [RoR](#lwp1seqewhg3)

ILROG Guideline: Role of RT in Patients With Relapsed/Refractory DLBCL [[Ng IJROBP '18]](https://www.sciencedirect.com/science/article/pii/S0360301617341871?via%3Dihub).

Radiotherapy for NHL (See Table 3 for early evidence supporting bridging RT with CART) [[Imber and Yahalom Cancer J '20](https://pubmed.ncbi.nlm.nih.gov/32496455/)]

* [[CAR T-Cell](#_q9ptcay0swp3)] Patterns of failure data suggests all necrotic lesions should be "bridged" with RT during after the leukapheresis stage when the CAR T-cells are being manufactured and the patient is being lymphodepleted *prior* to CAR T-Cell administration (A roughly 2-5 week window). Other indications suggest disease sites with high metabolic activity in lesions ≥ 2 cc in cross sectional area or ≥ 20 cc in metabolic volume are at increased risk of progression following CAR-T therapy.
* BWH/Dana-Farber [[Tseng IJROBP '15](https://www.ncbi.nlm.nih.gov/pubmed/25835625)]: Retro. Salvage RT for relapsed/refractory NHL.
  + 110 patients with 121 sites. MFU nearly 5y.
  + Median dose 37.8 Gy. Over half and nearly half of curative and palliative patients received ≥ 39.6 Gy.
  + Response rate over 85%.
  + 5y LC for curative patients 66%. 5y PFS for curative patients 34%.
  + Refractory disease and lack of response to initial chemotherapy but not dose were associated with short TTLR.
  + Despite doses of ≥ 39.6 Gy, 2y LC was only 61% for definitive patients with refractory disease or who did not respond to initial chemotherapy.
* Hematopoietic cell transplantation for DLBCL and FL: Current controversies [[Epperla Heme Onc SCT '17](https://www.ncbi.nlm.nih.gov/pubmed/28633038)]
  + 20-30% mortality at 1 year.

* **PARMA** [[Sud Heme '08](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2898124/#R4)]: **Salvage Plt and Ara-c based chemo ± ASCT**. IFRT 26-35/20 if ≥ 5 cm or extranodal.

ASCT is standard of care.

* + 213 pts. 163 intermediate grade, 52 high grade. Only 27 patients in the second relapse. 1987-1994.
  + EFS 46→ 53%.
  + OS 12→ 32%.
  + Chemo sensitive patients with 5y PFS 43%, while chemo resistant 1y OS 22%.
* **CORAL** [[Gisselbrecht JCO '12](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3646314/)]: demonstrated no role for Rituximab maintenance after ACST.
* **How I manage patients with Relapsed/Refractory DLBCL** [[Gisselbrecht BrJHeme '18](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6175435/)].

About 50-75% of failures after ASCT occur at initial sites of disease. IFRT may improve LC and PFS.

* + MSKCC retro: Chemosensitive relapsed or primary refractory DLBCL→ HIDAC→ ASCT ± IFRT.
    - IFRT improved LC and PFS, DFS, but not OS.
  + University of Rochester retro: 176 pts. As above. IFRT improved LC by 10% and even OS on MVA.
* **ALLG HDNHL04/TROG 03.03** [[Wirth IJROBP '19](https://www.ncbi.nlm.nih.gov/pubmed/30553941)]: Prospective. **Peri-transplant RT** to disease sites at registration.  
  Radiation in the up-front setting has an important role in decreasing relapses.
  + 55 NHL (n=22) and HL (n=23) pts.
    - RT: 30 Gy IFRT. Delivered post-transplant. CR 30 Gy, while PD 36-40 Gy for HL and 40-50 Gy for NHL.
    - All relapsed/refractory sites treated. Contiguous equivocal sites included when safe to cover.
  + Original sites that were unirradiated have a 15-35% incidence of relapse in original sites.
  + Original sites that were irradiated have a 4-7% incidence of relapse in original sites.

## 

## [Toxicity](#_oqhi8xeg79db)

* Rituximab can reactivate hepatitis B.
* Tumor lysis syndrome: Hydration, allopurinol, rasburicase, alkalinization of urine (Na-bicarb).

## 

## [Treatment Planning](#_oqhi8xeg79db)

See INRT or ISRT in the [[General Treatment Planning](#_d5y4iwywaoda)] section. As of 2020, IFRT is effectively dead.

**eContour**: [[MALT (conjunctiva)](http://econtour.org/cases/99)], [[MALT (lacrimal gland)](http://econtour.org/cases/98)], [[MALT (parotid)](http://econtour.org/cases/46)], [[Follicular (inguinal)](http://econtour.org/cases/41)]

**ARRO**: [[DLBCL case](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/HeadNeckDLBCL-NGT.pdf), [contour](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/HeadNeckDLBCL-NGT-Contour.pdf)], [[Orbital MALT](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/Orbital.pdf)]

ISRT in Adult Lymphomas: An Overview of ILROG Guidelines[[Wirth IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/32272184)] [RoR](#8tnt1mw76a6)

Must-Read article from 2020: ILROG's [[Making Every Single Gray Count](#gq1ic3qggdvh)].

ILROG Guidelines: Role of RT in Patients With Relapsed/Refractory DLBCL [[Ng IJROBP '18]](https://www.sciencedirect.com/science/article/pii/S0360301617341871?via%3Dihub). [RoR](#_brilw0sh9mf2)

ILROG Guideline: Modern RT for Nodal NHL - Target Definition and Dose Guidelines [[Illidge IJROBP '14]](https://www.sciencedirect.com/science/article/pii/S0360301614000649?via%3Dihub). [RoR](#lwp1seqewhg3)

ILROG Guideline: Modern RT for Extranodal NHL - Field and Dose Guidelines [[Yahalom IJROBP '15]](https://www.sciencedirect.com/science/article/pii/S0360301615000504?via%3Dihub). [RoR](#3ulp2e2jakqh), [PCNSL](#kix.mmiq0lal9y9s)

* If treating both sides of diaphragm (this pretty much never happens - med onc will give a million chemo regimens to avoid RT in advanced disease, even in the context of CT-based residual), then traditionally needed to split treatment with two week break in between to spare marrow/toxicities.

Indolent Lymphoma: G1-2 follicular, CLL/SLL, MALT (see section below).

ILROG Guideline: Modern RT for Extranodal NHL - Field and Dose Guidelines [[Yahalom IJROBP '15]](https://www.sciencedirect.com/science/article/pii/S0360301615000504?via%3Dihub). [RoR](#3ulp2e2jakqh), [PCNSL](#kix.mmiq0lal9y9s)

24/12 appears to be reasonable for indolent lymphoma [[Lowry RTO '11](#kix.k3nodad2fzof)], but 20% fail at five years (although Rituximab was not used in this study). Therefore, NCCN recommends 24-30 Gy for indolent lymphomas.

* Stage I-II, Gr I-II: MS 10-15y, 10y DFS 50%, 10y OS 70%.
  + Transformation to DLBCL in up to 20% of patients on watchful waiting or rituximab monotherapy.
  + ISRT alone: **24-30 Gy**. RT alone is NCCN preferred for stage I or contiguous stage II.
  + RT is the only curative modality.
* Stage II bulky - IV: MS 8-9y.
  + Observation if asymptomatic or non-bulky. Beware: Transformation to DLBCL without curative RT.
  + If symptomatic, bulky, or steady progression:
    - Chemo: R-CHOP or BR (bendamustine-rituxan) or RCVP or palliative RT: Boom boom or 30/10.
  + Relapsed: Radioimmunotherapy (Ibritumomab - CD20 with Y-90). Must biopsy relapsed follicular.
  + Transformation to DLBCL: Clinical trial, radioimmunotherapy, chemo ± rituxan ± ISRT or ISRT alone.
* **Radioimmunotherapy** (RIT) [[Witzig JCO '12](http://ascopubs.org/doi/full/10.1200/JCO.2012.46.2663)]:
  + Relapsed/refractory low-grade follicular or transformed B-cell NHL, CD20+.
  + 60-80% response with 20-40% CR.
  + Ibritumomab (Zevalin): Anti-CD20 w Y-90 (β emitter). For consolidation after induction for follicular lymphoma, first line, or relapsed/refractory. *Zevalin - "Z" is close to "Y" - Y-90.*
    - Half life 2.7d. Pretreat w unlabeled rituximab 1w prior to admin to improve biodistribution.
    - Toxicity: 85% G3-4 cytopenia with nadir at 8w. 2% develop MDS/AML.
  + Tositumomab (Bexxar): Anti-CD20 w I-131 (β and ៵ emitter - two ៵s), Theragnostics.
  + Main toxicity of Zevalin and Bexxar: myelosuppression, thrombocytopenia .
  + C/I: Hypersensitivity to murine proteins, ≥ 25% BM involvement, ≤ 15% BM cellularity, plt <100k, Hgb < 8, ANC < 1.5k, T Bili > 2, Cr > 2, pregnancy/nursing [[Witzig JCO '02](http://ascopubs.org/doi/full/10.1200/JCO.2002.11.076)].
* **Palliative splenic RT for CLL**: **0.25 Gy**-1 Gy qday or 2-3x/w **to 4 Gy**- 10 Gy.
  + **Splenic irradiation for splenomegaly** [[Zaorsky CTR '17](https://www.sciencedirect.com/science/article/pii/S0305737216301414?via%3Dihub)]
  + Typically in the context of MPD or CLL.
  + Most common fractionation 10/10 over 2 weeks, but 5/5 may be used.
  + Monitor blood counts.
  + Response rate 85-90%.

Aggressive lymphoma: e.g. **DLBCL** (e.g. GCB, PMBCL), **G3 follicular**, mantle cell.

ILROG Guideline: Modern RT for Extranodal NHL - Field and Dose Guidelines [[Yahalom IJROBP '15]](https://www.sciencedirect.com/science/article/pii/S0360301615000504?via%3Dihub). [RoR](#3ulp2e2jakqh), [PCNSL](#kix.mmiq0lal9y9s)

* **Stage I-II** (30%): For early stage dz, RT dec relapse by 50-60%, but no difference in OS.
  + **F** (< 7.5 cm, IPI 0-1): R-CHOP x**3c**→ ISRT 30-36 for D1-3 (Cat 1) or 40-50 Gy for PR vs. R-CHOP x6c.
    - DLBCL: 5-7 cm in size is considered bulky. A few years ago it was 10 cm.
  + **U** (bulky, IPI 2-4): R-CHOP x**6c** ± ISRT 30-36 Gy preferred, but may do 3c with ISRT as above.
    - ISRT 30-36 Gy for CR, 40-50 Gy for PR.
      * If PR, repeat PET/CT after RT. If D4+, biopsy. If it is positive for tumor, treat it as refractory.
* **Stage III-IV** (70%):
  + R-CHOP x**6**-8. Consider ISRT 30-36 Gy to initially bulky. Upfront transplant investigational.
    - R-CHOP 21 for 6c is standard of care. There is no advantage of q2w R-CHOP.
    - Obtain PET2 or PET4.
      * If responding, continue to 6 cycles.
      * If no response or progressive, biopsy then treat as per relapsed, refractory.
* **High grade**: Burkitt's, lymphoblastic, double hit DLBCL.
  + Chemo + clinical trial
  + Lymphoblastic, Burkitt's: Treat as per ALL.
  + HyperCVAD, limits RT role.
* RT (36 Gy) for limited stage III, bulky disease, persistent PET positive disease, skeletal involvement.
  + **Mantle-cell**: R-CHOP or hyperCVAD ± R.
    - Stage I/II (rare): IFRT alone (30 Gy).
    - Stage IIX/III/IV: (HyperCVAD alt w HD-MTX + ARA-C) + Rituxan→ HD CTX + ASCR.
  + **DLBCL of bone**: CHOP x6c→ 45/25 w 36 Gy whole bone w 2 cm margin[[1](https://www.sciencedirect.com/science/article/pii/S0360301610005213?via%3Dihub)], or 1 cm pre-chemo GTV[[2](https://www.sciencedirect.com/science/article/pii/S0360301615000553?via%3Dihub)].
    - Prefer to base off of **pre-chemo GTV** (***not* whole bone**), so get MRI in tx position prior to chemo.
    - PTV of 0.5-1 cm depending on immobilization.

* + **DLBCL of testicle**: Treat contralateral testicle too. 25-30 Gy [[Cheah Blood '14](http://www.bloodjournal.org/content/123/4/486.long?sso-checked=true)]
    - Orchiectomy→ R-CHOP x6 w high dose **MTX x4**→ RT to contra testicle/ipsi scrotum.
    - Measure scrotum separation. Anterior electron field according to thickness.
    - Frog leg. Tape up penis to the abdominal wall. Scrotum is immobilized with bolus under and around.
    - 5y PFS 75%, 5y OS 85%.
  + **DLBCL of breast**: Whole breast, don't treat elective nodes.
  + **DLBCL of brain**: Slit lamp exam, flash orbits if positive. Otherwise, treat posterior orbits. 23.4 vs. 36.
  + **DLBCL intraocular**: Entire globe, ONs to level of OC. Iso at posterior border to reduce brain divergence.

Relapse/refractory: Second line chemo ± HIDAC→ ASCT.

ILROG Guidelines: Role of RT in Patients With Relapsed/Refractory DLBCL [[Ng IJROBP '18]](https://www.sciencedirect.com/science/article/pii/S0360301617341871?via%3Dihub). [RoR](#_brilw0sh9mf2)If not a chemo candidate, RT alone to 40-55 Gy.

