

Head and Neck: DLBCL

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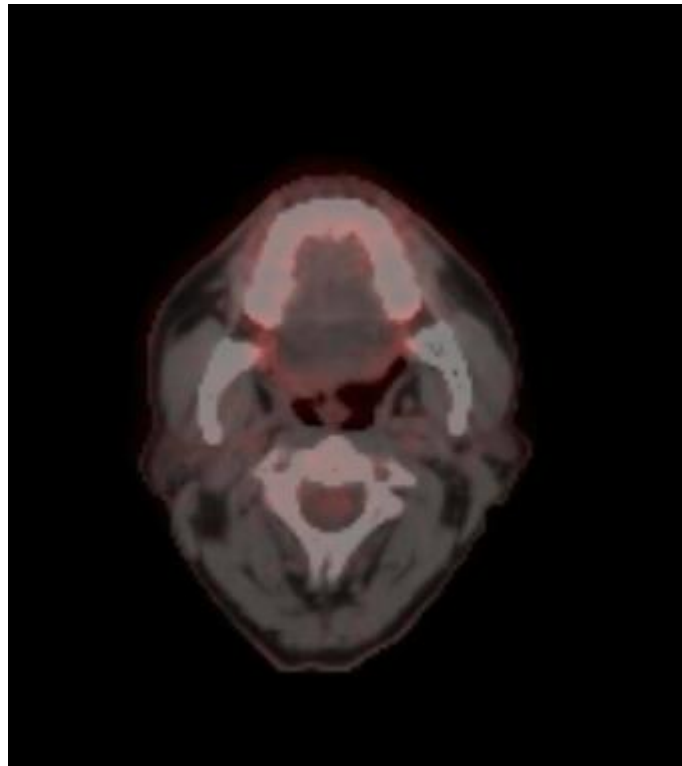
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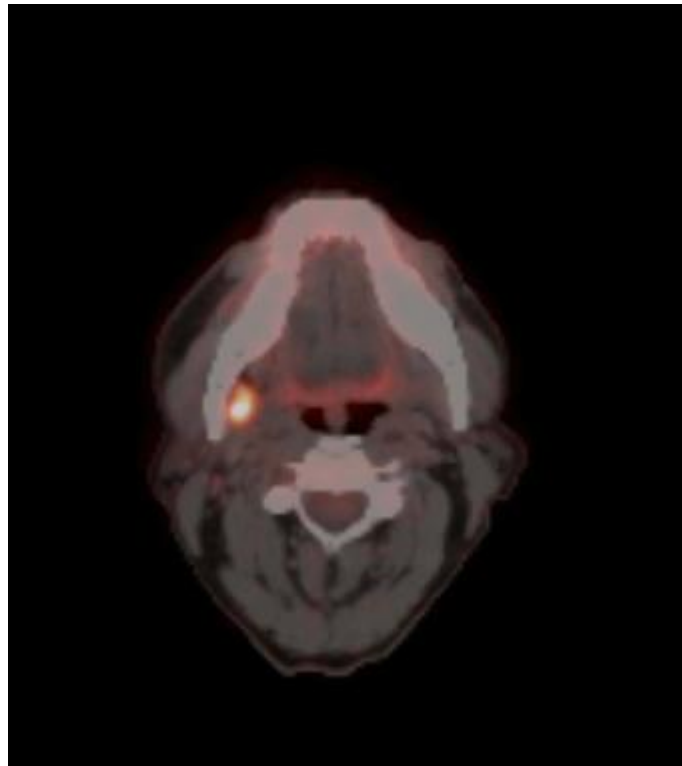
Case

- 60 yo male
- Presented with right cervical LAD
- PE: large, palpable right neck mass in the submandibular region
 - No other palpable adenopathy

