Head and Neck: DLBCL

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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
PET/CT Scan
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

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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 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            | Easy       | Requires expert cytopathologist |
|                | Relatively painless | Unable to evaluate histology |
|                | Office-based procedure | |
|                | Very small needle | |
| Core needle    | Easy       | Slightly larger needle than FNA |
|                | Relatively painless | |
|                | Office-based procedure | |
|                | Standard histopathology | |
|                | Able to assess tissue architecture | |
|                | Able to obtain cell surface markers | |
| Excisional     | Standard histopathology | Requires procedure suite or OR |
|                | Able to assess tissue architecture | Larger incision |
|                | Able to obtain cell surface markers | 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     |                                             |

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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+

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# 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 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 Table

| 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

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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

| Regimen   | Components                                                                 |
|-----------|---------------------------------------------------------------------------|
| 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

**Stage I, II**
- IPI = 0
  - RCHOP x 6
  - or
  - RCHOP x 3 + RT (30 Gy)
- IPI ≠ 0
  - RCHOP x 6 + RT (30 Gy; 36 Gy if bulky; 40-45 Gy if FDG avid)

**Stage III, IV**
- RCHOP x 6-8, RT in select cases (bulky, paraspinal, refractory, prep for SCT)

RCHOP: R- Cyclophosphamide, Cisplatin, Vincristine, Prednisone
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<br> Normal LDH: 80%<br> PS 0-1: 97%<br> % stage II: 33%<br> Excl. bulky stage II | 401 | 1) CHOP x 3 + RT<br> 2) CHOP x 8                   | RT vs. no RT:<br> 5 yr PFS 77% vs. 64% (p=0.03)<br> 5 yr OS 92% vs. 72% (p=0.02)<br> * 8 yr update: no survival advantage with RT |
| ECOG 1484           | Median age: 59<br> PS 0-1: 92%<br> % stage II: 68%<br> % bulky: 31%                | 399 | CHOP x 8<br> If CR (n=215):<br> 1) RT<br> 2) No RT<br> If PR (n=71) → RT | Complete response: RT vs. no RT:<br> 6 yr FFS 70% vs. 53% (p=0.05)<br> 6 yr OS 79% vs. 67% (p=0.23)<br> Partial response:<br> 6 yr FFS 63%<br> 6 yr OS 69% |
| GEELA LNH 93-1      | Median age: 47<br> Normal LDH<br> PS 0-1<br> % stage II: 32%<br> % bulky: 11%     | 647 | 1) CHOP x 3 + RT<br> 2) ACVBP                      | CHOP + RT vs. ACVBP:<br> 5 yr EFS 82% vs. 74% (p=<0.001)<br> 5 yr OS 90% vs. 81% (p=0.001) |
| GELA LNH 93-4       | Median age: 68<br> Normal LDH<br> PS 0-1<br> % stage II: 32%<br> % bulky: 9%      | 574 | 1) CHOP x 4 + RT<br> 2) CHOP x 4                   | RT vs. no RT:<br> 5 yr EFS 64% vs. 61% (p=0.56)<br> 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%  |
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
## Chemo vs. Chemo-RT in the Pre-PET and Pre-R Era

| TRIAL             | PT CHARACTERISTICS                                      | NO. | TREATMENT ARMS                      | RESULTS                                                                 |
|-------------------|---------------------------------------------------------|-----|-------------------------------------|-------------------------------------------------------------------------|
| SWOG 8736         | Median age: 59                                          | 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 |
|                   | Normal LDH: 80%                                         |     |                                     |                                                                         |
|                   | PS 0-1: 97%                                             |     |                                     |                                                                         |
|                   | % stage II: 33%                                          |     |                                     |                                                                         |
|                   | Excl. bulky stage II                                    |     |                                     |                                                                         |
| ECOG 1484         | Median age: 59                                          | 399 | CHOP x 8                            | 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% |
|                   | PS 0-1: 92%                                             |     |                                     |                                                                         |
|                   | % stage II: 68%                                          |     |                                     |                                                                         |
|                   | % bulky: 31%                                            |     |                                     |                                                                         |
| GEELA LNH 93-1    | Median age: 47                                          | 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) |
|                   | Normal LDH                                              |     |                                     |                                                                         |
|                   | PS 0-1                                                  |     |                                     |                                                                         |
|                   | % stage II: 32%                                          |     |                                     |                                                                         |
|                   | % bulky: 11%                                            |     |                                     |                                                                         |
| GELA LNH 93-4     | Median age: 68                                          | 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) |
|                   | Normal LDH                                              |     |                                     |                                                                         |
|                   | PS 0-1                                                  |     |                                     |                                                                         |
|                   | % stage II: 32%                                          |     |                                     |                                                                         |
|                   | % bulky: 9%                                             |     |                                     |                                                                         |
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%

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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 | p 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
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% |
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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
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
Treatment Summary: DLBCL

**Stage I, II**
- **IPI = 0**
  - RCHOP x 6
  - or
  - RCHOP x 3 + RT (30 Gy)

- **IPI ≠ 0**
  - RCHOP x 6 + RT (30 Gy; 36 Gy if bulky; 40-45 Gy if FDG avid)

**Stage III, IV**
- RCHOP x 6-8, RT in select cases (bulky, paraspinal, refractory, prep for SCT)