Early-stage Classical Hodgkin Lymphoma (CHL): Can We Eliminate Radiation Therapy for Most Patients?

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Learning Objectives

• Describe the challenges associated with the management of early stage CHL and the need to develop individualized treatment options

• Review the evidence from recent clinical trials evaluating the use of chemotherapy alone for early stage CHL

• To understand the evolving criteria used in interpretation of PET scans (Deauville Criteria)

• To understand the potential use and limitations of PET scans in guiding treatment decisions in early stage CHL
Stage I-II Classical Hodgkin Lymphoma (CHL)
Evolution of “The Gold Standards”

• Late 1960’s-1970’s: Extensive Radiation Therapy (RT)
• Late 1970’s-1990’s: Aggressive combined modality therapy (CMT) with extended field RT
• Mid 1990’s: Reduced intensity CMT with involved field RT
• Current CMT: Further reduction in chemotherapy with involved nodal/involved site RT
• Current focus: PET-adapted strategies to assess if RT can be eliminated
Evolution of Radiation Therapy

- Involved Field Radiation Therapy (IFRT)
  - Treats entire lymphoid regions defined by arbitrary anatomic landmarks

- Involved Site Radiation Therapy (ISRT)
  - Targets only the specific volume initially involved with minimal margins

- Involved Nodal Radiation Therapy (INRT)
  - Special case of ISRT where pre-chemo PET-CT in treatment position required
  - More accurate volume definition of treatment field
Evolution of RT: IFRT vs INRT


Implications for Transition to IFRT
Clinical Evidence of Reduction in Breast Cancer Risk

63% reduction in Relative risk of breast cancer

Stage I-II CHL
ABVD X 4 + IFRT: Established Standard of Care
Long-Term Results (12 years)

Freedom From Progression (FFP)
93% vs 94%

Overall Survival (OS)
96% vs 94%

Stage I-II CHL: Key Issues

- Definition of “favorable” vs “unfavorable” early stage disease
- Can risk-adapted strategies be employed to omit radiation therapy?
- Considerations for the treatment of patients with bulky mediastinal disease
- Future considerations
  - Incorporation of novel agents
  - Identification of biological subsets to guide therapy
Stage I-II CHL: Key Issues

• Definition of “favorable” vs “unfavorable” early stage disease
Risk Factors in Early Stage CHL

**Risk Factors: Variably defined**

<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>≥1 extranodal lesion*</td>
<td>Age ≥ 50 years</td>
<td>Bulk &gt; 10 cm</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>≥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>

Outcomes in Early stage CHL Using Risk Definitions: GHSG, EORTC, or NCCN

All definitions work largely because of significant overlap in risk factors

# HL Clinical Trial Treatment Groups
## Europe vs North America

<table>
<thead>
<tr>
<th>Europe (GSHG, GELA, EORTC)</th>
<th>USA/Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early favorable Stage</td>
<td>Early favorable Stage</td>
</tr>
<tr>
<td>CS I, IIA, B</td>
<td>Limited stage</td>
</tr>
<tr>
<td>No risk factors</td>
<td></td>
</tr>
<tr>
<td>Early unfavorable Stage</td>
<td>Early unfavorable Stage</td>
</tr>
<tr>
<td>CS I, IIA, B</td>
<td></td>
</tr>
<tr>
<td>(Intermediate)</td>
<td></td>
</tr>
<tr>
<td>B Sx</td>
<td></td>
</tr>
<tr>
<td>ESR &gt; 50 mm</td>
<td></td>
</tr>
<tr>
<td>Bulky disease</td>
<td></td>
</tr>
<tr>
<td>&gt; 2-3 nodal sites</td>
<td></td>
</tr>
<tr>
<td>Men over 40 y of age</td>
<td></td>
</tr>
<tr>
<td>Advanced stage</td>
<td>Advanced stage</td>
</tr>
<tr>
<td>CS III-IV, Selected CS IIB</td>
<td></td>
</tr>
</tbody>
</table>

Early Stage Classical Hodgkin Lymphoma (CHL)

Expected outcomes and goals of therapy in 2016

<table>
<thead>
<tr>
<th></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 with risk factors)</td>
<td>80-85</td>
<td>Increase Efficacy <em>without</em> any increase in toxicity</td>
</tr>
</tbody>
</table>