* Recent ILROG guidelines to give 36-40 Gy pretransplant only to PET+ persistent disease.
* **Refractory disease**:
  + CR to salvage: 30-40 Gy.
  + PR to salvage: 40-50 Gy.
  + RT alone: 40-55 Gy.

## 

## [Follow up](#_oqhi8xeg79db)

* H&P with labs q3-6 mo x5y.
* Imaging q6m x2 years, then as clinically indicated

## 

## [Future Directions](#_oqhi8xeg79db)

See NCTN Trial Portfolios by Disease Site: [[Lymphoma](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Lymphoma_Trials.pdf)]

Note how none of these trials are asking radiation questions...

* **A051301** [[NCT02443077](https://clinicaltrials.gov/ct2/show/NCT02443077)]: Phase III. **± Ibrutinib during and following AutoSCT**.
  + Relapsed/Refractory DLBCL.
* **A051701** [[NCT03984448](https://clinicaltrials.gov/ct2/show/NCT03984448)]: Phase II/III. (**DA-EPOCH or R-CHOP**) ± **Venetoclax (ABT199)**.
  + Newly diagnosed MYC/Bcl2 double hit or double expressing.
* **S1608** [[NCT03269669](https://clinicaltrials.gov/ct2/show/NCT03269669)]: Phase II. **Obinutuzumab +** (**Umbralisib vs. Lenalidomide vs. Combo chemo**)
  + Relapsed/Refractory Follicular Lymphoma. *Recall: Radiotherapy is the only curative modality for stage I-II FL, yet, patients on this trial could have omitted radiotherapy initially.*
* **EA4181** [[NCT04115631](https://clinicaltrials.gov/ct2/show/NCT04115631)]: Phase II. **BR/CR vs. BR/CR-A vs. BR-A**.
  + Mantle cell, untreated with cyclin D1 (BCL1) expression and/or t(11;14). Patients ≤ 70y.
  + BR/CR: Bendamustine+Rituximab/Cytarabine.
  + BR/CR-A: Adds Acalabrutinib.
  + BR-A: Omits Cytarabine.
* **EA4151** [[NCT03267433](https://clinicaltrials.gov/ct2/show/NCT03267433)]: Phase III. **Minimum residual disease→ Maintenance Rituximab ± AutoSCT**.
  + Mantle cell lymphoma, evaluation of transplant and minimal residual disease post-initial induction therapy.

# [MALT Lymphoma](#_oqhi8xeg79db)

**eContour**: [[MALT (conjunctiva)](http://econtour.org/cases/99)], [[MALT (lacrimal gland)](http://econtour.org/cases/98)], [[MALT (parotid)](http://econtour.org/cases/46)]

**ARRO**: [[Orbital MALT](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/Orbital.pdf)]

ILROG Guideline: Modern RT for Extranodal NHL - Field and Dose Guidelines [[Yahalom IJROBP '15]](https://www.sciencedirect.com/science/article/pii/S0360301615000504?via%3Dihub). [RoR](#3ulp2e2jakqh), [PCNSL](#kix.mmiq0lal9y9s)

**MALT lymphoma** (**aka** **Extranodal marginal zone BCL**): t(11:18).

Note: MZL can be extranodal (MALT - 5-10% NHL), nodal (1% NHL), or splenic (< 1% NHL).

* Stomach (65% of MALT), ocular adnexal, skin, thyroid, parotid, lung, breast.
* Most Stage I-II (60-70%). Typically stage IE - limited to mucosa or submucosa.
  + II1 - limited to stomach and perigastric nodes.
  + II2 - limited to stomach and non-perigastric nodes.
  + IIE - involves adjacent organs.
  + IV - disseminated disease.
* Associations with MALT:
  + Gastric - H. Pylori.
  + Orbital - C. psittaci. Doxycycline has a 50% response rate [[Ferreri JCO '12](http://ascopubs.org/doi/full/10.1200/JCO.2011.41.4466?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed)], therefore NCCN prefers ISRT.
    - ORR for lymphoma regression 65% w 15% CR of lymphoma.
  + Cutaneous - Borrelia burgdorferi.
  + Small bowel - Campylobacter jejuni.
  + Splenic - HDV.
  + Salivary - Sjogren's syndrome.
  + Thyroid - Hashimoto.
* Workup: Examine other potential sites such as **eyes**, **skin**.
  + Endoscopic biopsy, H. pylori testing. If negative, test for t(11;18) which has < 5% response to abx. Submucosal invasion, persistent monoclonal spike and higher failure [[Wündisch JCO '05](http://ascopubs.org/doi/full/10.1200/JCO.2005.02.3903)].
  + Try rapid urease on bx specimen, if negative, urea breath test, blood Ab, stool Ag.
  + EUS, PET/CT for MALT - only 40% Sn for gastric, otherwise very good! [[Perry EJH '07](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1600-0609.2007.00895.x)]
* **European multi-institutional** [[Wündisch JCO '05](http://ascopubs.org/doi/abs/10.1200/jco.2005.02.3903)]: Prospective. **Antibiotic eradication→ EGD monitoring**.  
  Antibiotics in H pylori for gastric MALT leads to excellent control and 80% CR.

Risk factors: t(11;18) RR3, ongoing monoclonality RR6, deep invasion of gastric wall, perigastric nodes.

* + 120 pts. Gastric MALT lymphoma stage IE, H. pylori (+).
    - Eradication with "**P**PI**A**mox**C**lari" or second line/penicillin allergic "**C**lari**O**meprazole**M**etro".
  + Time to CR can be slow. Around 60% of CRs in 3 mo, 25% of CRs in 12 mo, 15% of CRs in > 12 mo.
  + CR 80% (n=116). Of those who achieved CR, EFS 98% (3/116).
  + Of 16 with residual disease, 100% achieved CR after 2nd line antibiotics.

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| --- |
| **Treatment paradigm** For stage III-IV, treat for symptoms, bulky disease, steady progression.   * **Stage IE** (Gastric): Consider RT if t(11:18) present.   + **Triple therapy**: **"PAC"** - **P**PI, **A**moxicillin and **C**larithromycin x 7-14 days.     - Substitute Metronidazole if penicillin allergic: **"COM"** - **C**larithromycin, **O**meprazole, **M**etronidazole.   + **Quadruple therapy**: PPI + **bismuth** subsalicylate (Pepto) + 2 abx (metronidazole, tetracycline).     - Do EGD ± bx at 3 mo. Antibiotics have 80% CR, 80% of those remain in CR [[Nakamura BMJ '12](https://gut.bmj.com/content/61/4/507.long)].       * If HP is positive, but asx, may observe. If HP positive and sx, second line abx.         + ISRT if fails second line antibiotics.       * If HP is positive, t(11:18)→ abx w EGD in 3 mo (< 5% response), straight to ISRT.   + If RT, treat the entire stomach and perigastric nodes to 30/20, or consider Rituximab if RT contraindicated.     - LRC > 90% with 30/1.5 Gy. * **Stage IIE-IV** (any adjacent or distant organ involvement)→ R-CHOP (treat as MZL).   + II1 - give antibiotics if H pylori positive.   + II2 - consider chemo if symptomatic.   + IIE - consider chemo (or ISRT?).   + IV - chemotherapy. |

[**Treatment Planning**](#_4c4268dmp1aa)

eContour: [[MALT (conjunctiva)](http://econtour.org/cases/99)], [[MALT (lacrimal gland)](http://econtour.org/cases/98)], [[MALT (parotid)](http://econtour.org/cases/46)]. ARRO: [[Orbital MALT](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/Orbital.pdf)]

ILROG Guideline: Modern RT for Extranodal NHL - Field and Dose Guidelines [[Yahalom IJROBP '15]](https://www.sciencedirect.com/science/article/pii/S0360301615000504?via%3Dihub). [RoR](#3ulp2e2jakqh), [PCNSL](#kix.mmiq0lal9y9s)

ISRT in Adult Lymphomas: An Overview of ILROG Guidelines[[Wirth IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/32272184)] [RoR](#8tnt1mw76a6)

* Fasting CT (at least 3-4 hours) with ~15-25 cc diluted oral contrast, 4DCT, breath hold.
* IV contrast if LN involved.
* Vac lock, arms up.
* AP-PA vs. 4 fields to empty stomach. Can use 3D/IMRT if needed to spare OARs.
* GTV if possible: Visible tumor based on description in EGD note.
* PTV to account for respiratory motion, may use 4DCT or DIBH (Pushes stomach away from heart). Generally, 2.5 cm around the outer gastric border.
* Place patients on PPI during radiotherapy. Consider antiemetic 1h prior to treatment.
* Be sure to block the kidneys.
* Stomach including gastroduodenal junction + 1-2 cm to 30/20 (1.5 - 2.0 Gy) fractions.
  + Gastric 24-30 Gy in 1.5-2 Gy fractions, other extranodal **24-30 Gy**.
    - LC 90-100%.
* Parotid: Can be bilateral; use 24/12.
* Orbital/Conjunctival: 24/12. Associated with chlamydia psittaci. Doxycycline has a 50% response rate, NCCN prefers ISRT.
  + [[ILROG guidelines](#gq1ic3qggdvh)] from 2020 suggest 4/2 [[is acceptable](#qpinxhuxa1c6)] for orbital low grade lymphomas (e.g. MZL, MALT, etc).
  + This is the only site of which we are aware where [[Boom Boom](#2ir15dd82frs)] *may* be definitive therapy.
* Breast/thyroid/lung/bowel MALT: can treat w surgery, if SM negative, no further Tx needed. SM+→ RT.

**Follow up**

* Gastric: EGD ± bx at 3mo, CR 80-90%, but the **minimum time to CR is 6 mo** (median ~15 mo).
  + Endoscopy at 3 mo, then q3-6 mo until resolution, then annually.
  + Some only do one endoscopy if CR.

# [Dura Mater Lymphoma](#_oqhi8xeg79db)

* Often suspected to be a meningioma.
* Almost always MZL that often remains localized to dural surfaces, although often have more than one lesion.
* If >1 lesion present, WBRT to 24 Gy with 12 Gy boost to involved sites. Otherwise, 30-36 Gy.

# [Orbital (Ocular Adnexal) Lymphoma (OL)](#_oqhi8xeg79db)

ILROG Guideline: Modern RT for Extranodal NHL - Field and Dose Guidelines [[Yahalom IJROBP '15]](https://www.sciencedirect.com/science/article/pii/S0360301615000504?via%3Dihub). [RoR](#3ulp2e2jakqh), [PCNSL](#kix.mmiq0lal9y9s)

* Involves conjunctiva, ocular adnexa, lacrimal gland, eyelid, retrobulbar soft tissues.
* Ocular adnexal lymphoma (OL) vs. intraocular lymphoma (IOL):
  + In contrast to IOL, OL is generally an indolent disease.
  + Most OL are low grade BCL such as MZL. *Less commonly FL or DLBCL.*
    - Poor prognosis: high grade dz, stage IVE, LDH, lacrimal gland involvement (40% nodes), dx.
  + Only 15% are bilateral. *Compared to ~80% of IOL.*
  + Average presentation at 70. *Compare to bimodal at 31y and 60y for IOL.*
* Workup: Look for salmon colored conjunctival mass. Fundoscopy, slit lamp.
  + MRI brain/orbits.
  + Ocular U/S.
  + CT C/A/P, or PET/CT if MALT [[Perry EJH '07](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1600-0609.2007.00895.x)]
* Orbital/Conjunctival: 24/12. Associated with chlamydia psittaci. Doxycycline has a 50% response rate, NCCN prefers ISRT.
  + [[ILROG guidelines](#gq1ic3qggdvh)] from 2020 suggest 4/2 [[is acceptable](#qpinxhuxa1c6)] for orbital low grade lymphomas (e.g. MZL, MALT, etc).
  + This is the only site of which we are aware where [[Boom Boom](#2ir15dd82frs)] *may* be definitive therapy.
  + Doxycycline - 50% response rate [[Ferreri JCO '12](http://ascopubs.org/doi/full/10.1200/JCO.2011.41.4466?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed)], NCCN prefers ISRT.
  + ORR for lymphoma regression 65% w 15% CR of lymphoma.
* Stanford [[Le IJROBP '02](https://www.redjournal.org/article/S0360-3016(01)02729-8/fulltext)]: Retro. **31 orbital MALT lymphomas to 34 Gy**.
  + 10y LC 100%. 10y OS 73%.
  + 5 distant failures w 10y PFS 71%.
  + No difference in pts treated with ± 34 Gy.
* **Long term outcomes and patterns of failure in orbital lymphoma** [[Parikh L&L '15](https://www.ncbi.nlm.nih.gov/pubmed/25356924)]: Retro. **30.6 Gy** to the involved orbit.
  + 79 pts. Stage IE. 1995-2012. MALT 75%, FL 25%. MFU 4y.
    - Half in orbit, the remainder split between lacrimal and conjunctiva.
  + All OOF failures.
  + 10y LC 100%, 10y DMFS 94%, 10y OS 98%.
* **Partial orbit radiation is acceptable** [[Binkley PRO '16](https://www.ncbi.nlm.nih.gov/pubmed/26935235)]: Retro. Meidan **30.6 Gy** to involved orbit.
  + 5y local failure 5% (n=32). MFU 4y.

