49: AGGRESSIVE NON-HODGKIN'S LYMPHOMA

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QUICK HIT: Non-Hodgkin's lymphoma (NHL) is a heterogeneous disease. Aggressive NHL is a loosely defined group of B- and T-cell histologies with survival measured in months for those untreated. T-cell histologies are aggressive but uncommon. Multiagent CHT is indicated in almost all cases of aggressive NHL. Diffuse large B-cell lymphoma (DLBCL) is the most common of the aggressive NHL and the subject of the majority of clinical data. Limited-stage DLBCL is typically treated with R-CHOP for either three cycles followed by ISRT to 30–36 Gy or R-CHOP for six cycles. After six to eight cycles, the role for consolidative RT is controversial in the setting of a CR. Advanced-stage DLBCL can be treated with R-CHOP for six to eight cycles with consideration of consolidation RT. When selecting for consolidative RT, risk factors such as bulk (≥7.5 cm), skeletal involvement, inability to tolerate full CHT, residual disease after CHT on PET/CT, and perhaps genetic factors can be considered, although no clear standard exists.

TABLE 49.1: General Overview of Treatment Paradigm for DLBCL	
Limited (Stage I–II)	R-CHOP x 3 cycles followed by: 30–36 Gy for CR 40–50 Gy for PR or R-CHOP x 6–8 cycles
Advanced (Stage III–IV)	R-CHOP x 6–8 cycles ± ISRT 30–36 Gy
Relapsed/Refractory	High dose CHT + autologous SCT +/– RT pre- or post-transplant

EPIDEMIOLOGY: Overall there are 72,240 cases of NHL expected in the United States in 2017, and 20,140 deaths with an incidence of approximately 1 in 50.[1] NHL is the seventh most common noncutaneous cancer and ninth most common cause of death. Slightly more common in males (lifetime risk 1.26:1). Approximately 50% to 60% of NHLs are classified as aggressive. Most common NHL: DLBCL (29%), follicular (26%), SLL/CLL (7%), MZL/MALT (9%), mantle cell (8%), MZL/nodal (3%), primary mediastinal DLBCL (2%) among others.[2,3] Aggressive NHL is more common in low-middle–income countries.

RISK FACTORS: NHL is a heterogeneous disease with a multitude of risk factors. Risk factors for any NHL[4]: older age, race, family history,[5] geographic region,[3] *viral infection* (EBV [NK-T-cell, Burkitt], HTLV-1, HHV8 [Kaposi sarcoma and various lymphomas in HIV+], hepatitis C [DLBCL and splenic MZL]), *bacterial infection* (H. pylori [gastric MALT], Chlamydia psittaci [orbital MALT], Borrelia burgdorferi [tick bite, mantle cell],[6] Campylobacter jejuni [intestinal MALT]), *autoimmune disease* (rheumatoid arthritis, Sjögren's syndrome, Lupus), *immune suppression* (HIV, organ transplant), *medication* (immunosuppressants, alkylating agents), *chemicals* (hair dye, pesticides), previous CLL/hairy cell leukemia (Richter's transformation into DLBCL in 5%–10%).

ANATOMY: 13 individual nodal groups identified in 1965 now define staging and include: Waldeyer's ring, cervical/SCV/occipital/pre-auricular, infraclavicular, axillary/pectoral, mediastinal, hilar, para-aortic, spleen, mesenteric, iliac, inguinal/femoral, popliteal,

and epitrochlear/brachial. Waldeyer's ring and the spleen are considered lymphatic but extranodal regions for staging purposes.

PATHOLOGY: NHL includes cancers originating from cells which normally differentiate into T or B lymphocytes, whether originating from the bone marrow or peripheral nodal tissues. 85% to 90% of NHLs derive from B-cell origins.[4] In contrast, leukemias derive from cells that differentiate into erythrocytes, monocytes, or granulocytes. Originally, it was thought that leukemias arose from the bone marrow and lymphoma arises from a mass lesion. Today, cell lineage, morphology, genetics, and immunotyping classify leukemia and lymphomas. Over 60 types of NHL are identified in the WHO 2016 classification, which does not attempt to differentiate into aggressive/indolent due to variable clinical behavior.[7] Many treat grade 3 follicular lymphoma similar to DLBCL.

