FOLLOW UP CARE OF PATIENTS WITH INDOLENT LYMPHOMAS

Dr. Kai Luecke, MD, FRCPC

Assistant Professor UBC, Hematology

DISCLOSURES

Any direct financial payments including receipt of honoraria	AbbVie, Astra-Zeneca, Gilead, Janssen, Sanofi
Membership on advisory boards or speakers' bureaus	AbbVie, Astra-Zeneca, Gilead, Janssen, Sanofi
Funded grants, research, or clinical trials	
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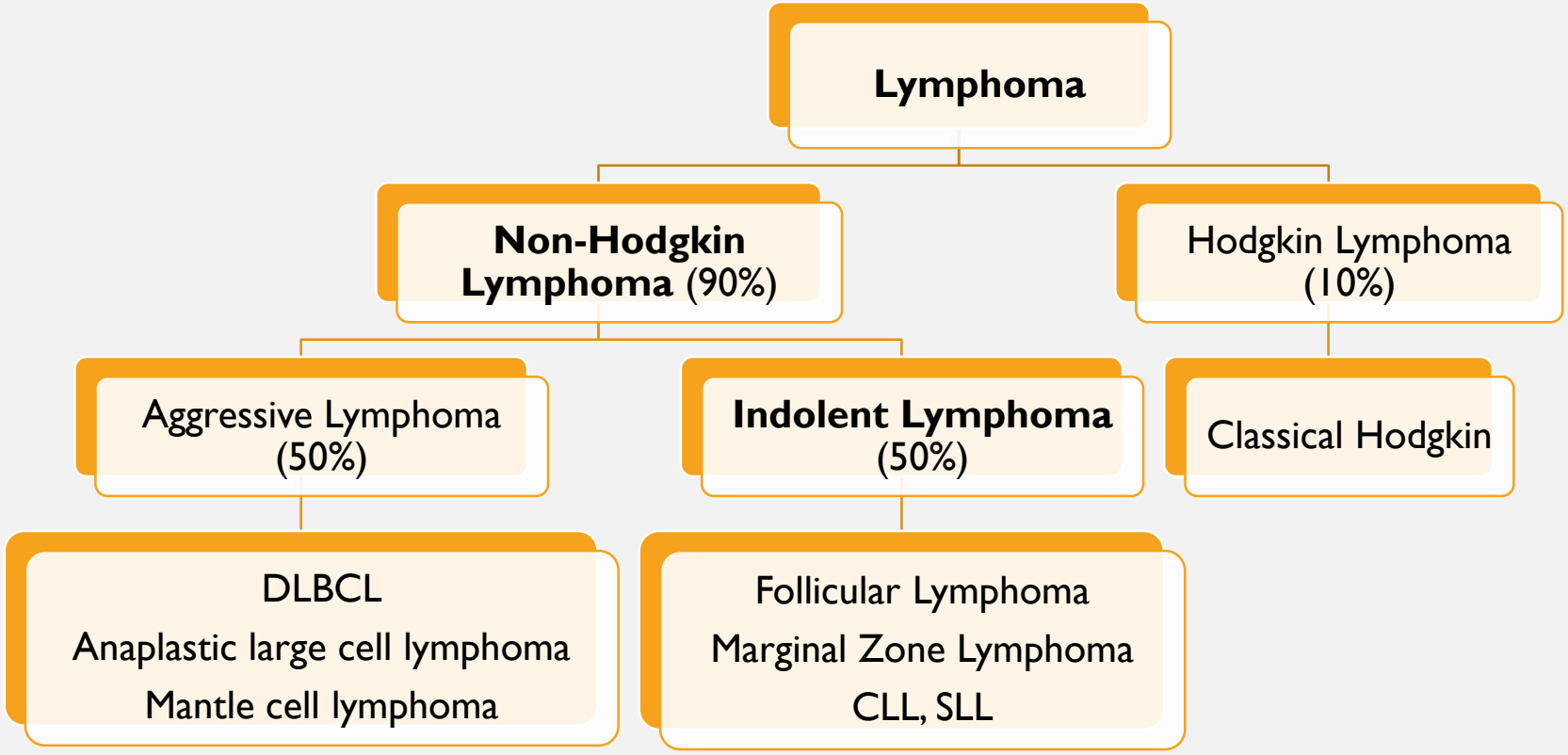
All other investments or relationships that could be seen by a reasonable, well-informed participant as having a potential to influence the content of the educational activity	

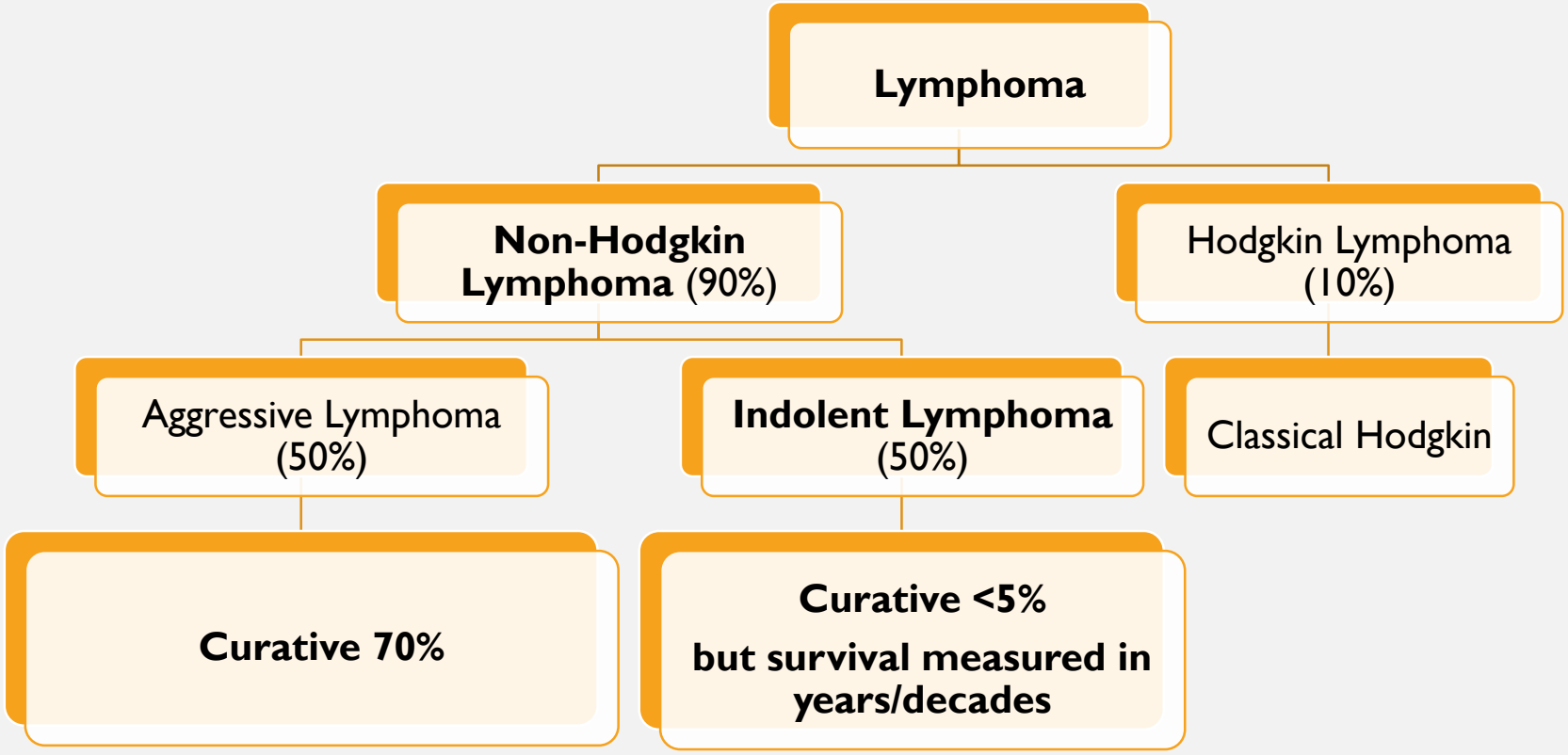
LEARNING OBJECTIVES

- Overview of indolent lymphoma subtypes
- Signs and symptoms of indolent lymphomas
- Survivorship, shared care and follow-up recommendations

