ICRO TEACHING COURSE
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LUCKNOW

Role of Radiotherapy in Pediatric NHL

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Introduction

- Since the late 1960s, treatment outcomes for pediatric patients with non-Hodgkin lymphoma have steadily improved.
- Even for patients with advanced disease, event-free survival rates are now 65-90%
- The mainstay of conventional therapy is multiagent chemotherapy tailored to the histologic subtype and the clinical stage of disease.
- In certain individuals with non-Hodgkin lymphoma, surgical resection and radiation therapy are also key components of definitive treatment.
- Newer therapies that target immunologic and biologic aspects of the lymphoma are still under development but beginning to appear in the clinical arena

Lymphoma

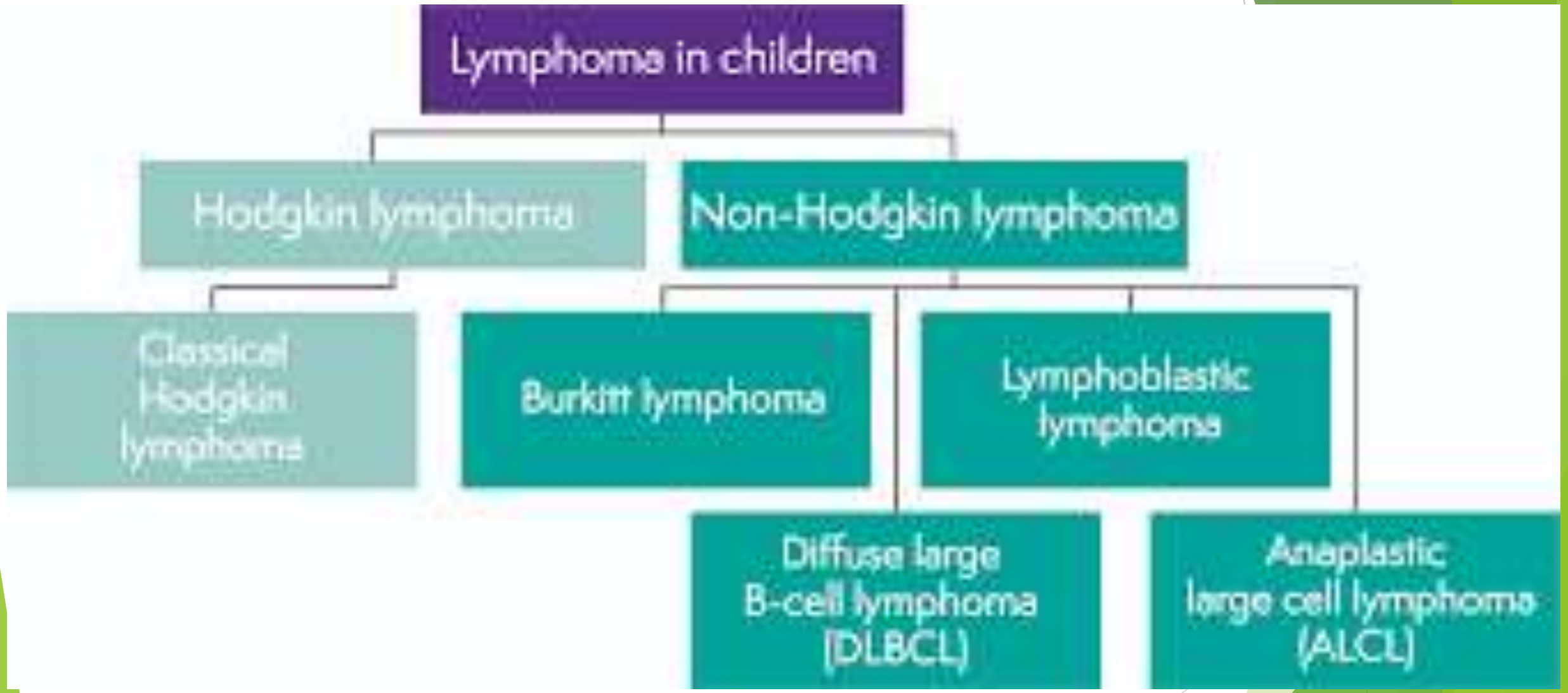
- Lymphoma is the third most common cancer in children, with an annual incidence of 13-14 per million children.
- The two broad categories of lymphoma, Hodgkin disease and non-Hodgkin lymphoma (NHL), have such different clinical manifestations and treatments that they are considered separately.