GENETICS: See Table 49.2.

TABLE 49.2: Common Translocations, Immunotype, and Clinical Pearls for Select "Aggressive" NHLs

Histology		Classic Genetics and Implications	Classic Immunotype	Pearls
B-Cell	Diffuse Large B-Cell Lymphoma (DLBCL)	t(14:18), BCL-2, BLC-6, ALK, many others	CD19+, CD20+, CD45+	Most common NHL. WHO 2016 subtypes: EBV+, germinal center, activated, primary cutaneous, ALK+, HHV8+, "double hit" (MYC and BCL2 or BCL6). Grey zone lymphoma is intermediate between DLBCL and Hodgkin's.
	Primary Mediastinal (Thymic) DLBCL	No classic translocations	CD19+, CD20+, CD5-	Anterior mediastinal (thymic) mass most common in young women. Treatment different than DLBCL.
	Mantle Cell	t(11:14), cyclin D1	CD19+, CD20+, CD5+	Older age and advanced stage more common. Radiosensitive.
	Burkitt	t(8:14) → C-MYC [transcription factor]	CD19+, CD20+, CD5-, CD10+	Classic "starry sky" appearance. Most common NHL in children, endemic type in Africa (jaw, EBV+). Also nonendemic (abdomen, visceral organs) and immune-deficient types
	Follicular, Grade 3B	Grade 3B genetically distinct from grades 1-3A	CD19+, CD20+	High-grade FL (especially grade 3B) is often treated as per DLBCL paradigm (grade 1-3A managed per low-grade NHL paradigm)
T-Cell	Peripheral T-Cell, NOS (PTCL)	t(7:14), t(11:14) or t(14:14)	Variable T-cell (±CD2, 3, 4, 5, 7)	Most common peripheral T-cell, older adults
	Anaplastic Large Cell	t(2:5) → ALK	CD30+, EMA+	More common in kids, good prognosis with ALK+. T-cell neoplasm.
	Angioimmunoblastic	No classic translocations	CD4+	Older adults
	Extranodal NK-T-Cell, Nasal Type	LOH 6q	CD2+, CD56+	More common in Asian males. EBV+ (EBV encoded RNA [EBER] by FISH)

(*continued*)

TABLE 49.2: Common Translocations, Immunotype, and Clinical Pearls for Select "Aggressive" NHLs (*continued*)				
Histology		**Classic Genetics and Implications**	**Classic Immunotype**	**Pearls**
Either	Lymphoblastic Lymphoma/ Leukemia	t(1:19), t(9:22)	TdT+	Nodal presentation of ALL and treated similarly. Can be T- or B-cell presentation

CLINICAL PRESENTATION: Most commonly presents with a painless enlarging LN. B symptoms (fever >38°C, drenching night sweats, weight loss >10% in 6 mos) or numerous other symptoms may be present (fatigue, anemia, pain, cord compression, SVC syndrome, etc.) depending on location and degree of involvement.

WORKUP: H&P with attention to constitutional symptoms (B symptoms), enlarged LNs, or hepatosplenomegaly.

Labs: CBC, CMP, β2 microglobulin, LDH, uric acid, hepatitis B testing (reactivation with rituximab), pregnancy test. Lumbar puncture with flow cytometry if symptomatic, testicular, double hit, HIV-associated, or epidural lymphoma (see CNS prognostic model for risk factors).[8]

Imaging: PET/CT is standard in almost all lymphoma histologies except certain low-grade histologies (extranodal MZL and SLL).[9–11] Uptake (SUV >10) in indolent lymphoma suggests transformation.[12,13] CT with contrast should also be obtained. Echocardiogram or MUGA if CHT dictates. EBV viral load for extranodal NK/T-cell, nasal type.