OVERVIEW


Lymphoma
Non-Hodgkin Lymphoma (90%)
Hodgkin Lymphoma (10%)
Aggressive Lymphoma (50%)
Indolent Lymphoma (50%)
Classical Hodgkin
DLBCL
Anaplastic large cell lymphoma
Mantle cell lymphoma
Follicular Lymphoma
Marginal Zone Lymphoma
CLL, SLL

OVERVIEW


Lymphoma
Non-Hodgkin Lymphoma (90%)
Hodgkin Lymphoma (10%)
Aggressive Lymphoma (50%)
Indolent Lymphoma (50%)
Classical Hodgkin
Curative 70%
Curative <5%
but survival measured in years/decades

2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms

Mature B cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B cell lymphocytosis*
B cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Lymphoplasmacytic lymphoma
▪ Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM*
μ heavy chain disease
γ heavy chain disease
α heavy chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases*
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Follicular lymphoma
▪ In situ follicular neoplasia*
▪ Duodenal-type follicular lymphoma*
Pediatric-type follicular lymphoma*
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
▪ In situ mantle cell neoplasia*
Diffuse large B cell lymphoma (DLBCL), NOS
▪ Germinal center B cell type*
▪ Activated B cell type*
T cell/histiocyte-rich large B cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV+ DLBCL, NOS*
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B cell lymphoma
Intravascular large B cell lymphoma
ALK+ large B cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
Burkitt lymphoma
High-grade B cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*
High-grade B cell lymphoma, NOS*
B cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
Mature T and NK neoplasms
T cell prolymphocytic leukemia
T cell large granular lymphocytic leukemia
Aggressive NK cell leukemia
Systemic EBV+ T cell lymphoma of childhood*
Hydroa vacciniforme-like lymphoproliferative disorder*
Adult T cell leukemia/lymphoma
Extranodal NK/T cell lymphoma, nasal type
Enteropathy-associated T cell lymphoma
Monomorphic epitheliotropic intestinal T cell lymphoma*
Hepatosplenic T cell lymphoma
Subcutaneous panniculitis-like T cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T cell lymphoproliferative disorders
▪ Lymphomatoid papulosis
▪ Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T cell lymphoma
Peripheral T cell lymphoma, NOS
Angioimmunoblastic T cell lymphoma
Anaplastic large cell lymphoma, ALK+
Anaplastic large cell lymphoma, ALK-*
Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
▪ Nodular sclerosis classical Hodgkin lymphoma
▪ Lymphocyte-rich classical Hodgkin lymphoma
▪ Mixed cellularity classical Hodgkin lymphoma
▪ Lymphocyte-depleted classical Hodgkin lymphoma
Post-transplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD*
Polymorphic PTLD
Monomorphic PTLD (B and T/NK cell types)
Classical Hodgkin lymphoma PTLD
Histiocytic and dendritic cell neoplasms
Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Indeterminate dendritic cell tumor
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumor
Disseminated juvenile xanthogranuloma
Erdheim-Chester disease*

Provisional entities are not listed.

* Changes from the 2008 classification.

WHO classification of the non-Hodgkin lymphomas (subclassified according to to clinical aggressiveness*)

The indolent lymphomas
B-cell neoplasms
Small lymphocytic lymphoma/B-cell chronic lymphocytic leukemia
Lymphoplasmacytic lymphoma (± Waldenstrom's macroglobulinemia)
Plasma cell myeloma/plasmacytoma
Hairy cell leukemia
Follicular lymphoma (grade I and II)
Marginal zone B-cell lymphoma
Mantle cell lymphoma¶
T-cell neoplasms
T-cell large granular lymphocyte leukemia
Mycosis fungoides
T-cell prolymphocytic leukemia
Natural killer cell neoplasms
Natural killer cell large granular lymphocyte leukemia
The aggressive lymphomas
B-cell neoplasms
Follicular lymphoma (grade III)
Diffuse large B-cell lymphoma
Mantle cell lymphoma¶
T-cell neoplasms
Peripheral T-cell lymphoma
Anaplastic large cell lymphoma, T/null cell
The highly aggressive lymphomas
B-cell neoplasms
Burkitt's lymphoma
Precursor B lymphoblastic leukemia/lymphoma
T-cell neoplasms
Adult T-cell lymphoma/leukemia
Precursor T lymphoblastic leukemia/lymphoma

OVERVIEW

- Most common indolent subtypes:
  - **Follicular Lymphoma**
  - **Marginal Zone Lymphoma** (+subtypes)
  - Lymphoplasmacytic Lymphoma / Waldenstrom
- Others, not being discussed today:
  - CLL/SLL
  - Myeloma
  - Cutaneous T-cell lymphomas

CLINICAL PRESENTATION

- Lymphadenopathy (waxing and waning), but generally progressive
- Cytopenias
- Splenomegaly, hepatomegaly
- Skin rashes, renal impairment, excessive fatigue, etc.
- B-symptoms:
  - Fever >38C
  - Weight-loss, >10% body-weight in past six months
  - Sweats, drenching

CLINICAL PRESENTATION

- Extranodal presentation:
  - CNS disease (almost always aggressive)
  - GI tract
  - Skin- or other organ-involvement
  - Bone marrow involvement

CLINICAL PRESENTATION

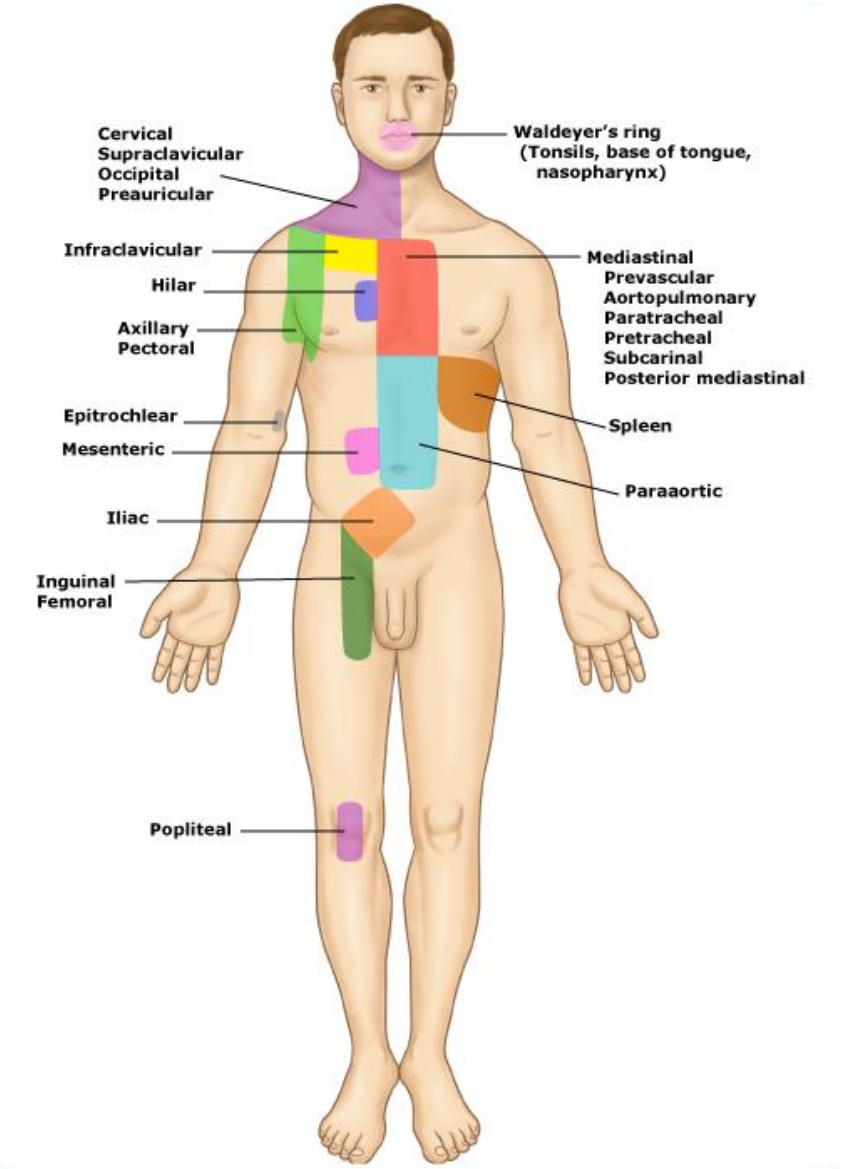
- Associated emergencies:
  - Spinal cord compression
  - CNS mass (seizure, headaches, visual changes, etc.)
  - Airway obstruction (mediastinal mass)
  - Pericardial tamponade
  - SVC obstruction
  - GI-/renal-obstruction
  - Tumor lysis syndrome (Ca, PO4, Creat, uric acid, LDH, etc.)

