Non-Hodgkin Lymphoma

BACKGROUND

What is the pathologic definition of NHL?

Answer

NHL is a monoclonal expansion of malignant B or T cells that lacks the pathologic characteristics of Hodgkin lymphoma (HL) (no Reed–Sternberg cells) and is typically characterized by nodal/focal involvement vs. the more disseminated presentation of leukemias.

How does the clinical presentation of NHL differ from that of HL?

Answer

NHL is more likely to be extranodal, is more likely to spread in a noncontiguous fashion, and has a prognosis that is more strongly affected by histologic subtype than HL.

What are the most common presenting signs or Sx of NHL?

Answer

Painless adenopathy (axillary, inguinal, and femoral) is the most common presenting sign of NHL. ∼30% of pts have B Sx. Waxing and waning adenopathy suggests an indolent form of NHL. Tumor bulk may cause airway compression, intestinal obstruction, urinary tract obstruction, or nerve impingement.

What are the B Sx?

Answer

The B Sx include unexplained fever >38°C (100.4°F), >10% body weight loss in 6 mos, or drenching night sweats.

What is the NCI working formulation for NHL?

Answer

The NCI’s working formulation groups NHL by clinical aggressiveness or grade with subgroups based on cell type or presentation.

Low-grade NHL: follicular (grades 1–2), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mucosa-associated lymphoid tissue (MALT) lymphoma, mycosis fungoides

Intermediate-grade NHL: follicular (grade 3), mantle cell, diffuse large B-cell lymphoma (DLBCL), natural killer (NK)/T cell, peripheral T cell, anaplastic large cell

High-grade NHL: Burkitt, lymphoblastic What is the WHO classification of NHL?

Answer

The WHO classification is based on morphology and cell lineage, dividing NHL into B- and T-cell/NK cell neoplasms. The indolent, aggressive, and highly aggressive subgroups roughly correlate to the aforementioned working formulation groups.

Is there a relationship b/t clinical aggressiveness and curability of NHL?

Answer

Advanced-stage indolent NHL is rarely curable. Intermediate-grade NHL may be curable even in advanced stages.

Without Tx, what is the life expectancy for pts with NHL of varying aggressiveness?

Answer

Pts with indolent NHL have survival measured in yrs. Pts with aggressive NHL have survival measured in mos, and those pts with highly aggressive Dz have an expected survival of wks.

What % of NHL is indolent, and what are the most prevalent subtypes?

Answer

∼35% of NHL is indolent by the WHO classification. The most common indolent NHL subtypes are follicular lymphoma (FL) (grades 1–2; 65%), CLL/SLL (18%), and marginal zone B-cell lymphoma (12%, most commonly MALT lymphoma).

What are the common cytogenetic abnormalities associated with indolent NHL?

Answer

t(14;18) is seen in 90% of FLs. This results in overexpression of antiapoptotic Bcl-2. Chromosomal deletions of 11q, 13q, and 17p, and trisomy 12 are associated with CLL/SLL. Trisomy 3 (60%) and t(11:18) (25%–40%) are associated with MALT lymphoma. c-myc overexpression t(8:14) is associated with Burkitt lymphoma.

How is FL graded?

Answer

FL demonstrates a mix of centrocytes (small, cleaved cells) and centroblasts (large, noncleaved cells). Grade correlates to the density of centroblasts (e.g., 0–5 centroblasts/high power field (hpf), grade 1; >15 centroblasts/hpf, grade 3).

What is SLL?

Answer

SLL is the same Dz entity as CLL but with a predominant manifestation in the spleen, liver, or nodes as opposed to peripheral blood or BM. What is Richter syndrome? What is its rate of occurrence?

Answer

Richter syndrome is the transformation of SLL or CLL into an aggressive lymphoma, most commonly DLBCL. It occurs in ∼5% of cases.

How is bulky Dz commonly defined in DLBCL?

Answer

Recent trials of DLBCL have defined bulk as Dz measuring at least 7.5 cm.

WORKUP/STAGING

What are the pertinent focused aspects of the physical exam in a person with suspected NHL?

Answer

The physical exam should include complete nodal assessment including epitrochlear and popliteal groups. Cervical adenopathy palpable above the hyoid bone should prompt an ENT exam. (The Waldeyer ring is more frequently involved in NHL than in HL.) Exam of other at-risk sites including the liver, spleen, testicles, bones, abdomen, and flanks is appropriate.

What lab studies should be performed?

Answer

Lab studies should include CBC with differential, CMP, LDH, β2- microglobulin, serum protein electrophoresis, HIV, hepatitis B virus (essential as it may reactivate with rituximab [Rituxan] Tx), and hepatitis C virus. BM Bx should be performed for all lymphomas. LP should be performed for CNS Sx, testicular or PNS involvement, or immunodeficiency. What imaging studies should be performed?

