ASTRO Refresher Course 2018: Lymphoma

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Disclosures

• No conflicts of interest to disclose.
Learning Objectives

• Integrate Lugano Classification / Deauville criteria into staging & workup

• Review role of RT in management of lymphoma:
  • Hodgkin lymphoma
  • Non-Hodgkin lymphoma
    • DLBCL
    • FL
    • MALT

• Implement modern radiotherapy techniques (ISRT)

*remains unchanged in Lugano Classification
### Staging / Summary of Changes

#### AJCC 2018

<table>
<thead>
<tr>
<th>STAGE</th>
<th>FEATURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymphatic site (i.e., Nodal region, Spleen, Waldeyer’s ring) or single extralymphatic site (in absence of nodal involvement – rare in HL)</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of ≥2 LN regions on same side of the diaphragm ± localized contiguous involvement of only one extranodal organ</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of LN regions on both sides of diaphragm</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse or disseminated involvement of ≥1 extranodal organs (i.e. CSF, BM, liver, lungs [<strong>not</strong> direct extension] ± associated LN involvement</td>
</tr>
<tr>
<td>B</td>
<td>Fever (&gt;38°C); drenching night sweats; weight loss &gt;10% (6 mos)</td>
</tr>
<tr>
<td>E</td>
<td>Involvement of extralymphatic tissue (by continuous growth from an involved lymph node or in close anatomic relation) that is <strong>treatable by irradiation</strong> (definition per HD10)</td>
</tr>
</tbody>
</table>

- Ann Arbor staging (Cotswold modification) → updated to the Lugano classification (next slide)
- “B” Symptoms → eliminated for NHL, kept for HL
- “X” subscript → X subscript for bulk eliminated, diameter of largest mass must be recorded
- Stage III → “E” lesion eliminated from Stage III, any E involvement with nodal disease above and below diaphragm is stage IV.
- Stage IIIS → Spleen involvement is no longer part of stage grouping
- Imaging → PA CXR no longer required for determination of bulk in HL or NHL
Work-up & Staging / Lugano Classification

- **H&P**
  - B-symptoms (weight loss, fevers, night sweats)
  - Palpation of all nodal groups and organomegaly
  - Spleen evaluation
    - Quantified: >13 cm is enlarged on CT

- **Labs**
  - CBC w/ differential
  - Metabolic panel / LFTs
  - ESR, LDH, HIV/Hep Panel

- **Imaging**
  - CT [n/c/a/p] w/ IV contrast
  - FDG-PET/CT
    - Standard staging for FDG-avid lymphomas
    - Response assessment using the 5-point scale
    - Scan frequency - Routine surveillance scans are discouraged

- **Tissue/Pathology**
  - Excisional biopsy
  - Bone marrow biopsy → *largely replaced by PET/CT*
    - No longer indicated for the routine staging of HL and most DLBCL

- **Prior to treatment**
  - Baseline MUGA scan (for doxorubicin)
  - Baseline PFTs (for bleomycin)

- **Progressive disease evaluation**
  - PPD progression of single site defines progression.
  - **SPD eliminated for progression**

What is Bulky?
Lugano Classification

➢ Largest tumor diameter (CT) should be recorded at staging when possible (HL/NHL)

➢ Per Lugano classification:
  ➢ ≥ 10 cm for Hodgkin lymphoma (7.0cm in Max transverse diameter (MTD) or Max coronal diameter (MCD), validated in early-stage cHL pts at MSK w/ worse RFS receiving chemo alone – Kumar et al. Haematologica. 2016 Oct)
  ➢ 6 - 10 cm suggested for diffuse large B cell lymphoma (7.5cm in UNFOLDER study)
  ➢ ≥ 6 cm suggested for follicular lymphoma (added to recent FLIPI score)
  ➢ Note: Limited studies on validation of these proposed sizes in current therapeutic era.

➢ Metabolic tumor volume (MTV) should be explored as potential prognosticactor
  ➢ “PET-CT Radiomics predict outcome in med chL” – S. Milgrom et al (MDA) Oral Session ASTRO 2017
    ➢ Using pre-chemo PET-based radiomic features to identify pts at high risk for refractory disease
    ➢ Extracted PET parameters: SUVmax; MTV: disease with SUV ≥ 2.5; TLG: MTV x mean SUV of MTV
PET-CT Response Assessment: What is the Deauville criteria?

Score 1-3 = PET negative
• 1 No uptake
• 2 Uptake ≤ mediastinum
• 3* Uptake > mediastinum but ≤ liver

Score 4-5 = PET positive
• 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

*for de-escalation studies, Deauville 3-5 considered positive

Eur J Nucl Med Mol Imaging 2010
Using PET/CT to Refine the Risk Stratification:

- PET-CT adds to the sensitivity of diagnostic CT → Essential in the era of ISRT
- Validation Study (prognostic value) based on Deauville criteria (stage IIB-IVB HL):
  - PET -ve (Deauville 1-3)=95% PFS at 3 years
  - PET +ve (Deauville 4-5)=28% PFS at 3 years
- Is there a role of interim PET staging to stratify patients to chemotherapy alone vs. chemotherapy + RT?
  - Primary objective of EORTC H10 & UK NCRI RAPID trials

Hodgkin Lymphoma

• Classical HL (CD15+/CD30+/CD20-)
• Early-stage Favorable
  • Stage I-II without risk factors
• Early-stage Unfavorable
  • Stage I-II with risk factors
• Advanced
  • Stage III-IV

<table>
<thead>
<tr>
<th></th>
<th>CD15</th>
<th>CD30</th>
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<th>CD45</th>
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<tr>
<td>Classical HL</td>
<td>+</td>
<td>+</td>
<td>-</td>
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</tr>
<tr>
<td>NLPHL</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
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</table>

• Nodular lymphocyte-predominant HL (CD15-/CD30-/CD20+)
Early-stage cHL: Prognostic Classification

