ASTRO Refresher Course

Lymphoma

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Duke University Medical Center
Hodgkin Lymphoma

Classical Hodgkin Lymphoma \((CD15+/CD30+/CD20-)\)

- Early-Stage Favorable
  - Stage I-II without risk factors
- Early-Stage Unfavorable
  - Stage I-II with risk factors
- Advanced
  - Stage III-IV

Nodular Lymphocyte-Predominant Hodgkin Lymphoma \((CD15-/CD30-/CD20+)\)
Hodgkin Lymphoma
Risk Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>GHSG (Eich et al. 2010; Engert et al. 2010)</th>
<th>EORTC (Ferme et al. 2007)</th>
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<td>≥ 3</td>
<td>≥ 4</td>
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<tr>
<td>LMA</td>
<td>Present</td>
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<tr>
<td>ESR &amp; B-symptoms</td>
<td>≥50, no “B” symptoms, ≥30, “B” symptoms</td>
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<td>ESR ≥50</td>
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<tr>
<td>Extranodal involvement</td>
<td>Present</td>
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## Hodgkin Lymphoma Risk Factors

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Favorable GHSG

• 1-2 sites of involvement
• No large mediastinal adenopathy
  – < 1/3 transverse diameter of the chest
• No extranodal involvement
• Favorable ESR/B-symptom profile
  – ≥50, no “B” symptoms
  – ≥30, “B” symptoms
Classical Hodgkin Lymphoma
   Early-Stage Disease

- Chemotherapy
- Chemotherapy + RT
### Randomized Trials Comparing Chemotherapy versus CMT

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Randomization</th>
<th>Progression-free survival</th>
<th>P-value</th>
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<td>Meyer (Canada)</td>
<td>276</td>
<td>ABVD X 4-6</td>
<td>86</td>
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<td>501</td>
<td>COPP/ABV X 4-6</td>
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<td>ABVD X 6 + RT</td>
<td>86 (5y)</td>
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CT + RT vs CT

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<td>Pavlovsky (1988)</td>
<td>70</td>
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<td>Meyer (2012)</td>
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Legend: CT + RT, CT
Systematic Review
Haematologica 2010;95:494

“Tumor Control”

All trials- HR 0.38 (95% CI 0.28-0.51)
Cochrane Review (2009)
Stage I-II (favorable)

n=1370

ABVD X 4
- IFRT 30 Gy
- IFRT 20 Gy

ABVD X 2
- IFRT 30 Gy
- IFRT 20 Gy

No PET Imaging
**HD10**  
Chemotherapy Comparison

### A. Chemotherapy Comparison

**Freedom from Treatment Failure (%)**

- 4×ABVD (groups 1 and 2)
- 2×ABVD (groups 3 and 4)

Difference at 5 yr, -1.9 percentage points (95% CI, -5.2 to 1.4)  
Hazard ratio, 1.17 (95% CI, 0.82 to 1.67)

**Overall Survival (%)**

- 4×ABVD (groups 1 and 2)
- 2×ABVD (groups 3 and 4)

Difference at 5 yr, -0.5 percentage points (95% CI, -2.6 to 1.6)  
Hazard ratio, 1.02 (95% CI, 0.61 to 1.72)

**No. of Patients at Risk**

- **4×ABVD**
  - Months: 596, 554, 532, 506, 479, 430, 330, 226, 131, 57, 6
  - Months: 594, 555, 530, 498, 473, 410, 314, 225, 131, 54, 9

- **2×ABVD**
  - Months: 596, 583, 575, 569, 562, 541, 471, 348, 227, 130, 24
  - Months: 594, 589, 578, 572, 567, 549, 482, 361, 239, 126, 36
HD10
Radiation Therapy Comparison

B  Radiation Therapy Comparison

---

**Freedom from Treatment Failure (%)**

- 30 Gy IFRT (groups 1 and 3)
- 20 Gy IFRT (groups 2 and 4)

Difference at 5 yr, −0.5 percentage points (95% CI, −3.6 to 2.6)
Hazard ratio, 1.00 (95% CI, 0.68 to 1.47)

---

**Overall Survival (%)**

- 30 Gy IFRT (groups 1 and 3)
- 20 Gy IFRT (groups 2 and 4)

Difference at 5 yr, −0.2 percentage points (95% CI, −2.0 to 1.7)
Hazard ratio, 0.86 (95% CI, 0.49 to 1.53)

---

**No. of Patients at Risk**

- **30 Gy IFRT**
  - Months: 575, 553, 526, 499, 471, 426, 328, 235, 139, 61, 8
  - 30 Gy IFRT
  - 20 Gy IFRT