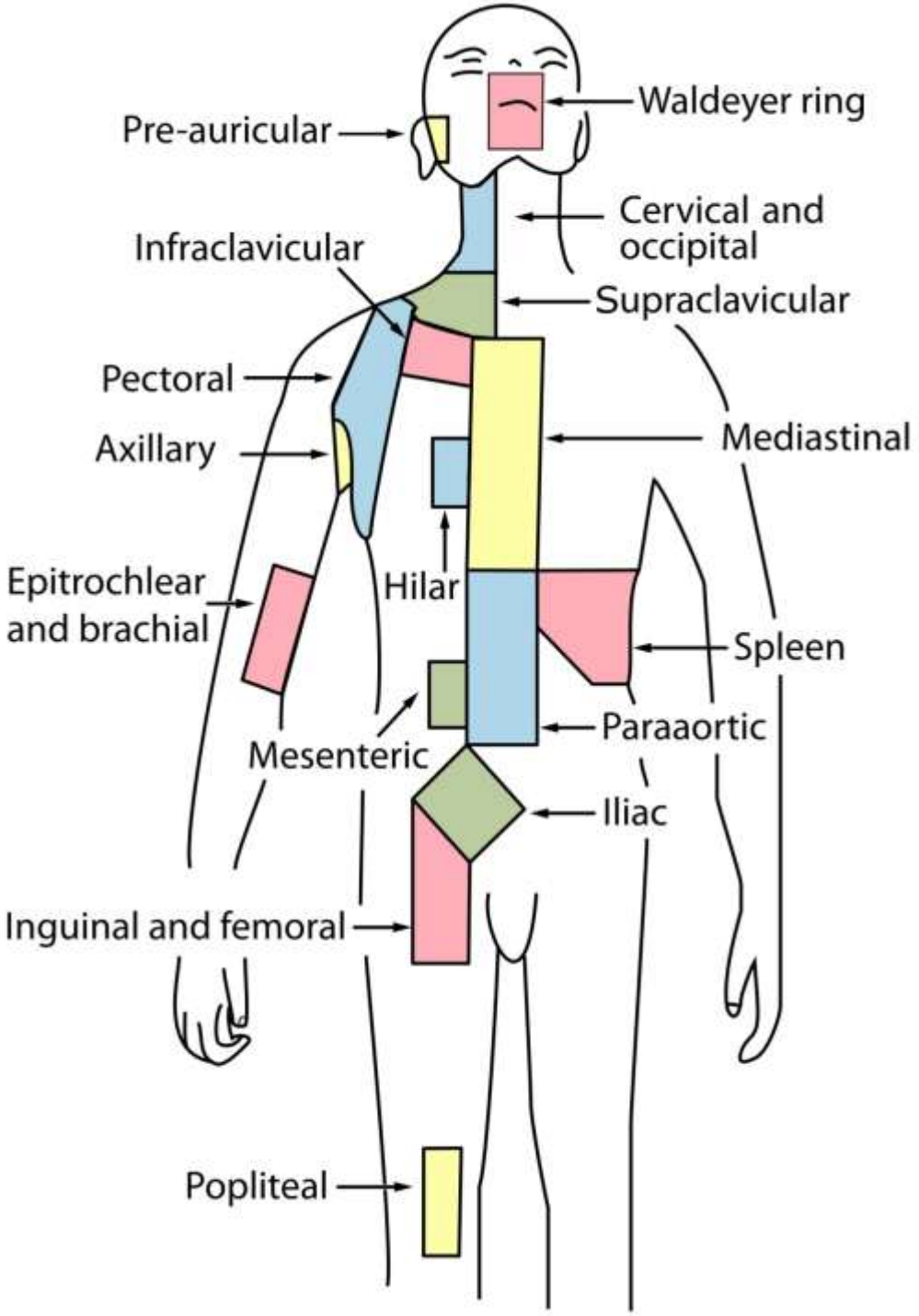
Pediatric Non-Hodgkin Lymphomas in Children: Diagnosis and Current Management

Pediatric lymphomas -

- Third most common malignancy in children Accounts for 13% of all childhood cancers.
- It’s incidence increases with increasing age in children.
- About 60% of the lymphomas are of the Non-Hodgkin variety.

Indian Pediatrics 2001; 38: 583-588


Lymphoma in children
Hodgkin lymphoma
Non-Hodgkin lymphoma
Classical Hodgkin lymphoma
Burkitt lymphoma
Lymphoblastic lymphoma
Diffuse large B-cell lymphoma (DLBCL)
Anaplastic large cell lymphoma (ALCL)


Waldeyer ring
Pre-auricular
Cervical and occipital
Infraclavicular
Supraclavicular
Pectoral
Axillary
Mediastinal
Epitrochlear and brachial
Hilar
Spleen
Paraaortic
Mesenteric
Iliac
Inguinal and femoral
Popliteal

Introduction

- Childhood NHLs - heterogeneous group of malignancies with variable histopathology, site of origin, and clinical manifestations.
- Diffuse, high grade, and poorly differentiated;
- Extranodal involvement is common,
- Dissemination occurs early and often.
- In the United States, NHL is diagnosed in approximately 800 children and adolescents younger than 20 years of age, each year.
- According to the Surveillance, Epidemiology, and End Results program of the National Cancer Institute,
  - *NHL accounts for about 8% of all cases of childhood cancer.*

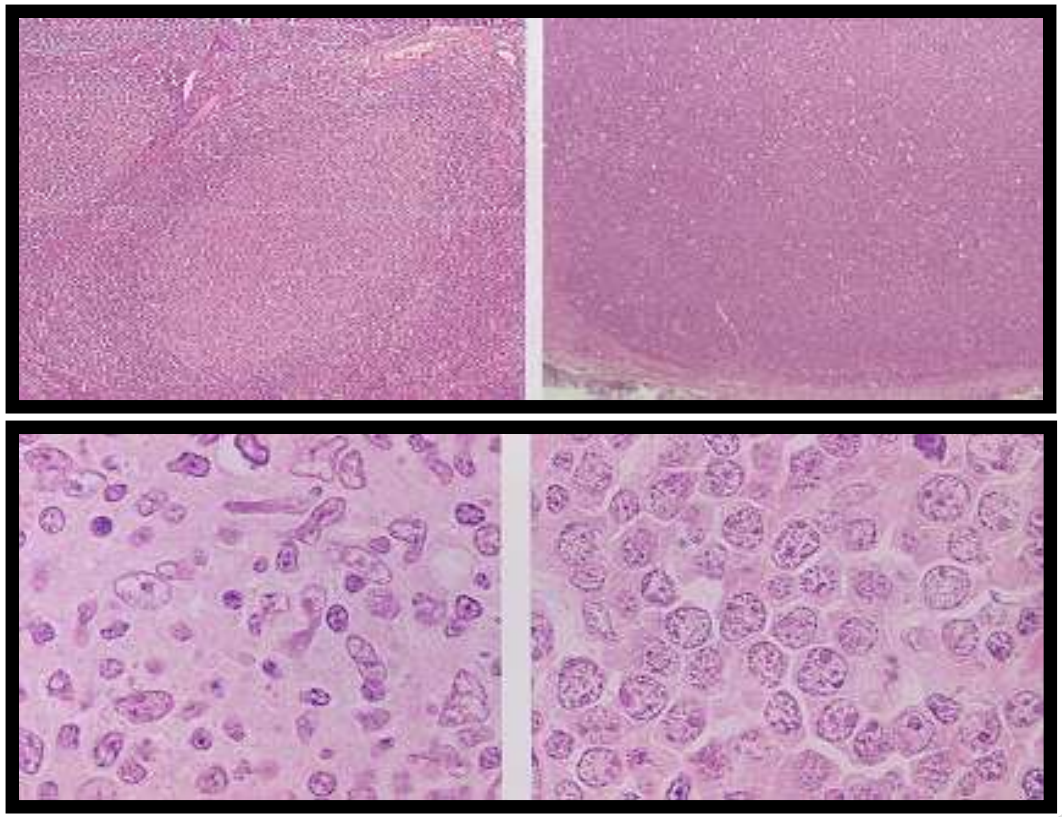
Histologic Classification of Non-Hodgkin's Lymphomas