Examples of Unfavorable Risk Factors for Stage I-II Hodgkin Disease

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>GHSG</th>
<th>EORTC</th>
<th>NCIC</th>
<th>NCCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>≥ 50</td>
<td>≥ 40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td>MC or LD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR and B symptoms</td>
<td>&gt; 50 if A; &gt; 30 if B</td>
<td>&gt; 50 if A; &gt; 30 if B</td>
<td>&gt; 50 or any B sx</td>
<td>&gt; 50 or any B sx</td>
</tr>
<tr>
<td>Mediastinal mass</td>
<td>MMR &gt; .33</td>
<td>MTR &gt; .35</td>
<td>MMR &gt; .33 or &gt; 10 cm</td>
<td>MMR &gt; .33</td>
</tr>
<tr>
<td>Nodal sites</td>
<td>&gt; 2*</td>
<td>&gt; 3</td>
<td>&gt; 3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>E lesion</td>
<td>any</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bulky</td>
<td></td>
<td>&gt; 10 cm</td>
<td></td>
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GHSG = German Hodgkin Study Group
EORTC = European Organization for the Research and Treatment of Cancer
NCIC = National Cancer Institute, Canada
NCCN = National Comprehensive Cancer Network

*The GHSG definition of nodal sites differs from the Ann Arbor system in that the infradiaphragmatic region is included with the bilateral cervical/supraclavicular, the bilateral hilar are included with the mediastinum, and the abdomen is divided into 2 regions, upper (spleen hilum, liver hilum, celiac) and lower.

- Objectives in Early-stage cHL:
  - Maximize # of cures and minimize late toxicity
  - Current standard is to follow a clinically risk-adjusted approach

Adapted from NCCN guidelines, 2018
Early-Stage cHL: NCCN guidelines

**Very Favorable**

- Stage IA, IIA<sup>nm</sup> (no bulky disease, <3 sites of disease, ESR <60, and no E-lesions)

  - ABVD x 2 cycles (category 1)<sup>im</sup>
  - or

  - HD10

  - Deauville 1-4°
    - [1°]: Low uptake, 2% or less.
    - [4°]: Moderately increased uptake (new or new site)
  - Involved-site radiation therapy (ISRT; 20 Gy)<sup>p</sup>
  - See Follow-up (HODG-14)<sup>n</sup>

**Favorable**

- Stage IA-IIA (no bulky disease)

  - ABVD x 3 cycles<sup>1i</sup> (Prefer to treat with chemotherapy alone)
  - or

  - EORTC H10

  - ABVD x 2 cycles<sup>1d</sup> (Preference to treat with combined modality therapy)
  - or

  - Stanford V x 8 weeks<sup>1j</sup>

  - Deauville 1-2°
    - [1°]: Low uptake, 2% or less.
    - [2°]: Moderately increased uptake.
  - ABVD x 1 cycle (total 4)<sup>1u</sup> (optional)
  - ABVD x 1 cycle (total 4)<sup>1u</sup> + ISRT (30 Gy)<sup>p</sup>
  - Deauville 3-4°
  - Deauville 5°
    - Biopsy
  - Negative
  - ISRT (20 Gy)<sup>p</sup>
  - See Follow-up (HODG-14)<sup>n</sup>
  - Positive
  - Biopsy
  - See Refractory Disease (HODG-16)

Adapted from NCCN guidelines, 2018
Early-stage cHL: Pre-PET Era Studies
Early Stage Favorable Disease: GHSG HD10

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

No PET Imaging

GHSG HD10 trial for Favorable Stage I-II HD

Early Stage Favorable Disease: GHSG HD10

**HD10 Chemotherapy Comparison**

**HD10 Radiation Therapy Comparison**

FFT 96%; OS 94.5%

**ABVD x 2 + 20 Gy = ABVD x 4 + 30 Gy**

Early Stage Favorable Disease: GHSG HD10

<table>
<thead>
<tr>
<th>Event</th>
<th>Chemotherapy Comparison</th>
<th>Radiation Therapy Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Groups 1 and 2 (N=596)</td>
<td>Groups 3 and 4 (N=594)</td>
</tr>
<tr>
<td></td>
<td>no. of patients/total no. (%)</td>
<td>no. of patients/total no. (%)</td>
</tr>
</tbody>
</table>

Acute toxicity (grade III or IV)†

- At least one event: 304/588 (51.7%) vs 194/585 (33.2%)
- Anemia: 7/588 (1.2%) vs 1/585 (0.2%)
- Thrombopenia: 3/588 (0.5%) vs 0
- Leukopenia: 138/588 (23.5%) vs 87/585 (14.9%)
- Nausea or vomiting: 79/588 (13.4%) vs 51/585 (8.7%)
- Mucositis: 7/588 (1.2%) vs 2/585 (0.3%)
- Gastrointestinal tract disorder or dysphagia: 11/588 (1.9%) vs 6/585 (1.0%)
- Respiratory tract disorder: 12/588 (2.0%) vs 2/585 (0.3%)
- Hair loss: 165/588 (28.1%) vs 89/585 (15.2%)
- Infection: 30/588 (5.1%) vs 10/585 (1.7%)
- Pain: 9/588 (1.5%) vs 14/585 (2.4%)
- Nervous system disorder: 12/588 (2.0%) vs 7/585 (1.2%)

- 46/528 (8.7%) vs 16/553 (2.9%)

Less grade 3/4 toxicity with 2 cycles ABVD or 20 Gy IFRT

Engert et al., NEJM 2010
ABVD x 4 c + IFRT 30 Gy vs. ABVD x 2 c + IFRT 20 Gy

At 10-years:

- PFS $\rightarrow$ 87.4% vs. 87.2% (NS)
- OS $\rightarrow$ 93.6% vs. 94.1% (NS)

*Non-inferiority of 2c+20Gy regimen holds true

Sasse et al., JCO 2017
Remember the GHSG Risk Stratification Factors...

- Any = Unfavorable
- None = Favorable
- BUT their nodal sites differ from Ann Arbor system....