- **20 Gy IFRT**

---

**No. of Patients at Risk**

- **30 Gy IFRT**
  - Months: 575, 570, 561, 556, 552, 535, 469, 352, 228, 125, 32
  - 20 Gy IFRT

- **20 Gy IFRT**
  - Months: 588, 583, 575, 568, 560, 539, 468, 346, 232, 131, 28
Favorable GHSG

- 1-2 sites of involvement
- No large mediastinal adenopathy
  - <1/3 diameter of the chest
- No extranodal involvement
- Favorable ESR/B-symptom profile
  - ≥50, no “B” symptoms
  - ≥30, “B” symptoms (*not well represented in HD10*)

2 cycles ABVD + 20 Gy RT
Unfavorable GHSG

- $\geq 3$ sites of involvement
- Large mediastinal adenopathy
  - $\rightarrow 1/3$ diameter of the chest
- Unfavorable ESR/B-symptom ratio
- Extranodal involvement
GHSG HD11
JCO 2010;28:4199

Stage I-II
(unfavorable)
n=1395

ABVD X 4

IFRT
30 Gy

BEACOPP X 4
(baseline)

IFRT
20 Gy

IFRT
30 Gy

IFRT
20 Gy

No PET Imaging
• Acute Toxicity
  • WHO grade 3-4 toxicity 74% (BEACOPP) vs 52% (ABVD)
  • WHO grade 3-4 toxicity 12% (30 Gy) vs 6% (20 Gy)

• Outcomes
  – Chemotherapy
    • No difference in any outcomes
  – Radiation therapy
    • BEACOPP: -0.8% (95% CI: 5.8 – 4.2%)
    • ABVD: -4.7% (95% CI: 10.3% - 0.8%)
EORTC-GELA HD-U
ASH 2005 Abstract

• CS I-II HL with risk factors (n=808)

• Randomized to:
  - ABVD X 6 + IFRT (36-40 Gy)
  - ABVD X 4 + IFRT
  - BEACOPP (baseline) X 4 + IFRT

EFS (4) 91%, 87%, 90% (p=0.38)
OS (4) 95%, 94%, 93% (p=0.98)
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

Statistics- FFTF primary endpoint
(A) Freedom From Treatment Failure (probability)

5-year FFTP (%) | 95% CI (%)
---|---
Arm A | 87.7 | 84.8 to 90.6
Arm B | 94.8 | 93.1 to 96.6

P < .001

Time (months)

No. at risk
Arm A | 765 730 709 664 595 505 439 361 288 223 142 94
Arm B | 763 730 702 671 599 523 463 367 297 235 170 111

(B) Overall Survival (probability)

5-year OS (%) | 95% CI (%)
---|---
Arm A | 96.8 | 95.2 to 98.4
Arm B | 97.2 | 95.8 to 98.6

P = .731

Time (months)

No. at risk
Arm A | 765 764 760 732 676 576 516 420 356 275 204 137 81
Arm B | 763 757 743 723 663 580 518 421 351 273 223 147 91
Unfavorable GHSG

- $\geq 3$ sites of involvement
- Large mediastinal adenopathy] – $> \frac{1}{3}$ diameter of the chest
- Unfavorable ESR/B-symptom profile
- Extranodal involvement

- ABVD X 4 + 30 Gy RT
- eBEACOPP/ABVD X 4 + 30 Gy RT
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<tr>
<th>Study</th>
<th>PFS (5)</th>
<th>Treatment</th>
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<tr>
<td>GHSG HD10</td>
<td>91.6%</td>
<td>ABVD X 2 + 20 Gy</td>
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<tr>
<td>GHSG HD11</td>
<td>87.2%</td>
<td>ABVD X 4 + 30 Gy</td>
</tr>
<tr>
<td>GHSG HD14</td>
<td>95.4%</td>
<td>eBEACOPP/ABVD X 4 + 30 Gy</td>
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</table>
Radiation Fields

• 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 with a margin to account for imaging limitations and disease specifics

• Involved Node
  – Based on 3D anatomy (GTV→CTV→PTV)
  – Includes original extent of disease with margin
Involved Site Radiation Therapy
IJOBP 2013 (in press)

• CTV- original extent of disease based on the pre-chemotherapy PET-CT
  – Adjusted to exclude uninvolved normal tissues
    • lung after chemotherapy-induced shrinkage
  – Expanded to account for imaging uncertainties and disease/treatment circumstances

• PTV- expansion to account for setup variations, organ motion (ITV)

• Logical treatment volumes based on region treated, adjacent normal tissues, dose, etc.
Deauville Criteria