* **Boom boom for orbital lymphoma** [[Fasola IJROBP '13](https://www.ncbi.nlm.nih.gov/pubmed/23726002)]: Retro. **4/2**.

Recall: Boom boom typically has a CR of 50% and a 2y local failure of 25% for low grade lymphoma [[UK FORT](#2ir15dd82frs)].

This study demonstrated a CR of 85%. Of those, none failed by 3y.

This is the only low grade lymphoma of which we are aware that Boom Boom is recommended as definitive therapy.

* + 20 NHL pts with 27 sites of ocular adnexal lymphoma. 2005-2011. M
  + ORR 96% with 85% CR. No patients with CR failed by nearly 3y.
  + Three patients (15%) experienced new sites of disease within the contralateral orbit.
  + No long term toxicity.
  + Can salvage with a repeat course.
* Toxicity
  + Cataracts occur in ~33% of patients after 2.5-6.5 Gy with 8y latent period.
  + Cataracts occur in ~66% of patients after 6.5-11.5 Gy with 4y latent period.
    - Lens opacification at doses >13-16 Gy.
    - 2 Gy/single fraction firm cutoff. Fractionation: < 4 Gy no cataracts, > 10 Gy 100% cataracts.
    - Cataracts are the classical deterministic (threshold) effect.
    - Stochastic effects have severity independent of dose (e.g. development of SMNs)
  + Loss of eyelashes occurs at 20 Gy and conjunctivitis can be seen at 30 Gy.
  + Retinal damage does not occur with < 24 Gy, but can occur when >34 Gy given.
  + Xerophthalmia TD 5/5 of 35 Gy.
  + See [[Toxicity](https://docs.google.com/document/d/17O0LOemBhckXGuuPBCh6u8vqBfc6lg88r46B8YctMXU/edit#bookmark=id.5a76zbq9fa6a)] section in CNS for more information.

## [Treatment recommendations](#_u3w4jkvaw541)

ARRO: [[Orbital MALT](https://www.astro.org/uploadedFiles/_MAIN_SITE/Affiliate/ARRO/Resident_Resources/Educational_Resources/Content_Pieces/Orbital.pdf)]

ISRT in Adult Lymphomas: An Overview of ILROG Guidelines[[Wirth IJROBP '20](https://www.ncbi.nlm.nih.gov/pubmed/32272184)] [RoR](#8tnt1mw76a6)

ILROG Guideline: Modern RT for Extranodal NHL - Field and Dose Guidelines [[Yahalom IJROBP '15]](https://www.sciencedirect.com/science/article/pii/S0360301615000504?via%3Dihub). [RoR](#3ulp2e2jakqh), [PCNSL](#kix.mmiq0lal9y9s)

Boom boom for orbital lymphoma may now be acceptable [[Fasola IJROBP '13](#qpinxhuxa1c6)].

* + Low-grade, limited disease: RT to 24-30.6 Gy with excellent LC >94%.
  + G2-3 or systemic disease with orbital involvement: CHOP + RT to orbit 30-36 Gy ± Ritux if CD20+.
  + DLBCL: 30 Gy for CR after chemo, 30-36 Gy for PR after chemo, 40-45 Gy for residual GTV after chemo.
  + Eyelid, conjunctival lesions may use anterior orthovoltage or electron fields. Suspect a lead shield in the beam to shield the lens (cuts down lens dose by 90-95%).
  + Lacrimal gland - cover the entire gland.
  + Conjunctiva: CTV includes entire conjunctival sac and local extensions to eyelid.
  + PTV margin usually 3-5 mm.
* Other salvage options include radioimmunotherapy with Y-90 or I-131 [[Esmaeli Ann Onc '09](https://academic.oup.com/annonc/article/20/4/709/206568)]

# [Intraocular lymphoma (IOL)](#_oqhi8xeg79db)

|  |  |  |
| --- | --- | --- |
| **PCNSL** | **IOL** | **OL** |
| Aggressive  DLBCL  Involves eyes 20% of the time  Bimodal: 35 (AIDS), or 60.  CNS  R-MPV→ HDCTX→ ASCT  R-MPV→ rdWBRT | Aggressive  DLBCL  Bilateral in 80%  Bimodal at 31 and 60y  Confined to neural structures  HD-MTX and Rituxan | Indolent  MALT  Bilateral in 15%  Average age 70y  Involves conjunctive, ocular adnexa, lacrimal gland, eyelid, retrobulbar soft tissues  CHOP or CVAD |

* **Extremely rare** subset of primary CNS lymphomas, accounting for 1-2% of extranodal lymphomas.
* Typically DLBCL. *Compared to low grade BCL such as MZL for OL.*
  + t(14;18) in ~55% of pts w PIOL [[Wallace '07](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1945012/)]
* Age of onset 50-60. More common in men. Bimodal distribution at 31y and 60y.
  + Just like PCNSL, age >60y is a poor prognostic indicator (less likely to rec WBRT).
* Ocular disease is bilateral in ~80% of cases. *Compared to ~15% for OL.*
* Most primary IOL patients will have CNS mets in 3y (60-80%). *Historically, these pts all rec'd WBRT at dx.*
  + 25% of pts with primary CNS lymphoma will develop IOL.
    - PIOL diagnosis requires confirmation of no CNS involvement w MRI and LP.
* Confined to neural structures. *Differ from OLs which involve uvea and ocular adnexa of orbit, lacrimal gland, conjunctiva.*
* There is no universal staging system.
* IHC: CD20, bcl-2, bcl-6, MUM1.
  + "Perivascular cuffing": Classic description of neoplastic B lymphocytes. CD 19/20/22 (B cells). BCL-6 (germinal center B-cells). IRF4/MUM1 (Late germinal center B-cell).
* Treatment recommendations: Give 36 Gy or consider intraocular MTX.
  + HD-MTX based intraocular/intravitreal chemotherapy with Rituxan common as per PCNSL.
  + CTV includes the entire globe, ON to the level of OC. PTV = 5mm. If treating bilaterally with opposed laterals, set iso at posterior border to reduce divergence in case of salvage WBRT.
* Recurrence rate is ~50%.

# [Primary CNS lymphoma (PCNSL)](#_oqhi8xeg79db)

[**StatPearls: Primary CNS Lymphoma (PCNSL)**](https://www.ncbi.nlm.nih.gov/books/NBK538148/) *Last update: 6/15/2019.*

**ILROG Guideline: Modern RT for Extranodal NHL - Field and Dose Guidelines** [[Yahalom IJROBP '15]](https://www.sciencedirect.com/science/article/pii/S0360301615000504?via%3Dihub). [RoR](#3ulp2e2jakqh), [PCNSL](#kix.mmiq0lal9y9s)

* ~4% intracranial tumors. 1,000 cases per year. 4 per million.
  + 3 fold increase over the past 30y! Initially due to AIDS (now declining), but still seeing incidence rise within immunocompetent, older adults in the last decade [[Villano BJC '11](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3241537/)].
  + LMD/CSF in 33% at dx. Retinal and vitreous seeding in 15-20% at time of dx [[Grimm Neuro '08](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4109164/)].
    - Do a **slit-lamp** ocular examination!
  + **Anatomy**: Periventricular, multifocal, crosses corpus callosum.
    - 90% supratentorial. Typically frontal lobe, deep white matter, periventricular.
    - 75% solitary mass. Up to 50% microscopically multifocal if immunocompetent, 100% if AIDS.
    - 20% synchronous ocular involvement.
    - < 5% of pts present with isolated spinal cord/meningeal involvement.
  + 90% **DLBCL**.
    - All are stage IE. Systemic NHL is often associated with orbital lymphoma.
    - B cells are typically not present in CNS.
      * "Perivascular cuffing": Classic description of neoplastic B lymphocytes. CD 19/20/22 (B cells). BCL-6 (germinal center B-cells). IRF4/MUM1 (Late germinal center B-cell).
  + **Systemic lymphoma**: > 95% of pts with PCNSL have negative lymphoma workup.
    - If systemic lymphoma is present, assume secondary CNS involvement.
    - High risk features of NHL: Burkitt, lymphoblastic lymphoma, immunocompromised, BM+, parameningeal presentation (NPX, PNS), testicular relapse.
  + **EBV is present** in 65% of immunodeficient, and 15% immunocompetent.
    - **Immunocompetent** median age **55**, with peak age 70. **M:F 2:1**.
      * Up to 50% multifocal.
    - **Immunodeficient** median age **35**, M:F > 9:1 (**95% males**).
      * Up to 80% multifocal (100% if AIDS).
* **AIDS**
  + Usually **100% associated with EBV** in cases of AIDS, NHL outside CNS with AIDS 30-50%.
    - Only 2-13% of AIDS develop PCNSL.
  + More likely to be multifocal if immunodeficient.
    - Microscopic exam demonstrates >90% multifocal dz ∴ chemo and/or WBRT recommended.
  + AIDS pts may have smaller ring-enhancing lesions, DDx = **toxoplasmosis**.
    - If CNS lymphoma, AIDS patients have MS 3-4 mo without significant benefit of WBRT [[1]](https://www.ncbi.nlm.nih.gov/pubmed/8058152).
* **Survival**
  + Unlike other extranodal NHL with a response of 90%, PCNSL is very radioresistant after RT alone w 5y OS 4%.
    - Long term survival becomes 15-20% when using MTX-based chemo ± RT. MS over 6 years on [MSKCC]
  + **Ocular lymphoma is uniformly fatal**. MS 6-18 mo.
    - No tx MS 1.5 mo.
    - WBRT MS 10-18 mo.
    - Chemo ± WBRT MS 44 mo.
  + 3y OS now nearly 90% with MS 6y for those who achieve CR (~60% after 5c R-MPV, ~80% after 7c R-MPV).
* **Workup**
  + **H&P**: testicular exam (testicular U/S for men > 60y), neuro exam, LN exam.
    - Ddx: Metastatic lymphoma (~5%), CNS tumors, mets, abscess, hemorrhage, MS, sarcoidosis, toxo (AIDS).
  + **Slit lamp eye exam**: Important for RT fields.
    - Retinal and vitreous seeding in 15-20% at the time of diagnosis [[Grimm Neuro '08](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4109164/)].
    - If ocular involvement, **vitrectomy** is diagnostic.
    - Conversely, 75% of pts who present with ocular lymphoma will develop CNS involvement.
    - If initially involved, then perform slit-lamp before and after chemotherapy.
  + **MRI brain** demonstrates a "cotton wool" appearance, usually homogenous with fuzzy borders.
    - Indistinct fluffy borders, strong contrast enhancement, ring enhancement esp in AIDS (central necrosis), T2 iso/hypointense, less edema than expected for glioma or mets.
    - Assess response w/i 2 mo of finishing tx [[Abrey JCO '05](http://ascopubs.org/doi/10.1200/JCO.2005.13.524)]. Repeat LP and/or slit lamp if initially positive.
      * CR: No steroids, normal slit lamp, LP and MRI.
      * Unconfirmed CR: Any steroids, minor slit lamp finding, negative CSF, Minor MRI enhancement.
      * PR: Slit lamp w decrease in vitreous cells/retinal infiltrate, LP+, ≥ 50% decreased enhancement.
      * PD: New ocular dz, LP+, ≥ 25% increase in enhancement or new lesion/site.
  + **MRI spine**: if sx or CSF positive.
    - Around 30% will have LMD or CSF involvement at diagnosis.
    - LP/CSF cytology (15-20cc): LP increased protein (85%), β2 microglobulin, and LDH; low glucose (33%).
    - If MRI and LP diagnostic, no biopsy necessary per NCCN.
  + PET/CT can replace CT.
    - Systemic dz only found in ~8% at diagnosis. Reserve for elderly or positive exam.
  + **Labs**: LDH, EBV, HIV, toxo (ELISA for antibody). LP at least 1 week after surgery.
    - AIDS patients: Toxoplasmosis titer and **BMBx**.
  + **Testicular U/S for men > 60y**.
  + **Hold steroids** until after biopsy.
    - If bx non-diagnostic on steroids, discontinue and re-biopsy on progression.
    - **Steroids**: 90% clinical response. 40% shrinkage. 10% CR on imaging. Recur weeks after discontinuation.
* **Risk factors**
  + Poor response to chemo, AIDS (OR 3.6k), multifocality, Age, poor KPS, LDH, CSF protein, deep location.
    - "Good risk" immunocompromised include AIDS with CD4 > 200.
  + **IELSG Prognostic scoring system for PCNSL** [[Ferreri JCO '03](http://ascopubs.org/doi/full/10.1200/JCO.2003.09.139?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed)]: 378 pts from 23 cancer centers, HIV negative.
    - RF: Age > 60, ECOG ≥ 2, LDH, high CSF protein, **deep location** (periventricular, BG, stem, CBL).
    - 2y OS for 0-1 / 2-3 / 4-5 factors of 80→ ~50→ 15%.
    - 2y OS for pts rec'd HD-MTX based chemo for 0-1 / 2-3 / 4-5 factors of 85→ 57→ 24%.
  + **MSKCC RPA** [[Abrey JCO '06]](http://ascopubs.org/doi/abs/10.1200/JCO.2006.08.2941?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed):   
    Patients under the age of 50 do best with a MS of nearly 10y.
    - 338 pts. MVA w age > 50 and poor KPS prognostic:
    - MS for < 50y / > 50y + KPS > 70% / > 50y + KPS < 70% of 8.5→ 3.2→ 1.1y .
* **Chemotherapy regimens**
  + **HD-MTX = 3.5**-8g/m2 to penetrate BBB. May be monotherapy in older adults.
    - After CR, consolidation w Ara-C or ASCT options.
    - In pts > 60y, WBRT with MTX has concern for neurotoxicity.
  + R-MPV is da real MVP for PCNS Lymphoma [[MSKCC](#kix.h2nxzvb803w7)].
    - Rituximab, MTX 3.5, Procarbazine, Vincristine q2w x5-7 cycles.
    - CR after 5 cycles is around 50%, while CR after 7 cycles is around 80%.
    - After CR, then consider reduced dose WBRT (23.4 Gy).
      * If there is no CR after 5c, give an additional 2 cycles.
    - 2 cycles Ara-C are commonly used as consolidative chemotherapy.
  + **RTOG 8806** [[Schultz JCO '96](http://ascopubs.org/doi/abs/10.1200/jco.1996.14.2.556)]: CHOP and CHOD ineffective due to poor BBB penetration.
  + **IELSG** [[Ferreri Lancet '09](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(09)61416-1/fulltext)]: **MTX** x4c **± Ara-C→ WBRT**.  
    Recall: CR after 5c / 7c of R-MPV of 60→ 80%. This study demonstrated 70% ORR.

