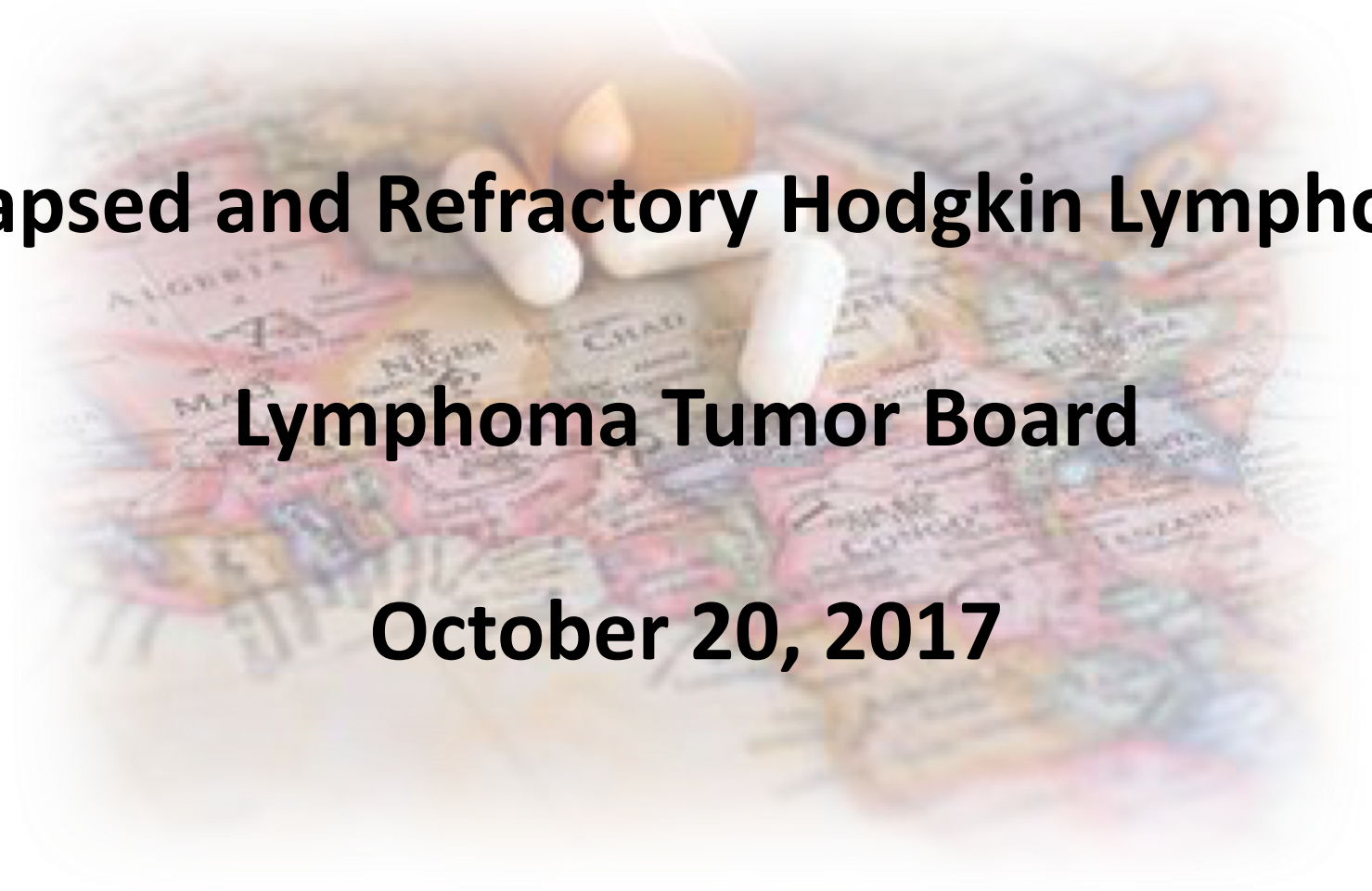


Relapsed and Refractory Hodgkin Lymphoma

Lymphoma Tumor Board

October 20, 2017

Thomas Hodgkin (1798-1866)

ON SOME MORBID APPEARANCES OF THE ABSORBENT GLANDS AND SPLEEN.

BY DR. HODGKIN.

PRESENTED BY DR. R. LEE.

READ JANUARY 10TH AND 24TH, 1832.

THE morbid alterations of structure which I am about to describe are probably familiar to many practical morbid anatomists, since they can scarcely have failed to have fallen under their observation in the course of cadaveric inspection. They have not, as far as I am aware, been made the subject of special attention, on which account I am induced to bring forward a few cases in which they have occurred to myself, trusting that I shall at least escape severe or general censure, even though a sentence or two should be produced from some existing work, couched in such concise but expressive language, as to render needless the longer details with which I shall trespass on the time of my hearers.

CASE I.

November 2, 1826. Joseph Sinnott, a child of about nine years of age, in Lazarus's ward, under the care of J. Morgan. His brother, his constant companion with whom he had habitually slept, died of phthisis a few months previously; he was much reduced by an illness of about nine months, during which time he had been subject to pain in the back, extending round to the abdomen. On his admission his belly was much distended with ascites. He had also effusion into the prepuce and scrotum. On the latter was a large ulcer induced by a puncture made to evacuate the fluid.

Head.—There was a considerable quantity of serous effusion under the arachnoid and within the ventricles. There were a few opake spots in the arachnoid, but this membrane was in other respects healthy. The pia mater appeared remarkably thin and free from vessels. The substance of the brain was generally soft and flabby, but no local morbid change was observable.

Chest.—The pleura on the right side had contracted many strong and old adhesions, in addition to which there were extensive marks of recent pleuritis. On the left the pleura was nearly or quite free from adhesion, but there was some fluid effused into

Etiology

Etiology - Hodgkin Lymphoma

Infectious agents

- EBV, may be involved in the pathogenesis. In as many as 50% of cases, the tumor cells are EBV-positive.
- Patients with HIV infection have a higher incidence of Hodgkin lymphoma compared with the population without HIV infection.

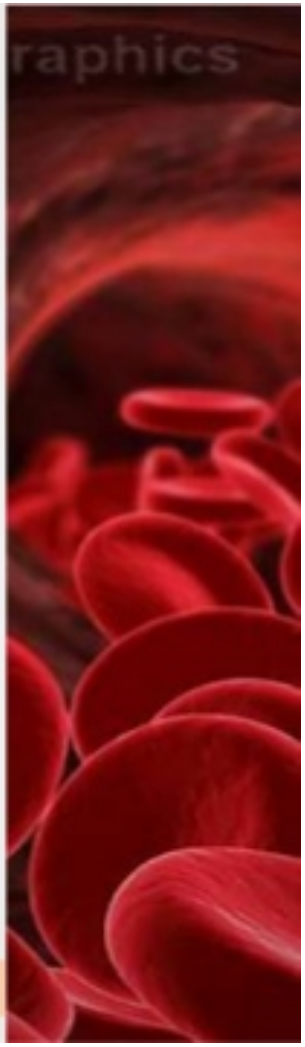
Genetic predisposition

- Approximately 1% of patients with Hodgkin lymphoma have a family history of the disease.