** The GHSG definition of nodal site differs from the Ann Arbor system in that the infraclavicular region is included with the ipsilateral cervical / supraclavicular, the bilateral hila are included with the mediastinum, and the abdomen is divided into 2 regions: upper (spleen hilum, liver hilum, celiac), and lower. **
Early-stage cHL: Pre-PET Era Studies

Early Stage Unfavorable Disease: GHSG HD11

- Overall 5-yr FFTF 85% & OS 94.5%
- BEACOPP + 30 Gy did not improve FFTF over ABVD x 4 + 30 Gy
- Concern for inferior PFS/FFTF for ABVD x 4+ 20 Gy arm
- Therefore, ABVD + 30Gy is standard of care

Early-stage cHL: Pre-PET Era Studies

Early Stage Unfavorable Disease: GHSG HD14

N=1,655
Primary endpoint = FFTF
Improved PFS (by 7.2%), Similar OS
Increased hematologic toxicity with BEACOPP: 80% vs 24%

Early-stage cHL: Modern PET-Era Studies
EORTC H10

Can PET help identify patients in whom RT can be omitted?

- 1° endpoint=PFS, Non-inferiority (allow ≤10% diff)
- Favorable disease per EORTC criteria:
  - Age <50
  - No bulky mediastinum
  - # nodal areas ≤3
  - ESR ≤ 50 if A or ESR ≤ 30 if B
- Note: 444 patients with favorable, early-stage HL (stage I/II)

Raemaekers et al., JCO 2014.
Planned Interim futility analysis after median follow-up of 1.1 years

Patients with early PET-negative disease (after 2 cycles of ABVD):

<table>
<thead>
<tr>
<th>Treatment</th>
<th># of pts</th>
<th># of events</th>
<th>HR</th>
<th>1-yr PFS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD x 3c + 30 Gy INRT</td>
<td>188</td>
<td>1</td>
<td>1.00</td>
<td>~100%</td>
<td>0.017</td>
</tr>
<tr>
<td>ABVD x 4 c</td>
<td>193</td>
<td>9</td>
<td>9.36</td>
<td>95%</td>
<td></td>
</tr>
</tbody>
</table>

Events = progression of disease (no deaths)

- Could not demonstrate non-inferiority in the experimental arm
- PET-negative experimental arm closed → patients in this arm converted if possible (within 6 weeks)
**EORTC H10 update – 2017**

Update for Early PET-negative pts (favorable), med f/u 5 years:

<table>
<thead>
<tr>
<th></th>
<th>ABVD (n=238)</th>
<th>ABVD+INRT (n=227)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Involved LN</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Uninvolved LN</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Both</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>5-yr PFS</td>
<td>87.1%</td>
<td>99.0%</td>
</tr>
<tr>
<td>5-yr OS</td>
<td>99.6%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Early PET-positive patients (favorable + unfavorable combined):

<table>
<thead>
<tr>
<th></th>
<th>ABVD (n=192)</th>
<th>BEACOPP (n=169)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>41</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>5-yr PFS</td>
<td>77.4%</td>
<td>90.6%</td>
<td>0.002</td>
</tr>
<tr>
<td>5-yr OS</td>
<td>89.3%</td>
<td>96.0%</td>
<td>0.062</td>
</tr>
</tbody>
</table>

Control: ABVD x 3 c → 30 Gy INRT

Experimental: ABVD x 2 c → BEACOPP x 2 c → 30 Gy INRT
# EORTC H10 update – 2017

Andre et al., JCO 2017

<table>
<thead>
<tr>
<th>Toxicity comparison</th>
<th>BEACOPPesc</th>
<th>ABVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>53.5%</td>
<td>30.3%</td>
</tr>
<tr>
<td>Anemia</td>
<td>4.9%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19.7%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Neutropenic fever</td>
<td>23.9%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Infection</td>
<td>5.6%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

**Control:** ABVD x 3 c → 30 Gy INRT

**Experimental:** ABVD x 2 c → BEACOPP x 2 c → 30 Gy INRT

*Chemo-escalation when PET2+ = increased toxicity...*
Early-stage cHL, Modern PET-Era Trials: UK NCRI RAPID Trial

Initial treatment: ABVD x 3

Re-assessment: if NR/PD, patient goes off study
FDG-PET scan performed

PET +ve; n=145
Deauville score 3-5
4th cycle ABVD then IFRT

PET –ve; n=420
Deauville score 1-2
Randomization

2003-2010, 602 pts
Favorable risk (63% by EORTC, 68% by GHSG)
Non-inferiority Trial (exclude ≥7% difference in PFS@ 3 yrs)

IFRT
30Gy
n=209

No further treatment
n=211

N = 602
• Stage IA/IIA cHL
• No bulky disease
• # of nodal sites not an exclusion factor*

Radford et al. ASH Dec 2012
Radford et al. NEJM 2015
UK RAPID trial: RT Fields (IFRT)

a) Neck node: whole ipsilateral neck
b) Neck and axilla: fields in continuity
c) Neck and mediastinum: whole R neck, lower L neck and mediastinum to 5cm below disease

d) Mediastinum: mediastinum and hilar nodes in continuity with 5 cm margin below. Lower neck included bilaterally

f) Axilla: To give a 5cm superior margin the field includes supra and infratclavicular regions

Radford et al., NEJM 2015
PET Scores after ABVD x 3c

- After 3 cycles ABVD - 571 pts had FDG PET CT scan:
- Deauville 5 point score *(centrally reviewed)*:
  - Score 1: 301 (52.7%) **74.7% PET NEGATIVE**
  - Score 2: 125 (22.0%)
  - Score 3: 90 (15.7%) **25.3% PET POSTIVE**
  - Score 4: 32 (5.6%)
  - Score 5: 23 (4.0%)
- 420 of 426 PET–ve pts randomized to IFRT (209) or NFT (211)
  - 6 not randomized; pt choice 3, clinician choice 2, error 1
- **26 in the IFRT arm did not receive RT**
  - 19 patient or clinician choice
  - 5 died in IFRT arm (before IFRT)
  - 1 had pneumonia
  - 2 withdrew consent

Radford et al. ASH Dec 2012
Radford et al. NEJM 2015
PFS in the Randomized PET-ve Population (ITT, n=420, med f/u 48 mos)

- 3 year PFS 94.5% IFRT vs 90.8% NFT (p=0.23) in favor of RT
- BUT <7% difference in PFS @ 3 yrs