Risk Factors: Variably defined

- Large mediastinal mass
- Extranodal lesions
- ≥ 3 nodal sites
- ↑ ESR
- age > 40
- MC histology
Case 1: Early Stage CHL

- 36-year-old woman presents with a 2-month h/o pruritus. She denies fevers, night sweats, or weight loss

- Exam: well appearing and has a 2 cm L neck mass

- PET/CT scan: bilateral supraclavicular nodes measuring ~ 2 cm (SUV 6-8) and an upper mediastinal node measuring 5 x 2 cm (SUV 11.1)

- Excisional biopsy: classical HL, nodular sclerosing type

- Labs: WBC 5.6 K/µL with a normal differential, Hgb 12.7 g/dL, plt 154 K/µL, ESR 45, normal renal and hepatic function

- Final Diagnosis: Stage II A CHL
Case 1: Therapy Choices for Stage IIA disease

1: ABVD x 2 + 20 Gy ISRT
2: ABVD x 4 + 30 Gy ISRT
3: Stanford V 8 weeks + 30 Gy ISRT
4: ABVD x 2 + Esc BEACOPP x 2 + ISRT
5: ABVD x 3-4
6: ABVD x 6

# Combined Modality Therapy in CT Era
Overall Survival > 94% in Early stage CHL

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Chemo</th>
<th>RT</th>
<th>OS (%)</th>
<th>Years</th>
</tr>
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<tbody>
<tr>
<td>Milan INT</td>
<td>70</td>
<td>ABVD</td>
<td>IF 30 Gy</td>
<td>94</td>
<td>12</td>
</tr>
<tr>
<td>GHSG HD10</td>
<td>1190</td>
<td>ABVD</td>
<td>IF 20-30 Gy</td>
<td>94.5</td>
<td>10</td>
</tr>
<tr>
<td>GHSG HD11</td>
<td>1395</td>
<td>ABVD Esc BEACOPP</td>
<td>IF 30 Gy</td>
<td>94.5</td>
<td>10</td>
</tr>
<tr>
<td>GHSG HD14</td>
<td>1431</td>
<td>ABVD 2+2</td>
<td>IF 30 Gy</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>EORTC H9U</td>
<td>277</td>
<td>ABVD</td>
<td>IF 30 Gy</td>
<td>95</td>
<td>4</td>
</tr>
<tr>
<td>Stanford/Kaiser G4</td>
<td>87</td>
<td>Stanford V</td>
<td>IF 30 Gy</td>
<td>94</td>
<td>12</td>
</tr>
</tbody>
</table>

Questions

• Can favorable patients receive less treatment?

• Should early stage unfavorable patients receive more treatment?

• Can we better select patients for chemotherapy alone?
NCIC H6 Trial: CT Adapted Therapy
Overall Survival and Freedom From Disease Progression

CT scans used to define response which is different from current paradigms which use PET scans

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

PET/CT Imaging
Potential Uses In CHL

• Staging: YES
• Response assessment: YES
  • End of therapy (EOT)

  • Treatment modification based on PET/CT
    • EOT
    • Interim

• Can modification of Rx based on EOT or interim PET/CT have the potential to select patients for treatment escalation or de-escalation?

• Do these modifications have the potential to improve outcomes?
Report ‘Wording’ Nightmares for Clinicians

Common report

• Excellent response, there is minimal residual uptake in a para aortic node which could represent treated disease. Residual lymphoma cannot be excluded.
Deauville 5-Point Scoring System

Score
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

The Prognostic Value of Interim PET Scan in Patients With Early Stage CHL

MD Anderson retrospective study using Deauville Criteria

Early Stage CHL

Does a reduction in therapy based upon a negative interim PET impact PFS?