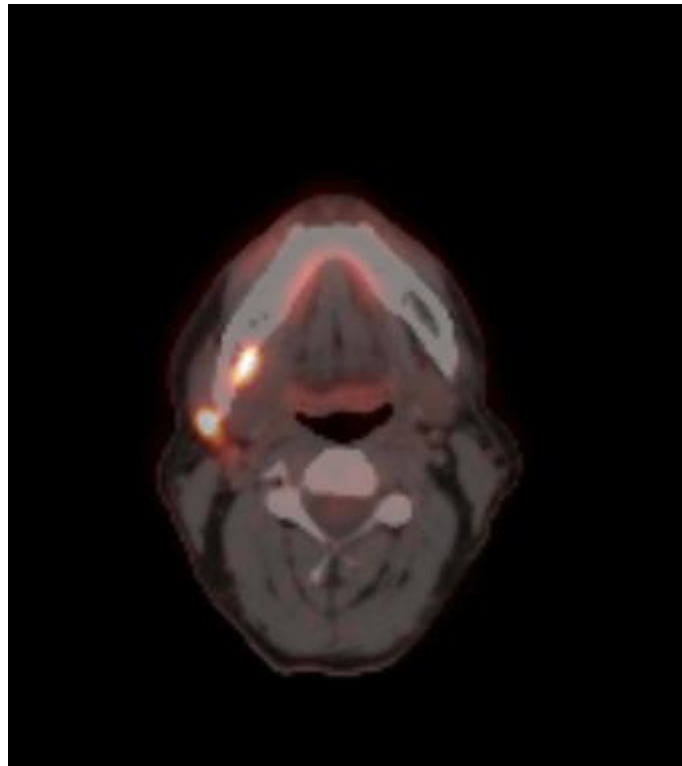
PET/CT Scan



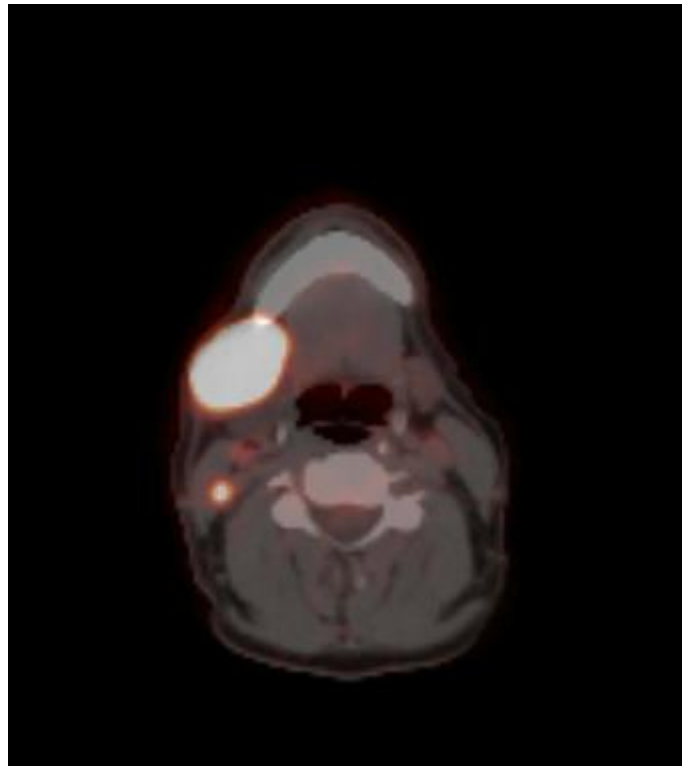
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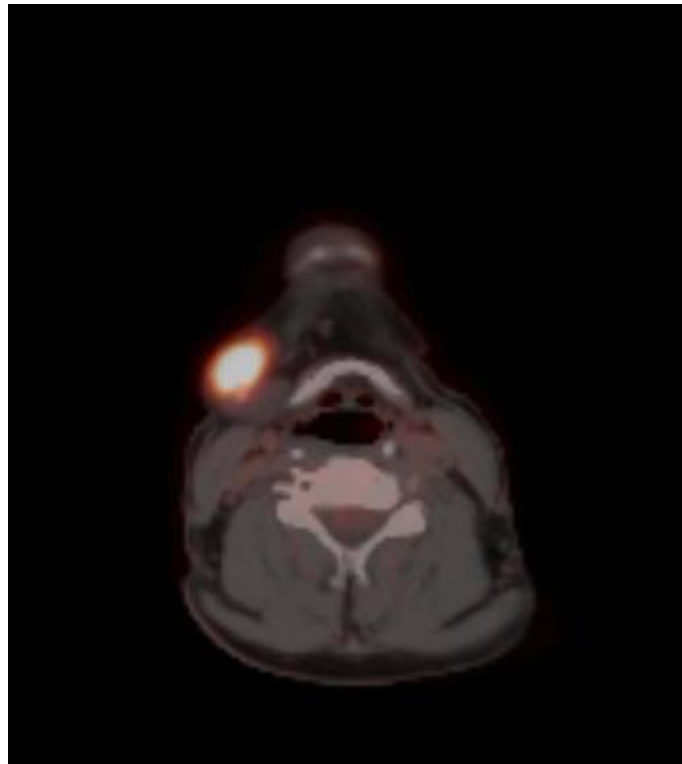
PET/CT Scan