Radford et al., NEJM 2015
PFS in the Randomized PET-ve Population
(“As-treated” Analysis, n=392)

➢ 3 year PFS 97.0% IFRT vs 90.7% NFT (p=0.03) in favor of RT

➢ Now ~7% difference in PFS @ 3 yrs

Radford et al., NEJM 2015
3 year OS 97.1 IFRT vs. 99.5% NFT (p=0.07) in favor of NFT

Radford et al., NEJM 2015
Summary of UK NCRI RAPID Study

➢ Analysis presented at 48.6 months and following 36 events

➢ Conservative definition: 74.7% of patients PET –ve after ABVD x 3
  ➢ Very conservative definition of PET results
  ➢ Central review of PET images at the Core Lab
  ➢ *Rarely does this happen in routine clinical practice*

➢ *ITT Analysis* in 420 PET –ve patients 3 year PFS 94.5% IFRT vs 90.8% NFT (p=0.23)

➢ *Per protocol (as treated)* analysis in 392 PET – ve patients 3 year PFS 97.0% IFRT vs 90.7% NFT (p=0.03) *in favor of RT*

➢ PET-negative after chemo still benefits from RT to *reduce risk of relapse*

Radford et al. NEJM 2015
Conclusions for PET-era Studies: EORTC H10/UK RAPID

- Using FDG PET, it may (or may not) be possible to identify patients with very favorable interim factors to omit consolidation RT.
- PET-negative patients after chemo still benefit from IFRT/INRT (↑PFS but same OS).
- Evaluating PET response after chemo allows for treatment adaptation → identify those with less responsive disease to tailor optimal treatment regimen.
- Field reduction from IFRT to INRT/ISRT is reasonable / validated.
- BEACOPP more toxic → intensification with BEACOPP in less responsive disease improves PFS and trend to improve OS (if PET2+).
- Longer follow-up required to establish the impact of a PET negative approach.
Advanced cHL: Role of RT

- Many patients have residual mass on CT after systemic therapy
- Modern studies incorporate response-adapted therapy with interim PET/CT

**GHSG HD15**

- End PET negative post-BEACOPP residual mass do not require RT
- In PET+ patients, RT may convert a PR (>2.5cm) to a CR

**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

Classical Hodgkin Lymphoma Summary

• Early-stage (I-IIA), favorable
  • Combined modality therapy (Chemo + RT)
    • ABVD x 2 + 20 Gy ISRT (GSHG HD10) [very favorable]
    • ABVD x 3 + 30 Gy ISRT (EORTC H10F / UK RAPID)
    • Stanford V (MOP-ABVE) x 8 weeks and 30 Gy ISRT

• Chemotherapy alone approach
  • ABVD x 3 cycles with NFT with expected slightly lower PFS (EORTC H10F / UK RAPID trials)
Classical Hodgkin Lymphoma Summary (continued)...

• Early-stage (I-II): bulky or unfavorable (by various risk stratifications)
  • Best outcomes with combined modality therapy...
  • Interim PET+ patients do worse, consider chemotherapy intensification
  • ABVD x 4-6 cycles and 30 Gy ISRT
  • Stanford V x 12 weeks and 30-36 Gy ISRT
  • eBEACOPP x 2 cycles f/b ABVD x 2 cycles and 30 Gy ISRT

• Advanced-stage: Stage III-IV
  • Chemotherapy with ABVD x 6+
  • Add ISRT to sites of bulky disease or incomplete response; 30 Gy for CR and 36-45 Gy for PR/Refractory disease *(Upcoming ILROG Guidelines. 2018)*
Nodular lymphocyte predominant HL (NLPHL)

- Comprises ~5% of Hodgkin lymphoma
- Distinct entity compared to cHL, CD 20+
- Best prognosis, usually early stage (I-II), non-bulky; rarely involves mediastinum, usually peripheral
- B-symptoms uncommon (<10%)
- May transform to DLBCL in 3-5% cases

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<td>-</td>
<td>+</td>
<td>+</td>
</tr>
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</table>
NLPHL: Management

- Stage IA/IIA non-bulky – ISRT alone
- Stage IA/II bulky or Stage IB/IIB – Chemotherapy + ISRT +/- Rituximab
- Multiple chemotherapy options: ABVD, CHOP, CVP, R
- ISRT – 30-36 Gy
- (ILROG) ISRT: *IS-CTV covers suspected subclinical disease (GTV + minimum adjacent lymph nodes in that site)*
  - Similar to RT for localized indolent NHL
- Relapses are late (> 5 years out) and can be either HL or DLBCL
NLPHL, Stage 1A
GHSG (1988-2009)

• Rituximab arm was worst, when compared to more limited treatment fields

Worst arm = Rituximab Alone

Eichenauer et al. JCO 2015
Non-Hodgkin Lymphoma

Topics to cover today

- Diffuse Large B-cell Lymphoma (DLBCL)
- Follicular Lymphoma (FL)
- Marginal zone Lymphoma (MALT)
DLBCL

- Most common NHL – 30%+
- Gene profiling – 3 separate subtypes (*different clinical behavior*):
  - **Germinal center B-cell (GCB)** – hypermutations, REL amplification, bcl-2 translocations – 64% 5-yr OS
  - **Primary Mediastinal B-cell (PMBCL)** – 59% 5-yr OS
    - Closely related to cHL-NS
  - **Activated B-cell (ABC)** – activation of NFkB – 30% 5-yr OS
  - “Double hit” or “triple hit” – more aggressive (systemically)
    - MYC translocation with either BCL2, BCL6 or both; in 2-12% of all cases
## 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>

### Overall Survival (5-yr)
- Low (0-1) – 73%
- Low intermediate (2) - 51%
- High intermediate (3) – 43%
- High (4-5) – 26%

*R-CHOP- Add ~10%

<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>≥ 1</td>
<td>70%</td>
</tr>
<tr>
<td>3</td>
<td>48%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AA-IPI</th>
<th>5-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>0</td>
</tr>
<tr>
<td>LI</td>
<td>1</td>
</tr>
<tr>
<td>HI</td>
<td>2</td>
</tr>
<tr>
<td>H</td>
<td>3</td>
</tr>
</tbody>
</table>