1. Rappaport	1966
2. Lukes and Collins	1974
3. Kiel	1974
3. Dorfman	1974
4. Bennet et al.,	1974
5. Lennert	1974
6. WHO	1976
7. Working Formulation	1982
8. REAL	1994
9. WHO	1999

Non-Hodgkin's Lymphoma Rappaport Classification

Nodular (follicular) Diffuse

Indolent



Aggressive

Small cell Large cell

World Health Organization (WHO) Classification of Lymphoid Neoplasms: B-Cell Neoplasms

- **Precursor B-cell neoplasm**
  - Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)
- **Mature (peripheral) B-cell neoplasms**
  - B-cell CLL/SLL
  - B-cell PLL
  - Lymphoplasmacytic lymphoma
  - Plasmacytoma, plasma cell myeloma
  - HCL
- **Marginal zone B-cell lymphoma**
  - Marginal zone B-cell lymphoma of MALT
  - Nodal marginal zone lymphoma (+/- monocytoid B-cells)
  - Splenic marginal zone B-cell lymphoma
- **FL**
  - Grade 1, 0-5 centroblasts/hpf
  - Grade 2, 6-15 centroblasts/hpf
  - Grade 3, >15 centroblasts/hpf
    - 3a, >15 centroblasts, but centrocytes still present
    - 3b, centroblasts from solid sheets with no residual centrocytes
  - Variants
    - Cutaneous follicle center
- **MCL**
- **DLCL**
  - Mediastinal (thymic) large B-cell lymphoma
  - Intravascular lymphoma
  - Primary effusion lymphoma
- **Burkitt's lymphoma/Burkitt cell leukemia**

Jaffe et al. *Ann Oncol*. 1998;9 (suppl 5):S25.

Non-Hodgkin's Lymphoma Working Classification

- Developed in 1980's
- NCI Investigators reviewed Rappaport, Lukes-Collins, and Kiel systems
- n=1175

- Goal was to clarify… now a new system!
- No consideration to B-cell or T-cell typing
- Goal was to group lymphomas according to aggressiveness (low, intermediate, high)

Non-Hodgkin's Lymphoma Working Classification

- Low Grade
  - Small Lymphocytic
  - Follicular small-cleaved cell
  - Follicular mixed small-cleaved and large cell
- Intermediate Grade
  - Follicular large cell
  - Diffuse small cleaved cell
  - Diffuse mixed small and large cell
  - Diffuse large cell
- High Grade
  - Large cell immunoblastic
  - Lymphoblastic
  - Small non-cleaved cell (Burkitt's and non-Burkitt's type)

Incidence of NHL per Million Person-Years

	Males				Females			
Age (y)	<5	5–9	10–14	15–19	<5	5–9	10–14	15–19
Burkitt	3.2	6	**6.1**	**2.8**	0.8	1.1	0.8	1.2
Lymphoblastic	1.6	2.2	**2.8**	**2.2**	0.9	1.0	0.7	0.9
DLBCL	0.5	1.2	2.5	6.1	0.6	0.7	1.4	4.9
Other (mostly ALCL)	2.3	3.3	4.3	7.8	1.5	1.6	2.8	3

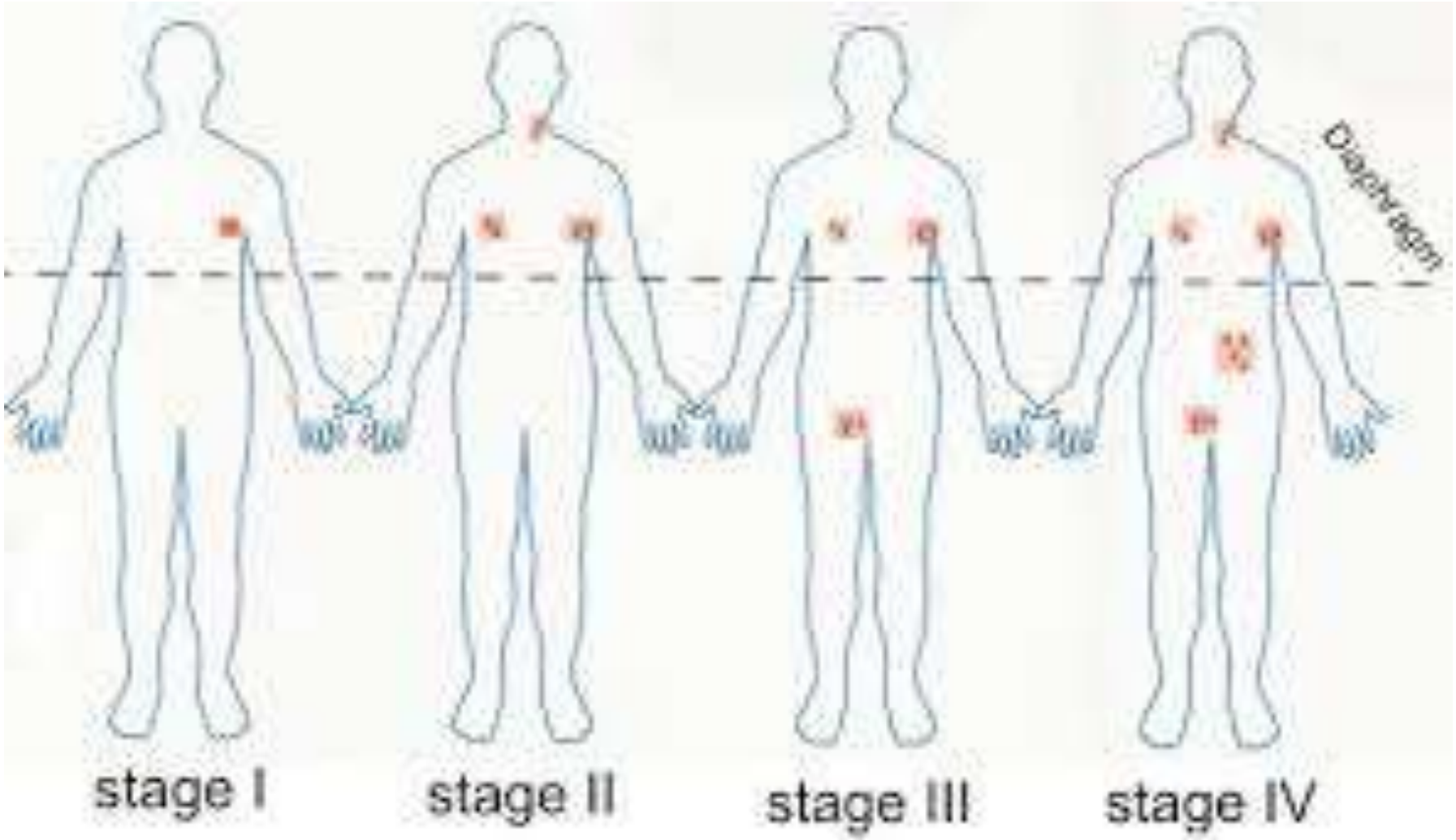
Indolent and aggressive histologies (more commonly seen in adult patients) are mostly found in older adolescents