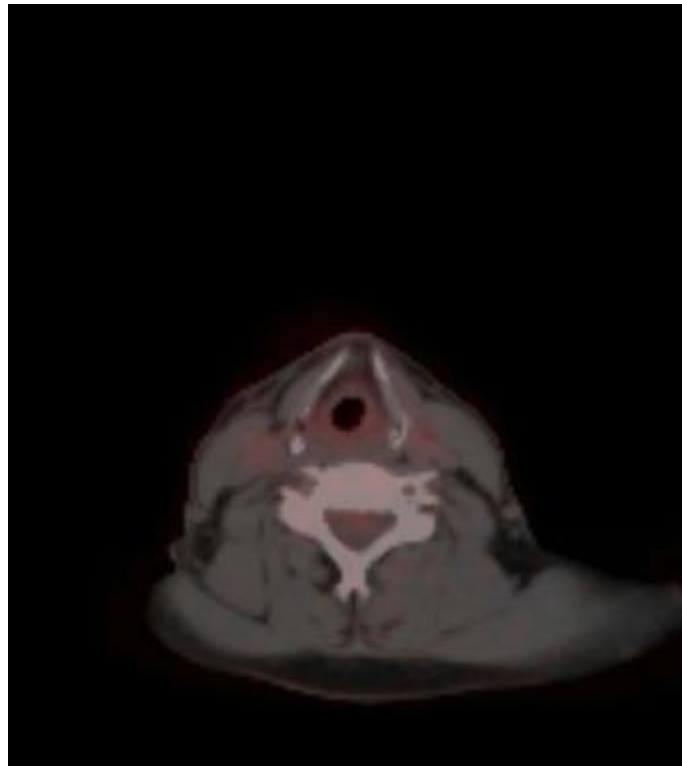
PET/CT Scan



PET/CT Scan



PET/CT Scan



Pathology

- Right excisional LN biopsy
- Diagnosis
 - DIFFUSE LARGE B CELL LYMPHOMA, Germinal Center-type
 - Ki-67: Greater than 95%
 - Positive for CD45, CD20, PAX-5, CD-10, BCL-6, and CD79a
 - Negative for CD3, CD5, pan keratin, HHV8, ALK-1, EBER, and MIM-1

NHL: Epidemiology

- >70,000 new cases of NHL per year in US
- ~19,000 estimated deaths
- NHL is 9th leading cause of death in men and 6th leading cause of death in women
- Most common subtype of NHL is DLBCL
 - Median age at presentation: 60
 - 40% with localized disease
 - 40-50% with extranodal disease
 - Common symptoms: painless LAD (axillary, inguinal, femoral), ~30% have B symptoms
- Indolent lymphoma: waxing and waning LAD

B Symptoms

- Any of the following:
 - Fevers: $T > 38\text{ C}$ (100.4 F)
 - Night sweats (drenching)
 - Weight loss: $>10\%$ loss over the past 6 months

DLBCL: Workup

- Excisional biopsy preferred
 - Adequate immunophenotyping to establish diagnosis via IHC or flow cytometry
 - IHC panel: CD20, CD3, CD5, CD10, CD45, BCL2, BCL6, Ki-67, IRF/MUM1
 - Cell surface marker analysis by flow: CD45, CD3, CD5, CD19, CD10, CD20
 - In certain situations:
 - Molecular analysis to detect gene rearrangements via FISH or IHC: BCL2, BCL6, MYC
 - Cytogenetics or FISH: t(14;18), t(8;14), etc.

Biopsy

Type of Biopsy	Advantages	Disadvantages
FNA	<ul style="list-style-type: none"> Easy Relatively painless Office-based procedure Very small needle 	<ul style="list-style-type: none"> Requires expert cytopathologist Unable to evaluate histology
Core needle	<ul style="list-style-type: none"> Easy Relatively painless Office-based procedure Standard histopathology Able to assess tissue architecture Able to obtain cell surface markers 	<ul style="list-style-type: none"> Slightly larger needle than FNA
Excisional	<ul style="list-style-type: none"> Standard histopathology Able to assess tissue architecture Able to obtain cell surface markers 	<ul style="list-style-type: none"> Requires procedure suite or OR Larger incision More painful

Courtesy of G. Walker

DLBCL: Workup

- B symptoms (fevers, night sweats, weight loss)
- PE: performance status; attention to node-bearing sites, including waldeyer's ring; note size of liver and spleen.
- Labs: CBC with diff, LDH, CMP, uric acid, Hep B
- Imaging: CT of C/A/P with contrast, PET-CT scan
- Bone marrow biopsy
- Calculate International Prognostic Index (IPI)
- Consider: cardiac w/u (MUGU scan, echo) if giving anthracycline based regimen, pregnancy test, beta-2-microglobulin, head and neck MRI, discuss fertility and sperm banking, HIV test
- LP if paranasal sinus, testicular, epidural, bone marrow with large cell lymphoma, HIV lymphoma, or more than 2 extranodal sites with elevated LDH.

Lymphoma Histology

B-cell	T-cell
DLBCL	Peripheral T-cell
Follicular	Precursor T lymphoblastic
SLL/CLL	Mycosis Fungoides
Lymphoplasmacytic	Anaplastic large cell
Plasma Cell / Myeloma	Adult T-cell
Marginal zone B-cell	
Mantle Cell	
Burkitt's lymphoma	
Precursor B lymphoblastic	

Immunophenotype

- B-Cell: CD19+, CD20+
 - Mantle Cell: CD5+
 - Follicular: CD10+ (germinal center)
 - MALT: CD5-, CD10-, CD23-
- T-Cell: CD2+, CD3+, CD7+, CD8+
 - Anaplastic large cell: CD30+

WHO Histology

Indolent	Aggressive	Very Aggressive
Follicular (G1-2)	DLBCL	Burkitt's
Marginal zone	Follicular (G3)	Precursor B lymphoblastic
MALT	Mantle	Precursor T lymphoblastic
Mycosis fungoides	Peripheral T cell	
NK Cell	Anaplastic large cell	
CLL		