[[IELSG 32](#kix.s5czz1yicuz5)] later demonstrated favorable outcomes with the addition of Rituxan and Thiotepa to MTX-AraC.

* + - 70 pts. NHL exclusively localized to CNS/eyes.
      * MTX 3.5 ± Ara-C 2g x4c q3w.
    - cCR 18→ 46%. ORR 40→ 69%.

* + **IELSG 32** [[Ferreri Lanc Heme '16](https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(16)00036-3/fulltext), ['17](https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(17)30174-6/fulltext)]: **MTX-Ara-C** x4c **± Ritux ± Thiotepa**→ **ASCT vs. WBRT**.

This study demonstrated 50% CR at most. Recall: CR after 5c / 7c of R-MPV of 50→ 80% per [[MSKCC](#kix.h2nxzvb803w7)].

Addition of Ritux and Thiotepa to MTX/Ara-C does best!

Lower dose WBRT might have produced more favorable outcomes. Although results were not significant, there was a slight trend in PFS benefit with WBRT. Nearly half received 45 Gy for partial response.

This group previously found no role in increasing dose beyond 36 Gy in the context of CR [[Ferreri IJROBP '11](https://www.sciencedirect.com/science/article/pii/S0360301610002695)].

* + - 227 immunocompetent pts.
      * MTX 3.5, Ara-C ± Rituxan 375 ± Thiotepa 30. Q3w.
      * RT: 36/20 WBRT + 9 Gy for PR (46%). Orbital shielding after 30 Gy (or 36 Gy if intraocular dz).
    - 30 mo cCR 23→ 30→ 49%.
    - 2y PFS for ASCT / WBRT of ~69→ 80% (p=0.17).
    - More heme toxicity with ASCT and two infectious deaths.

* + **CALGB 50202** [[Rubenstein JCO '13](http://ascopubs.org/doi/full/10.1200/JCO.2012.46.9957)]: **R-MTX/TMZ→ Ara-c/Etoposide without WBRT**.

This study demonstrated 70% CR at most. Recall: CR after 5c / 7c of R-MPV of 50→ 80% per [[MSKCC](#kix.h2nxzvb803w7)].

This trial was designed at least in part due to the neurotoxicity demonstrated in [RTOG 93-10], at 45 Gy WBRT which is rarely used anymore.

* + - CR 66%. 2y PFS 57%, comparable to previous regimens with WBRT.
      * HD-MTX 8, R 375. TMZ 150 d7-11 on each of the first 6 mo.
* **RTOG 8315** [[Nelson IJROBP '92]](https://www.sciencedirect.com/science/article/pii/036030169290538S?via%3Dihub): Phase II. **WBRT 40 Gy + 20 Gy boost** to tumor **+ 2 cm**. No chemo.

Conclusion: Dose escalation in absence of chemotherapy with poor outcomes, 90% IFF within 2 cm boost margin.

* + 41 pts. MS 12 mo. **60% recurrence** in brain.
  + Of 28 total failures, 90% recurred locally and 75% had local-only failure.
    - Nearly 90% recurred within 60 Gy volume.
* **MSKCC** [[Abrey JCO '00](http://ascopubs.org/doi/full/10.1200/JCO.2000.18.17.3144)]: **MPV x5c→ 45 Gy WBRT** with 30-40 Gy ocular if involved. All rec'd consolidation Ara-C x2c.

Neurotoxicity is over 10x greater in patients > 60y.

Patients greater than the age of 60 appear to have no OS benefit with the addition of WBRT, though the cause of death is much less likely due to tumor progression in patients who receive WBRT.

* + 52 pts. 30 pts rec'd WBRT. 22 pts older than 60y deferred RT. 1992-1998. HIV negative. MFU 33 mo.
    - MTX 3.5, procarbazine 100, VCR 1.4 q2w.
  + 56% cCR, 33% PR.
  + 3y PFS 65%. Around 1/3 relapsed in the brain alone, mostly distant from the initial site.
  + 10 of 16 pts (63%) who rec'd salvage tx achieved CR, with MS from time of relapse 27 mo.
  + Neurotoxicity after WBRT for < 60y / > 60y of 6→ 83%.
  + Patients > 60y had a MS of 33 mo, regardless in receipt of WBRT.
    - Although MS equivalent, cause of death more likely progression of dz in absence of WBRT.
    - Nearly half of pts who defer RT die due to tumor, < 10% if prior WBRT.

* **RTOG 9310** [[DeAngelis JCO '02](http://ascopubs.org/doi/full/10.1200/JCO.2002.11.013), [JNO '05](https://link.springer.com/article/10.1007%2Fs11060-004-6596-9)]: **MPV x5c→ WBRT** (**45**/25 **or 36**/30 (1.2 Gy) **BID**)→ **Ara-C** **x2c**.  
  45/30 switched to 36/30 BID (1.2) due to late toxicity, and was just as effective.

This trial likely resulted in less patients above the age of 60 getting WBRT for PCNSL.  
Modern, preferred regimen (not recognized as top option in NCCN): ~60% CR after 5c R-MPV. ~80% CR after 7c R-MPV.

If CR, deliver 23.4 Gy WBRT. If PR after 7c, give 30-36 Gy WBRT with 45 Gy boost to gross disease. Then, Ara-C x2c.

* + Phase II. 98 immunocompetent pts with newly diagnosed PCNSL. 40% above the age of 60.
    - MVP x5c (MTX 2.5, Procarbazine, Vincristine). IT MTX 12 mg between cycles.
    - Only 16 pts got BID, while 63 pts got 45 Gy.
  + 58% CR, 36% PR. CR did not influence survival outcomes.
  + 2y OS 64%, 5y OS 32%. MS 3y.
    - MS for < 60y / > 60y of 50→ 22 mo.
  + Severe delayed neurotoxicity in 52%, mainly clinically diagnosed leukoencephalopathy (14→ 19% for > 60y).
  + G3+ 73% (2/3 related to myelosuppression). G5 10% (6→ 16% for > 60y).
* G-PCNSL-SG1 [[Thiel Lanc Onc '10](https://www.sciencedirect.com/science/article/pii/S1470204510702291), [Korfel Neuro '15](https://n.neurology.org/content/84/12/1242.long)]: **HDMTX x6c ± 45/30 WBRT**.

This trial used MTX monotherapy and had much lower CR than other trials (typically, 50-70% CR). There is a suggestion of worsening OS with omission of WBRT. Suggested higher neurotoxicity with WBRT. Lower dose WBRT might have provided better outcomes.

"The role of WBRT is controversial because delayed neurotoxicity limits its acceptance as standard of care"

* + 551 immunocompetent pts, 318 tx PP. 2000-2009. 80% did not get ifosfamide. MFU 7y.
    - 2000-2006: HD-MTX 4 q2w. 2007-2009: Added ifosfamide. No WBRT arm got Ara-C if no CR.
  + CR 35%, PR 19% This is much lower CR than other trials.
  + 2y PFS ~30→ 44%. PFS HR ~0.6, greatest benefit appears for less than CR to HDMTX.
  + PP: MPFS ~12→ 18 mo (p=0.14). MPFS from last HDMTX of 12→ 26 mo.
  + ITT: MPFS 10→ 15 mo, MPFS from last HDMTX of 12→ 19 mo.
  + MS ~36 mo.
    - Trend to OS for < CR with addition of WBRT, HR 0.74 (p=0.10).
  + Neurotoxicity by clinical exam ~26→ 49% (p=0.054); Delayed neurotoxicity by CT / MRI in 46→ 71%.

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| **Modern WBRT for PCNSL**: Rad oncs rarely deliver WBRT 45/30 anymore due to severe delayed neurotoxicity in at least half of patients, especially pronounced for patients > 60 years [[RTOG 93-10](#kix.nv4dacheztsq)]. It is rare for patients to come into the clinic after 5c or 7c of R-MPV (60-80% CR, 95% ORR) [[MSKCC](#kix.h2nxzvb803w7)], as current preference seems to be utilizing different chemo regimens to achieve CR and omit RT until salvage [[IELSG 32](#kix.s5czz1yicuz5), [CALGB 50202](#kix.kgz19z5wb14k)]. Consolidative RT after CR or PR to R-MPV appears to be an excellent option:   * Give WBRT at 5c (if CR) or 7c (regardless of response). CR rates after 5c / 7c of R-MPV of 50→ 80%. * WBRT dosage for CR / PR of 23.4→ 30-36 Gy. Some consider 45 Gy boost to residual, but it is a multifocal process.   + For PR, ILROG recommends 36-45 Gy WBRT (1.5 to 1.8 Gy/fraction).   + For PR, NCCN recommends 30-36 Gy WBRT with 45 Gy boost to residual.   + For PR, e.g., 36/24 (1.5 Gy) + 43.2/24 (1.8 Gy) SIB would be acceptable per NCCN and ILROG. * When utilizing R-MPV, adjuvant chemotherapy after RT, such as Ara-C x2c, is recommended. * MS is an impressive 6y! Also, MS for patients above the age of 60y in the historical / modern era of 1.5→ 5.5y. * CR subgroup appears to have a 5y OS of 80% [[MSKCC](#kix.h2nxzvb803w7)].   See [[ILROG](#kix.mmiq0lal9y9s)] guidelines. |

* **MSKCC** [[Shah JCO '07](https://ascopubs.org/doi/full/10.1200/JCO.2007.12.5062), [Morris JCO '13]](https://europepmc.org/articles/pmc5569679): **R-MPV x5**-7**c + WBRT** (**45/30 if PR, 23.4/13 if CR**)**→ Ara-C x2c**.

Reduced dose WBRT to 23.4 Gy and Ara-C x2 after R-MPV x5-7c has good control and minimal neurotoxicity.

About half of patients will have CR after 5c of R-MPV, while CR after 7c 80%. Also, 5y OS is 80%!

* + 30 pts. Rituximab, MTX **3.5**, Procarbazine, Vincristine x5c q2w. CSF+ rec'd IT MTX 12 mg between cycles.
    - CR dose reduction due to high rates of severe neurotoxicity in pts > 60y who rec'd 45 Gy in earlier trials.
  + 2y OS 67%. CR 67%. No major neurotoxicity, in fact improvements in all tested domains.
  + 21 pts CR→ 19 pts 23.4 Gy (2 refused). 2y OS 89%, 2y PFS 79%.
  + Follow-up 2013 study [[Morris JCO '13]](https://europepmc.org/articles/pmc5569679): 52 pts. Median age 60. Median KPS 70.
    - CR in 60%. 50% CR after 5c, or 80% CR after two additional cycles with 16% PR (95% response).
      * CR (23.4 Gy): 2y PFS 77% w MPFS 7.7y. **5y OS 80%**. MS NR with nearly 6y of follow-up.
      * Of the 31 pts who rec'd rdWBRT, 12 pts progression-free and completed neuropsych evals up to 48 mo. At baseline, cognitive impairment evidence across several domains.
        + After induction chemo, significant improvement in executive and verbal memory.
        + No evidence of significant cognitive decline during follow-up, except for motor speed.
    - MPFS 3.3y, MS 6.6y.

* + - Of the 22 pts ≥ 60y, 9 alive without progression, 10 with progression, and 3 died without progression.
      * There were no deaths from neurotoxicity.
      * Elderly pts with MS 5.5y. Previously reported to be 1-1.5y MS.

* **RTOG 0227** [[Glass JCO '16](http://ascopubs.org/doi/full/10.1200/JCO.2015.64.8634)]: **R-MTX/TMZ** x5c**→ WBRT 36/30 BID** (1.2 Gy)**→ TMZ**.

Recall: CR after 5c / 7c of R-MPV of 60→ 80%. This study demonstrated 50% CR.