Features of aggressive lymphomas!

CLINICAL PRESENTATION

- Clinical exam:
  - Lymphoid survey:
    - Waldeyer's ring
    - Peripheral lymphnode stations
    - Liver/spleen
    - Other (occipital, preauricular, epitrochlear, popliteal)
  - Chest/lung/cardiac
  - Abdomen/pelvis

Lymph node regions in lymphoma



Lymph node regions used to determine stage in lymphoma.

UpToDate®

CLINICAL PRESENTATION

- Investigations:
  - Imaging studies (CT with contrast)
  - Labs: CBC, diff, creatinine, LDH, electrolytes
  - Rule out other causes: infections, autoimmune,
- Lymph-node-biopsy: progressive size, persistent (>4-6 wks), enlarged (>2cm)
  - FNA ----- BAD!!!
  - ***Core Bx*** ----- GOOD
  - ***Excisional Bx*** ----- BEST!!! 

CLINICAL PRESENTATION

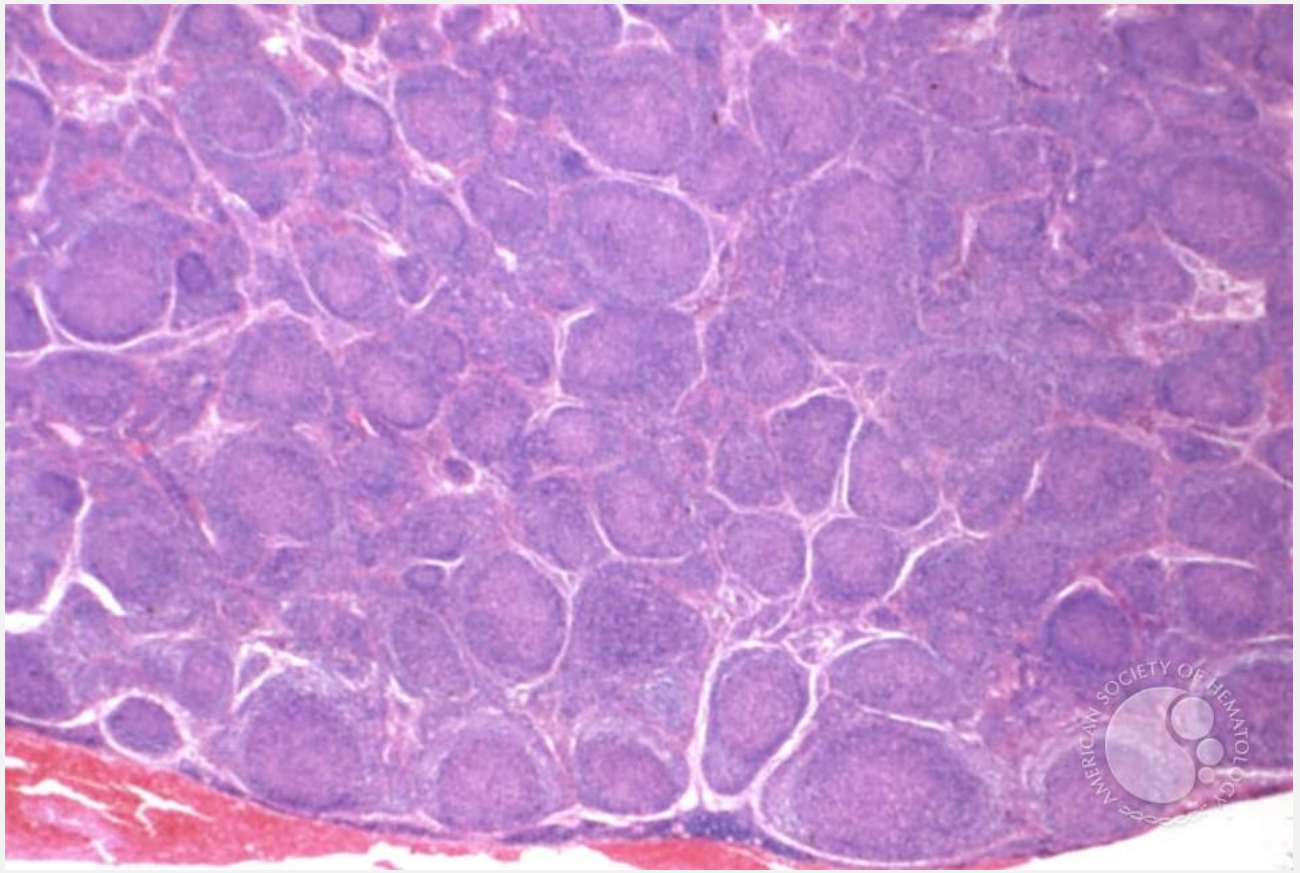
- Tissue diagnosis is paramount PRIOR to referral to oncologist!
  - Without a definitive diagnosis, unable to provide treatment recommendation
  - Differential diagnosis of lymphadenopathy is broad:
    - Infections
    - Reactive, drugs, etc.
    - Autoimmune
    - Sarcoid
    - Malignancy including lymphoma, solid cancer, etc.

Follicular Lymphoma - 1.