UV radiation exposure

- May have a protective effect against lymphomagenesis through mechanisms that may be independent of vitamin D

Source: http://emedicine.medscape.com/article/201886-overview#aw2aab6b2b3

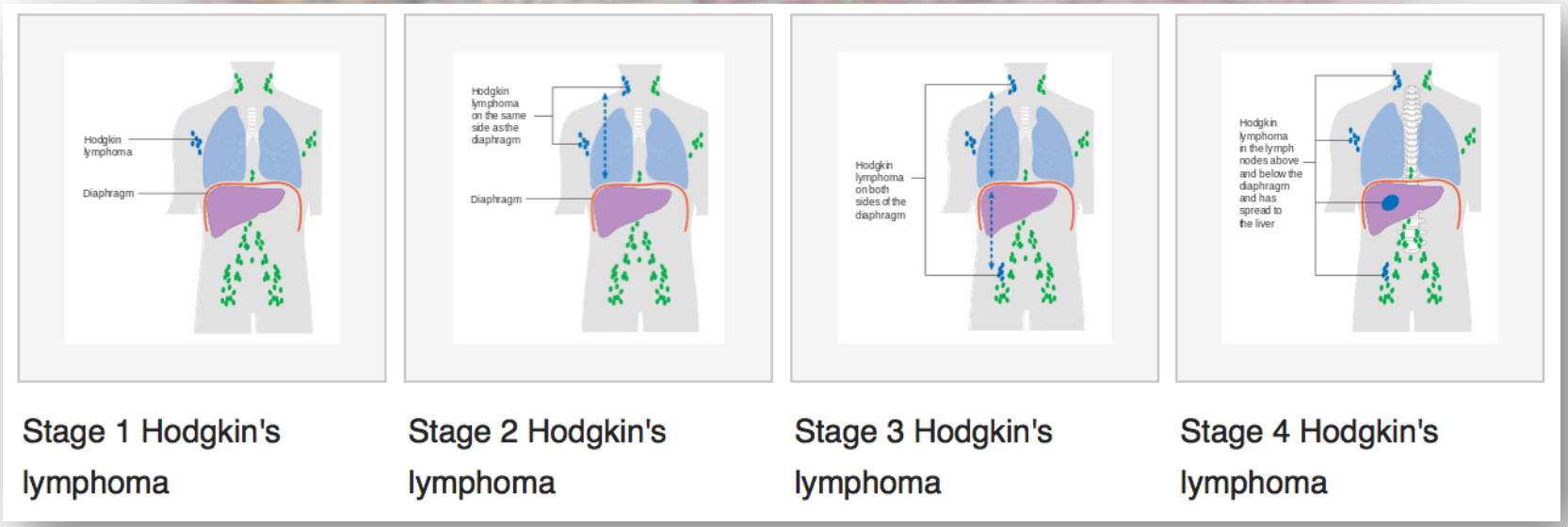


Subtypes of Classical Hodgkin Lymphoma (cHL)*

- Nodular sclerosing HL
  - Most common subtype
  - Composed of large tumor nodules
  - Nodules show scattered lacunar classical Reed Sternberg (RS) cells that are reactive
- Mixed-cellularity subtype
  - Common subtype
  - Composed of numerous classic RS cells with inflammatory cells
  - Frequently associated with EBV infection
  - Can be confused with “cellular” phase of nodular sclerosing CHL.
- Lymphocyte-rich
  - Rare subtype
  - Has most favorable prognosis
- Lymphocyte-depleted
  - Rare subtype
  - Composed of large numbers of pleomorphic RS cells with intermixed with reactive lymphocytes, which can be confused with DLBCL
- *~5% of patients have “nodular lymphocyte predominant Hodgkin lymphoma”

Staging of Hodgkin Lymphoma (HL)

- Stage I
  - Involvement of single lymph node region
  - Typically, cervical nodes or single extralymphatic site (stage IE)
- Stage II
  - Involvement of two or more lymph node regions on **same** side of diaphragm
  - One lymph node region and a contiguous extralymphatic site (IIE)
- Stage III
  - Involvement of two or more lymph node regions on both sides of the diaphragm
  - Can include spleen (IIIS) and/or limited contiguous extralymphatic organ sites (IIIE, IIIES)
- Stage IV
  - Disseminated involvement of one or more extralymphatic organs



HODGKIN LYMPHOMA STAGING[1]

Table 1

Definitions of Stages in Hodgkin's Disease[2]

Stage I Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (I_E).

Stage II Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional lymph node(s), with or without involvement of other lymph node regions on the same side of the diaphragm (II_E).

Note: The number of lymph node regions involved may be indicated by a subscript (eg, II_3).

Stage III Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE), by involvement of the spleen (III_S), or by both (III_{E+S}).

Stage IV Disseminated (multifocal) involvement of one or more extralymphatic organs, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

A No systemic symptoms present

B Unexplained fevers >38°C; drenching night sweats; or weight loss >10% of body weight (within 6 months prior to diagnosis)

Adapted with permission from the American Association for Cancer Research: Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31(11):1860-1.

[1]For additional information regarding the staging of Hodgkin lymphoma, refer to: Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano Classification. J Clin Oncol 2014;32:3059-3068.

[2]PET scans are useful for upstaging in stage I-II disease. If there is PET positivity outside of disease already identified, further clinical investigation is recommended to confirm or refute the observation. PET scans are usually positive in patients with HIV infection, even in the absence of Hodgkin lymphoma.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL STAGING FOR CLASSICAL HODGKIN LYMPHOMA (CHL)[i]

Clinical Stage	Bulky Disease[i] (mediastinal or peripheral)	Number of nodal sites[i]	Erythrocyte sedimentation rate (ESR)	Guidelines Page
IA	No	1	<50	HODG-3 or HODG-4
IB	No	1	Any	HODG-6
IIA, no extralymphatic (E) lesions	No	<3	<50	HODG-3 or HODG-4
IIA ± extralymphatic (E) lesions	No	<4	<50	HODG-4
	No	≥4 or	≥50	HODG-6
	Yes	Any	Any	HODG-7
IIB ± extralymphatic (E) lesions	No	Any	Any	HODG-6
	Yes	Any	Any	HODG-7
III-IV	Yes/No	Any	Any	HODG-10

[i]For definitions of bulky disease and lymph node regions, see HODG-A.