1. No uptake above background
2. Uptake ≤ mediastinal blood pool
3. Uptake > mediastinal blood pool but ≤ liver
4. Uptake moderately increased compared to liver
5. Uptake markedly increased compared to liver
Deauville Criteria

1. No uptake above background
2. Uptake $\leq$ mediastinal blood pool
   NEGATIVE
3. Uptake $>$ mediastinal blood pool but $\leq$ liver
   Negative or Positive (treatment de-escalation)
4. Uptake moderately increased compared to liver
5. Uptake markedly increased compared to liver
   POSITIVE
Advanced Hodgkin Lymphoma

- **Chemotherapy**
  - ABVD X 6 +/- RT
  - eBEACOPP X 6 +/- RT
    - GHSG HD9 (8 cycles eBEACOPP > COPP-ABVD)
    - GHSG HD15 (6 cycles eBEACOPP + PET-directed RT)

- **Role of RT controversial**
  - All sites for limited stage III disease
  - Original sites of bulky disease
  - PET positive site(s) after chemotherapy
Nodular Lymphocyte Predominant HL

NLPHL usually…

• CD20+; CD15- and CD30-
• Presents with early-stage disease (~80%)
• Peripheral adenopathy (central sparing)
• Slow progression (late relapses), perhaps with a tendency to transform to NHLs
• Do relapse, but survive relapses better than patients with classic HL
European Task Force on Lymphoma
JCO 1999;17:776

Hodgkin's-Specific Failure-Free Survival (relapse, death from HL, death from NHL)

Diagnosis
- LRCHD
- 27 / 115
- LPHD
- 54 / 219

p = 0.57

FFS (years) HD-specific
GHSG trials (1988 to 2002)
JCO 2008;26:434

Freedom From Treatment Failure

Probability

FFTTF (months)

LPHL
cHL
Treatment
NLPHL

CS IA, IIA → Observeaa → See Follow-up HODG-15
or ISRTm → Restage

CS IB, IIB → Chemotherapybb ± Rituximab ± ISRTm → Deauville 1-3° → Observe
or
Deauville 4-5° → Observe, if asymptomatic or
Second-line therapy (See HODG-18)
or RTm (if no prior RT)

CS IIIA, IVA → Chemotherapybb ± Rituximab ± RTm → Deauville 1-3° → Observe
or Observation (category 2B) or
Local RT (palliation only)

CS IIIB, IVB → Chemotherapybb ± Rituximab ± RTm → Deauville 4-5° → Observe, if asymptomatic or
Second-line therapy (See HODG-18)
or RTm (if no prior RT)
German Hodgkin Study Group
Annals of Oncology 2005;16:1683

IA without risk factors (n=131)

Log-Rank: p=0.8037
EF-RT: 100%
IF-RT: 92%
CM: 97%
I-IIA without bulky disease (10 cm)
N=88
NLP HL
Radiation Fields
Relapsed Hodgkin Lymphoma
Lancet 2002;359:2065

Figure 3: Freedom from treatment failure for patients with relapsed chemosensitive Hodgkin’s disease

Number of patients
BEAM-HSCT  61  43  34  25  13  8  7  0
Dexa-BEAM  56  27  20  15  10  8  5  1
Hodgkin Lymphoma
Conclusions

- Early-stage favorable (ABVD X 2 + 20 Gy ISRT)
- Early-stage unfavorable (ABVD X 4 + 30 Gy ISRT)
- Advanced disease (ABVD X 6 +/- ISRT)

- Current studies
  - Evaluating interim PET to adapt therapy
    - Escalation- more aggressive chemotherapy
    - De-escalation- elimination of RT; fewer chemotherapy cycles
  - Brentuximab
Non-Hodgkin Lymphoma
Non-Hodgkin Lymphoma

- Diffuse Large B-cell Lymphoma
- Follicular Lymphoma
- Marginal Lymphoma
- Plasmacytoma/Myeloma
- Cutaneous Lymphomas
- NK/T-cell Lymphoma, Nasal Type
DLBCL

Pearls

• ~50% stage I-II; ~50% stage III-IV
  – ~80% stage III-IV in FL

• ~40% have extranodal disease
  – rare in FL (except bone marrow)

• “Double hit” DLBCL- t(14;18) and MYC rearrangements- more aggressive

• Testicular DLBCL- propensity to involve CNS and contralateral testicle (prophylactic RT)

• Primary mediastinal DLBCL- unique entity
The IPI
NEJM 1993;329:987

Age (≤ 60 vs > 60)  
LDH (nl vs abnl)  
PS (0-1 vs 2-4)  
Stage (I-II vs III-IV)  
Extranodal dz (0-1 vs >1)  

OS (5)  
Low (0-1) – 73%  
Low intermediate (2) - 51%  
High intermediate (3) – 43%  
High (4-5) – 26%