Genotype

Translocations

- $t(8;14)$ – Burkitt's lymphoma (c-myc)
- $t(11;14)$ – Mantle cell lymphoma (bcl-1)
- $t(11;18)$ – MALT lymphoma
- $t(14;18)$ – Follicular lymphoma (bcl-2)

Ann Arbor Staging

- I Single lymph node group
- II Multiple lymph node groups on same side of diaphragm
- III Multiple lymph node groups on both sides of diaphragm
- IV Multiple extranodal sites or lymph nodes and extranodal disease

- X Bulk (> 10cm)
- E Extranodal extension or single isolated site of extranodal disease

- B/A B symptoms

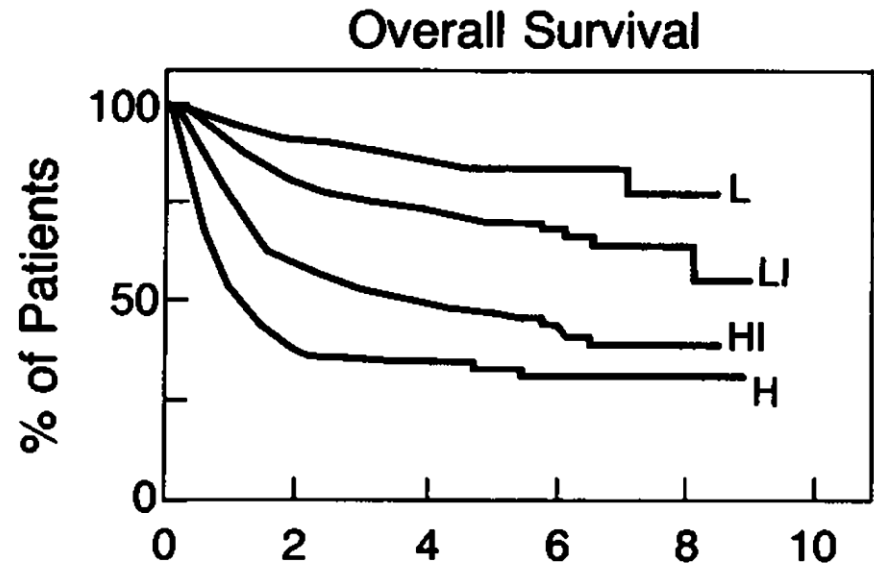
Case

- 60 yo male
- Right cervical LAD in 5/2013
- No B symptoms
- Bx: DLBCL
- Stage IA
- What else should we focus on in w/u?



International Prognostic Index (IPI) Score

- Age > 60
- Performance status ≥ 2
- LDH > normal
- Extranodal sites, > 1
- Stage 3 or 4



Score	Risk Group	5 Year OS (- R)	3 Year OS (+ R)
0-1	Low	76%	91%
2	Low-intermediate	51%	81%
3	High-intermediate	43%	65%
4-5	High	26%	59%

Rule of thumb: for R-CHOP, add 15% to 5-year OS

Shipp et al NEJM 1993

Case

- 60 yo male
- Right cervical LAD
- No B symptoms
- Good PS, normal LDH
- Bx: DLBCL
- Stage IA
- IPI = 0
- Tx recs?



