The Management of Lymphoma

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Disclosures

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• Ownership or Investment Interests
  • None

• Leadership Positions
  • eContour.org – Disease site expert
Conflicts of Interest

• None
Objectives

• Review the current treatment paradigms and evidence in the management of
  • Non Hodgkin Lymphoma
    • DLBCL, PMBL, GZL
    • Follicular Lymphoma
    • MALT
    • Cutaneous Lymphoma
  • Hodgkin Lymphoma
• Understand principles of modern radiotherapy
  • Involved Site Radiotherapy
  • Long term Toxicities of Radiotherapy
Non-Hodgkin Lymphoma
DLBCL
Incidence of NHL in the United States 2016

Total mature NHL = 112,380

- CLL/SLL 20,980 (19%)
- DLBCL 27,650 (25%)
- Follicular lymphoma 13,960 (12%)
- Marginal zone lymphoma, 7460 (7%)
- Peripheral T-cell lymphoma, 3950 (4%)
- Mantle cell lymphoma, 3320 (3%)
- Lymphoplasmacytic lymphoma* 2330 (2%)
- Hairy cell leukemia†, 1910 (2%)
- Mycosis fungoides, 1620 (1%)
- Burkitt lymphoma/leukemia, 1480 (1%)
- Others 1710 (1%)

*This includes hairy cell leukemia.
The heterogeneity of DLBCL

- DLBCL NOS
- DLBCL co-existent with other lymphomas (FL, MALT)
- Grade 3 FL
- Intravascular large B cell lymphoma
- DLBCL associated with chronic inflammation
- EBV+ DLBCL of elderly
- ALK+ DLBCL
- T-cell rich large B cell lymphoma
- Primary CNS DLBCL
- Primary cutaneous DLBCL

- Double Hit DLBCL
- Double expression DLBCL
- Primary Mediastinal Large B-cell lymphoma
- Gray Zone Lymphoma
Workup and Staging

- Pathology
  - Cell of Origin
  - Favorable vs. Unfavorable molecular profile
- PET/CT
  - Staging
  - Bone Marrow Involvement
- CSF sampling in select patients
Molecular Profiling

- **Cell Of Origin (COO)**
  - **Ger**minal C**enter B Cell**
  - **Act**ivated **B Cell**
- **GCB**
  - 50% incidence
  - 3 y OS ~80%
- **ABC**
  - 30% incidence
  - 3 y OS~40%

- **3 common microarray IHC algorithms**
  - **Hans**: CD10, BCL6, MUM1
  - **Choi**: GCET1, MUM1, BCL6, FOXP1
  - **Tally**: GCET1, CD10 (GCB)
    - MUM1, FOXP1 (ABC)
    - LMo2

- **Gene Expression Profiling using RNA is more reliable**
Oncogenic Pathways for DLBCL

Dunleavy et. al. Oncology 2014
High Grade B-cell Lymphoma – DH/DE

- **MYC** – transcription factor on Ch 8q
  - Translocations in ~10% DLBCL
  - GCB subtype

- **BCL2** – anti-apoptotic function
  - T(14;18) translocation in 20-30% DLBCL
  - GCB subtype

- **BCL6** – transcription repressor

- **Double hit** ~ 6% of all patients
  - Detected by FISH
  - BCL2 and MYC translocations (90% GCB)
  - BCL6 and MYC translocations (can be ABC)
High Grade B-cell Lymphoma – DH/DE

• Double expression = expression without translocation
  • Can be either GCB or ABC subtype
  • MYC ~ > 40% expression
  • BCL2 ~ > 50% expression
  • BCL6 ~ > 30% expression

• DH and DE DLBCL have been shown to have significantly poor OS compared to DLBCL NOS independent of IPI score and COO
DH/DE DLBCL

Figure 1. In DLBCL, there is a relationship between cell of origin and over-expression of BCL2 and MYC. Most cases of double-hit lymphoma are of germinal center B-cell (GCB) origin whereas most cases of double-expreser lymphomas (without rearrangements) are of activated B-cell (ABC) origin.
GCB vs. ABC patients treated with R-CHOP
Double Hit vs. DLBCL NOS
Green et al. JCO 2012, 30(28): 3460-3467

6% DH (majority had GCB COO)
Median survival 13 months vs. 95 months; 3 y OS 46% vs. 75%; PFS 6 months vs 95 months
Double Expression vs. DLBCL NOS
Green et al. JCO 2012, 30(28): 3460-3467
DLBCL

International Prognostic Index

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>IPI</th>
<th>AA-IPI (age ≤60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Serum LDH &gt; 1 x nl</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PS 2-4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 1 EN site</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Stage III-IV</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Rituximab adds ~ 10% to OS for each IPI score

OS by IPI and Age-Adjusted-IPI

Shipp et al. NEJM 329:987, 1993
NCCN-IPI in the Rituximab Era

![NCCN-IPI Table]

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;40 to ≤60</td>
<td>Low</td>
</tr>
<tr>
<td>&gt;60 to &lt;75</td>
<td>Low-intermediate</td>
</tr>
<tr>
<td>≥75</td>
<td>High</td>
</tr>
<tr>
<td>LDH, normalized</td>
<td></td>
</tr>
<tr>
<td>&gt;1 to ≤3</td>
<td>Low</td>
</tr>
<tr>
<td>&gt;3</td>
<td>Low-intermediate</td>
</tr>
<tr>
<td>Ann Arbor stage III-IV</td>
<td></td>
</tr>
<tr>
<td>Extracranial disease</td>
<td></td>
</tr>
<tr>
<td>Performance status ≥2</td>
<td></td>
</tr>
</tbody>
</table>

* = Disease in bone marrow, CNS, liver/GI tract, or lung.

![NCCN-IPI vs IPI Graphs]

Figure 1. NCCN IPI vs IPI in risk stratification in the NCCN DLBCL training cohort.
Patterns of Care in DLBCL
Vargo et al. JCO 2015; 33: 3710-3717

47% CMT in 2000
32% CMT in 2012
Patterns of Care in DLBCL
Vargo et al. JCO 2015; 33: 3710-3717
Patterns of Care in DLBCL
Vargo et al. JCO 2015; 33: 3710-3717

OS: 64% vs. 55% @ 10 y (p<0.001)

Figure 2. Overall survival probabilities on multivariable analysis by treatment modality (A) without propensity score and (B) with propensity score, adjusting for potential imbalances between treatment modalities because of lack of randomization.
DLBCL
Pre-Rituximab Era

The SWOG Randomized Study
CHOP X 8 vs CHOP X 3 + IFRT

- Stages I-IIIE (non-bulky)
- IFRT was 40-55 Gy
- Chemo alone (x8)
  - serious toxicity (p=.06)
  - heart failure (p=.02)
  - myelosuppression (p=.09)
  - Not able to complete regimen (p=.01)
- Chemo-RT
  - improved survival
  - Improved lymphoma control

SWOG 8736: Updated Results

- Median f/u= 8.2 yrs
- FFS curves overlap at 7 years
- OS curves overlap at 9 years
- Late relapses and lymphoma deaths in CMT arm


Miller et al. - ASH, 2001
Stage-Adjusted IPI for Stage I-II Patients

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Stage-Adjusted IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60</td>
<td>1</td>
</tr>
<tr>
<td>Serum LDH &gt; 1 x nL</td>
<td>1</td>
</tr>
<tr>
<td>PS 2-4</td>
<td>1</td>
</tr>
<tr>
<td>Stage II</td>
<td>1</td>
</tr>
</tbody>
</table>

OS by Stage-Adjusted IPI

* CHOPx3+RT arm:

<table>
<thead>
<tr>
<th>SA-IPI</th>
<th>5-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>94%</td>
</tr>
<tr>
<td>&gt; 1</td>
<td>70%</td>
</tr>
<tr>
<td>3</td>
<td>48%</td>
</tr>
</tbody>
</table>