Biopsy: At least a core needle biopsy but preferably excisional biopsy should be performed for adequate pathologic evaluation including morphology, nodal architecture, genetic and immunoprofiling. FNA is insufficient. A negative PET is usually sufficient at ruling out bone marrow involvement of DLBCL.[14,15] Bone marrow biopsy remains standard for most other NHL (~20% risk of BM involvement for aggressive NHL vs. 50%–80% of indolent NHLs).

PROGNOSTIC FACTORS: Age, bulk (classically defined as ≥10 cm or >1/3 thoracic diameter, but more recently defined as ≥7.5 cm). Germinal center subtype more favorable than nongerminal center as defined by tissue microarray (combination of CD10, BCL6, and MUM1).[16] Multiple prognostic models exist for pts with aggressive NHL treated with CHT. See Tables 49.3 and 49.4. The IPI[17] is classic (mnemonic "LEAPS": LDH, extranodal sites, age, performance status, and stage). NCCN-IPI is most recent (improved discrimination of low and high risk). Mantle cell may be best classified using the MIPI.[18] The Deauville (5-point) score is used to interpret PET scans and is prognostic, particularly at the end of treatment. This consists of five levels. Level 1 includes no update above background; level 2 is uptake less than or equal to mediastinal blood pool; level 3 is uptake above mediastinal blood pool but less than or equal to liver uptake; level 4 is uptake moderately above liver; and level 5 is uptake markedly greater than liver or new lesions.[19]

NATURAL HISTORY: Aggressive lymphoma, loosely defined, includes cancers with survival measured in months if untreated, as compared to indolent lymphoma, with survival measured in years. Compared to Hodgkin's disease, the pattern of spread is less predictable and can skip nodal levels/sites.

TABLE 49.3: Classic IPI Prognostic System (1993[17]) and NCCN-IPI (2014[20]) for Aggressive NHL

	IPI		Age-Adjusted IPI		NCCN-IPI	
	Factor	*Score*	*Factor*	*Score*	*Factor*	*Score*
Age	>60	1	*N/A*	1	>40 to ≤60 >60 to <75 ≥75	1 2 3
LDH	High	1	High	1	>1xULN but ≤3xULN >3xULN	1 2
Extranodal Sites	≥2	1	*N/A*	1	Bone marrow, CNS, liver/GI tract, lung	1
Performance Status (ECOG)	≥2	1	≥2	1	≥2	1
Stage (Ann Arbor)	III–IV	1	III–IV	1	I–II vs. III–IV	1

ULN, Upper limit normal.

TABLE 49.4: Aggressive NHL Outcome by IPI Score (see Table 49.3 for risk factors)

	Original IPI (Prerituximab)[17]			Age-Adjusted IPI[17]				IPI in Rituximab Era[21]			NCCN-IPI[20]		
Risk Group	Score	5-yr OS	5-yr RFS	Score	5-yr OS (≤60 y/o)	5-yr OS (>60 y/o)	5-yr RFS	Score	3-yr OS	3-yr PFS	Score	5-yr OS	5-yr PFS
Low	0–1	73%	70%	0	83%	56%	86%	0–1	91%	87%	0–1	96%	91%
Low-intermediate	2	51%	50%	1	69%	44%	66%	2	81%	75%	2–3	82%	74%
High-intermediate	3	43%	49%	2	46%	37%	53%	3	65%	59%	4–5	64%	51%
High	4–5	26%	40%	3	32%	21%	58%	4–5	59%	56%	≥6	33%	30%