Answer

The imaging workup should include CT neck, chest, abdomen, pelvis (N/C/A/P). PET is appropriate in most cases but may be less useful in indolent lymphomas with variable FDG-avidity. MRI brain should be performed for CNS Sx, testicular or PNS involvement, or immunodeficiency. How is NHL staged?

Answer

NHL is staged similar to HL using the Ann Arbor (AA) system:

Stage 1: involvement of 1 LN region or localized involvement of 1 extralymphatic organ or site (IE)

Stage 2: involvement of ≥2 LN regions on the same side of diaphragm or localized involvement of 1 associated extralymphatic organ or site and its regional LN, with or without involvement of other LN regions on same side of diaphragm (IIE)

Stage 3: involvement of LN regions on both sides of diaphragm, which may also be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE)

Stage 4: multifocal involvement of ≥1 extralymphatic organ, with or without associated LN involvement, or isolated extralymphatic organ involvement with distant nodal involvement

Note: Pts with B Sx are designated with a B, otherwise with an A. Pts with splenic involvement are designated with an S. Pts with bulky Dz are designated with an X. Pts with extranodal Dz are designated with an E.

TREATMENT/PROGNOSIS

What are prognostic factors for NHL?

Answer

Although grade remains the most important factor, several attempts have been made to combine multiple prognostic factors into a single numerical prognostic index to determine prognosis within a grade stratification of NHL. The most well-known is the International Prognostic Index (IPI) based on aggressive NHL. Derivatives of the IPI include the age adjusted, stage adjusted, and revised-IPI. Other derivatives include the FLIPI (for FL) and the MIPI (for mantle cell lymphoma).

What factors are included in the IPI?

Answer

IPI factors: Age >60 yrs, ECOG PS ≥2, LDH > normal, >1 Extranodal group, AA Stages III–IV (Mnemonic: APLES)

Estimate the 5-yr OS for aggressive NHL based on the number of IPI factors, in the pre-rituximab era.

Answer

Number of IPI factors as associated with 5-yr OS in the pre-rituximab era: Low: 0–1 factors → 73%

Low-intermediate: 2 factors → 51%

High-intermediate: 3 factors → 43%

High: 4–5 factors → 26%

What were the Dz characteristics and the Tx strategies employed for the pts whose outcome data were used to generate the IPI formulation?

Answer

The data used to generate the IPI come from 2031 adult patients treated for aggressive NHL of any stage with a combination-chemotherapy regimen containing doxorubicin as part of a phase 2 or 3 study between 1982 and 1987. (Shipp et al., NEJM 1993)

What is the R-IPI for intermediate-risk NHL incorporating the use of rituximab?

Answer

The R-IPI incorporates the same 5 factors as the standard IPI but with substantial changes in the prognosis of these pts.

Estimate the 5-yr OS for aggressive NHL based on the number of R-IPI factors.

Answer

Number of R-IPI factors as associated with 5-yr OS:

0 factors: 94%

1–2 factors: 79%

3–5 factors: 55%

(Sehn LH et al., Blood 2007)

What factors are included in the FLIPI?

Answer

FLIPI factors: Hgb <12 g/dL, Age >60 yrs, Stages III–IV, ≥5 extranodal Sites, LDH > normal (Mnemonic: FLIPI is a HASSL). Note: These are FLIPI-specific nodal sites, not AA nodal groups.

Estimate the 5-yr OS based on the number of FLIPI factors.

Answer

Number of FLIPI factors as associated with 5-yr OS:

0–1 factors: 90%

2 factors: 80%

3–5 factors: 55%

(Solal-Celigny P et al., Blood 2004)

What was demonstrated by the Stanford retrospective series supporting RT alone in the management of stages I–II, low-grade FL?

Answer

The Stanford series of 177 pts treated from 1961–1994 (MacManus MP et al., JCO 1996) demonstrated an MS of 13.8 yrs, 5-, 10-, and 15-yr RFS of 55%, 44%, and 40%, respectively, and 5-, 10-, and 15-yr OS of 82%, 64%, and 44%, respectively. RT-included IFRT, EFRT, and total lymphoid irradiation. Doses ranged from 35–50 Gy. Age <60 yrs was associated with better OS and FFR. Only 5 of 47 pts who reached 10 years without relapse developed recurrence subsequently.

What was demonstrated in the retrospective Stanford series of stages I– IIA, low-grade FL not treated immediately?

Answer

In this series, 43 highly-selected pts (11 pts stage I) with a median age of 58 yrs rcvd no initial Tx for various reasons. At a median f/u of 86 mos, 63% had not been treated. Estimated OS at 5, 10, and 20 yrs were 97%, 85%, and 22%, respectively. (Advani R et al., JCO 2004)

Has adj chemo demonstrated a benefit in randomized trials of early-stage, low-grade FL?