R-CHOP- Add ~10%
DLBCL

• Early-Stage Disease
  – Chemotherapy (R-CHOP)
  – Chemotherapy + Radiation Therapy

• Advanced Disease
  – Chemotherapy
    • RT for limited stage III, bulky disease, persistent PET positive disease
GELA (LNH98-5)
NEJM 2002;346:235; JCO 2005;23:4117

Patients (n=399), age 60-80 y/o; Stage II-IV DLBCL

Randomized to:
A. CHOP X 8
B. R-CHOP X 8

Rituximab- Chimeric monoclonal antibody to CD20 (B-cells)
Improved outcomes irregardless of IPI score
ECOG 1484
JCO 2004;22:3032

- Stage I-II diffuse aggressive lymphomas
  - DLBCL 80%
- Bulky stage I, IE, II
  - 68% stage II
  - 31% bulky (>10 cm)
- 8 cycles of CHOP. If CR by CT, then randomized to:
  - Consolidation RT (30 Gy)
  - Observation
- Primary endpoint- disease-free survival (20%)
ECOG 1484
Disease-Free Survival

![Graph showing disease-free survival with CHOP and CHOP + RT groups. The Log-rank two-sided P value is 0.05.]

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<td>Obs</td>
<td>24/93</td>
<td>11/69</td>
<td>6/58</td>
<td>2/50</td>
<td>2/45</td>
<td>4/36</td>
<td>2/22</td>
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(# events/# at risk)
ECOG 1484
Overall Survival

Log-rank two-sided $P=.24$

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(# events/# at risk)
• Stage I-II intermediate or high-grade NHL
  – 75% DLBCL
• Stage I (67%) or non-bulky stage II
• Randomized to:
  – CHOP X 8
  – CHOP X 3 + RT (40-55 Gy)
• Primary endpoint- not stated
SWOG 8736
Progression-free survival

More toxicity in CHOP X 8

Overall Survival
82% vs 72% (p=0.02)
• Younger patients (< 61 years) with stage I-II aggressive NHL
  – 81% DLBCL

• No risk factors

• Randomized to:
  – 3 cycles of ACVBP + consolidation CT
  – 3 cycles of CHOP + RT (40 Gy)

• Primary endpoint- event-free survival (10%)
Overall survival - 82% vs 74% (p<0.01)
Substantial toxicity.
GELA LNH 93-4
JCO 2007;25:787

• Older patients (> 60 years) with stage I-II aggressive non-Hodgkin lymphoma
  – 80% DLBCL
• No risk factors (bulky disease, elevated LDH, poor performance status)
• 4 cycles of CHOP
• Randomized to:
  – Consolidation RT (40 Gy)
  – Observation
• Primary endpoint event-free survival (10%)
RT markedly delayed and 12% didn’t receive it
Local failure 7% vs 18% (crude rates)
Stage I-II DLBCL
Conclusions

• Consolidation RT decreases risk of relapse at treated sites and overall risk of relapse
  – Local failure- 4-7% (crude)
• 3 cycles of R-CHOP inadequate for most patients
• Older patients, especially those with favorable disease and/or comorbidities, may derive less benefit from RT
Radiation Therapy in the Rituximab and PET Era
Benefit of RT with Rituximab
JCO 2010;28:4170

- MD Anderson retrospective analysis
  - N=327 received 6-8 cycles of R-CHOP and in CR by PET
- Stage I-II (37%) or stage III-IV (63%)
- RT (30-40 Gy) vs no RT
Progression-free Survival

JCO 2010;28:4170

HR (MVI)- 0.32
Overall Survival

JCO 2010;28:4170

HR (MVI) - 0.19
Italy
Leukemia and Lymphoma 2011;52:1867

• Retrospective evaluation of patients from two prospective GISL trials
• Patients (n=182) with DLBCL treated with R-CHOP X 6 +/- RT (physician discretion)
  – RT (n=40)
  – No RT (n=142)
• RT patients younger, more early-stage disease, more bulky disease
A: OS by consolidative IF-RT

Cumulative probability

- RT no
- RT yes

Follow-up, months

HR = 0.34; P = 0.143

B: EFS by consolidative IF-RT

Cumulative probability

- RT no
- RT yes

Follow-up, months

HR = 0.28; P = 0.035
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

Courtesy A. Ng
30 Gy vs 40-45 Gy

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
Summary

- Stage I-II DLBCL
  - R-CHOP X 3-6 cycles
  - ISRT (30 Gy) decreases risk of relapse by ~60%