Shipp et al. NEJM 1993;329:987
DLBCL: early-stage

**SWOG 8736**

- **Stage I, IIij,k**
  - Nonbulky (<7.5 cm)
    - RCHOP° x 3 cycles + RT^p (category 1)
    - or
    - RCHOP° x 6 cycles ± RT^p,q
  - Bulky (≥7.5 cm)
    - RCHOP° x 6 cycles ± RT^p,q

**UNFOLDER**

- See Pre RT Evaluation (BCEL-4)

Adapted from NCCN guidelines, 2018
DLBCL: Pre-Rituximab Era Studies

SWOG 8736: CHOP X 8 vs. CHOP X 3 + IFRT

- Stages I-IIE (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 overall survival
  - Improved lymphoma control (PFS)

SWOG 8736 finally a published update..

Continued Risk of Relapse Independent of Treatment Modality in Limited-Stage Diffuse Large B-Cell Lymphoma: Final and Long-Term Analysis of Southwest Oncology Group Study S8736

Deborah M. Stephens, Hongli Li, Michael L. LeBlanc, Soham D. Puvvada, Daniel Persky, Jonathan W. Friedberg, and Sonali M. Smith

(A) Progression-free (PFS)

(B) Overall Survival (OS)
5-year PFS and OS were **initially improved** in patients with limited-stage DLBCL receiving CHOP3RT versus CHOP8 in S8736.

Extended survival data with more than 17 years of follow-up showed **similar outcomes**, with continuous treatment failure and without a PFS plateau in either arm.

Important – prolonged observation of clinical trial patients and possible unique biology of limited-stage DLBCL.

Take home point: **CHOP x3 + RT = CHOP x8**

**Note:** IFRT to 40-55 Gy
Single Arm prospective Phase II Study:
Stage I-II DLBCL patients (at least 1 RF)
R-CHOP + IFRT

Lower impact of R in limited stage (5% vs 15% in advanced stage)

Biological explanation: molecular fingerprint GCB in 3/4 of cases (demonstrated lower benefit of R)

Persky et al. JCO 2008
Eligibility: early-stage DLBCL, aged 18-60, aa-IPI=1 or IPI=0 with bulky disease (\( \geq 7.5 \text{ cm} \))

Pts with bulky and/or extranodal disease randomized to 1 of 4 arms (n=285):

- Arm I: R-CHOP 21 x 6 alone
- Arm II: R-CHOP 21 x 6; if CR → IFRT
- Arm III: R-CHOP 14 x 6 alone
- Arm IV: R-CHOP 14 x 6; if CR → IFRT
Patients randomized to receive IFRT or not irrespective of PET response

Termination of No RT arm

3y EFS: 81%  
p=0.004

3y EFS: 65%

Held. ICML RT Workshop, 2013
DLBCL: Rituximab Era Studies
MD Anderson Experience

- 469 pts with DLBCL (30% received consolidative RT)
- Among 291 pts treated with R-CHOP and achieved CR, RT associated with significantly higher 5y PFS & OS
- MVA: RT associated with significantly improved PFS (HR, 0.19) and OS (HR, 0.32)

Phan J et al. JCO. 2010
Phase III randomised trial

Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial

**DLBCL: RT Dose**

**Patient Eligible**

- 1001 pts.

**Low Grade Lymphoma**

- 361 pts.

  **Randomize**

  - 12 fractions
    - 24Gy
    - 180 pts.

  - 20-30 fractions
    - 40-45Gy
    - 181 pts.

**Intermediate or High Grade Lymphoma**

- 640 pts.

  **Randomize**

  - 15 fractions
    - 30Gy
    - 319 pts.

  - 20-30 fractions
    - 40-45Gy
    - 321 pts.

Lowry et al. Radiotherapy & Oncology. 2011
DLBCL: RT Dose

Caveats:
- Included patients w RT alone or receiving salvage / palliative RT
- Limited chemotherapy data, largely without Rituximab
- No functional imaging for response-based therapy (from induction chemotherapy)
Phase II Study of **Dose-Reduced** Consolidation Radiation Therapy in Patients with Diffuse Large B-Cell Lymphoma;

- C. Kelsey et al., Oral Session ASTRO 2017

R-CHOP x4 → If PET-neg (Deauville 1-3), ISRT de-escalation to **20Gy (vs. 30Gy)**

- Primary endpoint: 5-yr Local Control
- n=62 (2010-2016)
- Stage: I- 39%; II- 40%; III- 6%; IV- 15%
- Bulky (≥ 7.5 cm): n=23 (40%); Bulky (≥ 10 cm): n=16 (28%)
- Median follow-up: 43 months (range, 1-81)
- 1 local recurrence + 6 distant recurrences
- **Need longer follow-up & validation in larger Phase II studies...**

RT Dose for DLBCL: Duke Phase II Study
DLBCL: Summary

- Stage I non-bulky, IPI 0-1
  - R-CHOP x 3-4 cycles and ISRT 30Gy
- Other Stage I/II
  - R-CHOP x 6 followed by ISRT 30Gy if CR on PET
  - If PR on interim PET, boost post-chemo GTV to 36Gy+
- Early-stage, aggressive histology (double/triple hit, Burkitt’s features)
  - da-R-EPOCH x 6 followed by ISRT 30Gy if CR on PET
  - R-CHOP X 6 followed by ISRT 30Gy if CR on PET
- Advanced, Stage III/IV
  - R-CHOP x 6 +/- ISRT (30-45Gy)
    - For bulky disease (JCO 2014; 32:1112)
    - Skeletal involvement (JCO 2013; 31:4115)
Follicular Lymphoma

- Most patients are Stage III-IV (70-85%)
- Patients should receive a bone marrow biopsy (up to 50% involvement)
- Course – chronic, relapsing indolent tumor
- Richter’s transformation in 30-65%
- Grade influences treatment