Answer

Several randomized trials have compared RT to RT + chemotherapy (ex. cyclophosphamide/vincristine/prednisone). These trials have failed to demonstrate an overall survival difference. However, several of these trials have demonstrated improved PFS with the addition of chemotherapy.

. Nissen NI et al., Cancer 1983

. Monfardini S et al., IJROBP 1980

. Carde P et al., Radiother Oncol 1984

. Yahalom J et al., Cancer 1993

. Kelsey SM et al., Med Oncol 1994

. MacManus et al., Hematological Oncology 2017

What is the evidence for reduced doses of RT to control FL?

Answer

A U.K. phase III trial randomized pts with indolent lymphomas (both follicular and marginal zone) to 40–45 Gy in 20–23 fx vs. 24 Gy in 12 fx. With a median f/u of 5.6 yrs, there was no difference in in-field failure, OS, or PFS. (Lowry et al., R&O 2011)

The Follicular Radiotherapy Trial (FoRT) phase III trial (Hoskin PJ et al., Lancet Oncol 2014) randomized pts (follicular or marginal zone) to either 24 Gy or 4 Gy and found better CR with 24 Gy (68% vs. 49%) and better local PFS, which was the primary endpoint. HR for time to local progression of 3.42 (p <0.0001). Nonetheless, the ORR to just 4 Gy was 81%. Given the relatively high response rates, ease of administration and min toxicity associated with 4 Gy, the authors concluded that this lower dose is a useful alternative for palliative Tx, when durable response might be less important.

What remains the Tx standard for localized, low-grade FL?

Answer

Locoregional RT to 24–30 Gy remains standard for stage I and contiguous stage II, grade 1–2 FL. However, observation, lower dose RT (4 Gy), and combined modality Tx are considered viable options depending on the pt and Dz characteristics.

What are the basic Tx principles for stages III–IV, low-grade FL?

Answer

No Tx is considered curative. Several randomized trials have indicated that therapy can be deferred without reducing survival. Tx is reserved for the following:

Symptomatic Dz

-Threatened end organ dysfunction

-Cytopenias

-Bulky Dz

-Steady Dz progression

-Clinical trial

-Pt preference

What is the evidence for radioimmunotherapy in advanced-stage FL?

Answer

SWOG S0016 randomized pts with advanced-stage FL to R-CHOP × 6 vs. CHOP-RIT with Bexxar (I-131-tositumomab, a CD-20 radiotherapeutic antibody). There was no difference in 2-yr PFS (80% vs. 76%) or 2-yr OS (93% vs. 97%). (Press OW et al., JCO 2013)

What is the role of RT for stages III–IV, low-grade FL?

Answer

In advanced-stage indolent lymphomas, RT is reserved for palliation of Sx.

What is a typical RT Tx for symptomatic stages III–IV FL?

Answer

24 Gy in 12 fx should be used when durable LC is needed. Otherwise, 4 Gy in 2 fx is an effective, convenient, and well-tolerated alternative, based on the FORT trial.

What is the role of RT in the Tx of CLL/SLL?

Answer

RT is used for palliation of symptomatic lesions. CLL/SLL does not respond as well to 4 Gy in 2 fx as FL or MZL. From various reports, the response rates of CLL/SLL to 4 Gy are ∼10%–25% CR, and ∼40%–50% PR. 4 Gy may be tried as a palliative dose; however, a higher total dose (e.g., 24– 30 Gy) may be needed, particularly if durable LC is a priority.

What is the role of RT in treating nodal MZLs?

Answer

Nodal MZL is rare and is managed like low-grade FL. RT may be used for definitive therapy in localized Dz and for palliation in advanced-stage Dz. What is the most common initial multiagent chemo used in the management of intermediate- or high-grade NHL?

Answer

The most common initial multiagent chemo used in NHL is R-CHOP, which uses the following drugs:

-Rituximab

-Cyclophosphamide

-Hydroxydaunomycin (Adriamycin)

-Vincristine (Oncovin)

-Prednisone

What are the current indications for RT in early-stage, intermediate- or high-grade NHL?

Answer

The inclusion of RT in early-stage, intermediate- or high-grade NHL is institution dependent. It may be included as consolidation after 3–4 cycles (i.e., an abbreviated course) of R-CHOP in favorable Dz, or in appropriately selected pts with a PR to chemo. Recent research has focused on identifying the subgroups of pts that benefit from consolidative RT, after experiencing a CR to rituximab and chemo. For example, the RICOVER noRTh study demonstrated improved outcomes in pts who rcvd consolidative RT to initially bulky sites of Dz. (Held et al., J Clin Oncol 2014;32(11):1112–8) Other work has demonstrated improved outcomes associated with RT to skeletal sites of involvement. (Held G et al., J Clin Oncol 2013;31(32):4115–

22) The results of ongoing randomized trials from the modern era are eagerly anticipated to further guide selection of candidates for RT.