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Unfavorable Risk Factors for Stage I-II Classical Hodgkin Lymphoma

Risk Factor	GHSG	EORTC	NCCN
Age		≥50	
Histology			
ESR and B symptoms	>50 if A; >30 if B	>50 if A; >30 if B	>50 or any B symptoms
Mediastinal mass	MMR > .33	MTR > .35	MMR > .33
# Nodal sites	>2*	>3*	>3
E lesion	any		
Bulky			>10 cm

GHSG = German Hodgkin Study Group
EORTC = European Organization for the Research and Treatment of Cancer

MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6

Definitions of Lymph Node Regions*

	Ann Arbor	EORTC	GHSG
R Cervical/SCL			
R ICL/Subpec			
R Axilla			
L Cervical/SCL			
L ICL/Subpec			
L Axilla			
Mediastinum			
R Hilum			
L Hilum			
Total	9	5	5

*Note that the EORTC includes the infraclavicular/subpectoral area with the axilla while the GHSG includes it with the cervical. Both EORTC and GHSG combine the mediastinum and bilateral hila as a single region.

International Prognostic Score (IPS) 1 point per factor (advanced disease)†

- Albumin <4 g/dL
- Hemoglobin <10.5 g/dL
- Male
- Age ≥45 years
- Stage IV disease
- Leukocytosis (white blood cell count at least 15,000/mm³)
- Lymphocytopenia (lymphocyte count less than 8% of white blood cell count, and/or lymphocyte count less than 600/mm³)

†From: Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin's disease: International Prognostic Factors Project on Advanced Hodgkin's Disease. N Engl J Med 1998;339:1506-1514. Copyright © 1998 Massachusetts Medical Society. Adapted with permission.

Note: All recommendations are category 2A unless otherwise indicated.
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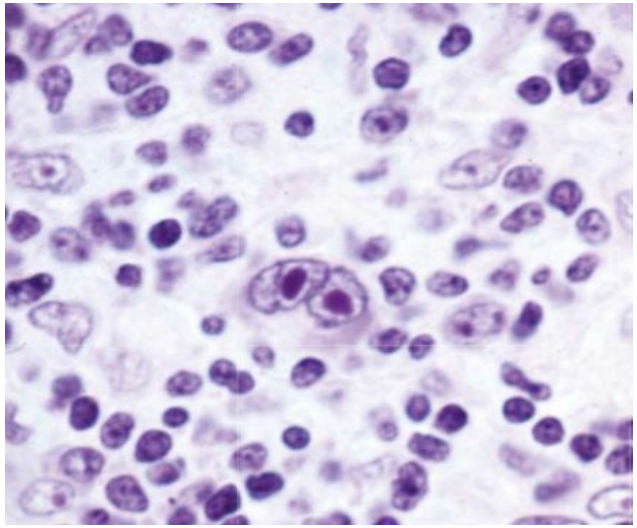
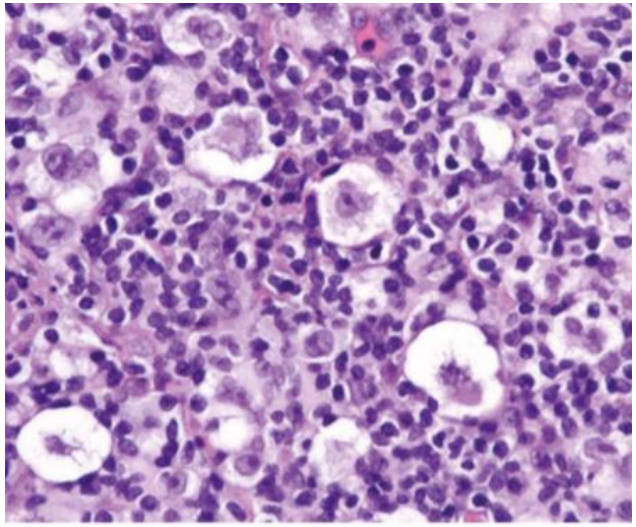
Classic Hodgkin lymphoma – Reed-Sternberg Cell Variants