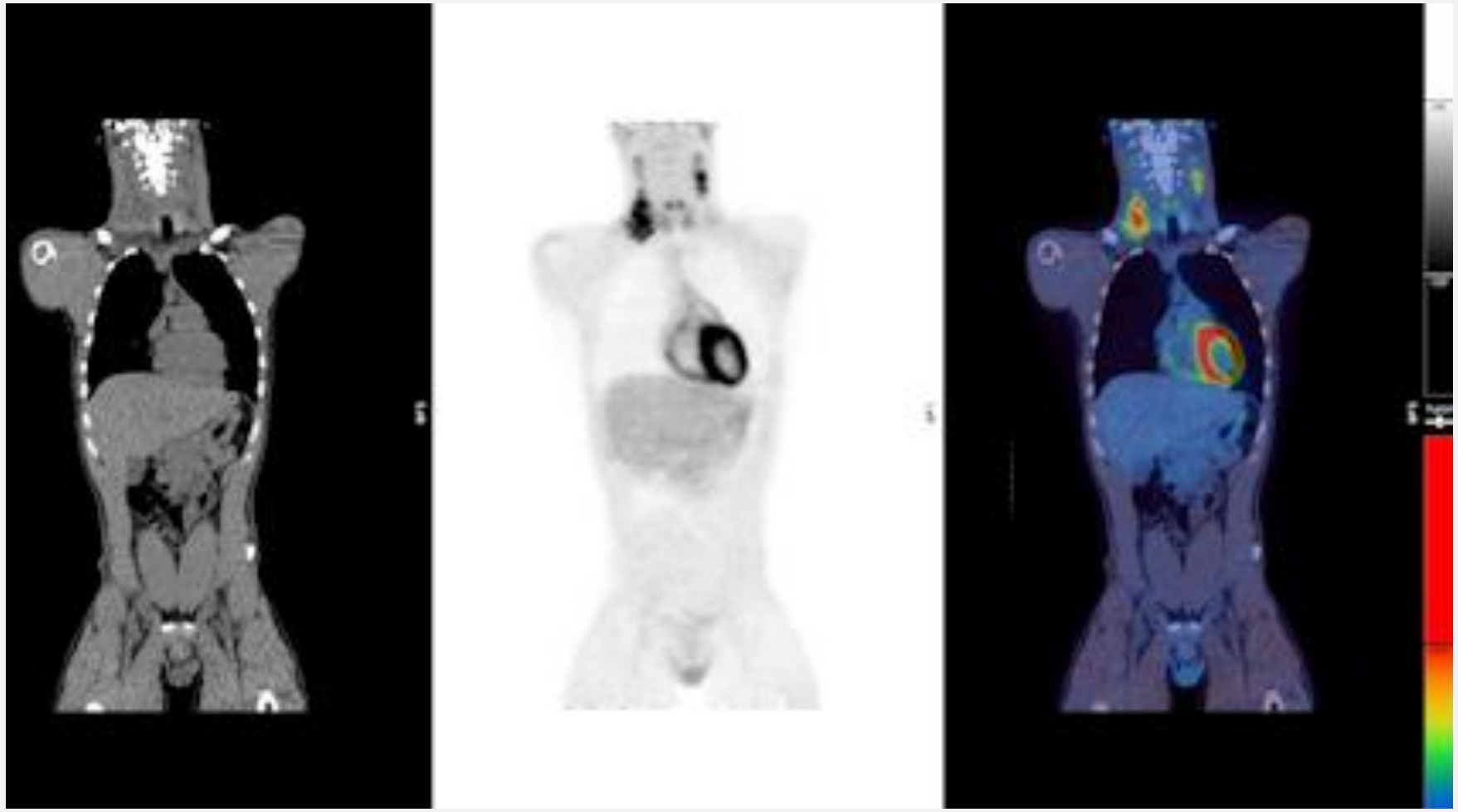
Image ID: 2050

Authors: Marshall Kadin

Category: Lymphoma: Mature B-cell and Plasma cell Neoplasms > Low-grade B-cell lymphoma > Follicular Lymphoma



STAGING



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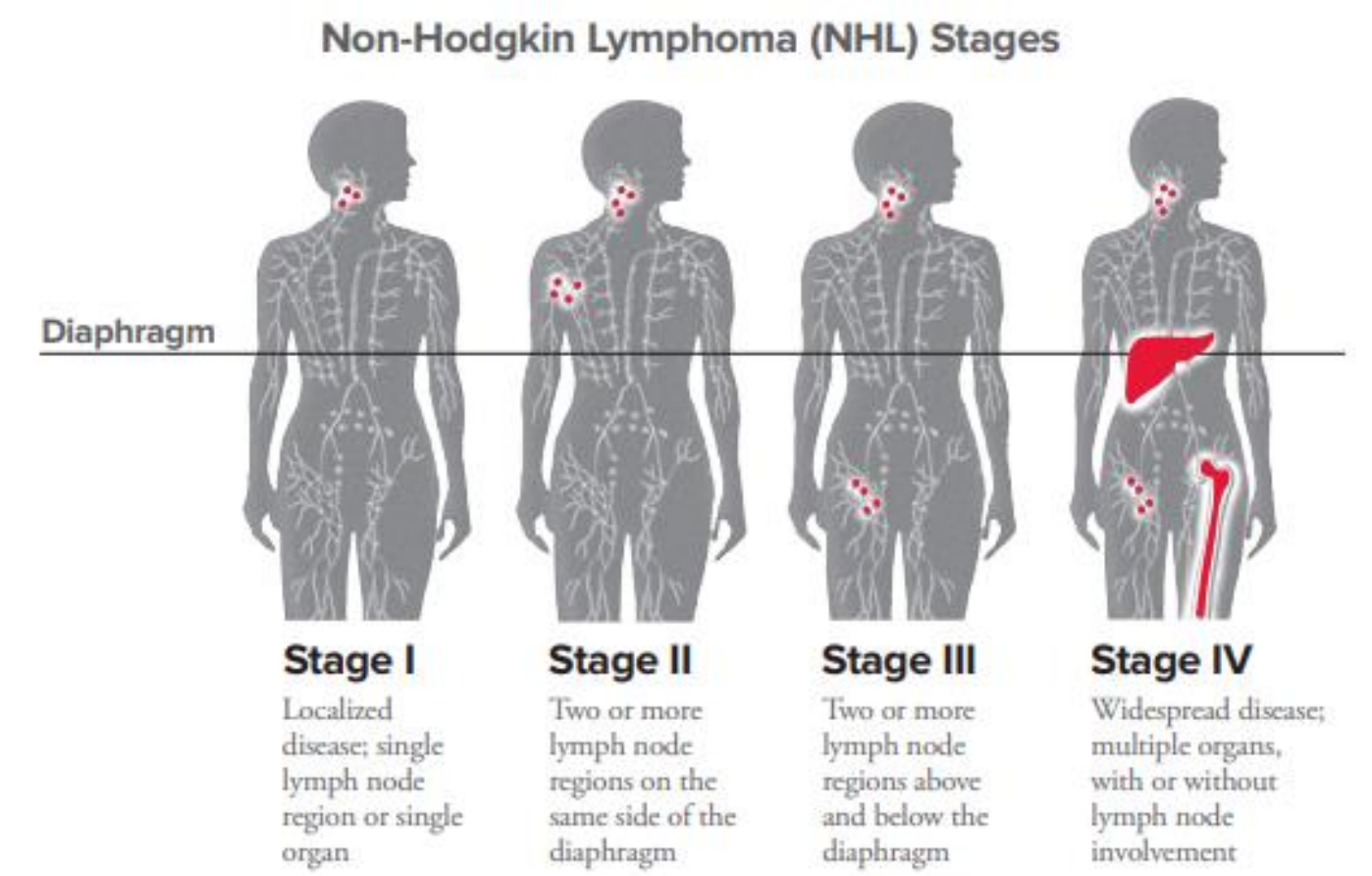

Non-Hodgkin Lymphoma (NHL) Stages
Diaphragm
Stage I
Localized disease; single lymph node region or single organ
Stage II
Two or more lymph node regions on the same side of the diaphragm
Stage III
Two or more lymph node regions above and below the diaphragm
Stage IV
Widespread disease; multiple organs, with or without lymph node involvement

TREATMENT

- Once diagnosis is established, refer to Oncology
- Additional testing might include:
  - PET, bone marrow, labs, Hep, HIV, echo, …
  - Ancillary tests determine stage, prognosis, fitness for treatment, etc.