<table>
<thead>
<tr>
<th>Grade</th>
<th>Characteristic</th>
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<tbody>
<tr>
<td>Grade 1</td>
<td>0-5 centroblasts/hpf</td>
</tr>
<tr>
<td>Grade 2</td>
<td>6-15 centroblasts/hpf</td>
</tr>
<tr>
<td>Grade 3</td>
<td>&gt; 15 centroblasts/hpf</td>
</tr>
<tr>
<td>3a</td>
<td>Centrocytes present</td>
</tr>
<tr>
<td>3b</td>
<td>Solid sheets of centroblasts</td>
</tr>
</tbody>
</table>

→ Treat as G1-2, or as G3B
→ Treat as DLBCL

Blood. 1997; 89: 3909-3918
Follicular Lymphoma Int’l Prognostic Index (FLIPI)

- This provides prognostic information that may be used to guide therapeutic options.
- This nodal area “map” is used to determine # of nodal sites in FLIPI-1 criteria and is different than the conventional Ann Arbor site map.

Adapted from NCCN guidelines, 2017
Follicular Lymphoma: early-stage, G1-2

Adapted from NCCN guidelines, 2018
Follicular Lymphoma: advanced-stage, G1-2

Adapted from NCCN guidelines, 2018
LymphoCare Study: PFS – “properly-staged” vs. not

National study: n=2,728
(similar to SEER patients)

Rigorous staging defined as:
computed tomography (CT) +/- positron emission tomography [PET] and a bone marrow assessment

Friedberg JW et. al, J Clin Oncol. 2012.
LymphoCare Study: PFS by Group of Treatment

Conclusion
In this largest, prospectively enrolled group of patients with stage I follicular lymphoma, variable treatment approaches resulted in similar excellent outcomes, which challenges the paradigm that XRT should be standard for this presentation.

Friedberg JW et. al, J Clin Oncol. 2012.
# Early Stage Follicular Lymphoma: Outcome with RT alone

<table>
<thead>
<tr>
<th>Institution</th>
<th>Author</th>
<th># of pts.</th>
<th>10 yr FFR</th>
<th>10 yr OS</th>
<th>10 yr DSS</th>
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<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>
</tr>
<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>
FL: British Columbia Study

Cancer 2010;116:3797

1986-2006
N=237
Stage I - 76%
Stage II - 24%

FFTPE - 49%
Early-stage (I-II), low-grade (1-2) Follicular Lymphoma

SEER data 1973-2004 of 6,568 patients

RT as initial treatment (34% of pts.) compared to no-RT

Disease-specific survival (DSS) and overall survival (OS) significantly better (P<0.0001; HR 0.65 and 0.73) at 5,10,15,20 years of follow-up

RT was a significant independent factor in multivariate analysis
FL: RT Dose

Phase III randomised trial
Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial

**PATIENT ELIGIBLE**
1001 pts.

**LOW GRADE LYMPHOMA**
361 pts.

- **RANDOMIZE**
  - 24Gy
    - 12 fractions
    - 180 pts.
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**INTERMEDIATE OR HIGH GRADE LYMPHOMA**
640 pts.

- **RANDOMIZE**
  - 30Gy
    - 15 fractions
    - 319 pts.
  - 40-45Gy
    - 20-30 fractions
    - 321 pts.

Lowry et al. Radiotherapy & Oncology. 2011
Subset analysis - no difference in subgroup treated with curative intent

British National Lymphoma Investigation
Radio & Oncol 2011;100:86
Conclusions: **24 Gy in 12 fractions is the more effective radiation schedule** for indolent lymphoma and should be regarded as the standard of care. **However, 4 Gy remains a useful alternative for palliative treatment.**

Hoskin et al. Lancet Oncology 2014
Indolent Lymphomas, Stage III-IV:

High Response Rates and Lasting Remissions After Low-Dose Involved Field Radiotherapy in Indolent Lymphomas

- Netherlands, n=109; mainly FL (90%), some MALT
- 52% with disease ≥ 5 cm (bulky)
- Prior regimens (median 2, range 0-11)
- IFRT: 4 Gy / 1-2 fx
- **ORR 92% (CR 61%, PR 31%, SD 6%)** more impressive than most systemic agents (chemo/targeted)!!
- 25 months median time to local progression (42 months in patients with CR)
- Well tolerated and effective **palliation using low-dose RT**

Follicular Lymphoma: Summary

- ISRT for low grade Stage I-II disease, G1-2 (non-bulky, or contiguous Stage I-II)
  - ISRT 24Gy alone
  - Can boost gross/bulky disease with ISRT margin to 30Gy
  - Expected outcomes – ~50% 10-year FFP
  - Patterns of failure – distant

- High grade Stage I-II disease (G3)
  - Follow DLBCL guidelines
  - R-CHOP x 3-6 cycles followed by ISRT 30Gy for CR

- Stage III or IV disease
  - RT for palliation, usually after systemic therapy (R-CVP; B-R; R-CHOP +/- maintenance R)
  - "Boom-Boom" regimen of 4Gy / 1-2 fractions, excellent palliative option

- **Remember:** For early-stage disease, RT is S.O.C., ISRT is safe/easily tolerated, RT dose is low (24Gy)
NHL – marginal zone lymphoma

- 10% of all cases of NHL
- (3) types
  - Nodal marginal zone lymphoma
  - **Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)**
    - Usually same chemotherapy as FL/low-grade lymphoma
  - Splenic marginal zone lymphoma
    - No need for immediate therapy
    - Consider splenectomy
NHL – MALT lymphoma

• Indolent; usually present stage IE or IIE
  • 60-70% present w/ stage I or II
  • 96% RFS with RT

• Common Sites
  • Stomach
    • H-Pylori
    • Represents 65% of MALT lymphomas
  • Orbital
  • Skin
  • Salivary glands
    • Sjogren’s
  • Waldeyer’s ring
  • Thyroid
    • Women more common than men
    • Hashimoto’s thyroiditis
    • DLBCL more common than MALT