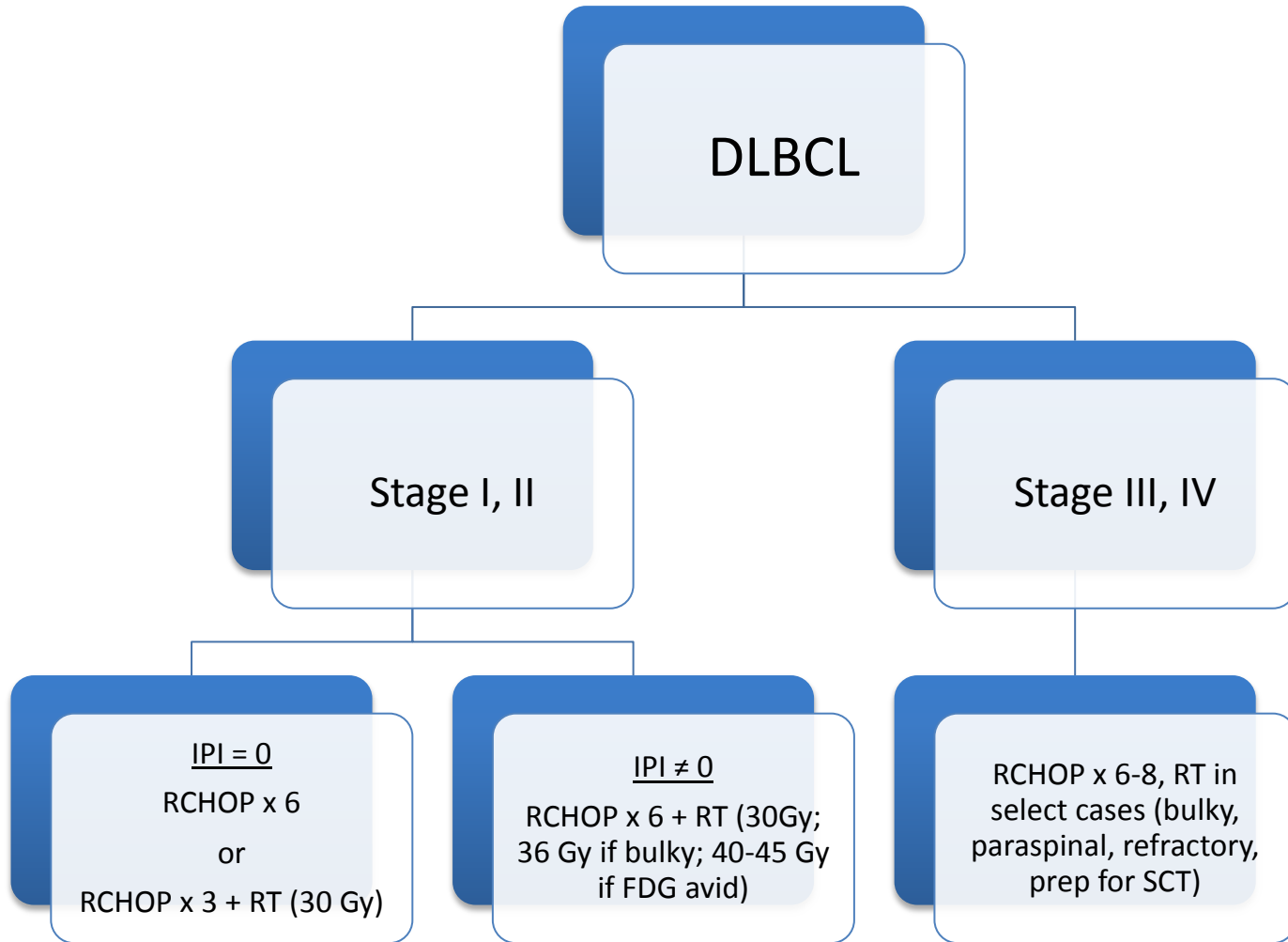
Case

- Treatment recommendations for non-bulky, stage I or II DLBLC, without adverse risk factors:
 - **R-CHOP x 3 cycles + RT**
 - Or
 - R-CHOP x 6 cycles +/- RT

Chemotherapy Regimens in Lymphoma

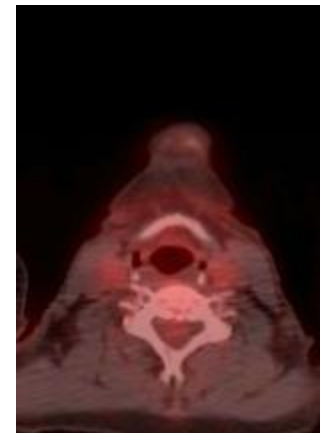
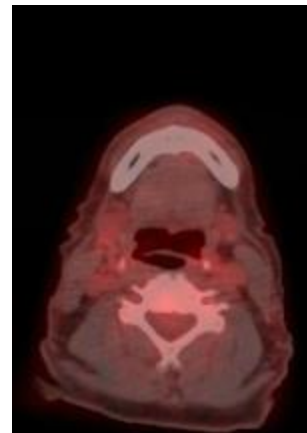
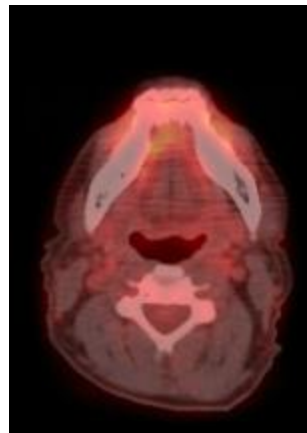
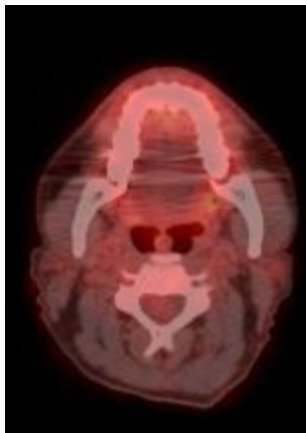
R-CHOP	rituximab, cyclophosphamide, adriamycin (hydroxydaunorubicin), vincristine (Oncovin), prednisone
CVAD	cyclophosphamide, vincristine, adriamycin, dexamethasone
EPOCH	etoposide, prednisone, vincristine (Oncovin), cyclophosphamide, adriamycin (hydroxydaunorubicin)
ABVD	adriamycin, bleomycin, vinblastine, dacarbazine
BEACOPP	bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone
COPP	cyclophosphamide, vincristine (Oncovin), procarbazine, prednisone
EBVP	epirubicin, bleomycin, vinblastine, prednisone
MOPP	mechlorethamine, vincristine (Oncovin), procarbazine, prednisone
Stanford V	mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, prednisone

Treatment Summary: DLBCL



Treatment Recommendations?