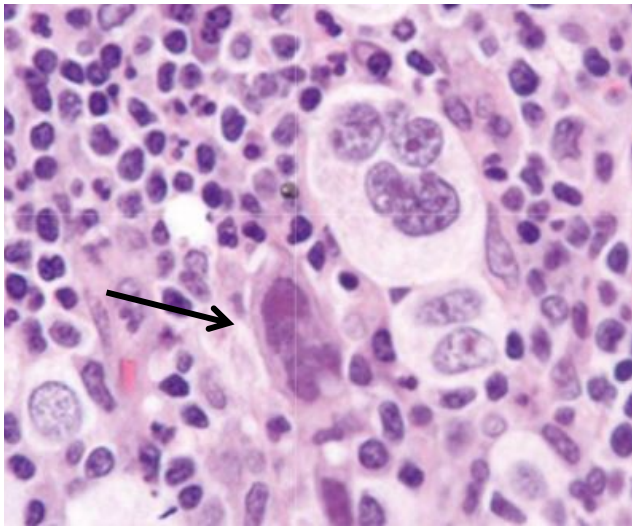
Classic RS Cell



Lacunar Cells



Mummified Cell



Emily Glynn

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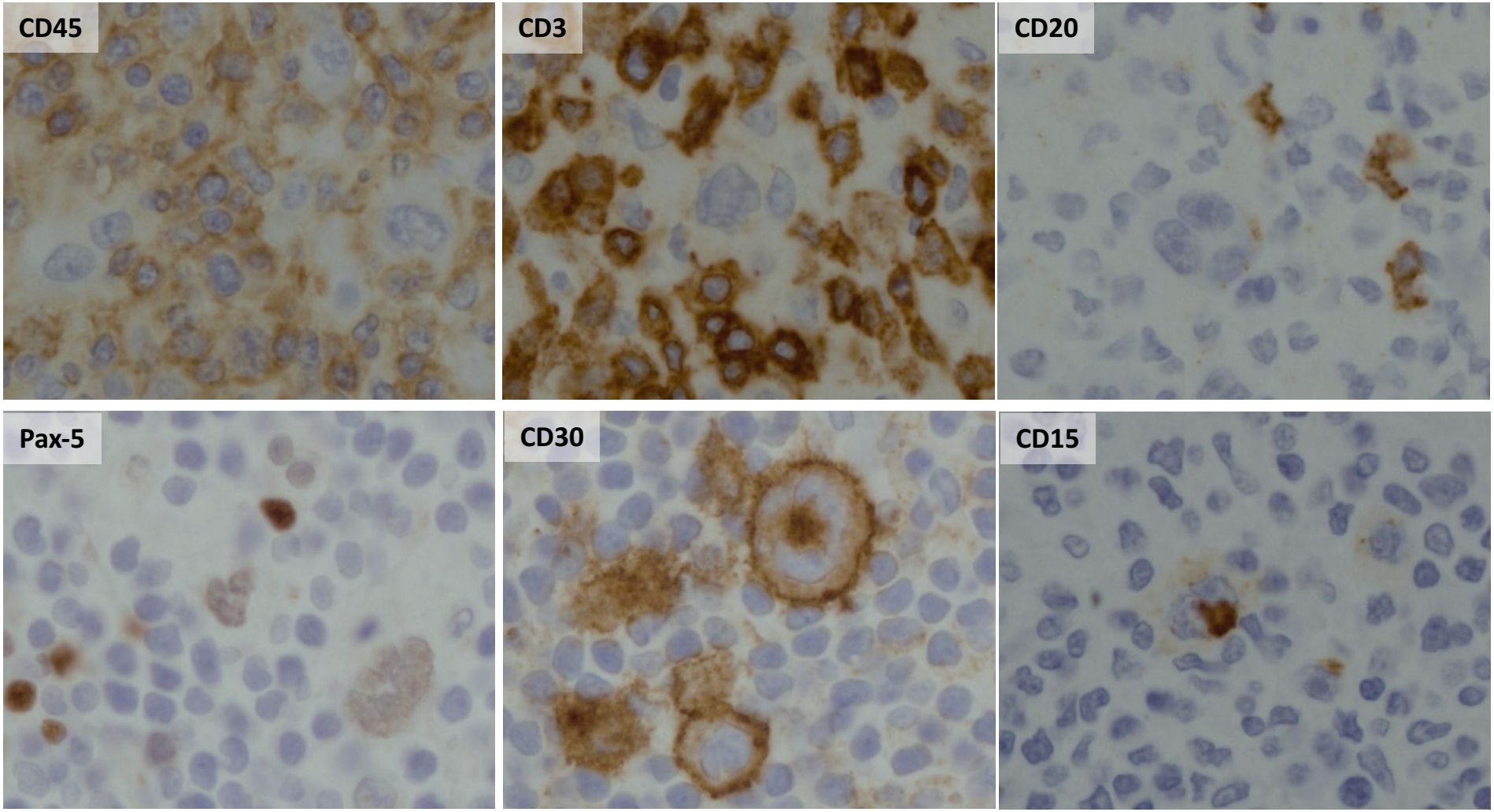
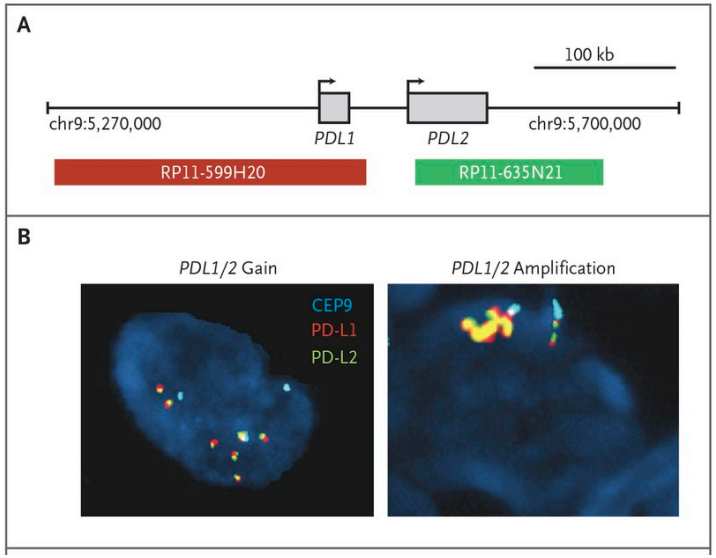
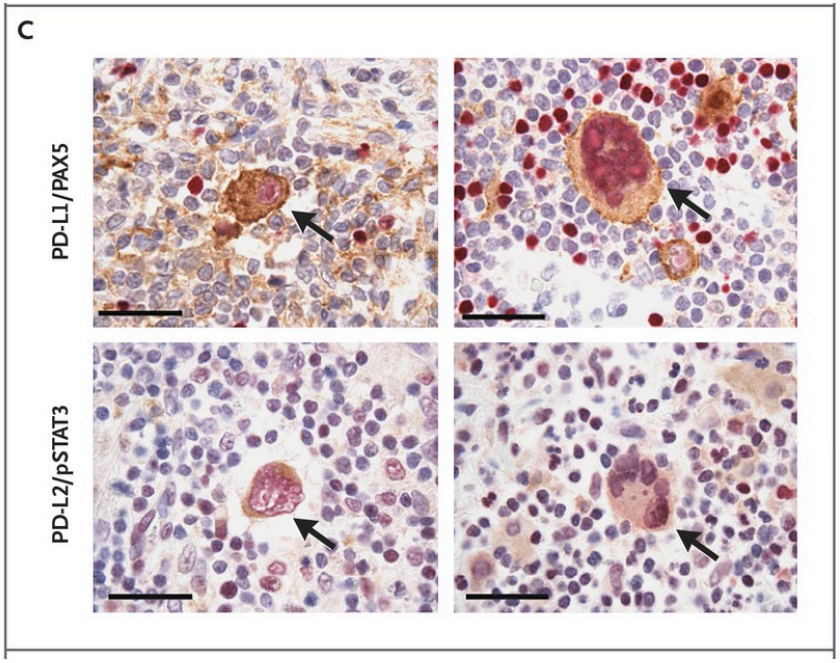
Classical Hodgkin Lymphoma - Immunophenotype



Genetic and Immunohistochemical Analyses of *PDL1* and *PDL2* Loci, PD-L1 and PD-L2 Protein Expression, and Epstein–Barr Virus Status in Patients with Hodgkin Lymphoma





D

Patient No.	Cytogenetic Alterations			IHC-positive HRS cells		Nuclear pSTAT3	EBER
	Polysomy 9p	*PDL1/2* Gain	*PDL1/2* Amplification	PD-L1	PD-L2		
1	+	–	–	+	+	+	–
2	+	–	–	+	+	+	–
3	+	–	–	+	+	+	–
4	+	+	–	+	+	+	–
5	+	+	–	+	+	+	–
6	+	+	–	+	+	+	+
7	+	+	+	+	+	+	–
8	+	+	+	+	+	+	–
9	–	+	+	+	+	+	–
10	–	–	+	+	+	+	–