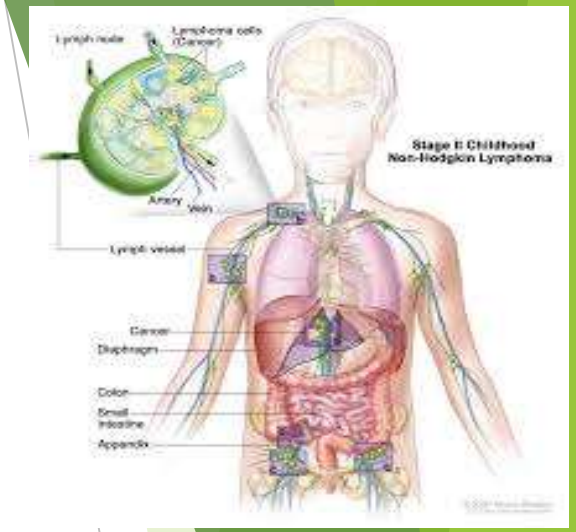
Diagnostic Evaluation

- History and physical exam.
- Pathologic examination of tumor cells.
- Immunophenotyping by immunohistochemistry and/or flow cytometry.
- Cytogenetics and/or fluorescence *in situ* hybridization (FISH).
- Bone marrow biopsy and aspiration.
- Lumbar puncture.
- Total-body imaging (CT- scan, PET, and MRI).
- Measurement of serum electrolytes, (LDH), uric acid, (BUN), and creatinine.
- Liver function tests.

Lymphoma Staging

- Murphy = Ann Arbor
- I: tumor at one site (nodal or extranodal = "E")
- II: two or more sites; same side of body (or resectable GI primary)
- III: both sides of body but not IV (& unresec. GI & mediastinal for NHL)
- IV: CNS or marrow involvement (Murphy); lung, liver, marrow, or bone for Ann Arbor (< 25% marrow)
- "B" sxs are defined for HD, as is "bulky disease"
- Head and neck (possibility of CNS involvement) is a further consideration for NHL
- PET or gallium


Diaphragm
stage I
stage II
stage III
stage IV


Stage II Childhood
Non-Hodgkin Lymphoma
Lymph node
Lymphoma cells
(Cancer)
Artery
Vein
Lymph vessel
Cancer
Diaphragm
Colon
Small intestine
Appendix

- Staging and response criteria were initially developed for Hodgkin lymphoma (HL) over 60 years ago,
- But not until 1999 were response criteria published for non-HL (NHL).
- Revisions to these criteria for both NHL and HL were published in 2007 by an international working group,
- Incorporating PET for response assessment, and were widely adopted.
- *After years of experience with these criteria, workshop including representatives of most major international lymphoma cooperative groups and cancer centers was held at the 11th International Conference on Malignant Lymphoma (ICML) in June, 2011* . (Lugano Switzerland) *to determine what changes were needed*

Chinese Clinical Oncology, Vol 4, No 1 March 2015

Major features of the Lugano classification

Staging

- PET-CT for staging of FDG-avid lymphoma histologies
- Modified Ann Arbor for extent of disease Treatment directed more by limited or advanced disease and prognostic/risk factors
- Elimination of bone marrow biopsies in Hodgkin and most diffuse large B-cell NHL
- Elimination of routine chest X-ray A and B only used for HL Elimination of “X”, but record largest mass diameter

Response assessment

- PET-CT is the basis of response assessment for all FDGavid histologies
- CR includes residual masses that are not FDG-avid
- Interpretation of PET using 5-point scale
- Increase of single node for progressive disease

History of Deau Ville Score

The scale was proposed in an international workshop attended by hematologists and nuclear medicine specialists in Deauville, France in 2009

Usage

- It is a simple tool based on visual interpretation of FDG-uptake.
- It takes advantage of two reference points of the individual patient, which have demonstrated relatively constant uptake on serial imaging.
- ***The two reference organs are the mediastinum (a.k.a. blood pool) and the liver***.
- **The scale ranges from 1 to 5, where 1 is best and 5 is the worst**.
- Each FDG-avid (or previously FDG-avid) lesion is rated independently:

1. No uptake or no residual uptake (when used interim)
2. Slight uptake, but equal to or below blood pool (mediastinum)
3. Uptake above mediastinal, but below or equal to uptake in the liver
4. Uptake slightly to moderately higher than liver
5. Markedly increased uptake or any new lesion (on response evaluation)

- *Some authors also use:*

•X for any lesion not overtly attributable to lymphoma ·

Assessment of treatment response

- Complete response (CR): scores 1, 2 or 3 together with the absence of FDG-avid bone marrow lesion(s) are interpreted as complete metabolic response (CR), irrespective of a persistent mass on CT
- Partial response (PR): a Deauville score of 4 or 5, provided:
  - uptake is decreased compared with baseline and
  - absence of structural progression development on CT
- Stable disease (SD), also called no metabolic response: a Deauville score of 4 or 5 without significant change in FDG uptake from baseline.
- Progressive disease (PD): a Deauville score of 4 to 5 with increasing intensity compared to baseline or any interim scan and/or any new FDG-avid focus consistent with malignant lymphoma ·

Caveat

It is often stated that DLBCL patients who demonstrate a complete metabolic response (Deauville 1) but have a residual mass of greater than 2 cm are at an increased risk of recurrence.