<table>
<thead>
<tr>
<th>Site</th>
<th>Infectious agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>H. pylori</td>
</tr>
<tr>
<td>Ocular adnexa</td>
<td>C. psittaci</td>
</tr>
<tr>
<td>Small intestine</td>
<td>C. jejuni</td>
</tr>
<tr>
<td>Spleen</td>
<td>HCV</td>
</tr>
<tr>
<td>Skin</td>
<td>Borrelia burgdorferi</td>
</tr>
</tbody>
</table>
Gastric Lymphoma (MALT)

• Presentation
  • epigastric pain ~ 72%
  • weight loss ~ 43%
  • nausea and vomiting ~ 30%
  • acute presentations
    • bleeding ~ 20%
    • perforation ~ 1%

• Diagnosis:
  • Previously – via gastrectomy
  • Currently – via endoscopy > 90%
  • Adequate biopsies essential: *Often multi-centric in stomach*
    • transformation seen in deeper layers
    • multifocal involvement
  • Limited to stomach, can involve duodenum and peri-gastric LN
Treatment of Gastric MALT

• Attempt antibiotic therapy if t(11:18) negative
  • Chromosomal aberration t(11;18) (q21;q21) → predictor of Abx resistance (JCO 2005; 23:8018)

• Wait for histologic confirmation of response / endoscopy
  • Minimum time to complete response: 6 mos (median=15 mos)
  • Response can be seen as late as 18 mos

• Failure of antibiotic therapy and/or H.pylori independent pathway
  • RT to stomach and perigastric lymph nodes
  • Chemotherapy (not preferred if stage I/II)

• Highly curable if local control achieved
  • In the past → surgery
  • Current s.o.c → RT alone → 90%+ CR/FFP rates...
Gastric MALT:
Simulation & Treatment Planning

- Simulate and treat fasting (3 hours)
- Oral Contrast if needed
- IV Contrast if LN are involved
- Vac-lock immobilization
- Arms up
- AP/PA vs. 3D-CRT vs. IMRT/VMAT
- Try to maximally spare kidney, liver, and bowel
- GTV if possible: Visible Tumor or based on description in EGD procedure note

- IS-CTV: Entire stomach including gastroduodenal junction + 2 cm
- PTV: Account for respiratory motion
  - Can use 4D-CT
- 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 (QA stomach/target)
- Loco-regional control rate (MSKCC, MGH, MDACC, France) – 95-98% at 5 years
RT Specifics: 3D-CRT/IMRT 30Gy/17-20fx

Block the Kidney(s)
MALT of Non-Gastric sites:

- Ocular Adnexa, Salivary glands, Lung, Skin
  - Definitive treatment for early stage disease is RT alone
  - Lower doses than gastric MALT
    - 24 Gy in 12 fractions
    - Can avoid toxicity
    - In Stage III/IV patients, can consider 4Gy in 1-2 fractions for local control
- Antibiotic response rates of 35-50% documented
  - Takes 6-24 months to see response
Contouring for Extra-Nodal Lymphoma

• **Orbit**
  - CTV: for most cases of indolent NHL, the entire bony orbit including definite or suspected extraorbital extensions
  - Lacrimal gland – treat the entire gland
  - Conjunctiva – CTV includes the entire conjunctival sac and local extensions to eyelid
  - PTV margin is normally 3-5 mm

Orbital MALT: Is it necessary to treat the whole orbit?

- N=12, median dose 25.2Gy to partial orbit
- All patients had a complete response to RT.
- Intraorbital recurrence developed in previously uninvolved areas not included in the initial target volume in 4 patients (33%) treated with partial orbit RT.
- All were salvaged by repeat RT or surgery.
- No patient treated with whole orbit RT developed intraorbital recurrence.

Pfeffer et al. IJROBP. 2004. 60, 527-530

Table 2. Patients with intraorbital recurrence (all had low-grade lymphoma and received a dose of 25.2–27 Gy)

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Initial site</th>
<th>Technique</th>
<th>Recurrence site</th>
<th>Retreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lacrimal gland</td>
<td>LAO 15-MeV electrons</td>
<td>medial orbital wall</td>
<td>25.2 Gy whole orbit</td>
</tr>
<tr>
<td>2</td>
<td>Medial conjunctiva</td>
<td>RAO 6-MV photons</td>
<td>Lateral conjunctiva</td>
<td>25.2 Gy whole orbit</td>
</tr>
<tr>
<td>3</td>
<td>Lateral conjunctiva and eyelid</td>
<td>2 oblique field photons</td>
<td>Medial conjunctiva</td>
<td>Resection</td>
</tr>
<tr>
<td>4</td>
<td>Right upper lateral</td>
<td>2 oblique field photons</td>
<td>Medial</td>
<td>25.2 Gy whole orbit</td>
</tr>
</tbody>
</table>

Abbreviations: Pt. No. = patient number; LAO = left anterior oblique; RAO = right anterior oblique.
Implementing modern RT techniques

- **Involved-site Radiation Therapy (ISRT)**
- (3) very important ILROG Guidelines

Modern Radiation Therapy for **Hodgkin Lymphoma:** Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group (ILROG)

Modern Radiation Therapy for **Nodal Non-Hodgkin Lymphoma**—Target Definition and Dose Guidelines From the International Lymphoma Radiation Oncology Group

Modern Radiation Therapy for **Extranodal Lymphomas:** Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group
Evolution of RT Volumes / Doses in Lymphoma

1978: Total nodal dose 30-44 Gy

Regional nodal involvement showed more than 80% reduction in 2018.

Involved field dose was reduced from 30-44 Gy to 20-30 Gy.

Involved site dose was further reduced to 20-30 Gy.

Specht L et al. IJROBP 2014
Involved Field Radiotherapy (IFRT) ?