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Deauville Scoring System

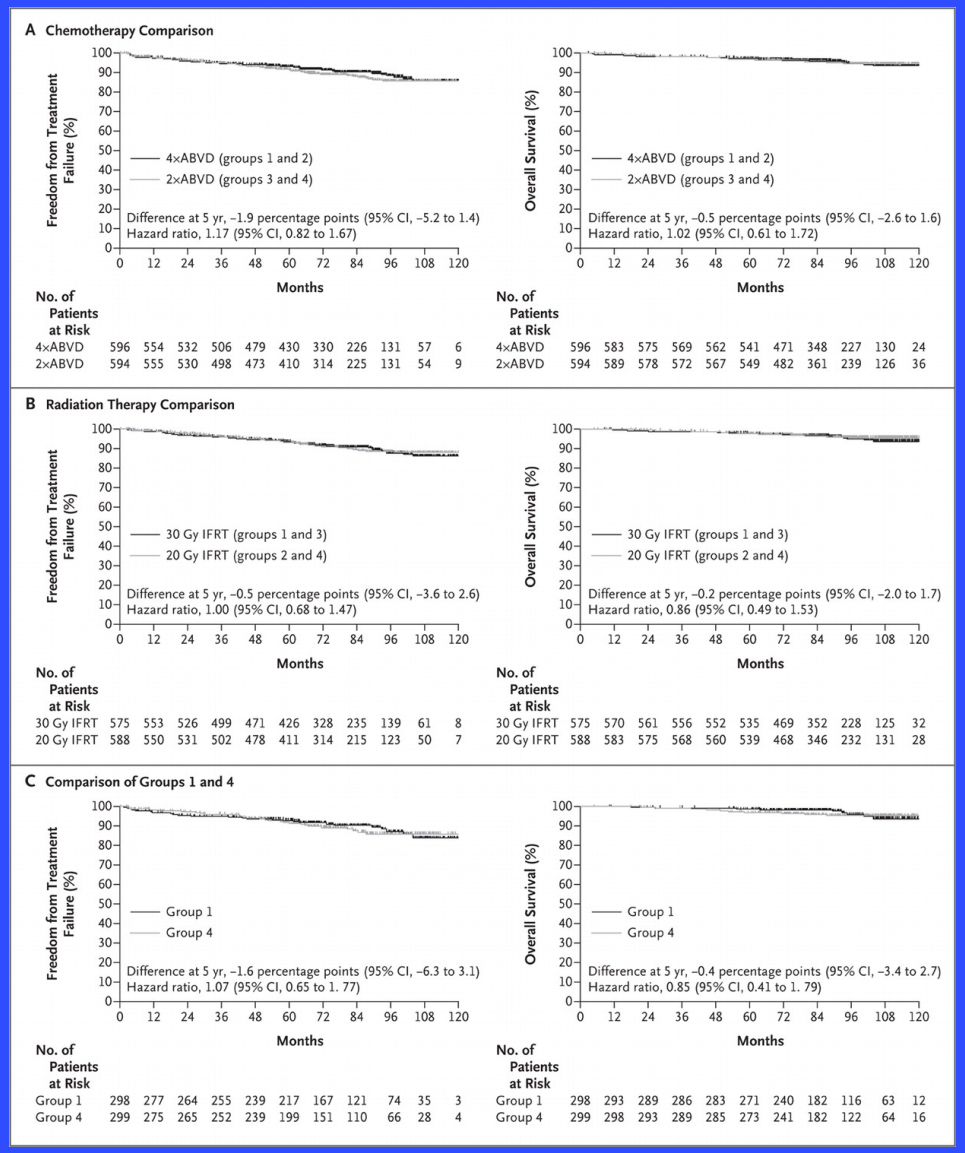
- Internationally accepted and utilized five-point scoring system for the fluorodeozyglucose (FDG) avidity of Hodgkin's lymphoma or NHL tumor mass seen on FDG PET.
- Scores of 1 and 2 are considered to be negative and 4 and 5 are considered to be positive. "Score 3 should be interpreted according to the clinical context but in many Hodgkin Lymphoma patients indicates a good prognosis with standard treatment."

Table 2.

Deauville 5-point scoring system.

Score	Uptake
1	No uptake
2	Uptake < mediastinum
3	Uptake > mediastinum but < liver
4	Uptake moderately more than liver, at any site
5	Markedly increased uptake at any site and/or new sites of disease

Treatment of limited stage Hodgkin lymphoma



Engert A et al. N Engl J Med 2010; 363:640-652

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Treatment of advanced stage Hodgkin lymphoma (1)

- Depends on patient age, performance status, stage of disease (limited/advanced), and patient preference

First Line Therapy – Advanced Stage Disease

- **ABVD** - Adriamycin, bleomycin, vinblastine, and dacarbzine
- Standard treatment of HL in the US
- Takes ~6 months
- **MOPP** – [Nitrogen] Mustard, Oncovin, Prednisone and Procarbazine
- Administered in four week cycles, often for 6 cycles.
- *Not often used, but a reasonable option for those with relapse or other complications.*
- **Stanford V regimen** - typically takes **half** as long as ABVD, but more intense chemotherapy schedule, and incorporates radiation.
- **BEACOPP** - treatment for stages > II, mainly used in Europe
- Approximately 10-15% higher with standard ABVD in advanced stages.
- More expensive due to use of G-CSF, more intense and more toxic
- Rituximab is not routinely used due to lack of CD20 surface expression on RS cells

Treatment of advanced stage Hodgkin lymphoma (2)

Second Line Therapy – Advanced Stage Disease

- **ICE**: Ifosfamide (Ifex), carboplatin (Paraplatin), and etoposide
- Given every 2 or 3 weeks for 2-4 cycles.
- **ESHAP or DHAP**: Etoposide, methylprednisolone (Solu-Medrol), high-dose cytarabine, (Cytosar-U), cisplatin (Platinol);
- OR, dexamethasone, high-dose cytarabine, and cisplatin.
- ESHAP or DHAP regimens are given every 3 weeks for 2 to 3 months.
- **GVD, Gem-Ox, or GDP**: Gemcitabine (Gemzar), vinorelbine (Navelbine), doxorubicin; OR gemcitabine and oxaliplatin (Eloxatin);
- OR gemcitabine, dexamethasone, and cisplatin.
- Gemcitabine-based regimens are either given 2 weeks in a row, followed by an off-week, or every other week.
- **Brentuximab vedotin (Adcetris)**: Brentuximab vedotin (Adcetris) is an antibody-drug conjugate – anti-CD30 coupled to monomethyl auristatin A
- Brentuximab vedotin is usually given every 3 weeks for up to 16 cycles, although sometimes it is given every 4 weeks.

CLINICAL PRESENTATION:
Classical Hodgkin Lymphoma[f]
Stage III-IV

PRIMARY TREATMENT[j]

Stage III-IV

- **ABVD[l] x 2 cycles** → **Restage with PET/CT[n,x]**
  - **Deauville 1-3[o]** → **ABVD x 4 cycles (total 6)[u] or AVD x 4 cycles[dd]** → **Observe or ISRT[p] to initially bulky or selected PET+ sites** → See Follow-up (HODG-14)
  - **Deauville 4-5[o]** → **ABVD x 4 cycles (total 6)[u] or Consider escalated BEACOPP x 4 cycles[l] (See HODG-12)** → **Restage with PET/CT[n]**
    - **Deauville 1-3[o]** → **Observe or ISRT[p] to initially bulky or selected PET+ sites** → See Follow-up (HODG-14)
    - **Deauville 4-5[o]** → **Consider ISRT[p] to PET+ sites (Deauville 4) or Biopsy**
      - Positive → See Refractory Disease (HODG-15)
      - Negative → **Observe[q] or ISRT[p] to initially bulky or PET+ sites** → See Follow-up (HODG-14)
- **or**
- **Stanford V[l] x 12 weeks (in selected patients if IPS <3)[cc]** → See HODG-11
- **or**
- **Escalated BEACOPP[l] x 6 cycles (in selected patients if IPS ≥4, age <60)[cc]** → See HODG-12