PROGNOSIS

- FLIPI (follicular lymphoma international prognostic index):
  - Age >60
  - Number of nodal sites >4
  - LDH elevated
  - Hemoglobin <120
  - Stage III/IV

10 year survival: low risk 70%; high risk 35%

TREATMENT

- Depending on staging investigations and patient factors:
  - Radiation in curative intend (limited tumor burden!)
  - Watch & wait in asymptomatic advanced stage
  - Single agent Rituximab in asymptomatic advanced stage

  - **Chemo-immunotherapy in symptomatic patients**

TREATMENT

- Current "standard" chemo-immunotherapy:
- Bendamustine + Rituximab (x6 cycles; 6 months)
- Rituximab maintenance (x8 cycles; 24 months)
  - STIL trial: response rate >90%; median PFS: 69.5 months, estimated survival at 10 years: 71%

StiL NHL 1-2003: BR vs R-CHOP in Newly Diagnosed FL

- Randomized, open-label phase III noninferiority trial
  - Primary endpoint: noninferiority of BR vs R-CHOP for PFS (decrease < 10% at 3 yrs)

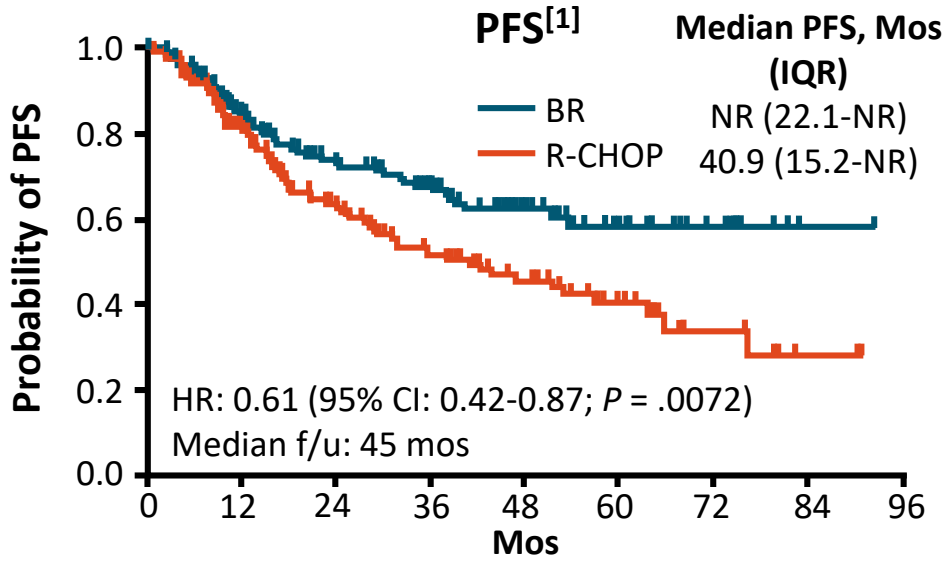
Stratified by histological subtype

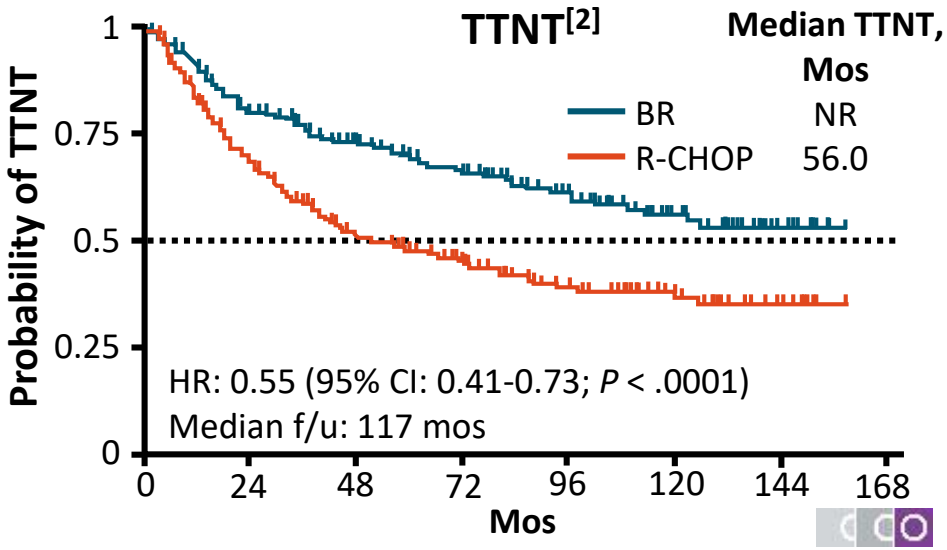
Treatment-naive patients with MCL or indolent CD20-positive lymphoma, including FL (N = 549)

- **BR** (n = 274*)
- **R-CHOP** (n = 275†)

*n = 261 assessed. †n = 253 assessed.

- No OS difference between arms
- Toxicity less with BR (SAEs: 19% vs 29% with R-CHOP)





1. Rummel. Lancet. 2013;381:1203. 2. Rummel. ASCO 2017. Abstr 7501.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Early Relapse of Follicular Lymphoma After Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone Defines Patients at High Risk for Death: An Analysis From the National LymphoCare Study

Carla Casulo, Michelle Byrtek, Keith L. Dawson, Xiaolei Zhou, Charles M. Farber, Christopher R. Flowers, John D. Hainsworth, Matthew J. Maurer, James R. Cerhan, Brian K. Link, Andrew D. Zelenetz, and Jonathan W. Friedberg

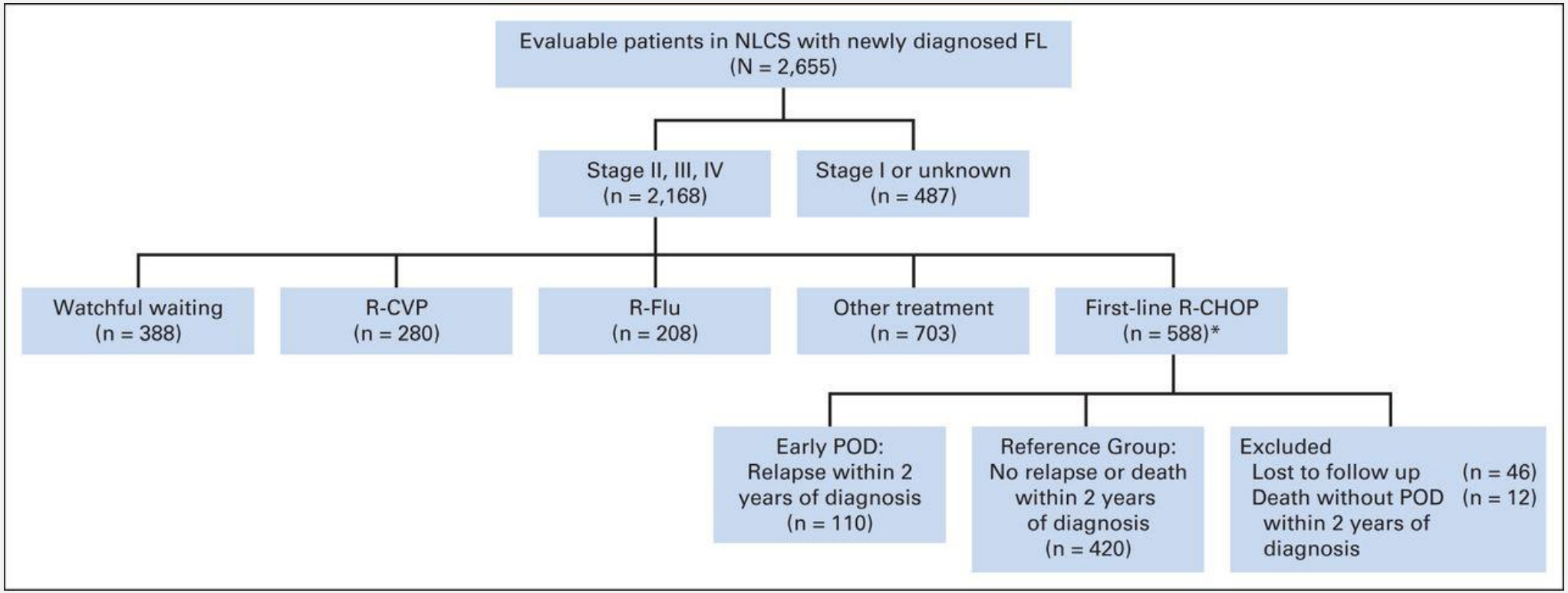

Fig 1. CONSORT diagram for participant selection. One patient who experienced progression of disease (POD) before receiving rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) was excluded. FL, follicular lymphoma; NLCS, National LymphoCare Study; R-CVP, rituximab with cyclophosphamide, vincristine, and prednisone; R-Flu, rituximab with fludarabine.