* + Phase I-II. R 375, MTX 3.5 q2w x5c. TMZ w4, w8, then 200 for nearly 1y.
    - Phase I: 13 pts w an increasing dose of TMZ (100/150/200).
    - Phase II: 53 pts. MFU 3.6y.
  + 2y OS 81%. 2y PFS 64%. Compare to [[9310](#kix.nv4dacheztsq)], with 2y OS 64% and 2y PFS 50%.
  + 51% CR, 34% PR.
  + G3+ 66% before WBRT, G3+ after WBRT attributable to chemotherapy 45%.
  + Cognitive function and QoL improved or stabilized after RT.
  + Improved MMSE at 3y more pronounced in pts ≥ 60y.
* **RTOG 1114** [[Omuro ASCO '20](https://meetinglibrary.asco.org/record/185073/abstract)]: Phase II. **R-MPVx5-7c (80% CR)→ ± WBRT (23.4/13 if CR)→ Ara-C x2c**.

When is rdWBRT going to be seriously considered as first-line for PCNSL?

* + 91 patients. Median age on WBRT arm nearly 70y! MFU 4.5y.
  + Median ITT PFS 25→ NR. 2y PFS 54→ 78%.
  + MS NR in either arm, with data still maturing.
  + Clinically defined moderate to severe neurotoxicity of ~11→ 14% (p=0.75)

* **Delaying WBRT for salvage** [[Nguyen JCO '05](http://ascopubs.org/doi/full/10.1200/JCO.2005.01.161)]: **Failed HD-MTX→ WBRT 36/24**.   
  For patients >60y, delaying WBRT until time of progression may decrease neurotoxicity rates.
  + 27 pts. 1994-2003. Majority of pts (67%) remained on steroids.
    - WBRT, no boost: 36 Gy (28-45). 7 pts boost: 36 Gy (19.6-40) w boost 10 Gy (10-21.6) or 12/16 Gy SRS.
  + ORR 74%; CR 37%, PR 37%.
    - 8 pts later progressed to recur at median 18.8 mo post-WBRT.
  + At the time of maximal response, KPS improved in nearly half and stabilized in 2/3.
  + MS after salvage WBRT 11 mo.
  + Late treatment neurotoxicity in 11% (n=3), associated w > 36 Gy and occurring at a median of 25 mo.

## [Toxicity](#_8xl8mj5300dm)

* Intraventricular chemo w HD-MTX and Ara-C with 9% rate of treatment-related death [[Pels JCO '03](http://ascopubs.org/doi/full/10.1200/JCO.2003.04.056)]
* According to [[RTOG 93-10](#kix.nv4dacheztsq)], 15% of patients > 60y w delayed severe neurotoxicity after WBRT.
  + However, [[02-27](#kix.ac2mevi6hc4s)] demonstrates cognitive function and QoL improved or stabilized after RT (36/1.2 BID).

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| **Modern RT for Extranodal Lymphomas: Field and Dose Guidelines** **from the ILROG** [[Yahalom IJROBP '15]](https://www.sciencedirect.com/science/article/pii/S0360301615000504?via%3Dihub).   * Doses around 45 Gy decrease risk of progression or relapse, but is Britney Spears toxic especially for > 60y. * There is [[suggestion of no benefit](#o0h8dmn48fu0)] above 36 Gy WBRT in the setting of effective chemotherapy. * For CR, 23.4 Gy WBRT appears to be acceptable without toxicity, even in the elderly [[MSKCC](#kix.h2nxzvb803w7)]. * In the salvage setting, 36 Gy appears to be acceptable [[Nguyen](#o36n6yt314q)]. * Given PCNSL is commonly a multifocal process, a "lesion boost" is not recommended in most cases. * PCNSL fields always include the ON and retina. Set the field anteriorly for potential future isocentric match. * If the eyes are involved prior to chemo, then WBRT should be extended to include the entire globe to 30-36 Gy. * Dosing recommendations:   + CR→ 24 Gy WBRT.   + PR or Salvage: 36-45 WBRT (1.5 to 1.8 Gy/fraction).   + Non-chemo candidates: 40-50 Gy WBRT (1.5 to 1.8 Gy/fraction).   + Palliation: WBRT 30-36/10-15. |

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## [Treatment](#_8xl8mj5300dm)

See the ILROG Guidelines above.

* WBRT includes cribriform plate and posterior 1/3 of the orbit (put BB at lateral canthus). Cover to C2/C3 "German helmet".
  + Get a slit lamp examination prior to chemo, if present, then include bilateral orbit to 36 Gy (flash eyes).
  + 3y OS nearly 90% with MS 6y for those who achieve CR (~60% after 5c R-MPV, ~80% after 7c R-MPV).
* **Age < 60 and KPS > 40** after steroids:
  + **R-MPV x5c** q2w. R-MPV = Rituxan, HD-MTX (3.5), Procarbazine, Vincristine.
    - **If CR**: ~60% CR after 5c R-MPV. ~80% CR after 7c R-MPV.
      * High dose chemo with stem cell rescue [[Omuro Blood '15](http://www.bloodjournal.org/content/125/9/1403), [Illerhaus Blood '12](http://www.bloodjournal.org/content/120/21/302) w 2y OS ~81%]
      * High dose Ara-C ± etoposide.
      * **rdWBRT** (23.4 Gy)→ high dose **Ara-C x2c**.
      * Continue monthly HD-MTX for up to one year.
    - **If < CR**, 2 more chemo cycles.
      * If CR after 7c (~80%)→ rdWBRT (23.4 Gy)→ Ara-C x2c.
      * **If < CR** after 7c, **full dose WBRT** (30-36 Gy WBRT with 45 Gy boost to gross dz - per NCCN).  
        Note: Boost to residual disease is not recommended in most circumstances per ILROG, given this is a multifocal process. Instead, ILROG recommends 36-45 Gy WBRT in 1.5-1.8 Gy/fraction.

Example which is acceptable per NCCN and ILROG for PR: 36/24 (1.5 Gy), with 43.2/24 (1.8 Gy) SIB to residual.

* + - * High dose Ara-C ± etoposide.
      * Best supportive care.
* **Age > 60 and KPS > 40** after steroids:
  + It is very reasonable to deliver 23.4 Gy rdWBRT for patients in CR after chemotherapy, [[regardless of age](#h6kwzldtev01)].
  + HD-MTX→ **If CR, Observe**. If < CR, WBRT.
  + If HD-MTX alone and failure >1y, may repeat HD-MTX, other systemic tx, or high dose chemo with stem cell rescue. Add WBRT prior to high dose chemo with stem cell rescue if failure < 1y after HD-MTX.
    - Salvage WBRT with CR ~40-60% and PR ~20-40% [[Nguyen JCO '05](http://ascopubs.org/doi/full/10.1200/JCO.2005.01.161?url_ver=Z39.88-2003), [Hottinger Neuro '07](http://n.neurology.org/content/69/11/1178.long)]
* **If KPS < 40 or renal dysfunction (no chemo), WBRT alone**.
  + Try steroids first. If KPS improves, chemo, otherwise 24-36 Gy WBRT with boost to 45 Gy (per NCCN).  
    ILROG recommends WBRT to 40-50 Gy in 1.5-1.8 Gy/fraction without a boost.
* If other metastatic disease, HDMTX + R-CHOP x6c followed by consolidative RT.
* If CSF+ or spinal MRI positive, consider IT-chemo. If there is no IT-chemo, consider focal spinal RT.
  + If LMD, consider CSI to **39.6 Gy** with additional 5.4-10.8 Gy to gross disease.
* If the eye exam is positive, IO chemo or RT to the globe.
  + CR 23.4 Gy, PR 36 Gy (not 45). RT to 36 Gy or chemo.
  + Local control after orbital RT > 90%. UF does 15-47.5 Gy (median 25.5 Gy) with 5y LC 98%.
* Boost is highly controversial. Consider 1-4 cm margins. Margins smaller than 4 cm around lesion associated with a higher failure rate and decreased overall survival per [[ILROG](#kix.mmiq0lal9y9s)].
  + CTV\_boost = GTV + 1-2 cm, up to 4 cm.

## [Follow up](#_8xl8mj5300dm)

* HP, Neuro exam and MRI q3mo x2y, q6mo to year 5, then annually.

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# [Plasmacytoma/Multiple Myeloma](#_e4a3jnknxfj8)

See NCTN Trial Portfolios by Disease Site: [[Myeloma](https://ctep.cancer.gov/initiativesPrograms/docs/nctn_trials/NCTN_Myeloma.pdf)]

**StatPearls: Lytic Bone Lesions** *Last update: 4/4/2019.*

[**StatPearls: Multiple Myeloma**](https://www.ncbi.nlm.nih.gov/books/NBK534764/)*Last update: 3/19/2019.*

ARRO: [[Solitary Plasmacytoma](https://www.astro.org/ASTRO/media/ASTRO/AffiliatePages/arro/PDFs/ARROcase_Plasmacytoma.pdf?utm_source=MagnetMail&utm_medium=email&utm_term=jeff.ryckman@gmail.com&utm_content=ARROgram%5F042320&utm_campaign=ARROgram%20April%20Monthly%20Announcement)]

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| **ASCO Guideline:** [**Treatment of Multiple Myeloma**](https://www.asco.org/research-guidelines/quality-guidelines/guidelines/hematologic-malignancies#/35681) *April 1, 2019*  **ILROG Guidelines: RT for Solitary Plasmacytoma and Multiple Myeloma** [[Tsang IJROBP '18](https://www.sciencedirect.com/science/article/pii/S0360301618308022?via%3Dihub)]  See the [[Treatment Planning](#_cree2ven8zqa)] section for more information.  Much lower doses are used for multiple myeloma. 40 Gy all day for SBP/SEP (35 Gy acceptable for SBP < 5 cm per ILROG).  Interestingly, treating 1-2 normal vertebral bodies above and below disease are obsolete for MM.  Cover hardware hardware within the CTV if there was potential seeding.   * Solitary Plasmacytomas are radiosensitive. RT is the standard of care. 5y LC 85-95%, 10y LC ~85%.   + CTV = GTV + 2-3 cm WRT anatomical boundaries.   + The most dreaded complication of SP is the transformation to multiple myeloma.  There appears to be a benefit in decreasing transformation to MM when RT is given concurrently with lenalidomide. * Dosing for SP:   + SBP < 5 cm: 35-**40 Gy** [[PMH Tsang IJROBP '01](https://www.sciencedirect.com/science/article/pii/S0360301600015728)]. *NCCN recommends 40 Gy at a minimum.*   + SBP > 5 cm: **40**-50 Gy.   + SEP: **40**-50 Gy.   + For SP with minimal BM involvement, total dose and fractionation can be modified (see MM dosing). * Dosing for MM:   + 30/10, 20/5, 8/1 reasonable. There is no definitive evidence for more durable control with 30/10 over 20/5, although 8/1 is less durable and preferred for patients who are [[poor prospects](#f7owkz2ou11s)] for survival. *Patients with CNS myeloma have an extremely poor prognosis, with 1y OS of ~20% and median survival of 2-6 mo.*   + ILROG recommends 30/10 over 20/5 for epidural disease with cord compression, large volumes, or retreatment.   + Dex 4 mg BID for cases with nerve root or cord compression to prevent pain flair, consider QID for symptoms.   + MDACC review suggests 20-25/10 effective and durable (< 3% re-irradiation) for tumors without frank cord compression or large paraspinal extent [QS](http://www.quadshotnews.com/2020/04/deuces.html) [[Elhammali Heme '20](http://www.haematologica.org/content/early/2020/01/03/haematol.2019.235804)]. * Determination of GTV:   + Field placements based on anatomic landmarks (e.g. 1-2 normal VB above and below) are obsolete. * Determination of CTV:   + SP: CTV = GTV + 0.5-3 cm. May use 0.5-1 cm axial for H&N. For long bones, use 2-3 cm CC esp if no MRI.     - It is acceptable to add the whole VB (or bone) in the CTV if there are no significant morbidity risks.     - ENI for SEP of H&N: Not recommended especially if MRI obtained. Waldeyer's ring does not mandate cervical nodal coverage.   + MM: No CTV margin is necessary in the setting of systemic disease. Whole bone coverage is not required, especially if receiving systemic therapy. |

* Derived from terminally differentiated B cells that produce and often secrete monoclonal immunoglobulins.
* Plasma cell neoplasms are ~1/5 of mature B-cell neoplasms in the USA. ~1-2% of US cancers diagnosed yearly, or 30k.
  + ≥ 90% are MM, only ~2-10% are solitary plasmacytomas (SPs). Definitive RT is the standard of care for SPs.
* 2:1 African Americans to Caucasians.
* SP 4:1 M:F with the median age of diagnosis 50-55y.
  + As opposed to SP, MM is generally incurable, with ~20% asx at diagnosis. Average age 10y greater than SP.

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| **Solitary Bone Plasmacytoma** (SBP) **vs. Solitary Extramedullary Plasmacytoma** (SEP) | | |
|  | **SBP** | **SEP** |
| **Incidence** | Most common. | Around 20-30%. |
| **Secretory** | Usually. May involve BM (< 10%). | No |
| **Transformation to MM** | 65-85% | 10-40% |
| **Timeframe** | Bimodal (2-3y esp if BM, 6-9y). | 10 years. |
| **Nodal involvement** | Less common. | More common (25% if H&N). |
| **Dx of SP**: Biopsy proven destructive bony or soft tissue lesion, Normal skeletal survey and pan-spine/pelvis MRI/CT (MRI especially for long bones or H&N), PET/CT optional but preferred and some consider it mandatory, no end-organ damage.  **Dx of SP with minimal BM involvement**: As above, but < 10% of BM. Over half transform to MM by 2-3 years.  Two or more plasmacytoma lesions, even in the setting of negative BMBx, are classified as MM.  Factors correlating with conversion to MM: ≥ 5 cm, > 40y, M-spike, spinal location, the persistence of M-protein >1y after RT. | | |

## [Solitary Plasmacytoma](#_rqr95ggtven3)

See the Summary Box above.