Table 1 Modified Lugano 5-point scale (5PS)

Score	Description
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately increased above liver at any site
5	Markedly increased uptake above liver at any site
NE	Not evaluable
X	Any areas of uptake not likely to be related to lymphoma

Note: Data from Cheson et al.[18]

Clinical findings in non-Hodgkin lymphoma

•Cervical or supraclavicular masses or adenopathy is/are firm, fixed, and nontender

•Dyspnea or stridor may occur in patients with a mediastinal mass

•In patients with superior vena cava syndrome, distended neck veins and plethora may be observed
•Decreased breath sounds are secondary to bronchial obstruction or pleural effusion

•Thoracic dullness to percussion may be present with pleural effusion.

•Abdominal distention or a mass may be present with or without tenderness, rebound tenderness, and/or shifting dullness

- Painful skin lesions suggest an anaplastic large cell lymphoma (LCL);
- Less common forms of cutaneous lymphoma (T-cell, blastic plasmacytoid dendritic) are typically nontender

•Obtundation, agitation, and meningismus may be observed in individuals with CNS involvement.

•Focal pain or swelling in the extremity may be present in patients with primary bone lymphoma.

Relatively uncommon physical findings include the following:

•Nasopharyngeal mass
•Parotid enlargement
•Nephromegaly
•Testicular enlargement

Clinical characteristics of NHL

Histologic subtype	Proportion of cases(%)	Most common site
Burkits lymphoma	35-40	Abdomen/ H&N
T	15	Mediastinum +adenopathy
B	3	Cutaneous<isolated nodes, bones
DLBCL	15-20	Nodes, abdomen &bones
Mediastinal	1-2	mediastinum
Anaplastic	15-20	Skin , bones, nodes

Prognosis and Prognostic Factors for Childhood NHL

In high-income countries and with current treatments, more than 80% of children and adolescents with NHL will survive at least 5 years,

Outcome depends on a number of factors, including clinical stage and histology

Prognostic factors for childhood NHL include the following:

- Response to therapy.
- Stage at diagnosis/presence of minimal disseminated disease (MDD).
- Sites of disease at diagnosis.
- Age.
- Immune response to tumor.

Treatment Options for Childhood Non-Hodgkin Lymphoma (NHL)

Treatment Group		Treatment Options
CNS = central nervous system; EBV = Epstein-Barr virus; MALT = mucosa-associated lymphoid tissue; PTLD = posttransplant lymphoproliferative disease; SCT = stem cell transplantation.		
Mature B-cell NHL:		
Burkitt and Burkitt-like lymphoma/leukemia	Newly diagnosed	Surgery (for stage I and II only) Chemotherapy with or without rituximab
	Recurrent	Chemotherapy with or without rituximab Allogeneic or autologous SCT
Diffuse large B-cell lymphoma	Newly diagnosed	Surgery (for stage I and II only) Chemotherapy with or without rituximab
	Recurrent	Chemotherapy with or without rituximab Allogeneic or autologous SCT

Primary mediastinal B-cell lymphoma		Chemotherapy and rituximab
Lymphoblastic lymphoma	Newly diagnosed	Chemotherapy
		Cranial radiation therapy for overt CNS disease only
	Recurrent	Nelarabine or nelarabine-containing chemotherapy regimens
		Chemotherapy
		Allogeneic SCT
Anaplastic large cell lymphoma	Newly diagnosed	Surgery followed by chemotherapy (for stage I)
		Chemotherapy
	Recurrent	Chemotherapy, brentuximab, and/or crizotinib
		Allogeneic or autologous SCT

Lymphoproliferative disease associated with immunodeficiency:

Lymphoproliferative disease associated with primary immunodeficiency	Chemotherapy with or without rituximab Allogeneic SCT
NHL associated with DNA repair defect syndromes	Chemotherapy
HIV-associated NHL	Chemotherapy with or without rituximab
PTLD	Surgery and reduction of immunosuppressive therapy, if possible Rituximab alone Standard or slightly modified chemotherapy with or without rituximab (for B-cell PTLD) Low-dose chemotherapy with or without rituximab (for EBV-positive B-cell PTLD)