- Stage III-IV DLBCL
  - R-CHOP X 6 +/- ISRT
    - Bulky disease (JCO 2014 epub)
    - Skeletal involvement (JCO 2013;31:4115)
German High-Grade NHL Study Group
JCO 2013;31:4115

• Retrospective evaluation of 9 prospective studies
• RT recommended for extranodal disease (but not mandatory)
• MVA- RT improved EFS (HR 0.3, p=0.001)
RICOVER-60
JCO 2014 (in press)

- Best arm of RICOVER-60
  - R-CHOP-14+2R + RT for bulky or E disease
- Compared with additional amended arm without RT
- Among patients with bulky disease, RT improved outcomes
Primary Mediastinal DLBCL
Pearls

• Clinicopathologic entity
• Arises from thymic B-cells (extranodal site)
• WHO- arises in anterior mediastinum +/- cervical/supraclavicular LNs without disease elsewhere
• M:F ratio- 1:2; Median age 30s
• 70% have bulky disease
• Unique molecular signature
Primary Mediastinal B-cell Lymphoma
Annals of Oncology 2006;17:123

- PMBCL: n=153
  - CHOP-like
  - MACOP-B/VACOP-B
  - R-CHOP
Primary Mediastinal versus DLBC NOS
OS (A) and PFS (B)

A

Cumulative Survival

Overall survival (y)

B

Cumulative Survival

Progression free survival (y)

PMLBCL

DLBCL
DA-EPOCH-R

No Radiation

NEJM 2013;368:1408
Primary Mediastinal DLBCL

Conclusions

- R-CHOP + RT
- DA-EPOCH-R +/- RT
Follicular Lymphoma
Follicular Lymphoma
Role of RT

• Stage I or limited stage II
  – Definitive RT

• Stage III-IV (or extensive stage II)
  – Palliative RT
Localized
LymphoCare Study
JCO 2009;10:1202

- 2004-2007
- n=2728
  - N=474 with stage I
- 265 sites
  - Private- 80%
  - Academic- 20%
Figure 3. Utilization of upfront external beam radiation therapy for localized low-grade follicular lymphoma in the United States is shown by decade.
British Columbia
Cancer 2010;116:3797

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

FFTF- 49%
1961-1994; N=177
Stage I - 41%; Stage II 59%

FFTFT - 44%
UK
Br J Cancer 1994;69:1088

N=208
Stage I- 100%
Low-grade NHL

FFTFF- 49%
Stage I Follicular Lymphoma

Dose & Field
• Patients (n=361) with low-grade NHL requiring RT (curative or palliative)
  – 59% FL 72% curative 70% stage I-II
  – 19% MZL 28% palliative

• Randomized to:
  – 40-45 Gy
  – 24 Gy
(a) Freedom from local progression

% of patients without local progression

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

0 1 2 3 4 5 6 7 8 9 10

PATIENTS at Risk
High dose 181 160 150 131 107 79 52 37 23 9 3
Low dose 180 159 147 119 101 83 54 38 24 10 1

Events Totals
High dose 38 181
Low dose 42 180

HR=1.13 95% CI=0.73-1.75
Subset analysis- no difference in subgroup treated with curative intent
British Columbia
Cancer 2010;116:3797

P=0.498

LNs + 0-5 cm margin
Stage I Follicular Lymphoma
Left Axilla

Dose
2 Gy qd to 30 Gy
1973-2004  
N=6568  
RT- younger, stage I, no extranodal disease

Figure 1. Non-Hodgkin lymphoma-specific survival with or without upfront external beam radiation therapy (RT) is shown. HR indicates hazard ratio.
Figure 2. Overall survival in patients with low-grade, stage I-II follicular lymphoma treated with or without upfront external beam radiation therapy (RT) is shown. HR indicates hazard ratio.
Stage III-IV
Patients (n=630) with symptomatic grade 1-2, stage III-IV FL

Randomized to:
A. CHOP X 6-8
B. R-CHOP
CVP vs R-CVP
JCO 2008;26:4579

- Previously untreated follicular lymphoma
- Stage III-IV
- 8 cycles of CVP vs R-CVP
Study group indolent Lymphomas (StiL)
Lancet 2013;381:1203

- Patients with stage III-IV indolent lymphomas
- Randomized to R-CHOP or B-R
- B-R better tolerated

---

Median (IQR; months)
- B-R: 69.5 (26.1 to not yet reached)
- R-CHOP: 31.2 (15.2–65.7)

HR 0.58 (95% CI 0.44–0.74)
p<0.0001

Number at risk
<table>
<thead>
<tr>
<th></th>
<th>B-R</th>
<th>R-CHOP</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>207</td>
<td>185</td>
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<td></td>
<td>169</td>
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<td>24</td>
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<tr>
<td></td>
<td>19</td>
<td>9</td>
</tr>
</tbody>
</table>