[f]Classical Hodgkin lymphoma (CHL) includes nodular sclerosis (NSHL), mixed cellularity (MCHL), lymphocyte-depleted (LDHL), and lymphocyte-rich (LRHL) subtypes.
[j]Individualized treatment may be necessary for older patients and patients with concomitant disease. See Management of Classical Hodgkin Lymphoma in Older Adults (HODG-F).
[l]See Principles of Systemic Therapy (HODG-B).
[n]An integrated PET/CT or a PET with a diagnostic CT is recommended.
[o]See PET 5-Point Scale (Deauville Criteria) (HODG-D).
[p]ISRT fields are generally smaller than IFRT fields. See Principles of Radiation Therapy (HODG-C).
[q]Complete response should be documented including reversion of PET to "negative" within 3 months following completion of therapy.
[u]Consider PFTs after 4 cycles of ABVD.
[x]The value of interim PET imaging is unclear for many clinical scenarios. All measures of response should be considered in the context of management decisions.
[cc]See International Prognostic Score (IPS) (HODG-A).
[dd]Adapted from the RATHL study: Johnson PW, et al. Hematol Oncol. 2015;33(suppl 1):102 (Abstract 008).

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Classification of relapsed/refractory Hodgkin lymphoma

Table 1.

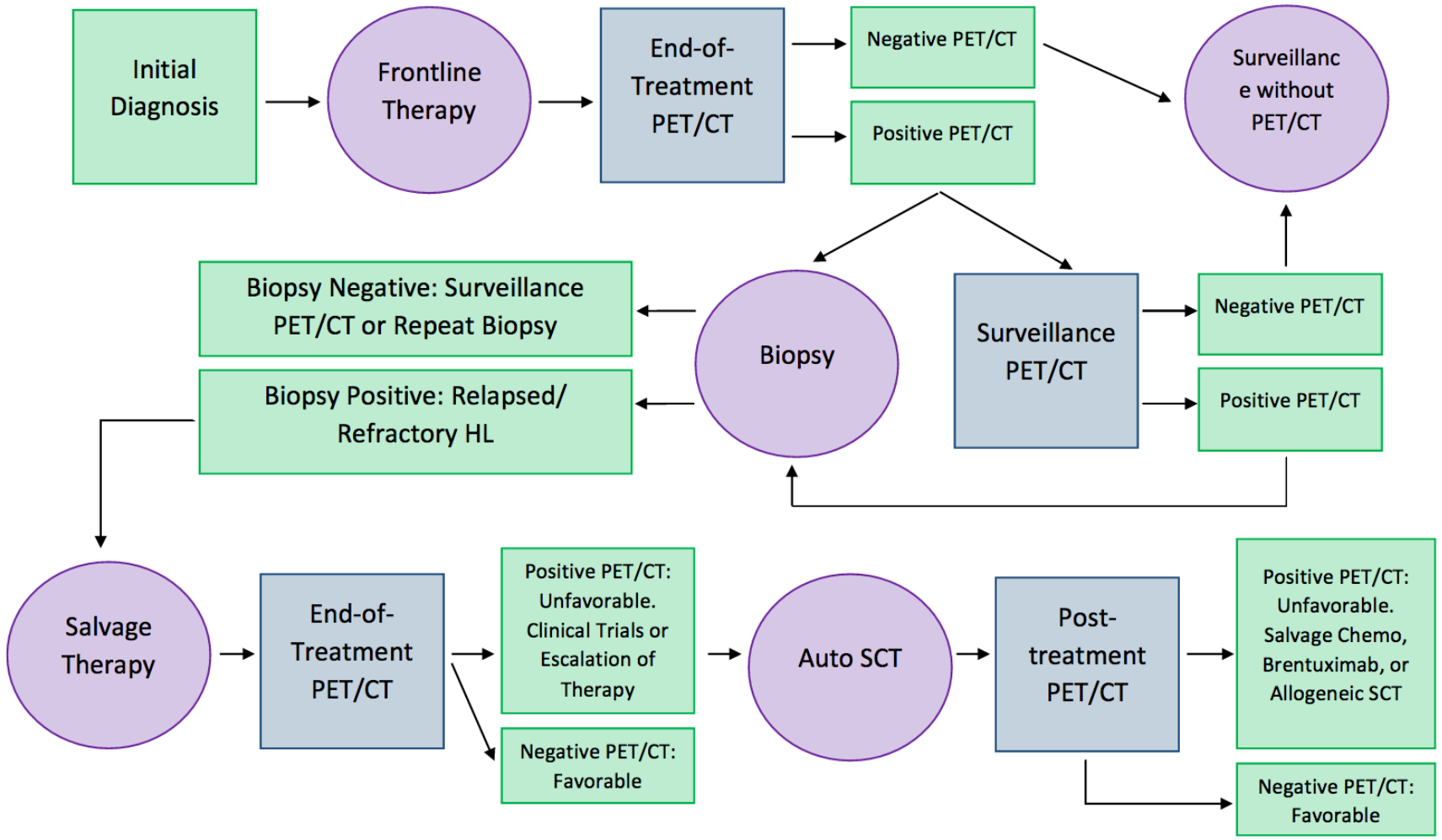
Classification of patients with relapsed and refractory HL in three risk groups: LYSA recommendations.

Subgroup	Prognostic factors
High-risk	Primary refractory disease[1] or relapse with two poor prognosis factors (early relapse[2] and stage III/IV at relapse)
Intermediate-risk	Relapse with only one poor prognostic factor (early relapse or stage III/IV at relapse)
Standard-risk	Relapse without risk factor (relapse > 12 months after end of treatment and stage I/II disease)

[1]Defined either by progression at any time during chemotherapy and up to 3 months after end of chemotherapy, or by failure to achieve at least PR with first-line therapy, or by persistence of significant (score 4 or 5/5) residual FDG metabolic activity using the quantitative 5-point scale Deauville score (DS). [2]Defined by time to treatment failure > 3 months but < 12 months after end of first-line therapy.