The involved field is **gone**: issues in delineating the radiation field in Hodgkin's disease

J. Yahalom¹* & P. Mauch²

¹Memorial Sloan-Kettering Cancer Center and Weill Medical College of Cornell University, New York, NY. ²Brigham and Women’s Hospital, Dana Farber Cancer Institute and Harvard Medical School, Boston, MA, USA

DOI: 10.1093/annonc/mdf616
Strategies to Improve the Therapeutic Ratio *(shrinking the CTV)*

- **Involved Field**
  - Based on 2D (bony) anatomy
  - Includes entire lymph node region

- **Involved Site**
  - Based on 3D anatomy (GTV→CTV→PTV)
  - Includes original extent of disease + margin to *account for imaging limitations* and disease site specifics

- **Involved Node**
  - Based on 3D anatomy (GTV→CTV→PTV)
  - Includes original extent of disease with margin
Requires optimal imaging

**Pre-chemo PET/CT MUST BE in treatment position**

Fusion with post-chemo planning CT

Tissue volume which contained the initially involved lymphoma tissue is contoured to allow for tumor shrinkage and other anatomic changes

Girinsky et al. Radiotherapy and Oncology. 2006

not a new concept...
Is ISRT/INRT safe for HL?

N=325

Patterns of Failure

The median time to relapse was 37 months (range, 10 to 106). A total of 12 relapses occurred, constituting an overall relapse rate of 4%. Four relapses occurred in the EFRT group, five in the IFRT group, and three in the INRT ≤ 5 cm group. LRR occurred in five (2%) of 325 patients: three in the EFRT group, two in the IFRT group, and none in the INRT ≤ 5 cm. All LRRs occurred in-field, with no marginal relapses in any of the three groups. Distant-only relapse occurred in 7 (2%) patients: one after EFRT; three after IFRT; three after INRT ≤ 5 cm. Of the 12 patients with relapsed HL, four died with HL; three were alive with active disease at the time of last follow-up, and five were successfully treated with second-line regimens and were disease free at the time of last follow-up.
INRT for FL: British Columbia
Cancer 2010;116:3797

Proportion of Patients

P=0.498

[d) IRRT INRT [LNs + 0-5 cm margin]

ASTRO Annual Refresher Course • Fort Lauderdale Marriott Harbor Beach Resort & Spa • March 2-4, 2018 #REFRESHER18
ISRT Principles – *our s.o.c*

- 1) Based on best available evidence, including evidence from large intergroup studies and the experience of ILROG members
- 2) Based on conventions defined by **ICRU Report 83** (GTV, CTV, ITV, PTV), *same as solid tumors*
- 3) **ISRT** is slightly larger volumes than **INRT** and smaller volumes than **IFRT** (ensure irradiation of all initially involved tissue volumes)
- 4) Based on modern 3D and functional imaging/planning techniques (CT, PET, MRI) *which may or may not be performed in the treatment positions*
- 5) Post-chemotherapy treatment planning CT

Modern Radiation Therapy for Hodgkin Lymphoma: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group (ILROG)
*Specht L. et al. IJROBP July 2014.*
ISRT Techniques

➢ **GTV**: Demonstrable tumor on imaging (applies when RT is used as single modality treatment for Stage 1A disease). Does not apply when treating post-chemotherapy volume, unless PR.

➢ **IS-CTV**: All initially involved sites (i.e. pre-Chemotherapy disease) expanded manually with **1.5cm margin cranio-caudally in the direction of potential lymphatic spread**. Expansions in other directions to include the involved nodes or any residual disease only. The IS-CTV should **not** extend into air, muscle planes or bone, (unless the disease is muscle or bone-invasive). If GTV was defined, it is expanded by 1cm isotropic margin.

➢ **IS-PTV**: CTV to PTV margins should be defined individually for each disease site and treatment center, depending upon their technique, set-up accuracy and consideration of internal organ motion. Typical margins are as below:
   ➢ Head and neck - 0.3cm
   ➢ Mediastinum – 1.0cm transversely and 1.5cm cranio-caudally if defined on free breathing CT. Add 8mm isotropic margin if defined on 4DCT.
   ➢ All other sites 1.0cm isotropic margin.
Supradiaphragmatic sites

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 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.
Infradiaphragmatic sites

Figure 3(a): Transverse sagittal and coronal views of an inguinal lymphoma patient. The pre-Chemotherapy nodal area is shown in yellow. The ISRT CTV is shown in red after SI expansion.

Figure 4(a): Transverse sagittal and coronal views of a para-aortic lymphoma patient. The pre-Chemotherapy nodal area is shown in yellow. The ISRT CTV is shown in red after SI expansion.
Treatment Techniques: AP/PA Fields

Treatment Techniques: IMRT

"Butterfly" IMRT Technique (MDA)
Voong et al.
Radiation Oncology. 2014

Proton Therapy: Dosimetric Comparison

The use of mDIBH significantly improved:

- Mean lung dose (FB: 11.0 Gy; mDIBH: 9.5 Gy; p<0.0001)
- Lung V20 (28% vs 22%; p<0.0001)
- Mean heart dose (14.3 Gy vs 11.8 Gy; p=0.003)
- **BUT** increased the mean breast dose (FB: 3.0 Gy; mDIBH 3.6 Gy; p=0.0005).

Charpentier et al. Practical Radiation Oncology. 2014. *Princess Margaret Cancer Centre*
ISRT Conclusions

• Modern radiotherapy for HL & NHL is highly individualized treatment restricted to limited treatment volumes
  • **Significant** volume reductions compared to previous IFRT techniques
• Modern imaging and radiotherapy **techniques/modalities** (IMRT, DIBH, Protons) should be used to limit irradiation of normal tissue, minimizing risk of long-term complications
• **Radiation oncologists treating HL & NHL should be involved as part of the multidisciplinary team in the initial treatment program for each patient and attempt to introduce imaging/planning procedures upfront**
• Integrated multidisciplinary approach will enable optimal outcome for patients
Summary & Key Points:

- Lugano classification / Deauville criteria
  - Work with radiology to report/integrate Deauville criteria into management
- Role of consolidation RT in cHL
  - ISRT improves recurrence by 50% and PFS/OS by 10%
- Consolidation RT in DLBCL
  - ISRT decreases risk of recurrence by 50-60%
- Role of definitive RT in localized FL and MALT lymphoma
  - FL: 50% long-term DFS with 24-30Gy ISRT
  - MALT: CR and LC > 90% (24-30 Gy)
- Understand and Implement Modern RT techniques – ISRT
  - Using solid tumor principles of GTV → CTV → PTV volume design
Thank you!