Miller et al. NEJM 339:21, 1998

Fisher, Miller et al. ASH Education Book, 2004
Phase II R-CHOP + IFRT in Stage I-II DLBCL patients with at least 1 risk factor
Persky et al. JCO 2008
DLBCL
SWOG 8736 – Final Results
Stephens et al. JCO 2016; 34:2997-3004

• Median F/U 18 years
• No difference is PFS or OS between 2 groups
• More late relapses in CHOP3RT but overall relapse rates same
• Median OS ~ 13 years
• No difference in the rate of 2\textsuperscript{nd} malignancies in 2 groups!
  • CHOP8 11% vs. CHOP3RT 12%
  • Most common NMSC, Lung CA, Breast CA
**DLBCL**

**Rituximab Era UNFOLDER trial**

**Aggressive NHL: UNFOLDER Trial**

- Eligibility: DLBCL, aged 18-60, aa-IPI=1 or IPI=0 with bulky disease (≥ 7.5 cm)
- Pts with bulky and/or extranodal disease randomized to 1 of 4 arms:
  - Arm I: R-CHOP 21 x 6 alone
  - Arm II: R-CHOP 21 x 6; if CR → RT
  - Arm III: R-CHOP 14 x 6 alone
  - Arm IV: R-CHOP 14 x 6; if CR → RT

**UNFOLDER Trial**

![Graph showing survival analysis](image)
DLBCL RICOVER-60

- 61-80 years
- Any stage or IPI
- 4 arm study
  - CHOP-14 x 6
  - R-CHOP-14 x 6
  - CHOP-14 x 8
  - R-CHOP-14 x 8
- Trial stopped at planned interim analysis due R-CHOP-14 x 6 showed improved PFS/OS

- Amendment of RICOVER-noRTh
  - R-CHOP-14 x 6 + 2 R and no RT
  - RT given to those with either bulky disease >7.5 cm or ENI
DLBCL RICOVER-60
Consolidation RT to skeletal sites
Held et al. JCO 2013 31:4115-4122

- MabThera & RICOVER-60 trials
- 292 patients
- 3 y EFS
  - 75% RT vs. 36% no-RT
  - p < 0.001
- 3 y OS
  - 86% RT vs. 71% no-RT
  - p = 0.064
- RT dose 39.6 Gy

Fig 3. (A) Event-free and (B) overall survival of patients with diffuse large B-cell lymphoma with skeletal involvement treated with and without radiotherapy to sites of skeletal involvement. Gold lines represent patients treated with (n = 133) and blue lines represent patients treated without (n = 28) radiotherapy to skeletal sites.
Chemotherapy intensification in DH DLBCL
R-EPOCH: MDACC series
Oki et al. BJH 2014, 166:891-901

- 10 y retrospective review
- 129 patients
- CR rate with R-CHOP 40%
  - EFS 22% OS 20%
- Poor PS and BM + did worse
- Consolidation SCT in CR
- CNS failure 13% @ 3 y
R-EPOCH vs. R-CHOP
CALGB 50303 – ASH 2016 abstract

• Phase III trial comparing DA-EPOCH-R x 6 vs. R-CHOP x 6
• Stage II or higher patients
• COO analysis done on all patients
• 5 y EFS showed no difference
• More acute hematologic toxicity and neuropathy in the EPOCH arm
• Subset analysis by COO and IPI pending
Phase III Trial on RT Dose

Radiotherapy and Oncology 2011;100:86

640 Sites of Aggressive NHL
82% DLBCL
67% stage I-II
73% as post-chemo consolidative RT
10% received Rituximab

30 Gy in 15 fractions
40-45 Gy in 20-23 fractions
**Median f/u 5.6 yrs:**

<table>
<thead>
<tr>
<th></th>
<th>30 Gy (n=319)</th>
<th>40-45 Gy (n=321)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5y FFLP</td>
<td>82%</td>
<td>84%</td>
<td>0.66</td>
</tr>
<tr>
<td>5y OS</td>
<td>64%</td>
<td>68%</td>
<td>0.29</td>
</tr>
</tbody>
</table>

**Caveats:**

- Included pts treated with RT alone or receiving salvage/palliative RT
- No chemo data, mostly without rituximab
- Lack of functional imaging to determine response to chemo

*Courtesy A. Ng*
2017 DLBCL Treatment Paradigm

• Stage I non-bulky IPI 0 or 1 (no unfavorable molecular features)
  • R-CHOP x 3-4 cycles and ISRT 30 Gy
  • R-CHOP x 6 and NFT?

• Other Stage I/II
  • R-CHOP x 6 followed by ISRT 30 Gy if CR on PET
  • if PR on PET, boost post-chemo GTV to 45-50 Gy

• Aggressive histology (ABC COO, DH/DE, Burkitt’s like features, Ki-67 index>90%)
  • da-R-EPOCH x 6 followed by ISRT 30 Gy if CR on PET
  • R-CHOP X 6 followed by ISRT 30 Gy if CR on PET
2017 DLBCL Treatment Paradigm

• Stage III & IV
  • R-CHOP x 6 cycles
  • Add RT to sites of bulky disease (> 5 cm) and skeletal sites ~ 30 Gy

• Relapsed & Refractory disease
  • Transplant candidates
    • Add RT after salvage chemo in the peri-transplant period
    • Pre-transplant 24-30 Gy in 20 fractions BID 6 hours apart
    • Post-transplant 30 Gy in 17-20 fractions
  • Non-transplant candidates
    • CR – 30 Gy
    • PR – pre-chemo disease to 30-36 Gy followed by post-chemo disease to 45-50 Gy
Primary Mediastinal Large B Cell Lymphoma (PMBL)

- Female predilection, median age 30s
- Majority present with early stage bulky disease
- Majority diagnosed as Stage I/II and without BM involvement
- Involves mediastinum+/-neck/SCF
- Arises from thymic B cells
- Distinct gene expression profiling
PMBL – CHOP +/- R
MINT trial  Rieger et al. Annals of Oncology 2013

Figure 2. EFS, and OS of PMBCL and DLBCL assigned to CHOP-like regimen alone or CHOP-like regimens in combination with rituximab.
PMBL: Da-EPOCH – R x 6 cycles
PMBL Role of Post-chemotherapy PET

IESLG-26 – Martelli et al. JCO 2014; 32: 1769-1777
Management of PMBL

• R-CHOP x 6 followed by ISRT 30 Gy for CR
• R-da-EPOCH x 6 cycles
  • Deauville 1-3 NFT
  • Deauville 4 Consider ISRT upfront or if + biopsy followed by ISRT
  • Deauville 5 ISRT 30 Gy with boost to residual disease
• Relapsed disease
  • If no prior RT, can salvage with RT alone
Mediastinal Gray Zone Lymphoma

• Synonyms
  • B-cell lymphoma, unclassifiable, with features between DLBCL and cHL
  • Large B-cell lymphoma with HL
  • HL-like anaplastic large cell lymphoma

• Large anterior mediastinal mass +/- SCF LN
  • Non-mediastinal gray zone lymphoma in older patients
    • Worse prognosis

• Male predominance, 20-40 y

• Morphology
  • Pleomorphic cells in dense fibrous stroma
  • Necrosis without neutrophilic infiltrate
Mediastinal Gray Zone Lymphoma

- da-R-EPOCH x 6 cycles
- 5 y EFS 62%
- 5 y OS 74%
- Relapsed patients treated with IFRT → CR
Management of Gray Zone Lymphoma

• Consolidate all early stage patients with ISRT
  • Regardless of chemotherapy (R-da-EPOCH vs. R-CHOP)
  • Regardless of post-treatment PET
• For CR, 30 Gy ISRT
• For PR, 30 Gy ISRT followed by 10-15 Gy boost to post-chemotherapy active disease
NHL
Follicular Lymphoma
Epidemiology

- Most common low grade NHL
- Incidence increases with age, median age – mid 60s
- Chronic, relapsing, indolent tumor
- 70-85% present with locally advanced disease
- Richter’s transformation in 30-65% of patients
- 50% have BM involvement @ diagnosis
Morphology