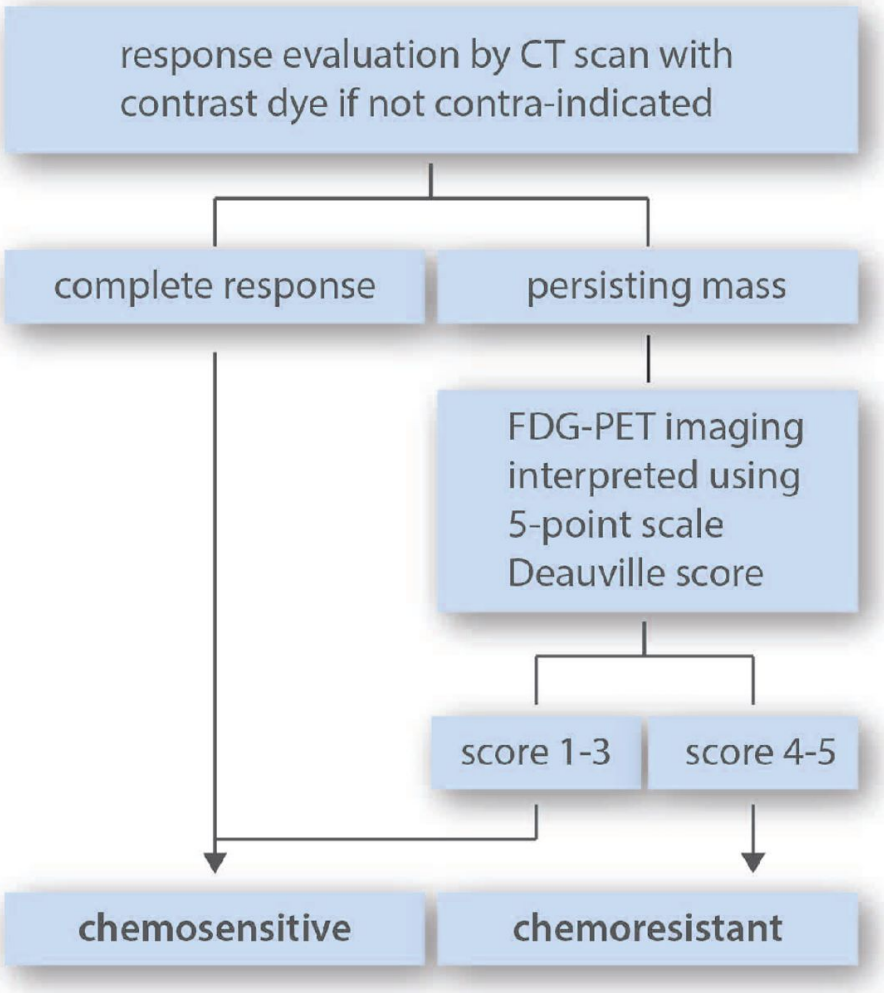
Treatment of relapsed/refractory Hodgkin lymphoma (3)

FIGURE. Evidence-Based Uses of PET/CT in Relapsed or Refractory Hodgkin Lymphoma



AJHO. 2016;12(9):8-13

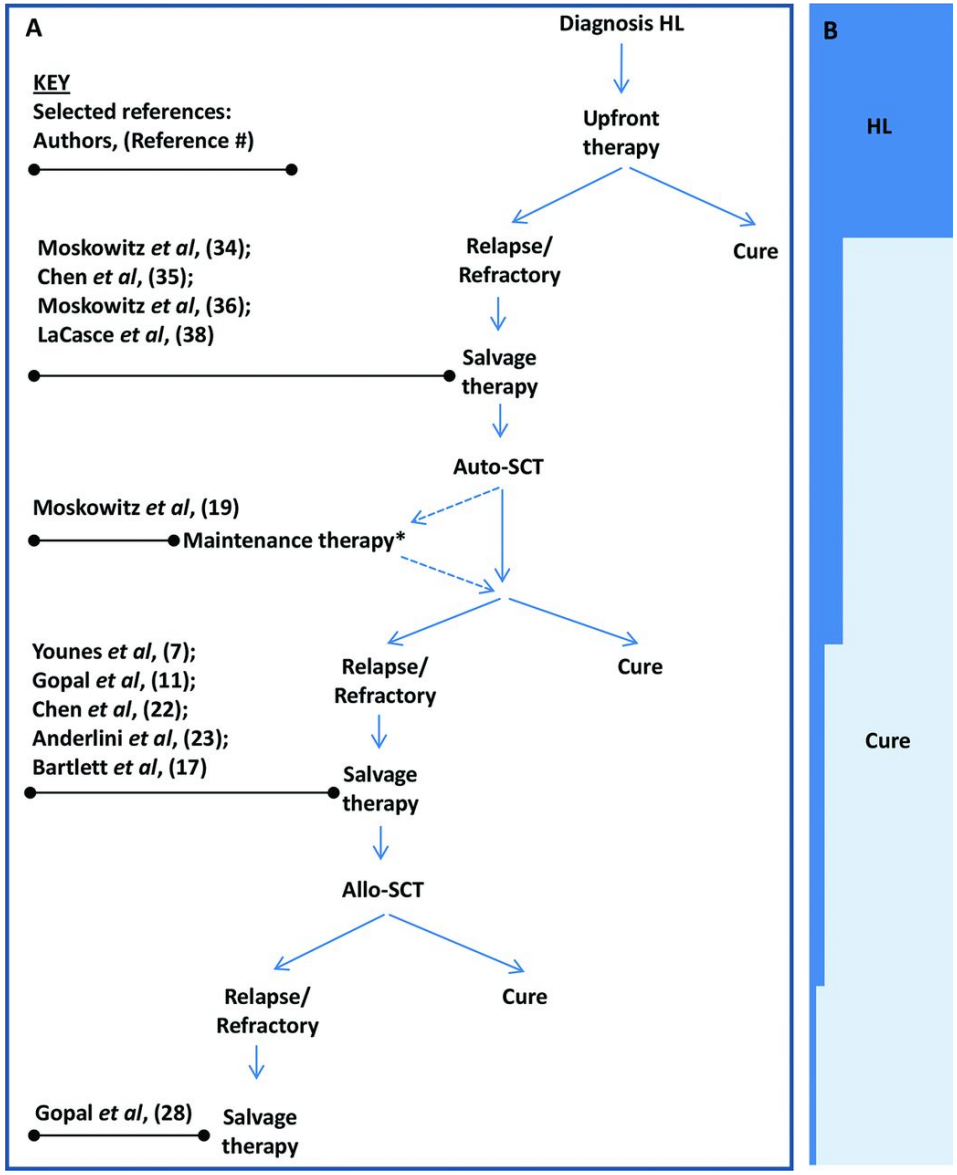
Definition of response to salvage chemotherapy: recommendations by the LySA HL committee



Eric Van Den Neste et al. Haematologica 2013;98:1185-1195

haematologica
Journal of the European Hematology Association
Published by the Ferrata Storti Foundation

Selected studies of Brentuximab Vedotin informing treatment of relapsed/refractory HL at different disease stages