STAGING

TABLE 49.5: Ann Arbor (Lugano) Staging System for Lymphoma**

I	One node or a group of adjacent nodes OR single extranodal lesions without nodal involvement (IE)	**A:** No systemic symptoms **B:** Unexplained weight loss >10% in 6 mos before diagnosis. Unexplained fever with temperatures above 38°C. Drenching night sweats. **E*:** Extranodal involvement. **X*:** Bulky disease (*Hodgkin's: >10 cm or mediastinal mass >1/3 the maximum thoracic diameter at T5-6 on PA CXR*).
II	≥2 nodal groups on the same side of the diaphragm OR stage I or II by nodal extent with limited contiguous extranodal involvement	
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	
IV	Additional noncontiguous extralymphatic involvement	

*Note that 2014 Lugano update suggests "X" and "A/B" modifiers are no longer necessary for NHL, and "E" unnecessary for stage III–IV disease.[22]
**Number of involved regions may be designated with a subscript (i.e., II_3).

TREATMENT PARADIGM

Observation: Unlike indolent lymphomas, there is generally no role for observation of aggressive lymphomas. Notable exceptions may be mantle cell with a low tumor burden.[23]

Surgery: Generally the role for surgery is limited to excisional biopsy.

Chemotherapy: CHT is the backbone of treatment for NHL. See Table 49.6 for regimens. Rituximab is an anti-CD20 antibody consistently demonstrated in the early 2000s to improve 5-yr OS for DLBCL by approximately 10% with minimal increase in toxicity.[24–26] R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, often given q21 days for six cycles. R-EPOCH consists of the same agents as R-CHOP but with etoposide and overall, across subtypes of DLBCL, did not demonstrate a benefit compared to R-CHOP in the CALGB/Alliance 50303 trial (although it is still an option in other subtypes, e.g., primary mediastinal DLBCL or double-hit DLBCL). Consolidation with autologous SCT is not routinely recommended for DLBCL but can be considered for "double hit" type.[27] CNS prophylaxis can be delivered to high-risk pts via either systemic MTX, intrathecal MTX or cytarabine.[8,9]

TABLE 49.6: Example Regimens for Aggressive NHL

Diagnosis	Common/Example CHT Regimens	Notes
DLBCL, Germinal Center Type	R-CHOPx6 ± RT	Good outcomes with standard R-CHOP
	R-CHOPx3 + RT	
DLBCL, Activated B-Cell Type	R-CHOPx6-8 ± RT	Studies suggest inferior outcomes with standard R-CHOP, some intensify CHT
	R-ACVBP + MTX/ Leukovorin[28]	
	R-CHOP + Lenalidomide[29]	
DLBCL, "Double Hit"	R-EPOCH	Outcomes with standard R-CHOP are inferior, consider CNS prophylaxis or autologous SCT
	RHyper-CVAD	
DLBCL, Transformed Follicular	R-CHOP x6 ± RT	Diagnosis: biopsy regions of PET SUV >10[13]
Follicular, Grade 3b	R-CHOP ± RT	As per DLBCL paradigm
Primary Mediastinal DLBCL	R-EPOCH x6 ± RT[30]	
	R-CHOP x6 + RT	
Mantle Cell	R-CHOP + Autologous SCT[31]	
	R-Hyper-CVAD/Cytarabine/ MTX[32]	
	R-CHOP + RT	Select stage I–II pts
	R-CHOP	Not curative
	Bendamustine + Rituximab	
	Many others	
Burkitt's	CODOX-M[33]	
	CALGB Regimen[34]	
	R-EPOCH[35]	

(*continued*)

TABLE 49.6: Example Regimens for Aggressive NHL (*continued*)		
Diagnosis	**Common/Example CHT Regimens**	**Notes**
	HyperCVAD[36]	
Extranodal NK-T-Cell, Nasal Type	SMILE + RT[37]	
	DeVIC + Concurrent RT[38]	
	GELOX + Sandwhich RT[39]	

Radiation

Indications: The role for RT in aggressive NHL is either for consolidation or palliation. For select patients unable to receive CHT or in early-stage mantle cell lymphoma, definitive RT may be appropriate. RT decisions should be based off the CHT regimen chosen and response to induction therapy. Historic technique was IFRT, modern technique is now ISRT (when treated after CHT). ILROG guidelines delineate the technique for involved-site RT.[40]