• B cell neoplasm derived from germinal (follicle) center cells
• Involved LN replaced with neoplastic follicles that are uniform in size
• Germinal centers contain monomorphous population of centrocytes

• Grades
  • 1 (small-cleaved cell)
  • 2 (mixed small and large cell)
  • 3 (large cell)
    • 3a vs. 3b controversial, not shown to be of clinical significance
    • Should be treated as DLBCL

• Any area of DLBCL in FL of any grade should be treated as DLBCL
Genetic profiling of FL

- IHC panel
  - CD20, CD3, CD5, BCL2, BCL6, CD21 or CD23
  - Ki-67 index, IRF4/MUM1, cyclinD1

- Molecular profiling
  - Antigen receptor gene rearrangement
  - BCL2 rearrangement
  - t(14;18)
  - BCL6
  - 1p36
  - IRF4-MUM1

<table>
<thead>
<tr>
<th>Grade</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1–2 (WHO 2008)</td>
<td>0–15 centroblasts per high power field (HPF)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>0–5 centroblasts per HPF</td>
</tr>
<tr>
<td>Grade 2</td>
<td>6–15 centroblasts per HPF</td>
</tr>
<tr>
<td>Grade 3</td>
<td>&gt;15 centroblasts per HPF</td>
</tr>
<tr>
<td>Grade 3A</td>
<td>Centrocytes present</td>
</tr>
<tr>
<td>Grade 3B</td>
<td>Centrocytes absent</td>
</tr>
</tbody>
</table>

HPF, high power field.
4 buckets of patients

- Typical FL
- FL with 1p36 translocation
  - Inguinal LN
  - Can be bulky
  - Low grade
  - Good prognosis
- Large B-cell lymphoma with IRF-4 translocation
  - HN location
  - Locally aggressive
  - Should be treated as high grade with chemotherapy and ISRT
- Pediatric-type FL
Low grade FL – Early Stage
FLIPI and GELF criteria

NCCN Guidelines Version 1.2017
Follicular Lymphoma (grade 1-2)

GELF CRITERIA\textsuperscript{a,b}
- Involvement of $\geq 23$ nodal sites, each with a diameter of $\geq 23$ cm
- Any nodal or extranodal tumor mass with a diameter of $\geq 27$ cm
- B symptoms
- Splenomegaly
- Pleural effusions or peritoneal ascites
- Cytopenia (leukocytes $<1.0 \times 10^9$/L and/or platelets $<100 \times 10^9$/L)
- Leukemia ($>5.0 \times 10^9$/L malignant cells)

FLIPI - 1 CRITERIA\textsuperscript{a,c,d}

<table>
<thead>
<tr>
<th>Age</th>
<th>$\geq 60$ y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ann Arbor stage</td>
<td>III–IV</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>$&lt;12$ g/dL</td>
</tr>
<tr>
<td>Serum LDH level</td>
<td>$&gt;$ ULN (upper limit of normal)</td>
</tr>
<tr>
<td>Number of nodal sites$^d$</td>
<td>$\geq 5$</td>
</tr>
</tbody>
</table>

Risk group according to FLIPI chart

- Low: 0–1
- Intermediate: 2
- High: $\geq 3$

Mannequin used for counting the number of involved areas.$^e$
### FLIPI and prognosis

**Table III. Prognostic scoring systems in FL- FLIPI and FLIPI2.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>FLIPI</th>
<th>FLIPI2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, stage, Hb, LDH, nodal areas</td>
<td>Low (0–1)</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Intermediate (2)</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>High (≥3)</td>
<td>27</td>
</tr>
<tr>
<td>Age, Hb, BM, β2M, nodal size</td>
<td>Low (0–1)</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Intermediate (2)</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>High (≥3)</td>
<td>27</td>
</tr>
</tbody>
</table>

Risk groups

<table>
<thead>
<tr>
<th>%</th>
<th>Low (0–1)</th>
<th>Intermediate (2)</th>
<th>High (≥3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year OS</td>
<td>91</td>
<td>78</td>
<td>52</td>
</tr>
</tbody>
</table>

| 5-year OS | 98 | 88 | 77 |

OS, overall survival.

Adverse factors: age >60 years; stage III-IV; Hb: haemoglobin concentration <120 g/L; lactate dehydrogenase (LDH) elevated above the upper limit of normal; nodal areas ≥5; β2-microglobulin (β2M) elevated above the upper limit of normal; bone marrow (BM) involvement; longest diameter of largest node > 6 cm (see Appendix 2).
Follicular Lymphoma

After Staging Evaluation

- Localized
  - Involved field radiation
- Advanced stage; low tumor burden
  - Observation or Therapy
- Advanced stage; high tumor burden
  - Therapy
• ISRT alone
• Immunotherapy alone: Rituximab
• Immunotherapy + Chemotherapy: R-Bendamustine, R-CHOP, R-CVP
• Combined modality therapy
• ISRT followed by consolidation immunotherapy
• Observation
Low Grade FL–Advanced Stage

Boom-Boom regimen of 2 Gy x 2-4 fractions offers excellent palliation
# Early Stage Follicular Lymphoma: Outcome with RT alone

<table>
<thead>
<tr>
<th>Institution</th>
<th>Author (year)</th>
<th># of pts.</th>
<th>10 yr FFR</th>
<th>10 yr OS</th>
<th>10 yr DSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNLI</td>
<td>Vaughn Hudson (1994)</td>
<td>208</td>
<td>47%</td>
<td>64%</td>
<td>70%</td>
</tr>
<tr>
<td>Royal Marsden</td>
<td>Pedlebury (1995)</td>
<td>58</td>
<td>43%</td>
<td>79%</td>
<td>NA</td>
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<tr>
<td>Stanford</td>
<td>MacManus (1996)</td>
<td>177</td>
<td>44%</td>
<td>64%</td>
<td>NA</td>
</tr>
<tr>
<td>PMH</td>
<td>Petersen (2004)</td>
<td>460</td>
<td>51%</td>
<td>62%</td>
<td>79%</td>
</tr>
<tr>
<td>SEER</td>
<td>Pugh (2009)</td>
<td>2222</td>
<td>NA</td>
<td>62%</td>
<td>79%</td>
</tr>
</tbody>
</table>
SEER - RT improved DSS and OS
Pugh et al. Cancer 2010; 116:3843-51
National Cancer Data Base- Early Stage FL
Vargo et al. Cancer 2015; 121:3325-3334
National Cancer Data Base- Early Stage FL
Vargo et al. Cancer 2015; 121:3325-3334

The text is about a study related to cancer data and early stage FL (Follicular Lymphoma). It includes survival curves with the following statistics:

- Curve C: Overall Survival
  - 12,013 patients
  - No Events: 20, 102
  - Event Times: 5,071, 18, 784
  - p-value: <0.0001

- Curve D: Overall Survival
  - 5,071 patients
  - Event Times: 5,981, 1,500
  - p-value: <0.0001
361 sites of low grade NHL

- 59% FL 1-2
- 68% Stage I-II

- 24 Gy in 12 fractions
- 40-45 Gy in 20-30 fractions
No difference in PFS or OS
FORT Trial for low grade lymphoma
4 Gy vs. 24 Gy

Hoskin et al. 4 Gy vs. 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomized phase 3 non-inferiority trial. Lancet Oncology 2014
Radiotherapy Fields
Campbell et al. Cancer 2010; 116:3797-3806

• BCCA series

• 1986-1998: Involved Regional Radiotherapy (IRRT) aka EFRT

• 1998 onwards: INRT = involved LN + upto 5 cm cranio-caudal margin aka ISRT
## Patterns of failure