- 60 yo male
- Stage IA DLBCL
- s/p 3 cycles R-CHOP
- PET CT and CT with contrast demonstrated **complete response (CR)**



“If I have a CR, why do I also
need RT?”

Chemo vs. Chemo-RT in the Pre-PET and Pre-R Era

TRIAL	PT CHARACTERISTICS	NO.	TREATMENT ARMS	RESULTS
SWOG 8736	Median age: 59 Normal LDH: 80% PS 0-1: 97% % stage II: 33% Excl. bulky stage II	401	1) CHOP x 3 + RT 2) CHOP x 8	RT vs. no RT: 5 yr PFS 77% vs. 64% (p=0.03) 5 yr OS 92% vs. 72% (p=0.02) * 8 yr update: no survival advantage with RT
ECOG 1484	Median age: 59 PS 0-1: 92% % stage II: 68% % bulky: 31%	399	CHOP x 8 If CR (n=215): 1) RT 2) No RT If PR (n=71) → RT	Complete response: RT vs. no RT: 6 yr FFS 70% vs. 53% (p=0.05) 6 yr OS 79% vs. 67% (p=0.23) Partial response: 6 yr FFS 63% 6 yr OS 69%
GEELA LNH 93-1	Median age: 47 Normal LDH PS 0-1 % stage II: 32% % bulky: 11%	647	1) CHOP x 3 + RT 2) ACVBP	CHOP + RT vs. ACVBP: 5 yr EFS 82% vs. 74% (p<0.001) 5 yr OS 90% vs. 81% (p=0.001)
GELA LNH 93-4	Median age: 68 Normal LDH PS 0-1 % stage II: 32% % bulky: 9%	574	1) CHOP x 4 + RT 2) CHOP x 4	RT vs. no RT: 5 yr EFS 64% vs. 61% (p=0.56) 5 yr OS 68% vs. 72% (p=0.54)

This still doesn't answer the question of needing RT with CR after R-CHOP chemo

None of these studies used rituximab:

- 1) Does rituximab obviate the need for RT?
- 2) **Will improved distant control with rituximab allow the local control benefit of RT to translate to an OS benefit?** Will answer this in a moment...

Local Control with RT after CR to Chemo

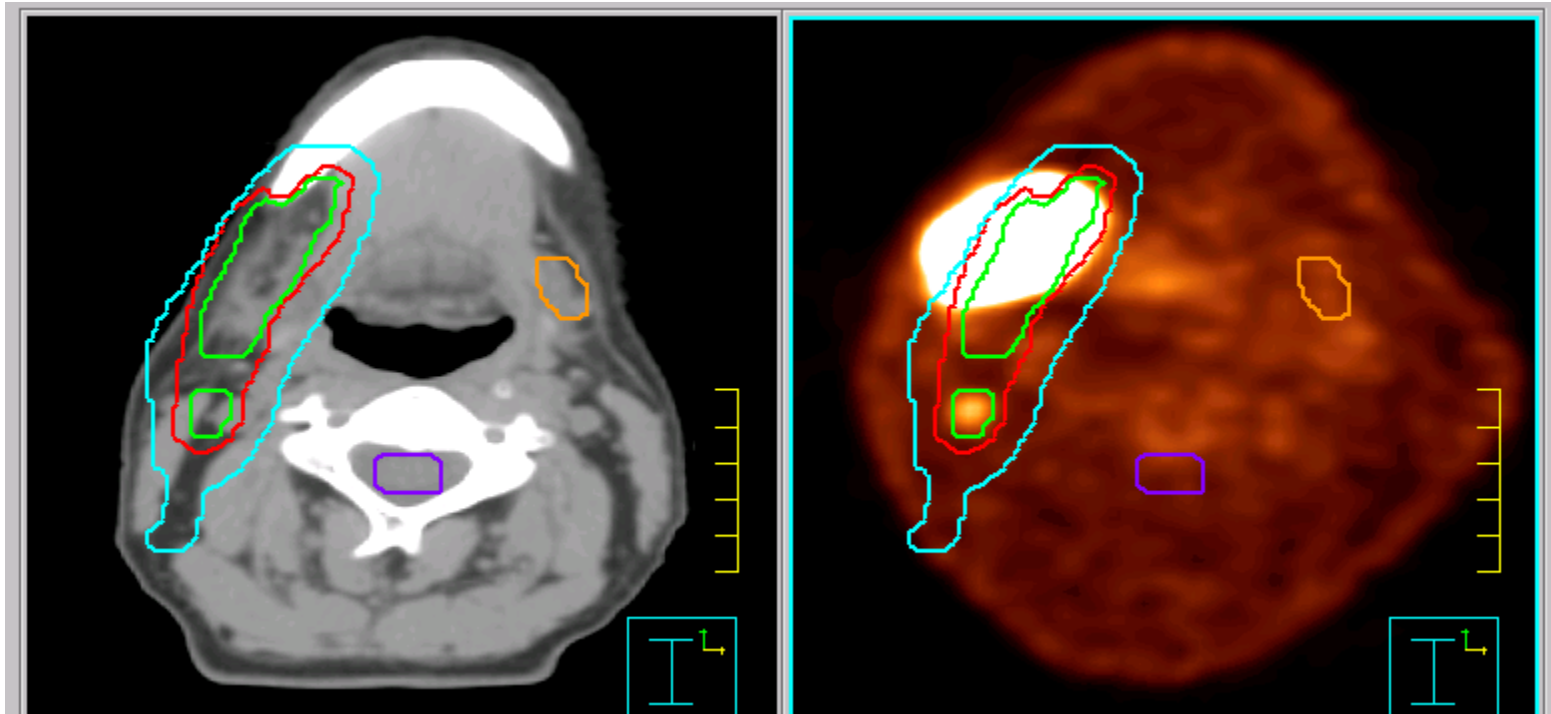
Study	# of pts in CR	Chemo	Median FU	Response assessment	RT dose (Gy)	LC
Zinzani, 1999	38	MACOP-B	39 mo	Gallium	30-36	100%
Kahn, 2006	16	CHOP x 4-6	40 mo	PET	Med: 30.6	100%
Halasz, 2010	39	R-CHOP	46.5 mo	PET	Med: 36	100%
Phan, 2010	142	R-CHOP in 70%	36 mo	PET	If no residual CT dz: 30; If > 5cm or residual CT dz: 36-39.6	100%
Dorth, 2012	79	R-CHOP in 65%	56 mo	Gallium (14%); PET (73%)	Med: 25	92%