Dose

TABLE 49.7: NCCN RT Dose Guidelines for Aggressive Non-Hodgkin's Lymphoma[9,10]		
Mantle Cell, stage I–II	RT alone	30–36 Gy
DLBCL*	Consolidation after CR	30–36 Gy
	Consolidation after PR	40–50 Gy
	Primary treatment (nonchemo candidate)	40–55 Gy
	Combined with SCT	20–36 Gy
	Scrotal RT after CHT	25–30 Gy
Peripheral T-Cell Lymphoma	Consolidation	30–40 Gy
Extranodal NK-T-Cell, Nasal Type	Concurrent with DeVIC	50 Gy
	Sequential after SMILE	45–50.4 Gy
	After GELOX	56 Gy
	RT alone	≥50 Gy
*Note that grade 3B follicular lymphoma is often managed according to DLBCL paradigm.		

Toxicity: Acute: Fatigue, skin erythema, other sequelae are site-dependent. Late: Site-dependent but include second malignancy, xerostomia, fibrosis, cardiotoxicity, and so on.

Procedure: See *Treatment Planning Handbook*, Chapter 10.[41]

EVIDENCE-BASED Q&A

Historically, what data exists regarding the role of RT in DLBCL?

Three cooperative groups (SWOG, ECOG, French GELA) investigated the role of consolidative IFRT after CHT with variable results in the pre-rituximab era. RT was effective at reducing in-field relapses but that RT only improved OS in the initial results of one trial (SWOG), though these studies used higher doses and older RT techniques. Overall, it appears that less-intense CHT with RT is comparable to intensive CHT alone. Toxicity is significant with intense CHT; therefore combined-modality treatment may be ideal for some pts.

Miller, SWOG 8736 (*NEJM* 1998, PMID 9647875, Update Stephens *JCO* 2016, PMID 27382104): PRT of 401 pts with localized intermediate or high-grade NHL stage I, IE (including bulky), nonbulky stage II or IIE disease. Bulk defined as ≥10 cm or >1/3 maximal chest diameter. Pts were randomized to CHOP x 8 cycles given q21 days vs. CHOP x 3 cycles followed by IFRT to 40–55 Gy. IFRT targeted any involved location pre-CHT. MFU 4.4 years. See Table 49.8. Long-term follow-up of a subset of original population (MFU 17.7 years) suggested continuous treatment failure despite RT in patients receiving limited CHT. **Conclusion: Combined-modality treatment is superior to CHOP alone and less toxic, although with long-term follow-up this did not persist.**

TABLE 49.8: Results of SWOG 8736 NHL			
SWOG 8736	**5-yr PFS**	**5-yr OS**	**Life-Threatening Toxicity**
CHOP x 8	64%	72%	40%
CHOP x 3 + RT	77%	82%	30%
p value	.03	.02	.06

Horning, ECOG 1484 (*JCO* 2004, PMID 15210738): PRT of 352 pts with early-stage diffuse aggressive lymphoma. Stage I with mediastinal or retroperitoneal involvement, bulky disease >10 cm, stage IE, II, or IIE included. Treatment was CHOP x 8 cycles, then restaging by CT. PR received 40 Gy IFRT. Pts with CR randomized to observation versus 30 Gy IFRT. MFU 12 years; 61% had CR; 31% of PR pts had CR after IFRT. See Table 49.9. **Conclusion: IFRT improved DFS but not OS.** *Comment: Powered for 20% OS difference.*

TABLE 49.9: Results of ECOG 1484 NHL		
ECOG 1484	**6-yr DFS**	**6-yr OS**
CHOP x 8 → PR → RT	63%	69%
CHOP x 8 → CR → Obs	53%	67%
CHOP x 8 → CR → RT	69%	79%
p value	.05	.23