* **SBP** (most common): Usually secretory. May involved bone marrow (< 10%).
  + **SBP→ MM 65-85%** in a bimodal distribution either 2-3y or 6-9y after presentation.  
    If SBP with minimal BM involvement (< 10%), then over half convert to MM by 2-3y.
  + Usually it does not involve nodes.
* **SEP** (20-30%): Most commonly located in H&N, upper aerodigestive tract (UAD). Usually non-secretory.
  + **SEP→ MM 10-30%** at 10y.
  + SEP is more commonly localized, and local therapy will achieve long term local control.
* **SEP more commonly involves nodes** (25% if H&N). SEP nodal involvement is less common if UAD tract.
  + Lymph node risk for SEP for UAD /non-UAD tract of 8→ 2.6%. Best prognosis for SEP in UAD tract.

* **France** [[Mignot IJROBP '19](https://www.ncbi.nlm.nih.gov/pubmed/31707123)]: Retro. ≥ 40 Gy **IMRT ± Concurrent Lenalidomide-Dexamethasone**.  
  Similarly to concurrent [[Rituximab/RT](#oufz0rscwg32)] for Follicular lymphoma, Lenalidomide-Dex/RT is effective for SP.  
  The dreaded complication of early-stage FL is transformation to DLBCL, similar to MM for SP.
  + 46 pts. 27 pts IMRT alone, 19 pts Lenalidomide-Dex/RT. 2007-2018. MFU 5y (short).
    - RT: 40 Gy for SBP, 46 Gy for SEP.
    - No consolidative therapy, chemotherapy or proteasome inhibitors allowed.
    - Lenalidomide 25mg/d x21d qmo x4c. First dose administered on the first day of RT.
    - Forty patients were SBP (87%), while only 6 were SEP (13%).   
      Note: SBP has around a 2x higher rate of transformation to MM than SEP.  
      There is no comment on the number of SP patients in this study with [[minimal BM involvement](#xwaho4phsfwq)].
  + 5y LC 96%. 5y MMFS 85%. 5y PFS 60%.
  + 5y MMFS 77→ 100%. 5y PFS 48→ 82%.
* **POEMS syndrome** (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) is a variant of MM with solitary or limited sclerotic bone lesions that often respond to RT with spontaneous improvement in neuropathy.

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|  | **MGUS** | **Smoldering MM** | **MM** |
| **Proteins** | Serum M-protein **< 3** g/dL | Serum M-protein ≥ 3 g/dL or Bence-Jones protein ≥ 500mg/24h |  |
| **BMBx** | BM plasma cells **< 10%** | BM plasma cells ≥ 10% | BM plasma cells ≥ 10% |
| **End organ damage** | No end-organ damage | No end-organ damage | End-organ damage |
| **Transformation/Progression** | 1%/y\* | 10%/y\*\*. | - |
| \*Initial size of the M-protein peak is predictive of the risk of transformation.  \*\*Risk of progression to symptomatic MM. Plasma cell labeling index >1% associated with higher progression to MM, poor OS [[1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2843123/)]. | | | |

## [MGUS and MM](#_rqr95ggtven3)

See table above.

* **MM**: ≥ 10% plasma cell + end-organ damage, hypercalcemia, renal insufficiency, anemia, or bone lesions, clonal BM plasma cells ≥ 60%, abnormal serum FLC ≥ 100 (involved κ) or < 0.1 (involved λ), >1 focal lesion on MRI > 5 mm.
  + Osteolytic lesions found in 70-80% of patients with MM. 20% are asymptomatic at diagnosis.
  + **End organ damage**: CRAB + frequent severe infections, amyloidosis, hyperviscosity syndrome.
  + Immunoperoxidase staining detects either κ or λ light chains, but not both, in the cytoplasm of BM plasma cells and cytogenetics detects recurrent alteration in ~60% of pts.

* + **Prognosis for elderly patients ( > 65y) presenting with cord compression** [[Rades BMC Cancer '16](https://bmccancer.biomedcentral.com/articles/10.1186/s12885-016-2325-y)]:
    - 1y OS ranges from 0% to 96%.
    - Poor predictors: ECOG-PS matters most, followed by non-IgG myeloma type, ambulatory status, and age.
  + Patients with CNS myeloma have an extremely poor prognosis, with 1y OS of ~20% and median survival of 2-6 mo.
* [**Revised ISS**](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4846284/):
  + I - β-2 micro < 3.5, albumin ≥ 3.5 dL and standard risk chromosomal abn by FISH and LDH < ULN. 5y OS 82%
  + II - not I or III. MS 83 mo.
  + III - β-2 micro ≥ 5.5. Stage III depending on ± chromosomal abn\* by FISH and/or LDH. MS 43 mo.  
    \*High-risk chromosomal abnormalities = del (17p), t(4;14), t(14;16).
* Chemo: Bortezomib and lenalidomide or carfilzomib and lenalidomide, each with dexamethasone.
  + Bortezomib - proteasome inhibitor.
* **ENDURANCE** [[Kumar ASCO '20](https://meetinglibrary.asco.org/record/186906/abstract)]: **Lenalidomide/Dexamethasone +** (**Bortezomib vs. Carfilzomib**).

TBL [QS](http://www.quadshotnews.com/2020/06/embrace-status-quo.html): Carfilzomib failed to additionally improve either progression-free or overall survival, meeting futility at its second planned interim analysis. In other words, bortezomib + lenalidomide + dex (VRD) remains standard initial therapy for most multiple myeloma.

* + 1,087 pts. Refractory MM. Excluded del17p,t(14;16), t(14;20), plasma cell leukemia, and high-risk GEP70 profile.
  + MPFS ~34 mo.
  + Side effects: Bortezomib - Neuropathy (reason why it is given subQ weekly). Carfilzomib - Cardiotoxicity.

## 

## [Treatment Planning](#_rqr95ggtven3)

ARRO: [[Solitary Plasmacytoma](https://www.astro.org/ASTRO/media/ASTRO/AffiliatePages/arro/PDFs/ARROcase_Plasmacytoma.pdf?utm_source=MagnetMail&utm_medium=email&utm_term=jeff.ryckman@gmail.com&utm_content=ARROgram%5F042320&utm_campaign=ARROgram%20April%20Monthly%20Announcement)]

ILROG Guidelines: RT for Solitary Plasmacytoma and Multiple Myeloma [[Tsang IJROBP '18](https://www.sciencedirect.com/science/article/pii/S0360301618308022?via%3Dihub)]. [RoR](#kix.54wzk8q4h2qy)

* Cover nodal areas in SEP if clinically involved. Involvement of Waldeyer's ring does not necessitate cervical nodal coverage. The incidence of lymph nodes in H&N SEP is around 25%, although less common if upper aerodigestive tract.
* **SP**: **Curative**. **Goal to prevent transformation to MM**, which is extremely common by 2-3y for minimal BM involvement or persistence of M-spike by one year after RT.
  + **40 Gy** is a good place to start. May consider 35 Gy if SBP < 5 cm (per ILROG, not NCCN), or > 45 Gy for SEP.
  + Studies suggest LC 100% for SEP dose > 45 Gy, while two studies [[1](https://www.sciencedirect.com/science/article/pii/S0360301605022236?via%3Dihub),[2](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1479355/)] suggest no dose response for SBP >30 Gy.
  + NCCN recommends 40-50 Gy despite evidence for no dose-response above 30 Gy.
* **MM**: **Goals are palliative**.
  + Be sure to [[prognosticate](#f7owkz2ou11s)] patients with cord compression. Bad prognosticators: bed-bound, non-IgG MM, > 65y.
  + Patients with CNS myeloma have an extremely poor prognosis, with 1y OS of ~20% and median survival of 2-6 mo.
  + Dex 4 mg BID for cases with nerve root or cord compression to prevent pain flair, consider QID for symptoms.
* Margins:
  + CTV including one VB above and below VB lesion is outdated and is now obsolete.
  + SP CTV margins: 2-3 cm with respect to anatomical boundaries. May use a 0.5-1 cm axial in H&N.
    - Utilize MRI for long bones and H&N. Prefer 2-3 cm CC for long bones. May include the entire bone.
  + MM CTV margins: Non-CTV margins necessary. Whole bone coverage is not required.

## [Follow up](#_rqr95ggtven3)

* SP: SPEP and UPEP q6mo. CBC, CMP with calcium, episodic skeletal surveys.
  + For patients with M-protein detectable prior to RT, the presence of M-protein at 1y after RT predicts a very high rate of transformation to MM.
  + Recommend re-imaging at 3-6 mo. It may take 6-8 mo for SP to maximally respond to definitive RT.
  + Periodic reimaging q4-6 mo may be considered for any residual tumor mass.

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# [PCL/CTCL](#_e4a3jnknxfj8)

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| **ILROG Guideline: Modern RT for Primary Cutaneous Lymphomas: Field and Dose Guidelines** [[Specht IJROBP '15](https://www.sciencedirect.com/science/article/pii/S0360301615000279?via%3Dihub)]  PC-Follicular center lymphoma, PC-MZL and PC-ALCL   * T1 are generally treated with "involved lesion RT". * Margins recommended from 0.5-5 cm, though 1-1.5 cm is recommended. * Depth margin is theoretically the same as lateral margins, but may be modified depending on the thickness of the lesion. * Most lesions can be effectively treated with 6-9 MeV. * Bolus is generally required. * Alternatively, superficial voltage (~100 kV) may be used. * Local control is excellent for PC-FCL and PC-MZL with reports ranging from 20-45 Gy, most commonly 24-40 Gy. * Dose ranges:   + EORTC/ISCL: 20-36 Gy for PC-MZL and ≥ 30 Gy for PC-FCL.   + NCCN: 24-30 Gy for PC-MZL, with a similar dose range for PC-FCL.   + There are few dose guidelines for PC-ALCL. 24-50 Gy has been reported, with the suggestion of 40 Gy recommended. ILROG recommends 24-30 Gy given reports of durable CR at this range. |

* PCLs account for ~20% of extranodal lymphomas or ~4,000 cases per year.
* **B-cell vs. T-cell and NK cell** (Non-cutaneous)
  + B cell (85%): DLBCL 33% > follicular 20% > MALT = B-cell CLL 5-10% > mantle cell 5%.
  + T cell (15%): T/NK cell, PTCL 6% > MF <1% < ALCL 2%. *T cell uncommon, but aggressive.*
* **Primary cutaneous lymphomas**

* + B cell (20-25%): PC-FCL (60%) > PC-MZL (25%) > PC-DLBCL, leg type (15%).

* + T cell (75-80%): MF most common type in the USA (50% of all PCLs). PC NK/TCL, nasal type in Asia.
    - Also PC-ALCL, Subcutaneous panniculitis-like TCL, PC ៵-δ TCL.
* **Workup**: PET/CT if not validated, but may be useful. Perform BMBx for PC-DLBCL, leg type.
  + Complete H&P, photography of skin lesions, LDH, SPEP may be indicated to exclude monoclonal gammopathy.

## 

## [**Palliative RT for indolent CTCL**](#_1n90fu1b692j)

* **Low dose palliative RT for indolent PC-BCL** [[Goyal J Am Acad Derm '18](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5961938/)]: **4-8/2 vs. 24-40/12-20**.  
  This study grouped 8/2 and 4/2 together and did not mention the number of pts who rec'd 8/2.
  + 54 B cell pts with 98 lesions, 2/3 PC-MZL. MFU 5y.
    - RT: Does not describe margins or energy used. Likely 1-2 cm w 6-9 MeV.
  + CR ~95%. For those who obtained CR, 1y LF 7→ 6% (p=0.07).
  + Acute erythema 16→ 78%.
  + Postinflammatory hyperpigmentation 8→ 40%.

* **Low dose palliative RT for Cutaneous B and TCL** [[Neelis IJROBP '09](https://www.sciencedirect.com/science/article/pii/S0360301608029519?via%3Dihub)]: **4/2** (**CBCL**) or **8/2** (**MF**). 20/8 for salvage.

CBCL: Palliative Boom Boom with CR of 75%, while 30% required re-treatment at a median of 6 months.

* + 31 T cell pts: 31 MF pts w 82 sx sites, initially 4/2 then later 8/2 (24 pts w 65 plaques). MFU 10 mo.
    - Half of MF pts previously rec'd 35/20 TSI on average 2.5y prior to current RT.
  + 18 B cell pts: 10 PC-MZL and 8 PC-FCL w 44 sx plaques and tumors. MFU 13 mo. Short follow-up.
    - RT: 2 cm margins of surrounding healthy skin, mostly 4 MeV. Perhaps too shallow (~1 cm 80% IDL)
  + CR for CBCL 75%. 13/44 (30%) re-tx at median of 6 mo due to persistent (8 pts) or recurrent (5 pts) sx disease.

Recall: [[FORT](#2ir15dd82frs)] trial with 25% LF at two years!