Figure 2  Progression-free survival  B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab.
PRIMA
Lancet 2011;377:42

A

PFS

HR 0.55 (95% CI 0.44-0.68); p<0.0001

Number at risk
Rituximab 505 472 445 423 404 307 207 84 17 0
Observation 513 469 415 367 334 247 161 70 16 0

B

HR 0.60 (95% CI 0.47-0.76); p<0.0001

Number at risk
Rituximab 505 483 455 441 414 312 209 91 17 0
Observation 513 487 452 417 380 286 170 71 18 0

C

HR 0.62 (95% CI 0.47-0.81); p=0.0004

Number at risk
Rituximab 505 484 459 444 428 325 220 93 19 0
Observation 513 492 460 425 393 302 188 75 20 0

D

HR 0.87 (95% CI 0.51-1.47); p=0.60

Number at risk
Rituximab 505 499 492 483 474 365 246 108 22 1
Observation 513 507 501 492 472 381 243 97 26 0
Stage III-IV Follicular Lymphoma Palliation

• Netherlands (JCO 2003;21:2474), n=109
• 52% with disease ≥ 5 cm
• Prior regimens (median 2, range 0-11)
• 2 Gy X 2 or 4 Gy X 1
• ORR 92% (CR 61%, PR 31%, SD 6%)
• 25 months median time to local progression (42 months in patients with CR)
• Well tolerated
Follicular Lymphoma
Conclusions

• Stage I/II
  – RT alone
  – 24-30 Gy
  – ISRT with appropriate CTV expansion (no chemotherapy)
  – Expected outcomes- ~50% 10-year FFP
  – Patterns of failure- distant

• Stage III-IV
  – R-CHOP +/- maintenance R, R-CVP, B-R
  – 2 Gy X 2 excellent palliative option
Marginal Zone Lymphoma
WHO Classification

- Nodal marginal zone lymphoma
- Splenic marginal zone lymphoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)
MALT Lymphoma

Pearls

• Locations
  – Stomach
  – Ocular adnexa (conjunctiva, lacrimal gland, retro-orbital space)
  – Salivary glands
  – Thyroid
  – Skin, lung, breast……anywhere

• Presentation- IE, no B-symptoms, very favorable outcomes

• Treatment
  – Antibiotics for *H. pylori* + gastric MALT
  – RT for localized disease elsewhere
Gastric MALT Lymphoma

- *H. pylori* provides the antigenic stimulus for promoting and sustaining lymphoma development
- 90% of cases are *H. pylori* positive
  - Endoscopy & *H. pylori* assessment (H&E/HpSS)
  - t(11;18)- poor response to antibiotics
  - EUS (depth of involvement)
  - CT C/A/P or PET-CT; bone marrow usually -
- Numerous studies show clinical response to *H. pylori* eradication
  - PPI, amoxicillin, clarithromycin
Hp+ Gastric MALT
JCO 2005;23:8018

• Multi-institutional European prospective study
• Patients with IE Hp positive gastric MALT
  – mucosa and submucosa; no LNrs
• Treated with antibiotics and PPI
• EGD monthly until histologic CR, then every 6-12 months
• Failure defined as no change after 2 months or only partial remission after 6 months
Hp+ Gastric MALT
JCO 2005;23:8018

• N=120
• *Hp* eradicated in 116/120 (97%); 4- 2nd line
• CR (*macroscopic and histologic*) achieved in 80% (96/120)
  – 1-28 months; 61% within 3 months, 88% within 12 months
• NR (n=11) or PR (n=13)
  – 8 had DLBCL; 1 had T-cell lymphoma
• Of the 96 who achieved CR…..
EFS 68%

- Death (n=7)
  - 0 from lymphoma

- Relapse
Hp+ Gastric MALT
JCO 2005;23:8018

120 patients with stage I1E Hp-positive gastric MALT lymphoma

Eradication of Helicobacter pylori

CR (n = 96)

PR/NC (n = 24)

Endoscopic-bioptic follow-up

CCR (n = 77)

hRD (n = 16)

Watch and wait

2nd CR (n = 16)

Relapse (n = 3)

2nd-line treatment

2nd-line treatment

2 deaths (DLBCL and T-cell lymphoma)

Duration in CR: Median 32 months (0-101)
Fischbach et al.
Gut 2007;56:1685

Gastric MALT lymphoma stage I
n = 108

Macroscopic CR
Histologic PR

Hp eradication

Minimal residuals
Hp negative after 12 months

CR n = 35 (32%)

Minimal residuals unchanged
n = 67 (62%)

PD n = 6 (6%)