<table>
<thead>
<tr>
<th>Pattern Description</th>
<th>Total $n = 237$</th>
<th>IRRT $n = 142$</th>
<th>INRT ≤ 5cm $n = 95$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS at 10 y</td>
<td>49%</td>
<td>48%</td>
<td>50%</td>
</tr>
<tr>
<td>Infield relapse only</td>
<td>3 (1%)</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Distant relapse without infield relapse</td>
<td>84 (35%)</td>
<td>54 (38%)</td>
<td>30 (32%)</td>
</tr>
<tr>
<td>Distant only</td>
<td>82</td>
<td>54</td>
<td>26</td>
</tr>
<tr>
<td>Regional only</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Regional + distant</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Distant &amp; infield relapse</td>
<td>11 (5%)</td>
<td>9 (6%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>
2017 Follicular Lymphoma Treatment Paradigm

• Stage I-II low grade (non-bulky)
  • ISRT alone
    • 24 Gy to initial volume with CC margin of 3-5 cm
      • If feasible, cone down to boost gross disease + 1.5-2 cm margin to 30 Gy

• Stage I-II low grade (bulky or any unfavorable molecular profile)
  • Chemotherapy (most common R-Bendamustine)
  • Consolidation RT to sites of bulky disease 24 Gy

• Stage I-II low grade (non-contiguous, non-bulky)
  • Chemotherapy alone

• Stage III-IV low grade
  • RT for palliation most commonly 2-4 Gy x 2-4 fractions

• Any high grade transformation
  • Follow DLBCL pathway
MALT

• MALT – extranodal Marginal Zone Lymphoma of Mucosa Associated Lymphoid Tissue

• 8% of NHL

• Infectious agents implicated in pathogenesis
  • Stomach: H. pylori
  • Ocular adnexa: Chlamydophila psittaci
  • Small intestine: Campylobacter jejuni
  • Spleen: HCV
  • Skin: Borrelia burgdorferi
MALT – The common sites

- STOMACH (H. pylori associated or independent)
- Orbital adnexa
- Salivary glands
- Skin
- Lung
- Thyroid
- Breast
- Bladder
- Dura
- Other organs
Gastric MALT

• Limited to stomach, can involve duodenum and peri-gastric LN
• Often multi-centric in stomach
• H. pylori dependent vs. independent
• H. pylori dependent
  • Treat with antibiotics as 1st line therapy
  • Lymphoma can regress, persist or progress
  • H. pylori eradicated in 97% with antibiotics
  • MALT eradicated in 80% of those patients with H. pylori eradication, 5 y EFS is 68%
• H. pylori independent
Workup

• Endoscopic Biopsy
  • H. pylori stain, if + then check for t(11;18)
  • If H. pylori negative by histopathology, check other non-invasive tests (stool antigen test, urea breath test, blood antibody test)
  • 70-90% are H. pylori +
Gastric MALT

Predictors of Antibiotic Failure

• 20% require a 2\textsuperscript{nd} course
• Median time from H. pylori eradication to CR of lymphoma on biopsy is 15 months
• Infiltration below the mucosa
  • 78% \rightarrow 43\% \rightarrow 20\%
• Nodal or adjacent organ involvement
• Chromosomal aberration t(11;18) (q21;q21)
  • Nuclear localization of BCL10 protein
  • Occurs in 30-40\% of MALT
  • 30\% response rate to abx
  • Rarely transform to DLBCL
• Relapse rates are 20-30\%
Who needs primary RT?

• H. pylori absent
• If H. pylori eradicated but lymphoma remains
  • After reasonable observation
  • Progression by EGD
  • Symptomatic
• Relapse after CR to Abx (H. pylori negative)
Gastric MALT
Simulation & Treatment Planning

• Simulate and treat on an empty stomach
• Oral Contrast if needed
• IV Contrast if LN are involved
• Vac-lock immobilization
• Arms up
• AP/PA vs. 3D-CRT vs. IMRT/VMAT
• Improvement in kidney, liver and bowel sparing
• GTV if possible: Visible Tumor or based on description in EGD procedure note
• CTV: Entire stomach including gastroduodenal junction

• PTV: Account for respiratory motion
  • Can use 4D-CT
  • Without 4D-CT at least a 2 cm margin for motion
• Dose: 30-30.6 Gy
  • 1.5 – 2 Gy per fraction
• Patient should be on a PPI during RT
• Consider an anti-emetic
• Daily CBCT
• Loco-regional control rate (MSKCC, MGH, MDACC, France, Japan) – 95-100% at 5 years
• Local recurrence is rare!
### Selected RT series for Gastric MALT

<table>
<thead>
<tr>
<th>Author et al.</th>
<th>No. of cases</th>
<th>Prospective study</th>
<th>After failure eradication Hp</th>
<th>Interval between Hp eradication and RT (median)</th>
<th>Radiotherapy doses</th>
<th>FU after RT years (range)</th>
<th>Response rate</th>
<th>DFS/ EFS</th>
<th>5 yr OS</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schechter [13]</td>
<td>17</td>
<td>Yes</td>
<td>5/17</td>
<td>?</td>
<td>30 Gy (28.5–43.5)</td>
<td>1.3 (0.9–8.6)</td>
<td>100%</td>
<td>100%</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Park [14]</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30 Gy (30–39)</td>
<td>-</td>
<td>100%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Yamashita [16]</td>
<td>11</td>
<td>No</td>
<td>6/11</td>
<td>12 mo</td>
<td>30 Gy</td>
<td>3.3 (0.2–12.2)</td>
<td>98%</td>
<td>100%</td>
<td>96.7%</td>
<td>0</td>
</tr>
<tr>
<td>Vrieling [17]</td>
<td></td>
<td></td>
<td>20 mo (6–44)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 1990</td>
<td>16</td>
<td>No</td>
<td>16/16</td>
<td></td>
<td>38 Gy (20–42)</td>
<td>?</td>
<td>100%</td>
<td>100%</td>
<td>89%</td>
<td>0</td>
</tr>
<tr>
<td>Tomita 2009</td>
<td>20</td>
<td>Yes</td>
<td>13/20</td>
<td>8 mo (4–14)</td>
<td>32 Gy (25.6–50)</td>
<td>4.1</td>
<td>100%</td>
<td>82.2%</td>
<td>96%</td>
<td>0</td>
</tr>
<tr>
<td>Goda [18]</td>
<td>25</td>
<td>No</td>
<td>14/25</td>
<td>10 mo (2–17)</td>
<td>30 Gy (20–35)</td>
<td>7.4 (0.6–16.2)</td>
<td>100%</td>
<td>-</td>
<td>93%</td>
<td>0</td>
</tr>
<tr>
<td>Present series 2015</td>
<td>53</td>
<td>Yes</td>
<td>53/53</td>
<td>22 mo (0–144)</td>
<td>30 Gy (1.3–16)</td>
<td>4.9</td>
<td>98%</td>
<td>98%</td>
<td>94%</td>
<td>0</td>
</tr>
</tbody>
</table>

RT = radiotherapy, FU = follow-up; DFS = disease free survival, OS = overall survival; CSS = cancer specific survival; Hp = *H. pylori.*

*FU = comprising various site extranodal MALT lymphomas with clinical not endoscopic FU.*

*Considering patients with MALT involvement of stomach only (other sites studied with) and studied for some after *H. pylori* eradication or *H. pylori* negative status.*

*Considering patients of the series treated after 1990 with low-dose RT.*

Please cite this article in press as: Ruskoné-Fourmestraux A et al. Exclusive moderate-dose radiotherapy in gastric marginal zone B-cell MALT lymphoma: Results of a prospective study with a long term follow-up. Radiother Oncol (2015), [httpdx.doi.org/10.1016/j.radonc.2015.08.029](httpdx.doi.org/10.1016/j.radonc.2015.08.029)
Non-gastric MALT

• Ocular Adnexa, Salivary glands, Skin
  • RT is primary therapy for early stage disease
  • Lower doses than gastric MALT
    • Primarily to avoid toxicity
    • 24 Gy in 12 fractions
    • In Stage III/IV patients, can consider 2 Gy x 2 fractions or 2 Gy x 4 fractions for local control
  • Less common to stain for C. psitacci in US
  • Antibiotic response rates of 35-50% documented in other countries
    • But takes 6-24 months to see response
Contouring for Extra-Nodal Lymphoma