What is the present Tx paradigm for advanced stage, intermediate- or high-grade NHL?

Answer

Advanced-stage, intermediate- or high-grade NHL Tx paradigm: R-CHOP × 6 cycles. IFRT may be considered for initially bulky sites, based on the RICOVER noRTh study, and for skeletal sites. (Held et al., 2013).

Estimate the prognosis of limited-stage aggressive B-cell lymphoma treated with R-CHOP and IFRT.

Answer

SWOG 0014 (phase II) enrolled 60 pts with limited-stage aggressive NHL and at least 1 adverse risk factor. Pts were treated with R-CHOP × 3 + IFRT: 4-yr PFS was 88%, and OS was 92%. (Persky DO et al., JCO 2008)

What is the long-term DFS for pts with localized DLBCL treated with RT alone? What were the typical Tx doses used in clinical trials?

Answer

Using 45–50 Gy to maximize LC, only 40% of pts with localized DLBCL had long-term DFS based on historical RT-alone data. (Chen MG et al., Cancer 1979; Sweet DL et al., Blood 1981; Kaminski MS et al., Ann Intern Med 1986)

What was demonstrated in the initial publication of the SWOG 8736 study comparing chemo alone to abbreviated CRT in localized intermediate- grade NHL?

Answer

In SWOG 8736, 401 pts with stage I or IE (including bulky Dz) and stage II or IIE (nonbulky) intermediate-grade NHL were randomized to CHOP × 8 cycles vs. CHOP × 3 + IFRT. RT doses of 40–55 Gy were employed. At 5-yr f/u, PFS and OS favored the combined therapy group (OS: 82% vs. 72%). (Miller TP et al., NEJM 1998) However, extended data with median 17.7 yrs f/u showed no difference in OS or PFS b/t the 2 groups and increased late relapses in the combined modality therapy arm. (Stephens DM et al., JCO 2016) These findings suggest that the use of RT cannot compensate for inadequate chemo.

What was demonstrated in the ECOG E1484 study randomizing postchemo complete responders to observation vs. IFRT?

Answer

In ECOG E1484, 352 pts with intermediate-grade, bulky stages I–IE or nonbulky stages II–IIE Dz were administered CHOP × 8 cycles. Complete responders (215 pts) were randomized to IFRT vs. observation. At 6 yrs, DFS favored IFRT (73% vs. 56%), but OS was equivalent. FFS was equivalent in partial responders administered IFRT (40 Gy) and in CR pts (30 Gy). Failure at initial sites was greater in pts not given IFRT. (Horning SJ et al., JCO 2004)

What was demonstrated in the GELA LNH-93-1 study comparing aggressive chemo vs. standard chemo and RT in pts less than or equal to 60 yo?

Answer

In GELA LNH-93-1, 647 pts ≤60 yo with low-risk (IPI 0), stages I or II, intermediate-risk NHL (extranodal or bulky Dz allowed) were randomized to doxorubicin/cyclophosphamide/vindesine/bleomycin/prednisone (ACVBP) × 3, then Mtx/etoposide/ifosfamide/cytarabine vs. CHOP × 3, then IFRT to 30– 40 Gy. ACVBP without RT improved 5-yr EFS (82% vs. 74%) and OS (90% vs. 81%) regardless of the presence of bulky Dz. (Reyes F et al., NEJM 2005) However, ACVBP is considered to be a toxic regimen (dose intensity 150% of CHOP; requires hospitalization to administer; associated with high rates of secondary acute myeloid leukemia and lung cancer); therefore, it is not used standardly.

What was demonstrated in the GELA LNH-93-4 study evaluating pts age

>60 yrs with low-risk, localized, intermediate-grade NHL?

Answer

In GELA LNH-93-4, 576 pts age >60 yrs with low-risk (age-adjusted IPI 0), stage I or II NHL (bulky [8%] or extranodal [56%] Dz allowed) were randomized to CHOP × 4 vs. CHOP × 4 + IFRT to 40 Gy. The 5-yr EFS (∼62%) and OS (∼70%) were equivalent in both Tx arms. (Bonnet C et al., JCO 2007)

What is the present Tx paradigm for relapsed intermediate- or high-grade NHL?

Answer

Relapsed intermediate- or high-grade NHL Tx paradigm: high-dose chemo + autologous stem cell transplant

FOLLOW-UP/TOXICITY

What are the expected RT toxicities associated with Tx of NHL?

Answer

The RT toxicities depend on the site of Tx. B/c of high rates of long-term survival and frequent Tx with doxorubicin; the cardiac effects of mediastinal RT are an important concern. The later age at presentation, when compared to HL, should be considered with respect to the risk of 2nd malignancies.