58 months f/u

36 months f/u
Risk Factors
JCO 2005;23:8018

- Ongoing monoclonality (RR 6.3, p=0.0007)
- t(11;18) (RR 3, p=0.004)
  - JCO 2005;23:8018

- Deep invasion of gastric wall

- Involved perigastric lymph nodes
  - Gut 2004;53:34-37
  - Gastroenterology 1997;113:1087
  - Ann Intern Med 1999;131:88-95
  - Gut 2001;48:297
# Radiation Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>RT dose</th>
<th>Outcomes</th>
<th>Patterns of Failure</th>
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<tbody>
<tr>
<td>1 Dana Farber</td>
<td>21</td>
<td>30 Gy</td>
<td>LC 21/21</td>
<td>2 patients failed distally</td>
</tr>
<tr>
<td>2 PMH</td>
<td>25</td>
<td>25-30 Gy</td>
<td>LC 15/15</td>
<td></td>
</tr>
<tr>
<td>3 Japan</td>
<td>8</td>
<td>30 Gy</td>
<td>LC 8/8</td>
<td></td>
</tr>
<tr>
<td>4 MSKCC</td>
<td>17</td>
<td>30 Gy</td>
<td>LC 17/17</td>
<td></td>
</tr>
</tbody>
</table>

1 Annals of Oncology 2007;18:672  
2 Cancer 2010;116:3815  
3 Gastroenterology and Hepatology 2010;25:804  
4 JCO 1998;16:1916
IEA H. pylori- Gastric MALT

- Simulation
  - Fasting 3h
  - 4D CT or BH
- Planning-
  3D/IMRT to avoid kidneys, liver, heart
- Dose- 1.5 Gy qd to 30 Gy
- Volume- Stomach with 2 cm margin
- Anti-emetics
IEA Parotid MALT
2 Gy qd to 24 Gy
IEA Conjunctival MALT
2 Gy qd to 24 Gy
Marginal Zone Lymphoma

Summary

• Most patients present with IE disease
• Radiation preferred approach
• RT technique
  – Field- whole organ
  – 24-30 Gy
• LC 95-100%; Survival excellent
• Disease in paired organs (eyes, parotid) tend to have higher relapse rates (distant relapse)
Plasma Cell Dyscrasias

- **MGUS**: Serum or urine M-protein without bone lesions, end-organ damage, and < 10% plasma cells in bone marrow
- **Smoldering myeloma**: >10% BM involvement but no bone lesions or end-organ damage
- **Multiple myeloma**: >10% BM involvement + 1 (M protein, bone lesions, plasmacytoma, organ damage)
- **Solitary Plasmacytoma**: Osseous or extramedullary plasmacytoma, <10% BM involvement, no end organ damage, +/- M protein
Solitary Plasmacytomomas

- Osseous or extraosseous
- Treatment- RT alone
- Dose- 40-45 Gy
- Volume
  - Osseous- Involved lesion + margin
  - Extraosseous- Involved lesion +/- regional LNs (H&N)

Osseous- 70% risk of myeloma
Extra-osseous- 35% risk of myeloma

Fig. 2. Actuarial probability of progression to multiple myeloma according to bone (dotted line) vs. extramedullary (solid line) solitary plasmacytoma in 258 patients ($p = 0.0009$).
Cutaneous Lymphomas

- T-cell (75%)
  - Mycosis fungoides (70%)
  - CD30 positive lymphoproliferative disorders (30%)
    - Lymphomatoid populosis
    - Primary cutaneous anaplastic large cell lymphoma
  - Primary cutaneous peripheral T-cell lymphomas, rare subtypes (1%)
    - Primary cutaneous gamma-delta T-cell lymphoma
    - Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma
    - Primary cutaneous CD4 positive small/medium T-cell lymphoma

- B-cell (25%)
  - Primary cutaneous marginal zone B-cell lymphoma (25%)
  - Primary cutaneous follicle center lymphoma (60%)
  - Primary cutaneous DLBCL, leg type (15%)
Primary Cutaneous B-cell Lymphoma
Dutch Cutaneous Lymphoma Group

Arch Dermatol 2007;143:1520

• N=153 (1985-2005)
• Re-classified according to WHO-EORTC
• All received radiation therapy
  – 20-46 Gy (median 40 Gy)
  – Tumor + 2 cm margin
• CR 99%
Disease-Specific Survival

- PCMZL (n=25)
- PCFCL (n=101)
- PCLBCL, LT (n=27)

Follow-up, mo
Cumulative Survival
Dutch Cutaneous Lymphoma Group
Arch Dermatol 2007;143:1520

Relapse-Free Survival

![Graph showing relapse-free survival rates](image)