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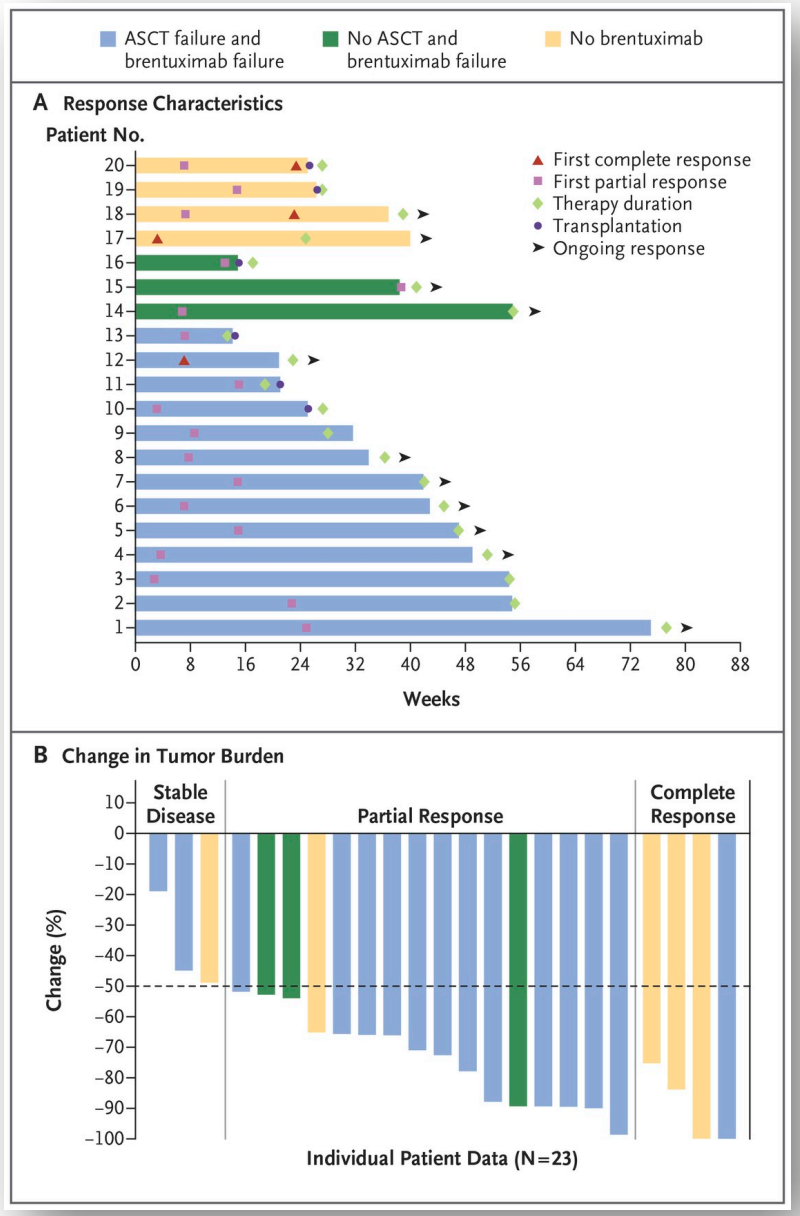
Response Characteristics and Changes in Tumor Burden in Patients with Hodgkin Lymphoma Receiving Nivolumab



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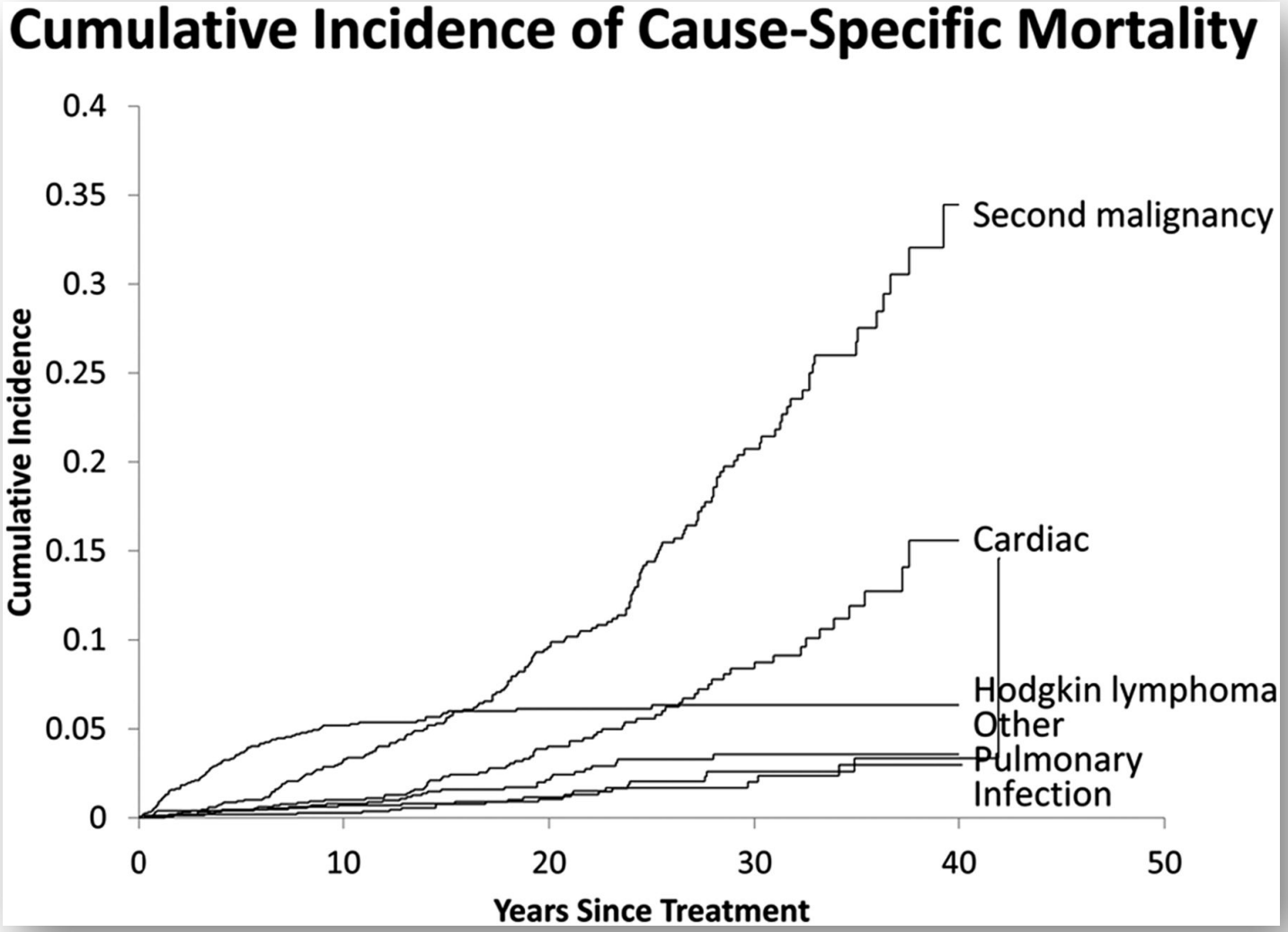
Cumulative incidence of cause-specific mortality in long-term HL survivors



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blood

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