ASTRO 2012

Treatment Plan

3060 cGy in 17 fx using IMRT to involved sites

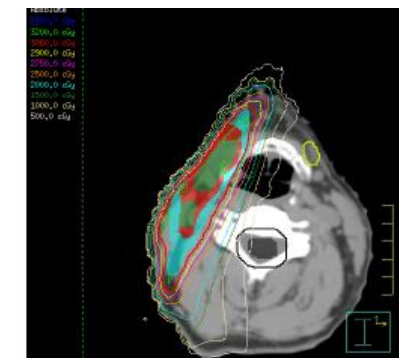
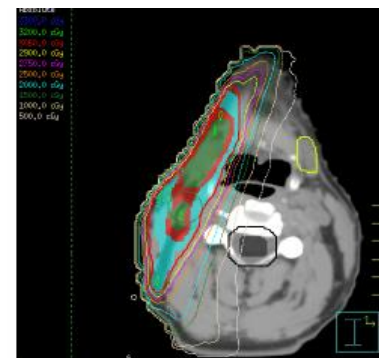
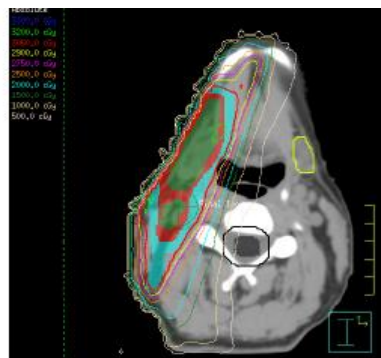
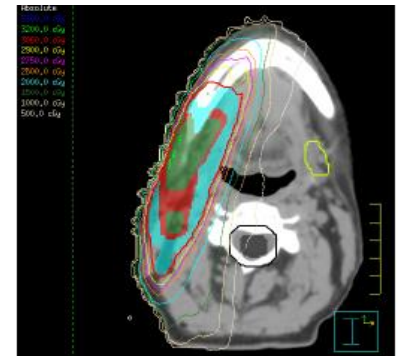
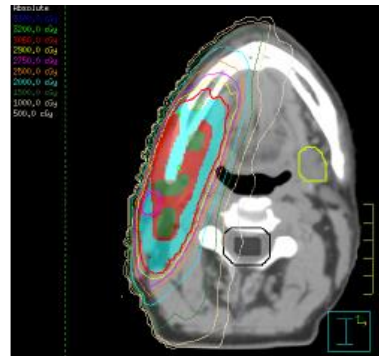
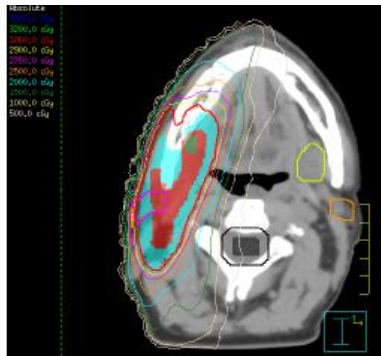
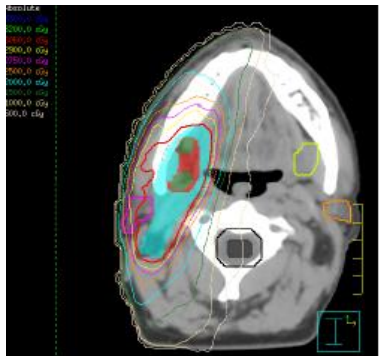
Pretreatment PET