Published in: Carla Casulo; Michelle Byrtek; Keith L. Dawson; Xiaolei Zhou; Charles M. Farber; Christopher R. Flowers; John D. Hainsworth; Matthew J. Maurer; James R. Cerhan; Brian K. Link; Andrew D. Zelenetz; Jonathan W. Friedberg; *Journal of Clinical Oncology* 2015 332516-2522.
DOI: 10.1200/JCO.2014.59.7534

Peak risk of progression is within the first 24 months of Dx

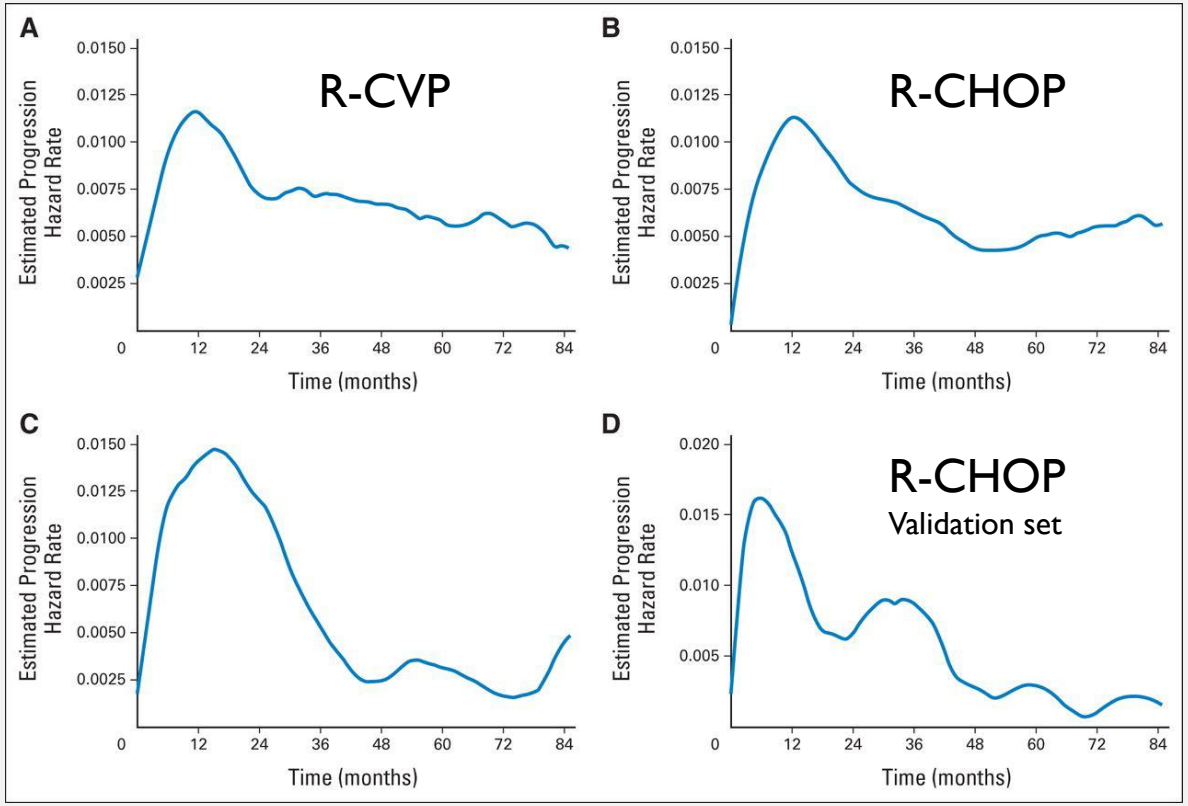

Fig 2. Estimated hazard of progression for the (A-C) National LymphoCare Study and (D) University of Iowa and Mayo Clinic Molecular Epidemiology Resource validation cohorts. (A) Rituximab with cyclophosphamide, vincristine, and prednisone (R-CVP); (B) rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); (C) rituximab with fludarabine (R-Flu); (D) validation set (R-CHOP).

Published in: Carla Casulo; Michelle Byrtek; Keith L. Dawson; Xiaolei Zhou; Charles M. Farber; Christopher R. Flowers; John D. Hainsworth; Matthew J. Maurer; James R. Cerhan; Brian K. Link; Andrew D. Zelenetz; Jonathan W. Friedberg; *Journal of Clinical Oncology* 2015 332516-2522.
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FL outcome after first progression following first-line therapy (RCHOP)