* + CR for MF with 4/8 Gy in 2 fractions of 30→ 92%.
  + **All pts** (CBCL and MF) **who failed to have CR were salvaged with 20/8, all achieving CR**.
  + Toxicity: 2 Gy x 2 may still cause temporary hair loss, no comment on 4 Gy x 2 toxicity.

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| ISCL/EORTC Staging for non-MF PCLs [[Kim Blood '07](http://www.bloodjournal.org/content/110/2/479.short?sso-checked=true)]   * T1: Solitary skin. a/b ± 5 cm. * T2: Regional skin. a/b/c 15/30 cm diameter. * T3: Generalized skin. b if ≥ 3 body regions. * N1: 1 LN region draining to current/prior skin invlmt. * N2: 2+ LN regions to current/prior or non-regional. * N3: Central lymph nodes. * M1: Extracutaneous non-LN disease present.   T2: Regional skin limited to 1-2 contiguous body regions.  T3: 2 Non-contiguous body regions, or ≥ 3 contiguous regions. |  |

## [Non-MF PCLs](#_1n90fu1b692j)

50% of all PCLs.

ILROG Guideline: Modern RT for Primary Cutaneous Lymphomas: Field and Dose Guidelines [[Specht IJROBP '15](https://www.sciencedirect.com/science/article/pii/S0360301615000279?via%3Dihub)]. [RoR](#_buun9ubd3cdd)

* **PC-DLBCL, leg type**: 15% of PC-BCL.
  + Poorer prognosis than PC-MZL and PC-FCLs. Tends to **relapse in non-cutaneous sites**, unlike other PC-BCLs.
  + Rapidly growing red to bluish tumors often located on LE. Often in elderly.
  + Solitary disease usually **R-CHOP x3**→ ISRT. Favor anthracycline-based chemo w rituximab.
    - RT alone ± rituximab if chemo is not tolerated.
    - Use **1-2 cm** margin on pre-chemo GTV.
    - Recommends 6-8 MeV.
    - ILROG says **36**-40 Gy recommended, favoring 40 Gy if no systemic tx.
* **PC-Follicular center lymphoma**: 60% of PC-BCL.
  + Most common PCBCL. Commonly indolent lesions on **scalp**, **forehead**. CD20+, CD79a+, bcl-6.
  + RT used as first-line, in-field recurrences rare.
  + 5y DSS 97% when RT used as primary treatment.
* **PC-Marginal zone lymphoma**: 25% of PC-BCL.
  + Typically deep-seated nodular or papular lesions on **extremities** or **trunk**. Extracutaneous involvement is rare.
  + RT used as first-line, in-field recurrences rare.
  + DSS ≥ 95% for localized disease.

* **PC-Anaplastic large-cell lymphoma** (**PC-ALCL**): 8% of PC-TCL, but >75% CD30+.
  + Median 60y. Compared to LyP, which is median age 30 and not malignant.
  + **Deeper** invasion (subQ), **horizontal** shape, usually **>2 cm** with ulceration, **solitary**, **persistent** and enlarging.
    - May be ALK positive (systemic - rare) or ALK negative (primary cutaneous).
    - If ALK is negative, one could consider ALK staining to be a systemic workup.
    - DUSP22.IRF4 (6p25.3) in 20-30% of PC-ALCL.
  + Systemic ALCL with poor prognosis, but PC-ALCL usually indolent with OS ≥ 90%.
  + Localized dz: ILROG 24-**30 Gy** [[Million IJROBP '16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5488803/)], NCCN 24-36 Gy or excision. **Previously 40 Gy** reported[[1](https://www.sciencedirect.com/science/article/pii/S0360301607042356?via%3Dihub)].
  + Multifocal disease with MTX, systemic retinoids, pralatrexate, brentuximab, or observation.
  + Workup: Include **HTLV-1**, which can be CD30+ and have an MF-like component, TTE (anthracycline use).
* **Treatment of PC-FCL, PC-MZL, PC-ALCL**:
  + Well established data for the former two, less established and ∴ broader spectrum of RT for PC-ALCL.
  + Workup: Expert dermatopathologist review. H&P, photography of lesion, LDH, consider SPEP.
  + T1-2 disease: RT and/or excision. May try obs or topical medications.
    - NCCN and ILROG say **24-30 Gy**, favor 30 Gy for PC-FCL/ALCL.
      * 20-36 Gy for PC-MZL, ≥ 30 Gy (36 Gy) for PC-FCL.
    - Typically 6-9 MeV.
    - Use **1-1.5 cm** margins (including deep) for PC-FCL and PC-MZL. May need up to 5 cm margins.
  + Boom boom (2 Gy x 2) with CR 72%, 30% req re-tx at median 6 mo [[Neelis IJROBP '09](https://www.sciencedirect.com/science/article/pii/S0360301608029519?via%3Dihub)].
    - After failure, all pts achieved CR with 20 Gy in 8 fractions.

* **Lymphomatoid papulosis** (**LyP**): CD4+ T cell, CD30+. Compared to PC-ALCL, median age 60y.
  + A lot of patients feel like this is just acne. But... it's not \*gasp\*. Median age of presentation 30y.
  + **Superficial** (dermis), **wedge** shape, size **< 2 cm**, **multiple** lesions, **regressing**, papulo/papulonodular.
  + A chronic lymphoproliferative disorder with diffuse papular, papulonecrotic, or nodular skin lesions.
  + Often generalized, common to have spontaneous regressions ("self healing") and chronic recurrences.
    - Most pts try: Topical OTC steroids, antifungals, anti-bacterials.
    - Often, no tx needed.
  + 5y OS/DSS 100%, but the risk of transforming to other lymphomas (MF, PC-ALCL, systemic ALCL, or HL).
  + Palliation with PUVA, MTX, IFN, topical/intralesional steroids, topical bexarotene.
* **Subcutaneous panniculitis-like TCL**:
  + α/β T-cell phenotype and solitary skin lesions ≥ **40 Gy**, typically with electrons. Little information available.
* **PC-៵-δ TCL**:
  + Often presents as generalized skin lesions. May respond poorly to systemic tx.
  + Give 24-30 Gy, but pts tend to relapse.
* **PC-NK/T-cell lymphoma, nasal type**:
  + Usually involves nasal cavity, paranasal sinuses, or waldeyer's ring.
  + Large chinese study suggests < 5% annual risk of failure once 3y out from RT for early-stage NKTCL [[Liu '19](https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2726713)]
  + Localized dz initially treated w **50 Gy** + **5-10 Gy boost** for residual.
  + Usually locally destructive and may extensively infiltrate the submucosa beyond macroscopically evident dz. Hence, the entire involved cavity and adjacent structures require irradiation.
  + Nasal CTV = bilateral NC, ipsi maxillary sinus, bilateral anterior ethmoid sinuses, hard palate.
    - Include the entire NP if near the posterior nasal aperture.
  + Include posterior ethmoid sinuses for disease extending to ant ethmoid sinuses.

# [Mycosis fungoides](#_1n90fu1b692j)

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| T1: < 10% BSA. a/b ± plaque.  T2:  **≥ 10%** **BSA**. a/b ± plaque.  T3: **≥ 1 cm** in diameter with deep infiltration (Tumor).  T4: Gen erythroderma > 80% BSA.  N1: Dutch G1 | NCI LN 0-2.  No atypical lymphocytes | ITC.  N2: Dutch G2 | NCI LN 3, a/b ± T-cell clone.  Early involvement w MF, cerebriform nuclei > 7.5 μm.  N3: G3-4 | NCI LN 4.  Loss of LN architecture. | |  |  |  |  |  | | --- | --- | --- | --- | --- | |  | **T1** | **T2** | **T3** | **T4** | | **N0** | **IA** | **IB** | **IIB** | **IIIA**  If B1: **IIIB**  If B2\*: **IVA1** | | **N1** | **IIA** | | | **N2** | | **N3** | **IVA2** | | | | | **M1** | **IVB** | | | |   B0: a/b ± clone.  B1: **> 5%** **Sezary** a/b ± clone.  B2: ≥ 1k cell/uL w + clone. |

**B1 does not influence staging** unless T4 (IIIB)

\*B2 disease automatically at least IVA1.

ILROG Guideline: Modern RT for Primary Cutaneous Lymphomas: Field and Dose Guidelines [[Specht IJROBP '15](https://www.sciencedirect.com/science/article/pii/S0360301615000279?via%3Dihub)]. [RoR](#_buun9ubd3cdd)

Total skin electron beam RT [[Zaorsky tweet](https://twitter.com/NicholasZaorsky/status/1226199181766938624?s=20)].

**ISCL/EORTC Staging for MF** [[Blood '07](http://www.bloodjournal.org/content/110/6/1713.long?sso-checked=true), Time for an update? [EMJ '18](https://www.emjreviews.com/hematology/article/staging-of-mycosis-fungoides-and-sezary-syndrome-time-for-an-update/)]

* **~50% of all CTCLs**, 70% of all PC-TCLs, **~2% of all lymphomas**. Only 600 new cases/year!
* Low grade NHL caused by skin-homing CD4+ T cells that form cutaneous lesions.
* Median age 55-60; risk factors black and male (2:1, 2.2:1). 2x likely if black.
* **Prognosis**:
  + Stage IA disease with excellent prognosis, prognosis similar to normal controls.
  + Stages IA-IIA (no tumor) with excellent px (unless Folliculotropic) MS 12-20y[[EMJ '18](https://www.emjreviews.com/hematology/article/staging-of-mycosis-fungoides-and-sezary-syndrome-time-for-an-update/)].
    - ~25% of early stage become refractory to skin-directed therapy and progress to tumor (IIB+).
  + Stages IIB-IVB w poor px, MS < 4y. Although some survive >10y, Stage IVA2-IVB MS < 12m.
    - Stage IIB may be worse than stage III. Tumors may be worse than generalized erythroderma.
  + Allogeneic SCT may be offered for pts in remission, but 1y mortality 15-20% w relapse rates up to 50%.
* **Workup**:
  + Full skin exam including soles, perineum, nails, auditory canals.
  + Biopsy: Minimum of **two areas** of involved skin, do PCR for the T-cell receptor genes.
    - Bx nodes if palpable, firm, irregular, clustered, or ≥ 1.5 cm diameter.
  + CBC, LDH, blood smear for sezary.
  + PET/CT or CT C/A/P indicated if N1 or T3 (any stage II).
  + Takes 6-24 mo to diagnose!! May look like [[LyP](https://docs.google.com/document/d/1gKy2Hpx7FxInjOpKIBkTFJWpqhJ3I-gSXz9eRwq-NSY#bookmark=id.737rzyynd38e)]; multiple bx may be req'd!
    - 70-80% diagnosed in early stages with skin involvement only. No LNs or internal organ involvement.
    - ~15% have LN involvement at Dx.
* **Histology**
  + 4 types: MF, Sezary, ATCL, Primary cutaneous CD30+ anaplastic lymphoma.
    - Folliculotropic and large-cell transformation carry a worse prognosis.
  + Related to these 3: Lymphomatoid papulosis [[LyP](https://docs.google.com/document/d/1gKy2Hpx7FxInjOpKIBkTFJWpqhJ3I-gSXz9eRwq-NSY#bookmark=id.737rzyynd38e)], Pagetoid reticulosis, follicular mucinosis.
  + Histopathologic hallmark: **Pautrier abscess** (microabscess) only in 20% of early stage disease.
  + Only 5% present with **Sezary Syndrome**: Leukemic variant of CTCL with widespread skin involvement.
    - Erythroderma (T4) + evidence of circulating T cell clones in blood.
    - Sezary cells > 5% is B1 disease. *B1 doesn't influence stage unless T4 (general redness).*
    - Sezary cell ≥ 1k cell/uL. *This is B2 disease, or stage IVA1.*
    - CD4/8 ≥ 10.
    - Increased lymphocyte count with chromosomally abnormal T-cell clone detected in blood.
      * Abnl expression of pan T-cell markers (CD2-5).
    - For diffuse erythroderma, around 41% will progress to extracutaneous disease. For T3 tumor (≥ 1 cm), 36%. For T2 (≥ 10% skin), only 10% will have extracutaneous manifestations [[1](https://onlinelibrary.wiley.com/doi/full/10.1002/cncr.27627)].
  + Phases: Premycotic phase (erythematous macule)→ Patch→ Plaque→ Tumor→ erythroderma (> 80% SA).
    - Patch→ plaque when lymphoid clones invade deeper into dermis and Pautrier abscesses are seen.
    - "**Rule of 9s**": Chest, Abdomen, Each arm, Each front leg. Groin 1%. Back and butt 18%.
    - **Palm = 1% SA**.

* **Stanford cd-TSEBT** [[Navi JAMA Derm '11](https://jamanetwork.com/journals/jamadermatology/fullarticle/427033)]: Retro. **Conventional dose TSEBT** (30-36 Gy) **T2 vs. T3** + 10-15 Gy boost.

This is the largest cohort of patients treated with conventional dose TSEBT.

Total skin electron beam RT [[Zaorsky tweet](https://twitter.com/NicholasZaorsky/status/1226199181766938624?s=20)]. See [[Treatment Planning](#_863hkgmxw2d)] section for more.