GTV

CTV

PTV



Appendix of Relevant Trials

- Summary of relevant trials for DLBCL

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ECOG 1484

- CHOP x 8
 - If CR, randomized:
 - Arm 1: Observation
 - Arm 2: RT to 30 Gy
 - If PR (28%) → 40 Gy
- Stratified by performance status (0-1), bulk (>10 cm), number of sites (> 3)

ECOG 1484

- In complete responders:
 - RT improved FFS: 70% vs. 53% ($p=0.05$)
 - No OS benefit: 79% vs. 67% ($p=0.23$)
- In partial responders (all received RT)
 - 6 yr FFS: 63%
 - 6 yr OS: 69%

ECOG 1484 Conclusions

- Patients with CR after CHOP benefit from RT (30 Gy)
 - Improved DFS and local control (53% vs. 70%, $p=0.05$)
 - No OS benefit
- Patients with PR treated with RT (40 Gy) had equivalent DFS and OS as patients with CR

GELA LNH 93-4

- 576 patients; aggressive lymphoma
- Age > 60 (“elderly”), but age adjusted IPI = 0
- Stage I or II
- Randomized
 - CHOP x 4, no RT
 - CHOP x 4 + 40 Gy IFRT

Bonnet et al JCO 2007

GELA LNH 93-4 Results

	CHOP x 4	CHOP x 4 + IFRT	<i>p</i> value
5 yr EFS	61%	64%	0.7
5 yr OS	72%	68%	0.6
Isolated local relapse	47%	21%	-
5 yr OS age > 70	70%	58%	0.1

Bonnet et al JCO 2007

GELA LNH 93-4 Conclusions

- Stopped early:
 - No difference on interim analysis
 - New evidence showing benefit of rituximab
- No advantage in adding RT
- GELA abandons RT as 1st line treatment of localized aggressive lymphoma: now R-CHOP

Bonnet et al JCO 2007

CHOP +/- RT Summary

- RT improves LC and possibly DFS, but not OS

CHOP-RT vs. Alternative Chemo

- SWOG 8736
- GELA LNH 93-1

SWOG 8736

- Stage I and IE, Non-bulky stage II NHL (DLBCL, FL, and Burkitt's)
- Randomized:
 - CHOP x 3 + IFRT to 40-55 Gy (n=200)
 - CHOP x 8 (n=201)

Miller et al. NEJM 1998

SWOG 8736

- Improved 5 yr PFS and OS in CHOP + RT arm

	CHOP x 3 + IFRT	CHOP x 8	P value
5 yr PFS	76%	67%	0.03
5 yr OS	82%	74%	0.02

Miller et al. NEJM 1998

SWOG 8736: Update

- Median follow up 8.2 years
- Loss of survival advantage in RT arm
- Conclusion: CHOP x 3 insufficient systemic therapy

GELA LNH 93-1

- Age < 61, aggressive lymphoma, stage I-II, IPI=0
- Randomized
 - CHOP x 3 + IFRT 40 Gy (n=329)
 - ACVBP* x 3 + Consolidation chemo** (n=277)

* doxorubicin, cyclophosphamide, vindesin, bleomycin, prednisone

** MTX, Ara-C, etoposide, ifosfamide

Reyes et al. NEJM 2005

GELA LNH 93-1

- Improved EFS and OS with intensified chemotherapy

	CHOP x 3 + IFRT	ACVBP x 3 + consolidation chemo	P value
10 yr EFS	74%	82%	<0.001
10 yr OS	81%	90%	0.001

Miller et al. NEJM 1998

CHOP-RT vs. alternate chemo: Summary

- RT cannot compensate for inadequate chemotherapy

Ng and Mauch JCO 2007

Local Control with RT after CR to R-Chemo

Study	# of pts in CR	Chemo	Median FU	Response assessment	RT dose (Gy)	LC
Zinzani, 1999	38	MACOP-B	39 mo	Gallium	30-36	100%
Kahn, 2006	16	CHOP x 4-6	40 mo	PET	Med: 30.6	100%
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ASTRO 2012

MDACC

- Retrospective review
- 469 DLBCL pts, any stage
- At least 6 cycles of R-CHOP
- 30% received consolidative RT
- Median f/u 36 mo

Phan et al. JCO 2010

MDACC

- Matched pair analysis: RT improved OS and PFS regardless of stage
 - PFS: hazard ratio 0.29
 - OS: hazard ratio 0.24
- OS benefit observed on multivariate analysis and matched pair analysis
- 100% LC at sites receiving IFRT

Phan et al. JCO 2010

MDACC Conclusions

- Retrospective evidence suggests a benefit for patients who receive R-CHOP followed by RT
- Among 291 pts treated with R-CHOP and achieved CR, RT was associated with a significantly higher 5 yr PFS and OS

Phan et al. JCO 2010

Treatment Summary: DLBCL