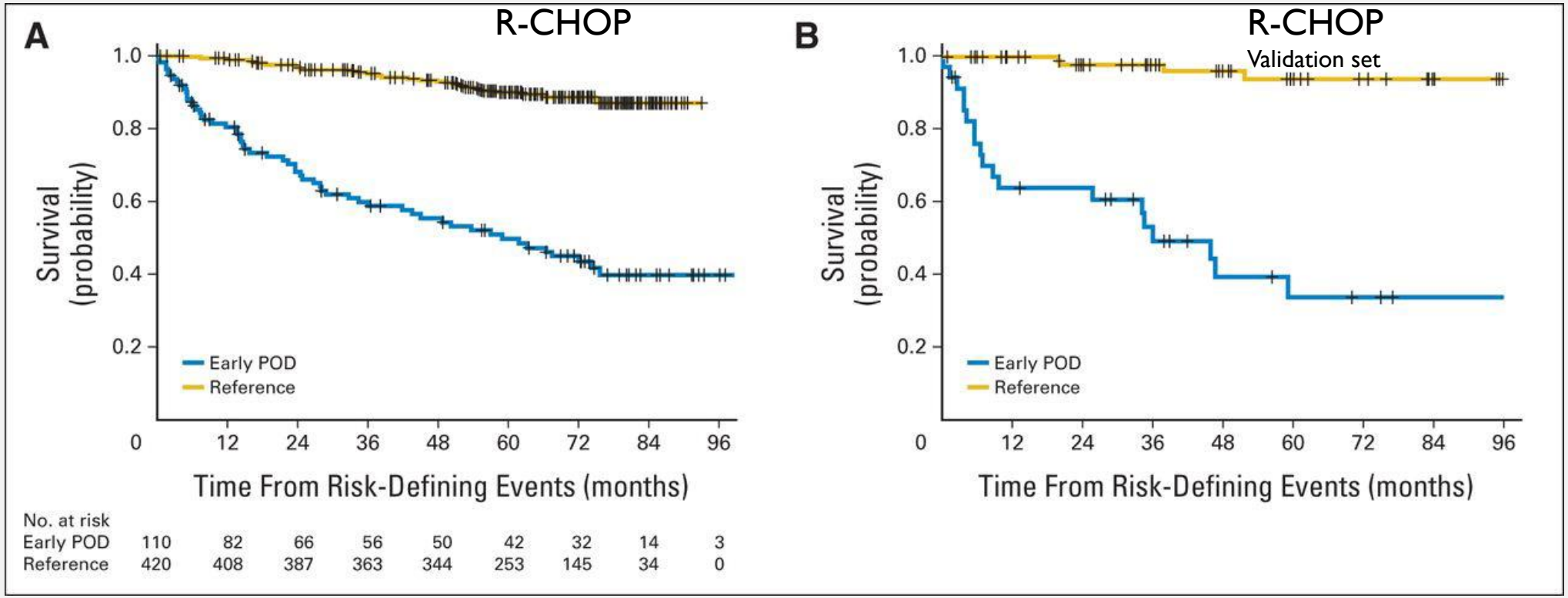
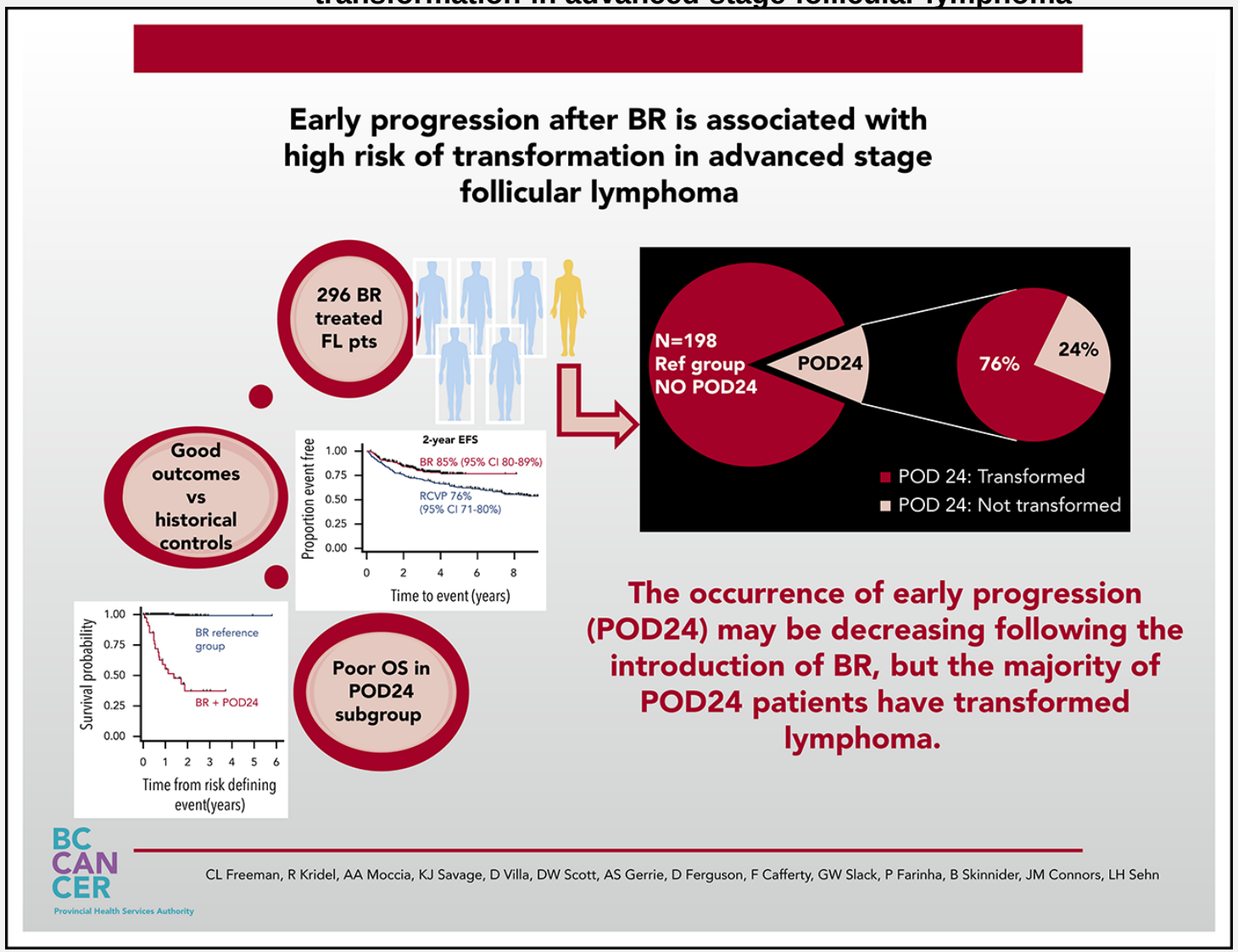


Fig 3. (A) Overall survival (OS) from a risk-defining event after diagnosis in patients who received rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy in the National LymphoCare Study group. Patients with early progression of disease (POD) had poor survival. Two-year OS was 68% (95% CI, 58.2% to 76.3%). Five-year OS was 50% (95% CI, 39.4% to 59.2%). OS in the reference group was 97% (95% CI, 94.6% to 98.1%) at 2 years and 90% (95% CI 86.2% to 92.4%) at 5 years. (B) Patients in the validation set who received R-CHOP with early POD also had inferior OS.

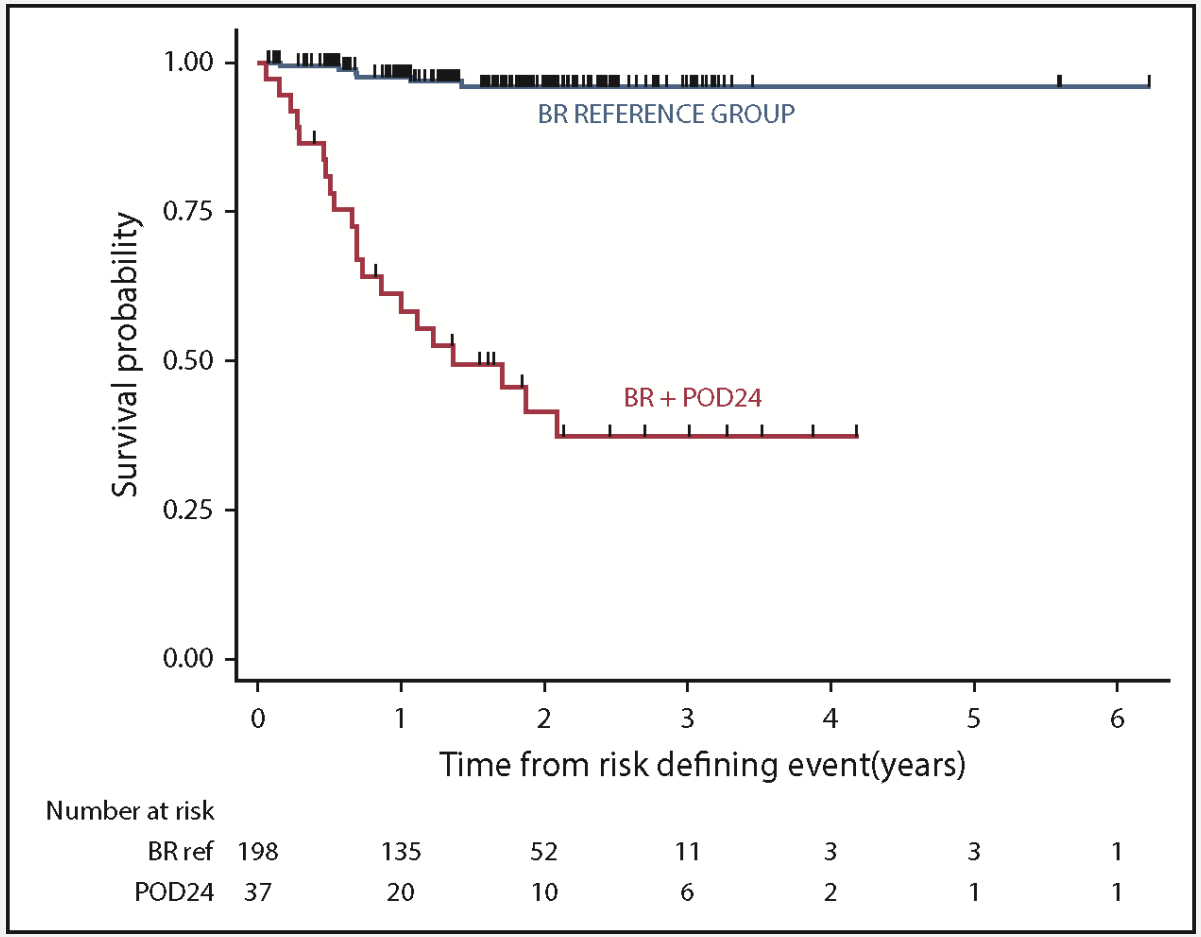
Published in: Carla Casulo; Michelle Byrtek; Keith L. Dawson; Xiaolei Zhou; Charles M. Farber; Christopher R. Flowers; John D. Hainsworth; Matthew J. Maurer; James R. Cerhan; Brian K. Link; Andrew D. Zelenetz; Jonathan W. Friedberg; *Journal of Clinical Oncology* 2015 332516-2522.
DOI: 10.1200/JCO.2014.59.7534