- Stomach: see previously
- Orbit
  - Conjunctiva – treat all of conjunctiva with electrons or superficial X-rays
  - Lacrimal gland – treat the entire gland
  - Orbit: Treat the whole orbit to the apex
- Testis
  - Treat the contralateral testis
- Breast
  - Treat the whole breast, no elective LN
- Skin
  - Add at least a 10 mm CTV margin on visible lesion
  - If resected, treat the entire length of the scar

Hoskin et al. Recommendations for Radiotherapy Technique & Dose in Extra-nodal lymphoma JCO 2016
Primary Cutaneous Lymphoma

<table>
<thead>
<tr>
<th>T cell lymphoma</th>
<th>~70%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indolent Clinical Behavior</strong></td>
<td></td>
</tr>
<tr>
<td>• Mycosis Fungoides and variants</td>
<td>50%</td>
</tr>
<tr>
<td>• Anaplastic Large Cell Lymphoma</td>
<td>8%</td>
</tr>
<tr>
<td>• Lymphomatoid papulosis</td>
<td>12%</td>
</tr>
<tr>
<td>• CD4+ small/medium pleomorphic</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Aggressive Clinical Behavior</strong></td>
<td></td>
</tr>
<tr>
<td>• Sezary syndrome</td>
<td>3%</td>
</tr>
<tr>
<td>• NK/T cell,</td>
<td>&lt;3%</td>
</tr>
</tbody>
</table>

## Primary Cutaneous Lymphoma

<table>
<thead>
<tr>
<th>B cell Lymphoma</th>
<th>~ 30%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indolent Clinical Behavior</strong></td>
<td></td>
</tr>
<tr>
<td>• Primary cutaneous MZL</td>
<td>7%</td>
</tr>
<tr>
<td>• Primary cutaneous Follicle Center Lymphoma</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Intermediate Clinical Behavior</strong></td>
<td></td>
</tr>
<tr>
<td>• Primary cutaneous DLBCL, leg type</td>
<td>4%</td>
</tr>
</tbody>
</table>
Mycosis Fungoides

• Median duration from lesion onset to diagnosis ~ 8-10 years

• Survival
  • Skin only >10 years
  • LN < 2 years
  • Visceral disease < 1 year

• Radiation is an excellent modality for palliation

• Dose/Fractionation
  • Fractionated 12-30 Gy in 4-15 fractions
  • Low dose radiation being used effectively
  • TSEBT doses have gone down to 12-24 Gy from 36 Gy
Low dose Radiation

Thomas et al. IJROBP 2013; 85:747-753

• 58 patients; 270 lesions
• Single fraction RT 7-8 Gy
• CR 94%
• Relapse rate 4%
Anaplastic Large Cell Lymphoma

- CD30 expressing subtype of PTCL
- Systemic ALK+ ALCL (younger patients, better prognosis)
- Systemic ALK- ALCL (older patients, worse prognosis)
- Cutaneous ALCL (ALK negative, propensity for local relapses, long term survival)
- Breast implant- related ALCL (ALK-, treat with removal of the implant)
- Systemic ALCL
  - Tends to advanced stage
  - Chemotherapy + ISRT for local disease (30-40 Gy)
Primary cutaneous Anaplastic Large Cell Lymphoma

Million et al. IJROBP 2016; 95:1454-1459

- Rapidly growing solitary or cluster of nodules, usually < 5 cm
- Can occur anywhere on the skin
- ALK negative
- 5 y OS ~ 85-100% but frequent cutaneous relapses
- ~ 30 Gy (30-45) is adequate for LC
- Risk of nodal involvement is ~ 10%
  - Nodal involvement – Chemotherapy + RT
- Multifocal lesions – systemic therapy
- Nodal involvement – Chemotherapy + RT
Extranodal NK/T cell lymphoma

- Prognostic Factors
  - EBV levels
  - Tumor invasiveness
  - NKPI
  - Antigen expression
    - Cutaneous lymphocyte antigen
    - COX-2
    - Loss of granzyme B protease inhibitor 9 (PI9)
  - Absolute lymphocyte count
    - <1x10^9/L

The overall survival from a study of 92 patients with nasal NK/T-cell lymphoma collected from multiple institutions as part of an international retrospective analysis.

NK/T cell lymphoma

- JCOG0211
- Concurrent chemoRT
  - 50 Gy + either 2/3rd or full dose DeVIC
- OS: 70 % @ 5 years (superior to 40% for RT alone)
- Only 2 “in-field” failures

Yamaguchi et al. Concurrent ChemoRT for Localized Nasal NK/T cell Lymphoma: JCOG 0211 update JCO 2012
Primary Cutaneous Follicle Cell Lymphoma

- Commonly solitary plaques
- Involve head, scalp, trunk
- Do not harbor t(14;18) translocation
- Germinal-center B cell origin
- Indolent clinical behavior
- RT alone is very effective with local control rates of 100%
  - 24-36 Gy, electrons
- Surgical excision alone has 25 % LRR
- Advanced disease can be treated with Rituximab
- Palliative RT is very effective with doses as low as 4 Gy in 2 fractions
Primary Cutaneous Marginal Zone Lymphoma

• Multifocal disease with patches, plaques or nodules
• Trunks or extremities
• In Europe associated with Borrelia burgdorferi
• RT is effective for localized disease
• 24-36 Gy, electrons
• Rituximab for advanced stages
• Palliative RT is very effective with doses as low as 4 Gy in 2 fractions
Primary DLBCL Leg Type

• Typically elderly women
• Rapidly progressive
• Genetic landscape similar to ABC-DLBCL
• Upfront systemic therapy with R-CHOP
• Consolidation RT for localized disease patients
  • 36-40 Gy
• If no chemotherapy, 40 Gy or higher
Primary RT for cutaneous B Cell lymphoma
Senff et al. (Dutch CLG) JAMA Dermatology 2007; 143: 1520-1526

- 153 patients
- 40 Gy; electrons
- Infield Relapse
  - PC MZL 0/25 pts
  - PC FCL 0/101 pts
  - PCDLBCL 2/27 pts
B cell cutaneous lymphomas
# Early Stage Hodgkin Lymphoma: Goals of Therapy in 2017

<table>
<thead>
<tr>
<th>Type</th>
<th>% Cure Rate</th>
<th>Therapeutic Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Favorable (Stage I-II)</td>
<td>90</td>
<td>Reduce Toxicity</td>
</tr>
<tr>
<td>Early Unfavorable (Stage I, II w/ risk factors)</td>
<td>80-85</td>
<td>Increase Efficacy <em>without</em> any increase in toxicity</td>
</tr>
</tbody>
</table>

*Courtesy: Ranjana Advani*
Trends in Radiation Therapy in Stage I-IV HL

Goyal et al. Clinical Lymphoma, Myeloma and Leukemia 2016
Early Stage Hodgkin Lymphoma

Risk Factors
• Large mediastinal mass
• Extra-nodal lesions
• ≥ 3 nodal sites
• Elevated ESR
• Age > 40
• MC/LD histology

Nodal grouping

<table>
<thead>
<tr>
<th>Definitions of Lymph Node Regions*</th>
<th>Ann Arbor</th>
<th>EORTC</th>
<th>GHSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Cervical/SCL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R ICL/Subpec</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Axilla</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Cervical/SCL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L ICL/Subpec</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Axilla</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediastinum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Hilum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Hilum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

*Note that the EORTC includes the infraduvalicular/subpectoral area with the axilla while the GHSG includes it with the cervical. Both EORTC and GHSG combine the mediastinum and both hila as a single region.
# Hodgkin Lymphoma Unfavorable Disease

<table>
<thead>
<tr>
<th>GHSG</th>
<th>EORTC</th>
<th>NCCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large mediastinal mass (ratio ≥ 1/3)*</td>
<td>Large mediastinal mass (ratio ≥ 0.35)</td>
<td>Large mediastinal mass (ratio &gt; 1/3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bulk &gt; 10 cm</td>
</tr>
<tr>
<td>≥ 1 extranodal lesion*</td>
<td>Age ≥ 50 yr</td>
<td></td>
</tr>
<tr>
<td>ESR ≥ 50 (A) or ≥ 30 (B)</td>
<td>ESR ≥ 50 (A) or ≥ 30 (B)</td>
<td>ESR ≥ 50 (A)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B-symptoms</td>
</tr>
<tr>
<td>≥ 3 nodal areas (out of 11 GHSG areas)</td>
<td>≥ 4 nodal areas (out of 5 supra-diaphragmatic EORTC areas)</td>
<td>≥ 4 nodal regions (out of 17 Ann Arbor regions)</td>
</tr>
</tbody>
</table>

Patients with CS I-II are staged unfavorable, if at least one of the listed risk factors is present.