* + 180 pts. 1970-2007. T2 ≥ 10% BSA (n=103), T3 ≥ 1 cm lesions (N=77). MFU 6.5y.
    - RT: Mean 36 Gy, local boosts 10-15 Gy to tumors or thick plaques.
    - Shadowed areas boosted to a median of 20 Gy.
  + ORR 100%. Overall CR for 30-36 Gy with local boosts of 10-15 Gy of ~60%.
  + CR of 75→ 50%. Duration of CR of 29→ 9 mo.
  + Multiple courses in 14 pts: CR is limited, with only 2/14 achieving a complete response. MS/PFS 29 mo.
  + OS at 5 / 10y of 59→ 40%.
  + MS of 11→ 5y.
  + MPFS of 9→ 3y.
  + Nearly all patients had mild to moderate radiation-induced dermatitis, partial or complete alopecia, nail dystrophy, and generalized xerosis. In most patients, radiation-associated toxicities were reversible, but time to recovery was variable and could last up to 2y.

* **Stanford/MDACC ld-TSEBT** [[Hoppe JAAD '15](https://www.sciencedirect.com/science/article/pii/S0190962214020593?via%3Dihub)]: 3 Phase II trials. **Low dose TSEBT** (12 Gy) + 12 Gy boosts.

Total skin electron beam RT [[Zaorsky tweet](https://twitter.com/NicholasZaorsky/status/1226199181766938624?s=20)]. See [[Treatment Planning](#_863hkgmxw2d)] section for more.

* + 33 pts. Most T2-T3 (2 patients T4). 2009-2012.
    - RT: 12 Gy, 1 Gy per fraction over 3 weeks (4 Gy/wk). Stanford regimen.
    - Supplemental boosts to tumors were limited to 12 Gy, typically with 6-9 MeV electron fields with 1 cm of tissue equivalent bolus.
  + ORR 88%. CR ~30% (n=9).
  + MTTR 8 weeks. Median duration of clinical benefit 16 mo.
  + Toxicities were mild and reversible.

* **UK Cutaneous Lymphoma Group** [[Morris IJROBP '17](https://www.ncbi.nlm.nih.gov/pubmed/28843374)]: Prospective. **12/8 in two weeks** **+ 8/2** (**or 12/3**) **boosts**.

Total skin electron beam RT [[Zaorsky tweet](https://twitter.com/NicholasZaorsky/status/1226199181766938624?s=20)]. See [[Treatment Planning](#_863hkgmxw2d)] section for more.

* + 103 pts. Most T2-T3. 2011-2016. MFU nearly 2y.
    - RT: 12 Gy, 1 Gy per fraction over 2 weeks (6 Gy/wk).
    - Self-shielded areas such as eyelids, perineum, soles, and scalp were treated with supplementary low dose superficial or electron beam RT to 8/2 (or 12/3 if too large or very symptomatic).
  + ORR 90%. CR 18%, PR 70%. SD 8%, PD 5%.
  + If CR, MTTR 7 mo. Median duration of clinical benefit 12 mo. MPFS 13 mo.
  + Median duration of clinical benefit for T2 / T3 of 17→ 9 mo.
  + MPFS for stage IB (T2) / IIB-III (T3-4) of 27→ 11 mo.
  + 2y OS for IB (T2) / IIB (T3 - tumor) / III (T4 - gen erythroderma) / IV of 94→ 51→ 74→ 0%.

## 

## [Treatment Planning](#_d5uyaxe3kzvz)

ILROG Guideline: Modern RT for Primary Cutaneous Lymphomas: Field and Dose Guidelines [[Specht IJROBP '15](https://www.sciencedirect.com/science/article/pii/S0360301615000279?via%3Dihub)]. [RoR](#_buun9ubd3cdd)

* **Skin only**: Topical nitrogen mustard, BCNU, steroids, imiquimod (TLR-7), PUVA, UVB, local or TSEBT.
  + Long term DFS with topical therapy is >85%.
  + **PUVA** is psoralen + UVA (long wave). UVB less penetrating (patches), UVA (some plaques). UVA activates 8-methoxypsoralen, which results in DNA cross-linking and apoptosis.
    - Administered q2-3d, then gradually increased to q1mo once CR achieved.
    - 70-90% CR but long term DFS remains poor. *~25% of early stage refractory to skin-directed therapy.*
* **Systemic**: Consider for extensive, advanced or refractory disease.
  + INF-α2A, Retinoids, Extracorporeal photochemotherapy (photopheresis), cytotoxic chemo (**MTX**, E, chlorambucil).
  + Vorinostat - Histone deacetylase inhibitor (HDAI).
  + Brentuximab: For some CD30+ CTCLs, may have up to 100% response.
  + **Photopheresis**: often for T4, use of leukapheresis to collect WBC→ PUVA→ transfuse back into the patient.
    - Response rate 40% w ~20% CR.
* **RT**: 4/2, **8/4**, 7-8/1, 12/3-4, 20-30 Gy in 2-3 Gy fx.
  + Prefer **8/2**, as CR for 4/8 Gy in 2 fractions of 30→ 92% [[Neelis IJROBP '09](https://www.sciencedirect.com/science/article/pii/S0360301608029519?via%3Dihub)].
  + Higher dose for large-cell or tumor stage. Local recurrence above 24 Gy is rare.
  + Consider 20-30 Gy in 2-3 Gy fx for thicker/larger lesions, though 12 Gy in 3-4 fx reasonable.
    - Doses in the 8-12 Gy range allow for re-treatment. Prefer 3-5 Gy per fraction as well tolerated.
  + Utilize **1-2 cm** margins, prefer >2 cm margin for limited T1 disease. LR is rare above 24 Gy.
  + 6-9 MeV electrons w 0.5-1.0 cm bolus.
  + TSEBT: Consider boost to "shadowed" areas such as perineum, scalp vertex, palms/soles, inframammary folds, panniculus.

### [TSEBT](#_jpvb9e4ko5f8)

See [[TSEBT](#_u15dt8ald0dz)] in the Heme introductory section for more information.

ILROG Guideline: Modern RT for Primary Cutaneous Lymphomas: Field and Dose Guidelines [[Specht IJROBP '15](https://www.sciencedirect.com/science/article/pii/S0360301615000279?via%3Dihub)]. [RoR](#_buun9ubd3cdd)

* **TSEBT in MF- A shift towards lower dose?** [[Chowdhary Chin Clin Onc '19](https://www.ncbi.nlm.nih.gov/pubmed/30525748)]

30-36 Gy is quite effective, particularly at inducing CR, but most patients eventually relapse. In these cases, conventional dose TSEBT is limited as RT toxicity is dose dependent. Therefore, clinicians are moving towards TSEBT 10-12 Gy as retreatment is an option.

* + The Stanford technique is the most commonly used TSEBT method. Conventional dose TSEBT consists of 30-36 Gy delivered over a period of 8-10 weeks.
  + Electron beams with 6-9 MeV are usually used to treat anterior and posterior treatment positions with both superior and inferior beam angulations. Two treatment cycles are delivered per week, with one cycle consisting of AP and two posterior oblique fields on day 1 then PA and two anterior oblique fields on day 2. A boost is given to areas that may be "underdosed" including the perineum, plantar surfaces, medial thigh, inframammary fold, behind pannus, or scalp. Beams pointed ± 18 degrees due to x-ray background dose of 2% strongly peaked in forward direction.
  + Generally speaking, 30 Gy used to be given in the past, but this was quite morbid with hypohidrosis and heat stroke upon re-irradiation to similar doses. Current trend is to use 12 Gy as it has fewer AE and is more amenable to re-irradiation. However, there is only ~30% CR, so consider focal boosts for tumors or on "shadowed" areas.
  + However, even when focal boosts are used for tumors, the median duration of CR is less than one year for patients with tumors ( ≥ 1 cm). Sometimes, boost prior to TSEBT may be warranted to decrease thickness of lesions beforehand.
  + Use external eye shields if no facial disease.
  + Patients with T2+ in CR to TSEBT may benefit from adjuvant therapy such as PUVA, photopheresis, or mechlorethamine.
* Conventional dose TSEBT (30-36 Gy): ORR approaches 100%. CR for 30-36 Gy with local boosts of 10-15 Gy of ~60%. CR for T2 / T3 of 75→ 50%. Duration of CR for T2 / T3 of 29→ 9 mo [[Navi JAMA Derm '11](#k9p1vasi49wy)].
  + More toxicity with standard higher dose, most all have skin irritation.
* Low dose TSEBT (12-20 Gy): ORR approaches 90%. CR only ~30%, even when focal boosts to tumors of 12 Gy utilized. MTTR 8 weeks. Median duration of clinical benefit 16 mo. Amenable to re-irradiation [[Hoppe JAAD '15](#ll8a5rw6xzfk)].
  + Lower dose favored due to ability to retreat (hypohidrosis, heat stroke).
  + CR for 12 / 30-36 Gy of 20→ 70% (n=20) [[Zhao IJROBP '17](https://www.redjournal.org/article/S0360-3016(17)32699-8/fulltext)].
  + Time to re-irradiation for 12 / 30-36 Gy of 3→ 10 mo.
* Consider boosting tumors with an additional 8-12 Gy (20-24 Gy total based on 12 Gy TSEBT) [[Morris IJROBP '17](#1bczowbwpilr)].
* Prescribed dose is **12**-36 Gy, generally 4-6 Gy per week.
  + Example: 1.5-2 Gy delivered per 2d/cycle, 4 d/week.
  + May consider a boost prior to TSEBT to decrease the thickness of lesions.
  + Example: Boost tumor lesions to 8/2 ("Bam bam") or 12/3 if large/very symptomatic, then 12 Gy total skin.
* EORTC criteria: 80% IDL ≥ 4 mm deep, with 20% IDL < 20 mm from skin surface.

# [Benign](#_e4a3jnknxfj8)

### [Orbital pseudotumor/lymphoid hyperplasia/pseudolymphoma](#_m7nmhxl6jtbu)

* [**StatPearls: Orbital Pseudotumor**](https://www.ncbi.nlm.nih.gov/books/NBK551576/)*Last update: 12/16/2019.*
* **Orbital pseudotumor** [[Mendenhall AJCO '10](https://insights.ovid.com/pubmed?pmid=19738455)].
* May occur in kiddos (5-15%) or adults.
* Very rare benign orbital mass where mature polyclonal lymphocytes are noted.
* Typically unilateral. Presents with sudden unilateral diplopia and proptosis.
* Dx of exclusion: Graves, lymphoma, lymphoid hyperplasia, RMS, nodular fasciitis.
* Tolosa-Hunt syndrome: Orbital pseudotumor w cavernous sinus involvement. Painful ophthalmoplegia.
* Workup: As per suspected [[IOL](#kix.ghkahk7i6o2n)]. MRI brain/orbit and biopsy if necessary.
* 80% ORR, 33% durable CR with corticosteroids, although up to 30% may progress to lymphoma [[Mombaerts Ophthal '96](https://linkinghub.elsevier.com/retrieve/pii/S0161-6420(96)30663-5)]
* Toxicity:
  + Try to limit the lens to < 8-10 Gy.
  + Diabetic pts at increased risk of RT retinopathy [[Wakelkamp Ophthal '04](https://www.aaojournal.org/article/S0161-6420(04)00337-9/fulltext)].
* Surgery or immunosuppression should be considered.
* EBRT 20/10 w 74-100% response.

### [Langerhans cell histiocytosis](#_m7nmhxl6jtbu)

* Radiotherapy of Langerhans' Cell Histiocytosis [[Olschewski SuO '06](https://link.springer.com/article/10.1007/s00066-006-1630-9)].
* Langerhans cell histiocytosis in adults: a case report and review of literature [[Lian Oncotarget '16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4951319/)].
* ~1,200 cases per year. Most common age 1-3. M:F 3:2.
* Single eosinophilic granulomas in bone, skin and lymph nodes; multiple sites typically liver, spleen, marrow, GI, CNS.
  + Kiddos: Bones. Adults: Lungs. Can present in any organ.
  + Single organ system such as bone in 55% of cases.
  + Skin involvement in 40% of cases.
* Typically single organ in older kids/adults, diffuse involvement in kiddos.
* Langerhans cells are APCs, typically found in skin, mucosa, lymphatics and spleen.
* Birbeck granules (S100, CD1a, "tennis rackets") on electron microscopy.
* Originate from **myeloid dendritic cell** precursors. Perhaps should reclassify as inflammatory myeloid neoplasm [[Berres '13](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3985340/)].
* Associated diseases: *Three names older, better px. Two hyphenated names younger, abysmal prognosis.*
  + Eosinophilic granuloma: < 2y, excellent prognosis.
  + Hans-Schuller-Christian: >2y, good prognosis. Triad of exophthalmos, DI, skull lesions.
  + Letterer-Siwe: < 2y, wasting, rash, otitis, LAD, bleeding, fulminant, acute, fatal.
* Workup:
  + H&P: Look for DI. This can occur in up to 50% of pts > 2y of age.
  + Labs, skeletal survey, biopsy.
* Treatment includes steroids, etoposide, vinblastine.
  + Give prednisone and vinblastine if multisystem involvement followed by re-evaluation.
  + Asymptomatic LCH lesions are typically observed.
  + Symptomatic bony lesions: Curettage/excision and/or local injection of steroids.
  + Symptomatic skin lesions: Topical therapy w nitrogen mustard, steroids, or systemic therapy..
* RT for ppx against bone fracture, dose to 6-8 Gy.
* DI: 15 Gy to pituitary/hypothalamus.
* Adults: 15-24 Gy in 2 Gy fractions.