Reyes, GELA LNH 93-1 (*NEJM* 2005, PMID 15788496): PRT of 647 pts <61 years of age with localized stage I–IIE aggressive lymphoma and no IPI risk factors. Pts randomized to CHOP x 3 cycles + IFRT versus ACVBP alone (doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) with MTX, etoposide, ifosfamide, and cytarabine consolidation. IFRT was 40 Gy/22 fx. MFU 7.7 years. See Table 49.10. Grade 3-4 toxicity worse in the ACVBP arm (12% vs. 1%). Initial site relapse more common in ACVBP arm (41% vs. 23%) but out-of-field relapse more common in CHOP arm (72% vs. 38%). **Conclusion**: **In young pts, intensive CHT alone is superior to CHOP+IFRT. ACVBP is not a standard regimen in the United States.**

TABLE 49.10: Results of GELA LNH 93-1 NHL			
GELA LNH 93-1	**CR**	**5-yr EFS**	**5-yr OS**
CHOP x 3 + IFRT	92%	**74%**	**81%**
ACVBP	93%	**82%**	**90%**
p value	NS	**<.001**	**.001**

Bonnet, GELA LNH 93-4 (*JCO* 2007, PMID 17228021): PRT of 576 pts >60 years of age with localized stage I–IIE aggressive NHL and no IPI risk factors. Pts randomized to CHOP x 4 cycles ± IFRT to 40 Gy. MFU 7 years. CR (89% vs. 91%), 5-yr EFS (61% vs. 64%),

5-yr OS (72% vs. 68%, $p = .5$) were no different with the addition of RT. **Conclusion: For older pts with favorable risk factors, CHOP alone appears adequate.**

What was the impact of rituximab on outcomes with chemotherapy alone?

The preceding historic trials were performed in the pre-rituximab era. The introduction of rituximab in the early 2000s markedly improved outcomes above CHOP alone, with approximately a 10% improvement in OS at 5 years.[24–26,42] *Therefore, many argue consolidation with RT is unnecessary, though there is no level I evidence to support this conclusion at this time.*

How many cycles of R-CHOP are necessary for DLBCL?

Trials performed either six or eight cycles for DLBCL given every 21 days. The RICOVER-60 trial directly addressed this question.

Pfreundschuh, RICOVER-60 (*Lancet Oncol* 2008, PMID 18226581): PRT of 1,222 pts, 61 to 80 years of age with aggressive B-cell lymphoma; 2x2 randomization: CHOP versus R-CHOP and six versus eight cycles (both q14 days, rather than conventional q21 days). IFRT to 36 Gy was recommended to sites initially ≥7.5 cm (bulky) or extranodal sites regardless of response. R-CHOP improved DFS and OS, but no difference between six versus eight cycles. **Conclusion**: **Six cycles of R-CHOP is the preferred regimen for elderly pts.**

Is consolidative RT necessary for early-stage DLBCL in the rituximab era?

This is a controversial question and use of RT has been declining.[43] *There may be some pts who benefit, but no high-quality data exists to guide decisions. Retrospective and nonrandomized data below supports the role of RT. This includes at least four large databases (NCDB, SEER, NCCN) and multiple retrospective reviews.*[43–50] *Of note, the German UNFOLDER trial randomizing bulky or ENE pts to either RT or No RT closed its two arms omitting RT early due to inferior EFS.*[51,52] *It is likely that a subset of pts with DLBCL benefit from RT, although this has not been clearly defined. Risk factors such as bulk, skeletal involvement, inability to tolerate full CHT, residual disease after CHT on PET/CT, and perhaps genetic factors can be considered.*[52]

Held, RICOVER-60 NoRTh (*JCO* 2014, PMID 24493716): After the completion of the RICOVER-60 trial, the protocol was amended and another 166 pts were accrued to the best arm of the RICOVER-60 trial (R-CHOPx6 q14 days) but sparing RT. The arm from the original trial (RT arm) was compared to the no RT cohort. MFU 39 months. MVA in the per-protocol population demonstrated worse EFS, PFS, and OS in those with bulky disease not treated with RT. **Conclusion: RT should be used in all patients with bulky disease, until PET-directed omission studies are completed. Further randomized trials are necessary.**