*Within the GHSG system, patients with CSIIB and a large mediastinal mass or ≥ 1 extranodal lesion are considered as advanced stage.

HL, Hodgkin’s Lymphoma; ESR, erythrocyte sedimentation rate; A, without B-symptoms; B with B-symptoms; GHSG, German Hodgkin Study Group; EORTC, European Organization for Research and Treatment of Cancer; NCCN, National Comprehensive Cancer Network.
What is Bulky disease?
Kumar et al. Haemtologica 2016;101:1237-1243

• Historical
  • Upright PA CXR
  • MMR >/= 1/3
  • MTR >/= 1/3
  • >10 cm
  • Lugano: single nodal mass >10 cm or MTR > 1/3

• MSKCC study
  • Maximal diameter >7 cm in transverse or coronal planes
What is Bulky disease?
Kumar et al. Haematologica 2016;101:1237-1243
What is Bulky disease?
Kumar et al. Haemtologica 2016;101:1237-1243

Relapse-free survival by presence of bulky disease (transverse or coronal max, diameter > 7cm) and treatment [chemotherapy alone (Chemo) vs. combined modality therapy (CMT)].
PET CT Response Assessment
Deauville criteria

1. No uptake
2. Uptake ≤ mediastinum
3. Uptake > mediastinum but ≤ liver
4. Uptake moderately higher than liver
5. Uptake markedly higher than liver and/or new lesions
X. New areas of uptake unlikely to be related to lymphoma

Score 1-3 = PET negative
Score 4 or 5 = PET positive

Early Stage Hodgkin Lymphoma

• In 2017, early stage patients can be stratified into 4 buckets of patients
  • FAVORABLE DISEASE
    • Stage I/IIA – no bulky disease, < 3 nodal sites, no extra-nodal disease, ESR<50
    • Stage IIA – no bulky disease, <4 nodal sites, ESR<50, +/- EN disease
  • UNFAVORABLE DISEASE
    • Stage I-IIB – non-bulky
    • Stage I-IIB bulky
Pre-PET Era trials
Early Stage Favorable Disease: GHSG HD10

SUPER FAVORABLE
- Stage I/II
- Non-bulky
- 1-2 sites of involvement
- No ENI
- ESR < 50 if no B symptoms
- ESR < 30 if B symptoms

GHSG HD10 trial for Favorable Stage I-II HD

- **CS I/II without risk factors**
- **4 x ABVD**
  - 30 Gy IF
- **4 x ABVD**
  - 20 Gy IF
- **2 x ABVD**
  - 30 Gy IF
- **2 x ABVD**
  - 20 Gy IF

*Large mediastinal mass: extranodal disease; high ERS: 3 or more areas involved*
Pre-PET Era Trials
Early Stage Unfavorable Disease: GHSG HD11

- Unfavorable: Bulky disease, ≥3 sites, EN dz, increased ESR+/- B symptoms (IIB+bulkly or IIB+EN dz excluded)
- BEACOPP + 30 Gy did not improve over ABVD x 4 + 30 Gy
- Concern for inferior PFS/FFTF for ABVD x 4+ 20 Gy arm
- 5 y FFTF 85% & OS 94.5%

Pre-PET Era Trials
Early Stage Unfavorable Disease: GHSG 14

GHSG HD14
JCO 2012;30:907

Stage I-II (unfavorable)
n=1655

ABVD X 4
RT- 30 Gy

eBEACOPP X 2
ABVD X 2
RT- 30 Gy

Increased hematologic toxicity with BEACOPP: 80% vs 24 %

Pre-PET Era Trials
Early Stage Unfavorable Disease: EORTC H9U

EORTC-GELA H9-U trial

treatment failure-free survival

- 6 ABVD-IF RX (276) 91%
- 4 BEACOPP-IF RX (255) 89%
- 4 ABVD-IF RX (277) 85%

Increased SAE with BEACOPP

Proportion Failure-Free

October 2007

P value = 0.27

Time since Randomisation, mo

Courtesy Dr Noordijk.
## Pre-PET Era Trials
### Early Stage Disease: Summary

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemotherapy</th>
<th>RT</th>
<th>PFS/FFT (%</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSHG HD10</td>
<td>ABVD x2 vs. ABVD x 4</td>
<td>IFRT (20-30 Gy)</td>
<td>96</td>
<td>94.5</td>
</tr>
<tr>
<td>GSHG HD11</td>
<td>ABVD x 4 vs. BEACOPP x 4</td>
<td>IFRT 30 Gy</td>
<td>85</td>
<td>94.5</td>
</tr>
<tr>
<td>GSHG HD 14</td>
<td>ABVD x 4 vs. ABVD x 2 + BEACOPP x 2</td>
<td>IFRT 30 Gy</td>
<td>94.8</td>
<td>95</td>
</tr>
<tr>
<td>EORTC H9U</td>
<td>ABVD x 4 vs. ABVD x 6 vs. BEACOPP x 4</td>
<td>IFRT 30-36 Gy</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>STANFORD G4</td>
<td>STANFORD V</td>
<td>IFRT 30 Gy</td>
<td>94</td>
<td>94</td>
</tr>
</tbody>
</table>

**OS ≥ 94% FFTF/PFS ≥ 85%**
Incorporating PET-CT in Hodgkin Lymphoma

• Early stage favorable disease
  • Can we use FDG-PET to de-intensify therapy?
    • Less chemotherapy
    • No XRT
  • UK NCRI RAPID, EORTC H10F, CALGB, GHSG HD 15

• Early stage unfavorable disease
  • Can we use FDG-PET to assess interim response and should we change therapeutic decisions based on early response?
    • Change chemotherapy course
    • RT vs. no RT
  • EORTC H10U, GSHG HD 17
# PET/CT response-adapted trials

## Early Stage Favorable Disease

<table>
<thead>
<tr>
<th>STUDY</th>
<th>TREATMENT</th>
<th>PFS (ITT)</th>
<th>PFS (PP)</th>
<th>OS (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UK RAPID</strong></td>
<td><strong>STANDARD:</strong> 3 x ABVD + 30 Gy IFRT if PET3 neg</td>
<td>94.6% (3y)</td>
<td>97.1%</td>
<td>97.1%</td>
</tr>
<tr>
<td></td>
<td><strong>EXPERIMENTAL:</strong> 3 x ABVD + NFT if PET3 neg 4 x ABVD + 30 Gy IFRT if PET3 pos</td>
<td>90.8% (3y) 87.6% (5y)</td>
<td>90.8% NR</td>
<td>99.0% 94.5%</td>
</tr>
<tr>
<td><strong>EORTC H10F</strong></td>
<td><strong>STANDARD:</strong> 3 x ABVD + 30 Gy INRT</td>
<td>100% (1y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>EXPERIMENTAL:</strong> 2 x ABVD + 2 x EB + 30 Gy INRT if PET2 pos 4 x ABVD + NFT if PET2 neg</td>
<td>NR 94.9% (1y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CALGB 50604</strong></td>
<td><strong>EXPERIMENTAL:</strong> 2 x ABVD + 2 x EB + 30 Gy IFRT if PET2 pos 4 x ABVD + NFT if PET2 neg</td>
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<tr>
<td><strong>GSHG 16</strong></td>
<td><strong>STANDARD:</strong> 2 x ABVD + 20 Gy IFRT</td>
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<tr>
<td></td>
<td><strong>EXPERIMENTAL:</strong> 2 x ABVD + 20 Gy IFRT if PET2 post 2 x ABVD + NFT if PET2 neg</td>
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</tbody>
</table>
### PET/CT response-adapted trials