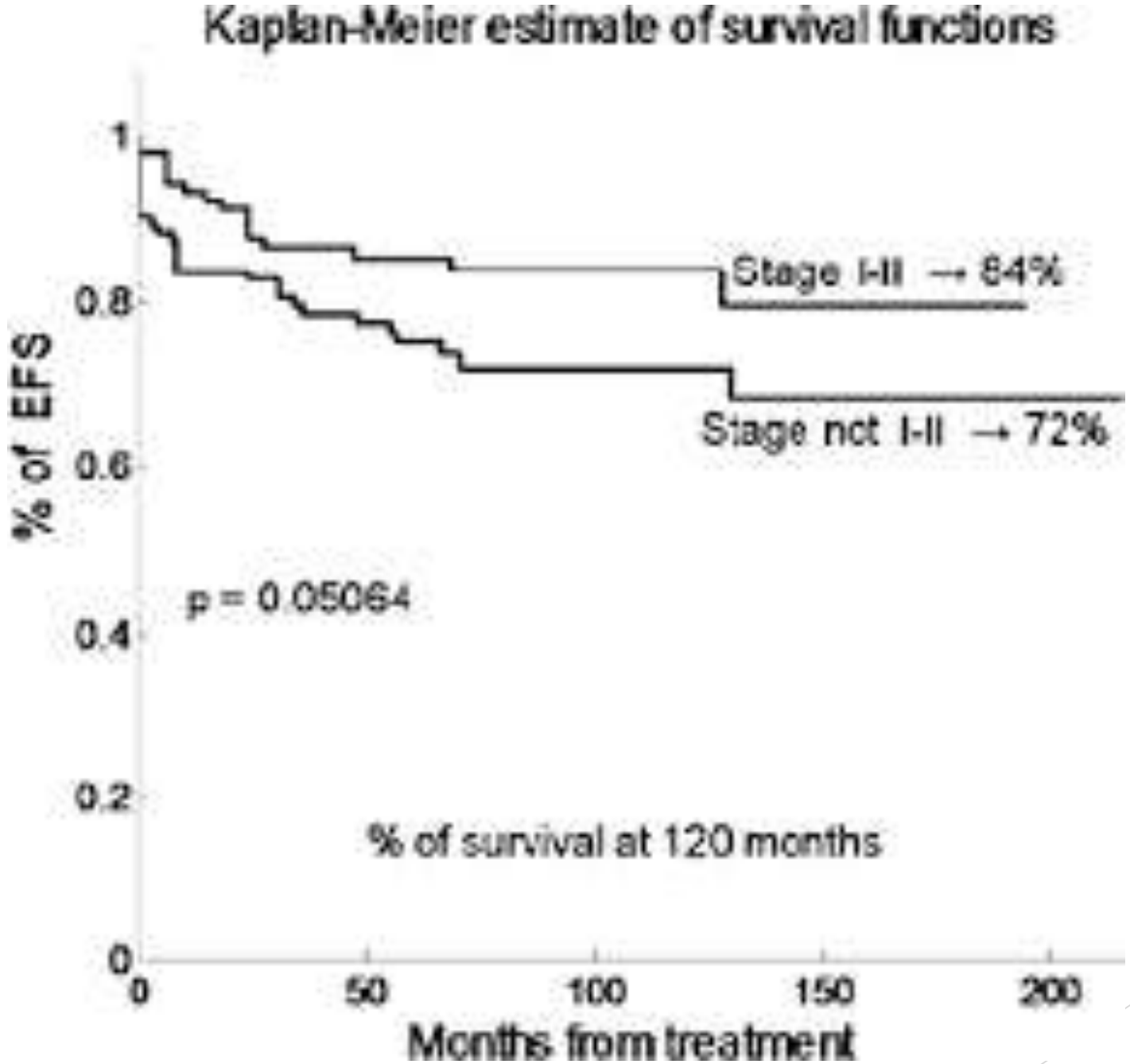
Rare NHL:

Pediatric-type follicular lymphoma	Surgery only
	Chemotherapy with or without rituximab
Marginal zone lymphoma	Surgery only
	Radiation therapy
	Rituximab with or without chemotherapy
	Antibiotic therapy, for MALT lymphoma
Primary CNS lymphoma	Chemotherapy
Peripheral T-cell lymphoma	Chemotherapy
	Radiation therapy
	Allogeneic or autologous SCT
Cutaneous T-cell lymphoma	No standard treatments have been established

THE ROLE OF RADIATION THERAPY IN THE TREATMENT OF PEDIATRIC NON-HODGKIN'S LYMPHOMAS

STEVEN C. CARABELL, MD,*,$ J. ROBERT CASSADY, MD,* HOWARD J. WEINSTEIN, MD,
Cancer 42:2193-2205, 1978.

- Between 1971 and 1976, 64 patients less than 18 years of age with non- Hodgkin's lymphoma were treated at Boston's Children's Hospital Medical Center-Joint Center for Radiation Therapy.
- A multimodality approach was used, consisting of radiation therapy (3500-4500 rad), surgery, and chemo- therapy.
- Since 1973, all patients have received a regimen initially comprising Adriamycin, Prednisone, 6-Mercaptopurine, Vincristine, and L-Asparaginase. Methotrexate was substituted for Adriamycin following a cumulative total dose of 450 mg/m2.
- The 5-year actuarial survival for all patients was 6l%, while relapse-free survival was 54%.
- The actuarial and relapse-free survival for patients presenting with localized disease was 75% and 72%, respectively.
- Median follow-up was 40 months and all relapses occurred within 24 months of initial therapy.
- A multidisciplinary approach, such as the current regimen, offers a good prognosis for this disease.


Kaplan-Meier estimate of survival functions
% of EFS
1
0.8
0.6
0.4
0.2
0
Stage I-II → 84%
Stage not I-II → 72%
p = 0.05064
% of survival at 120 months
0
50
100
150
200
Months from treatment