Held, German Pooled Analysis (*JCO* 2013, PMID 24062391): Pooled analysis of data from nine randomized trials including 3,840 pts with aggressive B-cell lymphoma; 7.6% had skeletal involvement. Skeletal involvement was associated with worse EFS after R-CHOP (EFS HR 1.5, $p = .048$). Rituximab was not found to improve outcome for pts with skeletal involvement. RT did improve EFS for pts with skeletal involvement (EFS HR 0.3, $p = .001$; OS HR 0.5, $p = .111$). **Conclusion: RT may benefit those with skeletal involvement.**

Lamy, Lysa/Goelams 02-03 (*ASH* 2014, Abstract 124[21]:393): Pts with nonbulky (<7 cm) stage I–II DLBCL treated with R-CHOP for four cycles (IPI of 0) or six cycles (IPI > 0), then randomized to 40 Gy IFRT or observation. Pts with PR (PET-assessed) after four cycles received six total cycles and RT. Preliminary report at MFU of 51 mos. 313 pts, 40% had extranodal sites; 84% CR after four cycles. EFS and OS no different in the ITT population.

For those in CR, 5-yr EFS 89% No RT versus 91% RT (p = .24). **Conclusion**: **Preliminary findings suggest RT consolidation is not necessary in nonbulky early-stage DLBCL.**

Is there a role for consolidative RT for advanced-stage DLBCL?

This is also a controversial question with less data available. NCCN suggests R-CHOP for six cycles and if CR is confirmed on PET, to consider RT to initially bulky sites or areas of skeletal involvement. RICOVER-60 probably provides the best data for this, as it included all stages (60% in the No RT cohort were stage III–IV). Retrospective data from MD Anderson,[53] *Duke*[46] *and observational data from the NCCN database also suggest a benefit.*[50]

What is the optimal radiation dose?

Classic trials often used doses >40 Gy but modern doses are lower as NHL is generally radiosensitive.

Lowry, UK (*Radiother Oncol* 2011, PMID 21664710): PRT with any histologic subtype of NHL requiring RT for local control. 640 sites were randomized to either high-dose RT to 40–45 Gy/20–23 fx versus low-dose RT. Low-dose arm was 30 Gy/15 fx for aggressive histologies and 24 Gy/12 fx for indolent histologies. MFU 5.6 years. No difference in response rates, in-field progression, PFS, or OS. Toxicity was reduced (but not SS) in the low-dose arm. **Conclusion: 24 Gy and 30 Gy is sufficient for indolent and aggressive NHL, respectively.**

How should response to treatment be evaluated for pts with NHL? Is interim PET predictive of outcome?

The updated Lugano Classification[22] *(named after Lugano, Italy where the conference took place) defines both staging and response assessment. See the manuscript for details, but in brief a CR should be defined as Deauville 1 to 3, without new lesions, no abnormal bone marrow uptake, regression of the nodal size to ≤1.5 cm in longest diameter and no organomegaly. A Deauville 3 is usually sufficient but may be considered abnormal if reduced-intensity CHT is used. Of note, a midtreatment PET is not clearly predictive of outcome (as opposed to Hodgkin's), and it is not recommended that therapy be altered due to the midtreatment PET.*[54]

How is primary mediastinal DLBCL managed?

Primary mediastinal DLBCL is a different entity than other forms of DLBCL and has a natural history between NHL and Hodgkin's disease. It should be managed with either R-EPOCH CHT for six to eight cycles or R-CHOP for six cycles with RT.[9,30] *There is minimal data investigating the omission of RT in these pts. Like Hodgkin's, midtreatment PET/CT is prognostic.*[55]

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