#### Early Stage Unfavorable Disease

<table>
<thead>
<tr>
<th>STUDY</th>
<th>TREATMENT</th>
<th>PFS (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC H10U</td>
<td><strong>STANDARD:</strong> 4 x ABVD + 30 Gy INRT&lt;br&gt;2 x ABVD + 2 x EB + 30 Gy INRT if PET2 pos&lt;br&gt;4 x ABVD + NFT if PET2 neg</td>
<td><strong>97.3 (1y)</strong>&lt;br&gt;<strong>NR</strong>&lt;br&gt;<strong>94.7% (1y)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>EXPERIMENTAL:</strong> 2 x ABVD + 2 x EB + 30 Gy INRT if PET2 pos&lt;br&gt;4 x ABVD + NFT if PET2 neg</td>
<td></td>
</tr>
<tr>
<td>GSHG HD17</td>
<td><strong>STANDARD:</strong> 2 x EB + 2 x ABVD + 30 Gy IFRT&lt;br&gt;2 x EB + 2 x ABVD + 30 Gy INRT if PET4 pos&lt;br&gt;2 x EB + 2 x ABVD + NFT if PET4 neg</td>
<td></td>
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<tr>
<td></td>
<td><strong>EXPERIMENTAL:</strong> 2 x EB + 2 x ABVD + 30 Gy IFRT&lt;br&gt;2 x EB + 2 x ABVD + 30 Gy INRT if PET4 pos&lt;br&gt;2 x EB + 2 x ABVD + NFT if PET4 neg</td>
<td></td>
</tr>
<tr>
<td>CALGB 50801</td>
<td><strong>EXPERIMENTAL:</strong> 2 x ABVD + 4 x EB + 30 Gy IFRT if PET2 post&lt;br&gt;6 x ABVD + NFT if PET2 neg</td>
<td></td>
</tr>
</tbody>
</table>
UK NCRI RAPID trial: Stage I-IIA favorable HL

Initial treatment: ABVD x 3
Re-assessment: if NR/PD, patient goes off study FDG-PET scan performed

PET +ve
- 4th cycle ABVD then IFRT

PET -ve
- Randomisation
  - IFRT
  - No further treatment

≤ 7% difference in PFS, 3 y PFS no less than 88% in NFT arm acceptable

UK NCRI RAPID Trial

PFS

A Intention-to-Treat Analysis

B Per-Protocol Analysis

<table>
<thead>
<tr>
<th>Intent-to-treat analysis</th>
<th>Per protocol analysis</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>PET neg, RT</td>
</tr>
<tr>
<td>3 y PFS</td>
<td>93.8%</td>
</tr>
<tr>
<td>3 y OS</td>
<td>97%</td>
</tr>
</tbody>
</table>
UK NCRI RAPID Trial
Conclusions

• Results... “did NOT show the non-inferiority of the strategy of NFT after chemotherapy in regard to PFS”

• “Nevertheless patients with early stage Hodgkin’s and negative PET findings after 3 cycles have very good prognosis either with or without consolidation radiotherapy”

• Either consolidation ISRT or NFT are reasonable options and the decision should be tailored to the patient

• + PET/CT after 3 cycles ABVD had prognostic value but GSHG/EORTC criteria did not

• 5 episodes of progression and 3 HL deaths in 23 patients in Deauville 5 patients
EORTC H10 Trial

Unfavorable: > 3 nodal areas, age ≥ 50, ESR ≥ 50 if no B, ESR ≥ 30 if B, MM > 0.33

PET - = Deauville 1 or 2

EORTC H10 Early Results

Progression-free survival
Favorable - PET2 negative

1-yr PFS: 94.9% vs. 100.0%
HR = 9.36 (79.6% CI: 2.45-35.73)
P-value = 0.017 < 0.102*

Progression-free survival
Unfavorable - PET2 negative

1-yr PFS: 94.7% vs. 97.3%
HR = 2.42 (80.4% CI: 1.35-4.36)
P-value = 0.026 < 0.098*

Table 2. Results of Interim Analysis in Patients With Early PET-Negative Disease

<table>
<thead>
<tr>
<th>Subset</th>
<th>No. of Patients</th>
<th>No. of Observed Events</th>
<th>HR</th>
<th>Adjusted CI*</th>
<th>Pt</th>
<th>1-Year PFS</th>
<th>%</th>
<th>Adjusted CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>168</td>
<td>1</td>
<td>1.00</td>
<td></td>
<td>.017</td>
<td>100.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Experimental</td>
<td>193</td>
<td>9</td>
<td>9.36</td>
<td>2.45 to 35.73</td>
<td>94.93</td>
<td>91.89 to 96.85</td>
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<td></td>
</tr>
<tr>
<td>Unfavorable</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>251</td>
<td>7</td>
<td>1.00</td>
<td></td>
<td>.026</td>
<td>97.23</td>
<td>97.17 to 98.48</td>
<td></td>
</tr>
<tr>
<td>Experimental</td>
<td>268</td>
<td>16</td>
<td>2.42</td>
<td>1.36 to 4.36</td>
<td>94.70</td>
<td>92.11 to 96.45</td>
<td></td>
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</tbody>
</table>
EORTC H10 Trial Modification

INRT after ABVD reduces treatment failure in both favorable and unfavorable patients – both no RT arms were closed

* PET2/-+ according to protocol criteria

Hodgkin - CS I/II – untreated - 15-70 yrs - supradiaphragmatic - no NLPHL
EORTC H10 Trial: What about the PET2+ patients?

5 y PFS 77% vs. 91% (p=0.002)
5 y OS 89% vs. 96% (p=0.062)
Increased toxicity in the escBEACOPP arm

13th ICML Presentation 2015
Clinical Advances in Hematology & Oncology August 2015
EORTC H10 conclusions

• There is still an important role for RT in early stage patients favorable and unfavorable patients regardless of interim PET response

• For favorable HL, if PET2- then 3 cycles ABVD + 30 Gy ISRT For unfavorable HL, if PET2- then 4 cycles of ABVD + 30 Gy ISRT

• PET2+ patients benefit from intensification of chemotherapy

• Field reduction from IFRT to INRT/ISRT is validated
Role of Radiotherapy in Advanced HL

• Majority of patients will have residual CT mass after chemotherapy
• Modern trials incorporate response-adapted therapy with Interim PET/CT
  • **RATHL**
    • Intensification of chemotherapy based on interim PET response
    • Escalation to BEACOPP may overcome negative prognostic impact of a + interim PET
    • Bleomycin toxicity is cumulative, so may consider ABVD → AVD if the interim PET is negative
  • **GHSG HD 15**
    • PET guided RT post-BEACOPP
    • End PET negative post-BEACOPP residual mass do not require RT
    • In PET+, RT converts a PR → CR
  • **CALGB 50801**
    • Start with ABVD x 2 followed by PET guided therapy
    • PET2 – negative patients got additional 4 cycles of ABVD with no RT
    • Early results show favorable outcomes omitting RT in early responders

Savage, et al. (BCCA) Abstract 579.
RATHL

- **Enrollment criteria**
  - IIB-IV, IIA with bulky thoracic disease or >3 LN sites
  - Pre-treatment PET

- **Treatment Paradigm**
  - 2 cycles of ABVD
  - PET-CT after 2\textsuperscript{nd} cycle; PET- was Deauville 1-3
  - If PET-, then ABVD x 4 vs. AVD x 4
  - If PET+, BEACOPP-14 x 4 cycles vs. BEACOPP-e x 3 cycles (not randomized)
    - PET after
    - If PET-, BEACOPP-14 x 2 cycles or BEACOPP-e x 1
    - If PET+, RT or salvage therapy
RATHL results