Early progression after bendamustine-rituximab is associated with high risk of transformation in advanced stage follicular lymphoma



Ciara L. Freeman,Robert Kridel,Alden A. Moccia,Kerry J. Savage,Diego R. Villa,David W. Scott,Alina S. Gerrie,David Ferguson,Fergus Cafferty,Graham W. Slack,Pedro Farinha,Brian Skinnider,Joseph M. Connors,Laurie H. Sehn, Early progression after bendamustine-rituximab is associated with high risk of transformation in advanced stage follicular lymphoma, Blood, 2019,

Early progression after bendamustine-rituximab is associated with high risk of transformation in advanced stage follicular lymphoma



Ciara L. Freeman,Robert Kridel,Alden A. Moccia,Kerry J. Savage,Diego R. Villa,David W. Scott,Alina S. Gerrie,David Ferguson,Fergus Cafferty,Graham W. Slack,Pedro Farinha,Brian Skinnider,Joseph M. Connors,Laurie H. Sehn, Early progression after bendamustine-rituximab is associated with high risk of transformation in advanced stage follicular lymphoma, Blood, 2019, Figure 1.

POST TREATMENT

- Historically, patients remain under care of Hematologist/Oncologist
  - Regular follow up of perfectly well patients every 3-6 months
  - Neglected other medical issues (HTN, DM, CAD, etc)
  - Lack of cancer screening
  - ++ referral to other specialist

  - Patient experiences anxiety, travel to cancer clinic, parking, etc

POST TREATMENT

- Proposition:
  - Transfer of care to primary care provider of patients with indolent lymphomas after their initial treatment if they achieved a complete remission after 2.5 years
  - Rational:
  - Excellent prognosis and low risk immediate lymphoma recurrence
  - Enable Hematologist/Oncologist to care for new patients/ patients on Tx
  - Decrease wait times for cancer patients
  - Decrease health care costs

SURVIVORSHIP

- **DISCLAIMER:**
- Limited evidenced based guidelines
- Level of evidence often: Expert Opinion
- Extrapolation from Hodgkin Lymphoma survivors

Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†☆

Table 7. Recommended follow-up after end of therapy

Examination	Details	Year 1-2	Year 3-5	Year >5
History	B symptoms (see Table 2)	Every 3-6 months	Every 6-12 months	Annually
Physical examination	Particular: peripheral LNs, liver, spleen	Every 3-6 months	Every 6-12 months	Annually
Laboratory work-up	Blood and differential count	Every 3-6 months	Every 6-12 months	Annually
	LDH, IgG levels	Every 3-6 months	Every 6-12 months	If progression suspected
Imaging (optional)	Abdominal ultrasound	Every 6 months	Every 12 months	If progression suspected
	CT neck, chest, abdomen	Every 6-12 months	Every 12-24 months	If progression suspected

CT, computed tomography; IgG, immunoglobulin G; LDH, lactate dehydrogenase; LN, lymph node.

SURVIVORSHIP

- Relapsed lymphoma
  - Yearly physical exam, focusing on lymphnode exam, spleen, liver
  - History, B-symptoms
  - Labwork, CBC, diff, LDH

  - Imaging???

Surveillance Imaging during First-Remission in Follicular Lymphoma Does Not Impact Overall Survival

Figure 1 — Descriptive Statistics Flow Chart

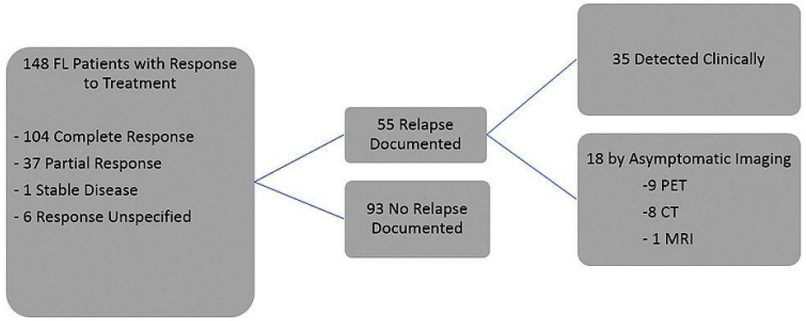
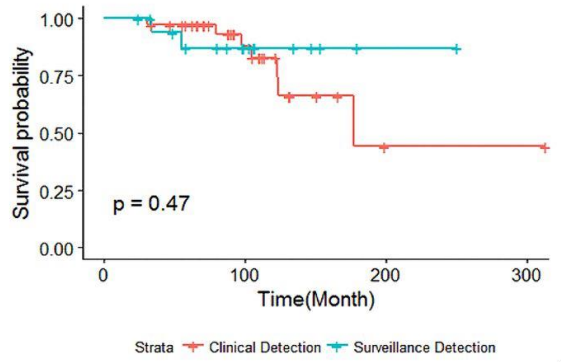


Figure 2 — OS for Clinical vs. Surveillance Method of Relapse Detection



				Overall Survival				
Group	No. of Subjects	Event	Censored	HR (95% CI)	P-val	Log Rank Test(Pval)	aHR (95% CI)	P-val
Clinical Detection	35	7 (20.0%)	28 (80.0%)	Ref.				
Surveillance Detection	18	2 (11.1%)	16 (89.9%)	0.56 (0.12, 2.71)	0.473	0.4664	0.64 (0.12, 3.47)	0.607

Max L. Goldman, BA,Chaejin Kim, PharmD,Zhengjia Chen, PhD,Oscar Calzada, BS,Michael C Churnetski, BS,Christopher Flowers, MD,Jonathon B Cohen, MDMS, Surveillance Imaging during First-Remission in Follicular Lymphoma Does Not Impact Overall Survival, Blood, 2017,

SUSPECTED RELAPSE

- Patient detects relapse in 71% (29% Medical Oncologist) *
  - No difference in survival!!!
- If relapse is suspected, **repeat imaging** and **biopsy**
- Contact Medical Oncologist
  - Multiple different treatment approaches:
    - Chemo-immunotherapy
    - radiation
    - Stem-cell transplantation

*Savage. et al.; Annals of Oncology Volume 25, issue 5. 2013

SURVIVORSHIP

- Long term side effects (Hodgkin Lymphoma):
  - Secondary malignancies, ongoing screening
  - CVD
  - Immunosuppression: yearly flu shot, pneumococcal, shingles, COVID (booster!)
  - Cognitive deficits, chronic fatigue,
  - Psychosocial dysfunction

- There is limited data in long term side effects for Non-Hodgkin Lymphoma

SUMMARY

- Lymphoma diagnosis should be suspected: progressive adenopathy/ B-symptoms
- Imaging studies and excisional biopsy are key in initial management
- Patients who achieve a complete remission with first line therapy have an excellent prognosis
- Post treatment follow up should include yearly physical exam focusing on lymphnode stations, basic labs (CBC, differential, LDH). Limited evidence for routine imaging studies
- Suspected relapse should trigger imaging and repeat biopsy
- Contact Medical Oncologist if questions or concerns

RESOURCES

www.bccancer.bc.ca "Health Professional" – "Cancer Management Guidelines"

- Phone:
  - Abbotsford: 604-851-4710
  - Kelowna: 250-712-3900
  - Prince-Georg: 250-645-7328
  - Surrey: 604-930-2098
  - Vancouver: 604-877-6098
  - Victoria: 250-519-5500

QUESTIONS

- Kai.Luecke@bccancer.bc.ca

- Please spare three minutes on a quick questionnaire about lymphoma:
- https://surveys.vch.ca/Survey.aspx?s=6fffae5c0b7346d1a821ebcd26a3a510
- Get a ***coffee card*** in appreciation of your input! (email to PQI@PHSA.CA)