- FCL: 72% recurrences cutaneous
- MZL: 80% recurrences cutaneous
- Leg-type: 44% recurrences cutaneous
Italian Study Group for Cutaneous Lymphomas  
Zinzani P L et al. JCO 2006;24:1376-1382

• N=467 (1980-2003) from 11 Italian centers
• Pathology reclassified WHO/EORTC
• RT or surgery for single/localized disease
  – 35-45 Gy
  – CR 98% for FCL/MZL and 81% DLBCL, leg type
• Chemotherapy for DLBCL, leg type or disseminated cutaneous involvement
  – CHOP
  – CR 76-86% for FCL/MZL and 80% for DLBCL, leg type
(A) Time-to-progression curve according to the WHO-European Organisation for Research and Treatment of Cancer (EORTC) diagnosis (P = .039); (B) overall survival of all patients; (C) disease-free survival of all patients; (D) overall survival by histology; (E) DFS according to extent of cutaneous disease
Overall survival of primary cutaneous follicle center lymphoma (PCFCL) and primary cutaneous large B-cell lymphoma, leg type (PCLBCL LT) further subdivided by site.
PCBCL
2 Gy qd to 30 Gy (MZL) - 36 Gy (FCC)
CD30+ Lymphoproliferative Disorders
CD30+ Lymphoproliferative Disorders

Lymphomatoid papulosis

- Indolent lymphoproliferative disorder
- Chronic, recurrent, self-healing skin disease
- Disappear within 3-12 weeks
- Typically multifocal
- Histologically indistinguishable from ALCL
- A monoclonal population may be detected
- 20% of patients may develop another malignant lymphoma

Cutaneous ALCL

- Cutaneous lymphoma
- Persistent/progressive entity
- Can spontaneously regress
- Typically solitary or localized group of nodules +/- ulceration
- Regional LNs+ in ~10%
Primary Cutaneous ALCL

RT alone- 40 Gy
Overall Survival

Cumulative Survival (%)

Follow-up (years)

Dutch Cutaneous Lymphoma Group
Blood 2000;95:3653-3661

- Lymphomatoid papulosis (n=118)
- CD30+ LTCL with concurrent skin and draining lymph node involvement (n=11)
- Primary CD30+ LTCL (n=79)
- Secondary CD30+ LTCL (n=11)

ALCL
RT - 99% CR
40% relapsed
90% of relapses cutaneous
CD30+ LP Disorders- Stanford

Disease-Specific Survival

- RT (ALCL)
  - 86% CR
  - 71% long-term control
Nasal NK/T-cell Lymphoma
1314 PTCL and NKTCL cases from 22 institutions

NKTCL- North America (5%), Europe (4%), and Asia (22%)
Patients (n=33) with IE or IIE untreated extranodal NKTCL, nasal type

RT
- 2 Gy qd to 50 Gy (lesion and entire nasal cavity and paranasal sinuses +/- LNs if involved)

Chemotherapy (DeVIC)
- Dexamethasone, etoposide, ifosfamide, carboplatin X 3 cycles
- Dose level 1 (2/3 DeVIC MTD)
Patients treated with 2/3rds DeVIC)
Phase II Trial (Korea)
JCO 2009;27:6027

• Patients (n=30) with IE or IIE extranodal NK/T-cell lymphoma, nasal type

• RT
  – 2 Gy qd to 40 Gy (lesion and margin +/- elective cervical LNs)

• Chemotherapy
  – Concurrent cisplatin (30 mg/m2 IV) with RT
  – Adjuvant etoposide, ifosfamide, cisplatin, dexamethasone X 3 cycles
Phase II Trial (Korea)
JCO 2009;27:6027

A

CHOP then RT

B

Overall Survival

Progression-Free Survival

Time (months)

CCRT + VIPD
Di-CHOP + RT

P = .044

P = .022

Time (months)
NCCN Guidelines Version 1.2014
Extranodal NK/T-Cell Lymphoma, nasal type

STAGE

No risk factors present →
Clinical trial or RT alone
or Concurrent chemoradiation
or Sequential chemoradiation

Presence of ANY risk factor →
Clinical trial or Concurrent chemoradiation
or Sequential chemoradiation

Stage I → Assess risk factors
Stage II
Stage IV

Extranodal → Stage I, II, IV

Risk factors (includes elements of NK/T-cell Lymphoma PI on NKTL-A)

- Age >60 y
- B symptoms
- ECOG PS ≥2
- Elevated LDH
- Regional node involvement
- Local tumor invasion (LTI); bone or skin
- Histologic evidence of high Ki-67 staining
- EBV DNA titer

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)


See Suggested Treatment Regimens (NKTL-B).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Questions