A. Progression-free Survival among Patients with Negative PET Findings

B. Overall Survival among Patients with Negative PET Findings

C. Progression-free Survival among Patients with Positive PET Findings

D. Overall Survival among Patients with Positive PET Findings
HL: GSHG HD15

Advanced-Stage HL: GHSG HD15

Stage IIbE, IIbX, III-IV HL

- escB x 8
- escB x 6
- baseline B14 x 8

No further treatment if CR or < 2.5 cm residual mass
If PR with persistent ≥ 2.5 cm mass → PET

RT to 30 Gy to only PET+ pts

4-year PFS rates of 92.6% (PET-) and 92.1% (PET+)

**Interpretation**
Treatment with six cycles of BEACOPP escalation followed by PET-guided radiotherapy was more effective in terms of freedom from treatment failure and less toxic than eight cycles of the same chemotherapy regimen. Thus, six cycles of BEACOPP escalation should be the treatment of choice for advanced stage Hodgkin's lymphoma. PET done after chemotherapy can guide the need for additional radiotherapy in this setting.
Classic Hodgkin Lymphoma Conclusions
Favorable Disease

Stage I/IIA – non-bulky, 1-2 nodal sites, no END, ESR<50

• CMT – ABVD x 2 cycles
  • Deauville 1-4
    • 20 Gy ISRT (GSHG HD10)
  • Deauville 5
  • Biopsy
    • Negative – 20 Gy ISRT
    • + Refractory disease pathway
Classic Hodgkin Lymphoma Conclusions
Favorable Disease

Stage I/IIA – non-bulky, <4 nodal sites, +/- END, ESR<50

• CMT - ABVD x 2 cycles
  • Deauville 1-2
    • ABVD x 2 cycles (total 4) + ISRT 30 Gy
  • Deauville 3-4
    • ABVD x 2 cycles (total 4) + ISRT 30 Gy
    • Can consider escalation to BEACOPP + ISRT 30 Gy
  • Deauville 5
    • Biopsy
• CMT – Stanford V x 8 weeks + ISRT 30 Gy
Classic Hodgkin Lymphoma Conclusions
Favorable Disease

Stage I/IIA – non-bulky, <4 nodal sites, +/- END, ESR<50

• Chemotherapy alone – ABVD x 3 cycles
  • Deauville 1-2
    • Observe (RAPID trial)
    • ABVD x 1 cycle (total 4)
  • Deauville 3-4
    • ABVD x 1 cycle (total 4) + ISRT 30 Gy
  • Deauville 5
    • Biopsy
Classic Hodgkin Lymphoma Conclusions
Unfavorable Disease

Stage I-II Unfavorable Non-Bulky

• ABVD x 4 cycles
  • Deauville 1-3
    • ISRT 30 Gy (total 4 cycles)
    • ABVD x 2 cycles (total 6 cycles) and no RT
  • Deauville 4
    • ABVD x 2 cycles (total 6 cycles)
      • Deauville 1-3 – ISRT 30 Gy
      • Deauville 4-5 – Re-biopsy
  • Deauville 5
    • Rebiopsy
• eBEACOPP X 2 + ABVD x2 + ISRT 30 Gy
• Stanford V x 12 weeks + ISRT 30-36 Gy
Classic Hodgkin Lymphoma Conclusions
Unfavorable Disease

Stage I-II Unfavorable Bulky

• ALL patients need RT!!!
• ABVD x 4 cycles
  • Deauville 1-3
    • ABVD x 2 cycles (total 6 cycles) + ISRT 30 Gy
    • ISRT 30 Gy (total 4 cycles)
  • Deauville 4
    • ABVD x 2 cycles (total 6 cycles) + ISRT 30 Gy
  • Deauville 5
    • Biopsy
• eBEACOPP X 2 + ABVD x2 + ISRT 30 Gy
• Stanford V x 12 weeks + ISRT 30-36 Gy
Radiotherapy Treatment Planning for Lymphoma
Transformation of RT Volumes / Doses in HL ISRT – Specht L et al IJROBP 2014

1978 → 80% reduction → 2013

<table>
<thead>
<tr>
<th>Total nodal</th>
<th>Regional nodal</th>
<th>Involved field</th>
<th>Involved site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose: 30-44 Gy → 20-30 Gy</td>
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</table>

Two thirds of women with early-stage HD do not require radiation of the axillae. Substantial reduction in breast, lung cancer risk, cardiac morbidity.
Historical RT Fields

Cutter et al. JNCI 2015; 107:1-9
IFRT is DEAD!!!!
Evolution of RT fields
IFRT to INRT/ISRT

Risk of Breast Cancer

Moskowitz, CS et al. *J Clin Onc*; 2014
Risk of Breast Cancer


*FIGURE 3.* Estimated cumulative incidence of breast cancer treated at (A) age 20 years or (B) age 30 years. Shaded areas illustrate the range of estimated cumulative incidence calculated with individual patient’s median ERR estimates.
Risk of Breast Cancer

Cardiac Toxicity

Fig 3 | Cumulative incidence of cardiac disorders among childhood cancer survivors by anthracycline dose

Fig 4 | Cumulative incidence of cardiac disorders among childhood cancer survivors by average cardiac radiation dose

Mulrooney et al. BMJ 2009
Cardiac Toxicity

Nimwegen et al. JCO 2016: 7.5% ERR per Gy
Involved Site RT (ISRT)

- **IRRT or EFRT**
  - Regional Field
  - Involved field + at least one adjacent clinically uninvolved region

- **IFRT**
  - Prior to routine use of CT-SIM
  - Based on fluoroscopy and bony landmarks
  - 2000 paper by Yahalom
  - Site of the clinically involved nodal group

- **INRT**
  - Origins in Europe for HD
  - Requires accurate pre-chemo or pre-biopsy information in treatment position

- **ISRT**
  - Compensates for sub-optimal pre-chemo/pre-biopsy information in terms of imaging
  - Slightly larger volumes that INRT (esp. cranio-caudally) but same principles as INRT
  - In most situations, ISRT will result in significantly smaller volumes than IFRT
Contouring

• GTV
  • Pre-chemotherapy GTV PET
    • FDG threshold? 40% of SUVmax
  • Pre-chemotherapy GTV CT
    • GTV edge better defined by CT
    • Other areas visible on CT but < 40% of SUVmax
    • Questionable LN in proximity to GTV
  • If incomplete response to chemotherapy or post-chemotherapy nodal remnant seen
    • Post-chemotherapy GTV CT
Pre-chemo PET/CT scan

PET+ volume

Gross tumour volume GTV

Courtesy: Lena Specht MD
Contouring

• CTV
  • Encompasses original GTV
  • Excludes normal structures that are clearly uninvolved
    • Muscle, bone, vessel, extra-nodal organs
  • Fuse pre-chemotherapy PET/CT with post-chemotherapy CT
    • Import pre-chemo GTV-CT and GTV-PET
  • Contour post-chemotherapy tissue volume taking into account tumor shrinkage and other anatomic changes = post-chemotherapy CTV
Figure 2(a): transverse, sagittal, and coronal views of a neck lymphoma patient. The pre-Chemotherapy nodal area is shown in yellow. The ISRT CTV is shown in red after SI expansion.
Mediastinum - CTV

Figure 1(a): transverse sagittal and coronal views of a mediastinal lymphoma patient. The pre-Chemotherapy nodal area is shown in yellow. The ISRT CTV is shown in red after SI expansion.

Figure 1(b): transverse view of most superior to most inferior extent of the mediastinum ISRT CTV.
Pulmonary Sparing Radiotherapy - DIBH

Free Breathing

Deep Inspiration Breath Hold (DIBH)
Cardiac Sparing Radiotherapy - DIBH

Free Breathing

Deep Inspiration Breath Hold (DIBH)
Cardiac Sparing Radiotherapy - DIBH

Free Breathing

Deep Inspiration Breath Hold (DIBH)
DIBH