Review article NEJM 1996

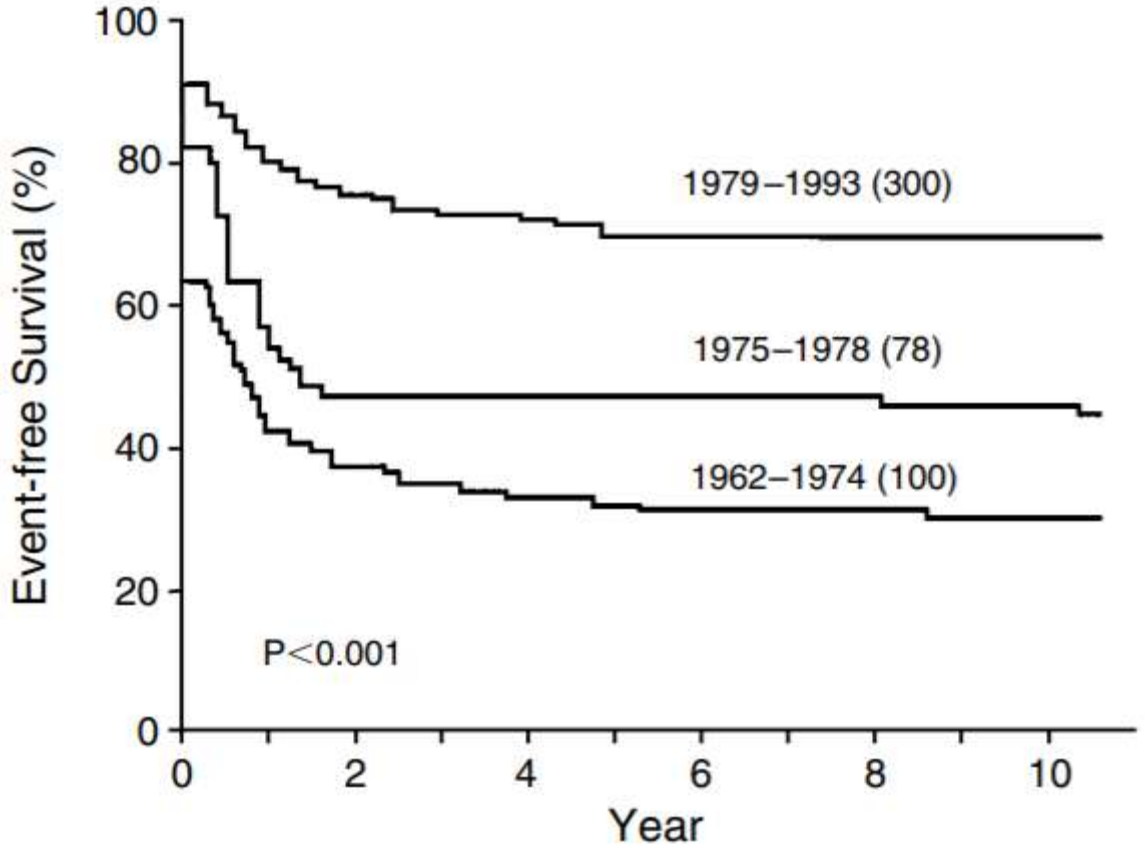


Figure 5. Event-free Survival of Patients with Non-Hodgkin's Lymphoma Treated from 1962 to 1993 at St. Jude Children's Research Hospital.

Balancing Act of Radiotherapy

chemotherapy

Radiotherapy

RADIOTHERAPY TREATMENT PLANNING:

1.POSITION/IMMOBILISATION

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

2.IMAGE ACQUISITION

Patients are 3D-planned using data from a CT planning scan.

- Contiguous slices with slice thickness of no more than 3mm taken through the region of interest.
- I.V .contrast is recommended to improve identification of nodal chains unless there are specific contraindications.

- Except in sites such as mediastinum and paraaortic region where blood, volume is relatively large
- Pre and post i.v. contrast planning CT scans are then required.
- It is recommended that each centre carry out a dosimetric analysis of the effects of contrast on the treatment planning calculations for individual anatomical sites.

VOLUME DELINEATION AND NOMENCLATURE

- Lymph node region atlases for CT planning have been published
- IFRT has been the standard with equivalence to wide field radiotherapy when used in combination with chemotherapy.
- ISRT has been utilized in recent pediatric Hodgkin Lymphoma protocols and in the recent 18-30 trial as a step to further reduce the radiation volume treated and hence probability of late effects.
- Validation from large data sets is awaited from the current clinical trials.
- Hoskin et al,(2013) recommended the adoption of ISRT for patients receiving combined modality treatment as long as appropriate pre-chemotherapy imaging is available.
- In this instance, FDGPET-CT would be advisable.
- If imaging is not available or radiotherapy is being used as sole therapy, IFRT should be used instead.
- Use of ISRT remains at clinician discretion with the patient fully counselled.

IFRT–CTV Definition

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

ISRT-CTV definition:

- IS-CTV includes all initially involved sites.
- Pre-chemotherapy imaging is used to define the superior and inferior extent of the original disease.
- This is expanded cranio-caudally by 1.5 cm in the direction of lymphatic spread to form the superior and inferior levels of the IS-CTV.
- In transverse plane, the IS-CTV includes the nodal chain (or organ) and any residual disease.
- It is not necessary to encompass entire
- Nodal regions (or adjacent ones either).
- CTV is
- Modified by hand to no text end in to air, muscle planes or bones unless evidence of direct invasion.

Planning target volume (PTV)

- CTV is expanded in 3D to create the PTV to account for organ motion and set-up error.
- These are to be defined individually for each disease site and treatment centre.
- For guidance typical margins areas follows.
- ▫ Head&Neck :5–10mm
- ▫ Mediastinum :10mm transversely & 15mm cranio-caudally
- ▫ All other sites :10mm

PLANNING/TECHNIQUE

3D planning using CT data Consider 4D imaging or DIBH technique for disease sites significantly affected by respiratory motion.

TREATMENT TECHNIQUE

- Conformal plan with field arrangements devised according to treatment site.
- A parallel-opposed field arrangement often remains the preferred beam arrangement.
- IMRT may be found beneficial for head and neck sites e.g.NK-T cell lymphoma of nasopharynx.

TREATMENT VERIFICATION

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

ON TREATMENT REVIEW DEFINITION & SCHEDULE GAP CATEGORY FOR MANAGEMENT OF UNSCHEDULEDINTERRUPTIONS

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

Non-Hodgkin Lymphoma(RT Dose)

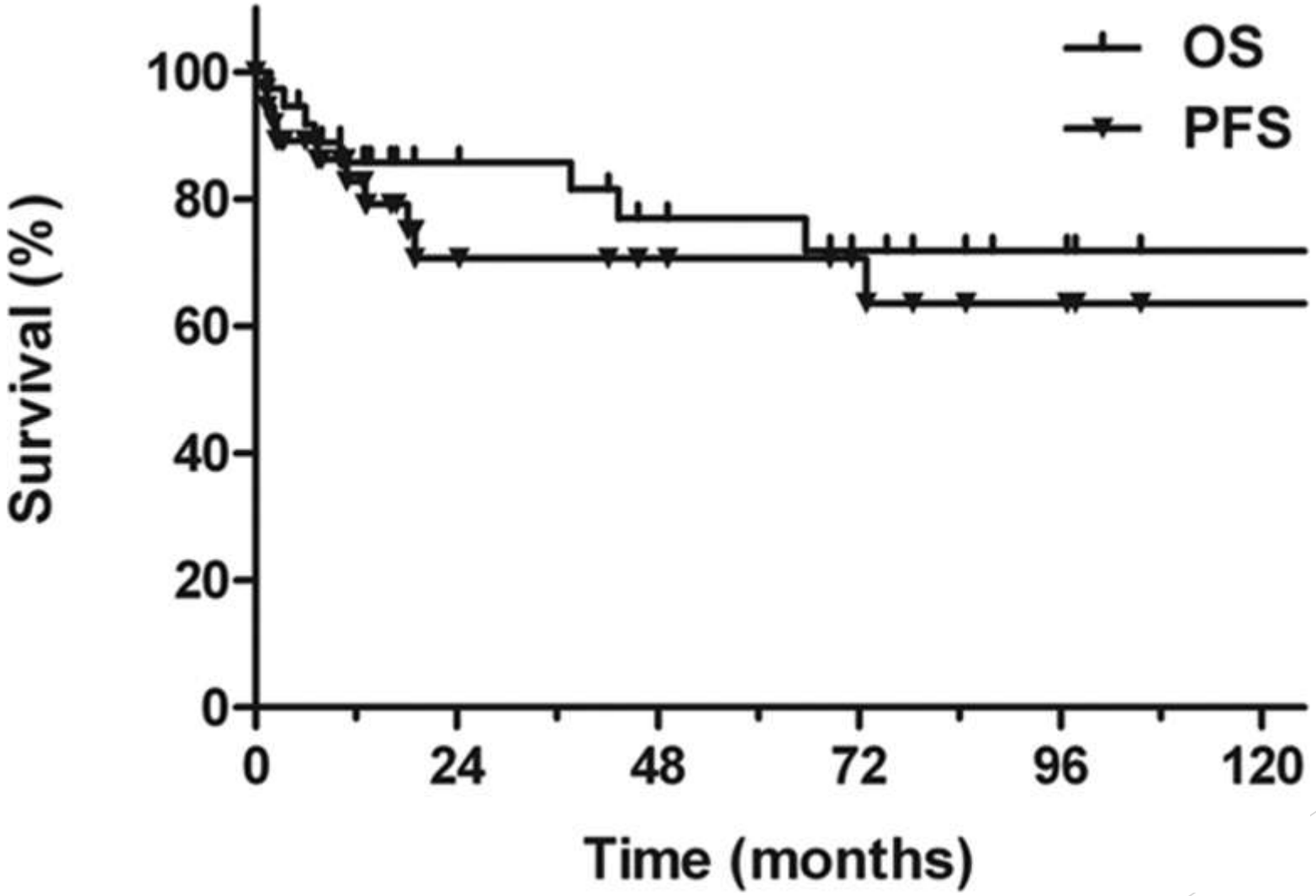
- High grade Lymphoma 30Gy/15-17fractions
- NK/T-cell Lymphoma requires higher doses of at least 50 Gy in 2Gy/fraction
- Primary CNS Lymphoma –Post chemotherapy 35-40 Gy in 1.8-2 Gy/fraction with boosting of residual volume to total of 45-50 Gy Low grade Lymphoma(e.g. Follicular Lymphoma) 24- 30Gy/12-15fractions

Examples of Palliative Schedules:

- 20-30Gy/5-10fractions
- 12Gy/4fractions
- 8Gy/single fraction
- 4Gy/2fractions(Boom Boom RT)

Primary radiotherapy showed favorable outcome in treating extranodal nasal-type NK/T-cell lymphoma in children and adolescents

Blood, 2009,



American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Zhao-Yang Wang,Ye-Xiong Li,Wei-Hu Wang,Jing Jin,Hua Wang,Yong-Wen Song,Qing-Feng Liu,Shu-Lian Wang,Yue-Ping Liu,Shu-Nan Qi,Hui Fang,Xin-Fan Liu,Zi-Hao Yu

AcuteToxicities:

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

LateToxicities

- Neck - Hypothyroidism
- Mediastinum - Pulmonary fibrosis
- Cardiac effects –Ischaemic heart disease, heart valve toxicity, pericarditis, pericardial effusion.
- Pelvis - Infertility Early menopause Late bowel and bladder toxicity
- Second malignancy –Breast cancer in young women

Follow-up = 4-6 weeks following completion of Radiotherapy

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STEVEN C. CARABELL, MD,$ J. ROBERT CASSADY, MD, HOWARD J. WEINSTEIN, MD, AND NORMAN JAFFE, MDT.5

(Cancer 42:2193-2205, 1978.)

Conclusion

- Radiation therapy, whether used as pri-mary therapy, as a supplement to multi- agent chemotherapy, or for CNS prophylaxis, has contributed to the markedly improved outlook for the child with NHL.
- However, a number of children still present with specific clinicopathologic settings for which current therapy is clearly inadequate.
- It is therefore critically important that childhood NHL be recognized as a complex group of conditions rather than one disease and that suitable stratification be performed so that future reports can be properly analyzed.
- Only in this manner will development of improved therapies be facilitated.

In contrast to the treatment of adults with NHL

The use of radiation therapy is limited in children with NHL.

- Early studies demonstrated that the routine use of radiation had no benefit for patients with low-stage (I or II) NHL.
- It has been demonstrated that prophylactic central nervous system (CNS) radiation can be omitted in patients with pediatric NHL.
- For patients with anaplastic large cell lymphoma and B-cell NHL who present with CNS disease, radiation can also be eliminated.

- Radiation therapy may have a role in treating patients who have not had a complete response to chemotherapy.
- Data to support limiting the use of radiation therapy in the treatment of pediatric NHL come from the Childhood Cancer Survivor Study.
- This analysis demonstrated that radiation was a significant risk factor for subsequent neoplasms and death in long-term survivors.

Summary

- Multiple recent trials demonstrated important role of RT as part of lymphoma therapy
- Doses of RT have decreased over time for most lymphoma cases
- Modern RT technique allows significant sparing of normal tissue
- Reduced doses and normal tissue exposure will limit side effects of RT

Although radiotherapy remains, as stated by;
James Armitage, former ASCO president and highly regarded lymphoma leader, “the most effective single agent in the treatment of lymphomas”,

Thank You!!!