Prospective Studies
UK NCRI RAPID Trial: Stage I-IIA Non-Bulky

C. Stage I/II (non-bulky)
   - 3 x ABVD
     - *PET –
       - Standard Arm
       - Experimental Arm
         - 30 Gy IFRT
         - No further treatment

≥7% difference in PFS
~ 36% would have been considered unfavorable by GHSG or EORTC criteria

## UK NCRI RAPID Trial: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Negative PET Findings</th>
<th>Positive PET Findings (N=145)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radiotherapy (N=209)</td>
<td>No Further Treatment (N=211)</td>
</tr>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Range</td>
<td>16–74</td>
<td>16–75</td>
</tr>
<tr>
<td>Sex — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>103 (49.3)</td>
<td>107 (50.7)</td>
</tr>
<tr>
<td>Female</td>
<td>106 (50.7)</td>
<td>104 (49.3)</td>
</tr>
<tr>
<td>Ann Arbor stage — no. (%)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>69 (33.0)</td>
<td>70 (33.2)</td>
</tr>
<tr>
<td>IIA</td>
<td>140 (67.0)</td>
<td>141 (66.8)</td>
</tr>
<tr>
<td>Favorable pretreatment features — no./total no. (%)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC criteria¹⁴</td>
<td>118/184 (64.1)</td>
<td>122/185 (65.9)</td>
</tr>
<tr>
<td>GHSG criteria¹³,²⁴</td>
<td>114/175 (55.1)</td>
<td>136/184 (73.9)</td>
</tr>
</tbody>
</table>


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UK NCRI RAPID Trial: Stage I-IIA Non-Bulky

UK NCRI RAPID Trial: Conclusions

• Overall excellent outcomes

• PET score after 3 cycles ABVD had prognostic value in terms of EFS but EORTC/GHSG pre-treatment stratification did not

• PET score 5 is a particularly adverse feature
  • 5 episodes of progression and 3 HL deaths in 23 patients

• Findings need to be validated in other series of patients with early stage CHL

• If confirmed the role of PET in individualized treatment planning is strengthened
PET scans scored according to the International Harmonization Project criteria
- PET negative: Deauville score 1 or 2

EORTC H10 Trial: PET– Group
Futility Confirmed in Both Arms

5-Point Scale (Deauville Criteria) for Interpretation of Interim-PET scans

1. No uptake
2. Uptake ≤ mediastinum
3. Uptake > mediastinum but ≤ liver
4. Moderately increased uptake compared to liver
5. Markedly increased uptake compared to liver or new areas of FDG uptake

CALGB 50604 Progression Free Survival
Post cycle 2 ABVD PET- and PET+ Patients

Follow-up time
Median: 2.1 years
Range: < 1 month – 4.3 years
1 Death (Suicide – PET+)

Est. 3-yr PFS Hazard Ratio
PET - 92% (84%-96%) 6.04 (1.82-20.08)
PET + 66% (32%-86%)

Courtesy Dr Strauss  ASH  2015
Stage I-II CHL: Key Issues

Considerations in patients with bulky mediastinal disease

• Responses not reported separately for bulk vs other factors in most studies

• Therapy varies across different study groups
  • GHSG: bulk alone: treated on early stage unfavorable studies
    • ie, HD11 and HD14
  • GHSG: bulk + EN/B symptoms: treated on advanced stage studies
    • HD15 (esc BEACOPP x 6)
  • North America: By and large treated as advanced disease
Randomized Phase III Studies Which Included Stage I-II X CHL

<table>
<thead>
<tr>
<th>Study (%) bulky mediastinal mass</th>
<th>Treatment Arm</th>
<th>N</th>
<th>Median Follow-up (yrs)</th>
<th>Overall Response Rate (%)</th>
<th>Outcome (% of pts)</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North American Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG 2496 (subset with stage I-IX mediastinal HL)(100%)</td>
<td>ABVD x 6–8 + 36 Gy IRFT</td>
<td>136</td>
<td>5.47</td>
<td>82</td>
<td>5-yr FFS: 85</td>
<td>5-yr: 95</td>
</tr>
<tr>
<td>Stanford V</td>
<td>131</td>
<td>5.47</td>
<td>86</td>
<td>5-yr FFS: 77</td>
<td>5-yr: 92</td>
<td></td>
</tr>
<tr>
<td>European Trials (Bulky subsets were not separately reported.)</td>
<td>EORTC H9-U[35,36] (NR)</td>
<td>ABVD x 6 + 30 Gy IRFT</td>
<td>276</td>
<td>NR</td>
<td>87</td>
<td>4-yr FFS: 94</td>
</tr>
<tr>
<td>EORTC H10-U[37] (NR)</td>
<td>ABVD x 4 + 30 Gy IRFT</td>
<td>277</td>
<td>NR</td>
<td>86</td>
<td>4-yr FFS: 89</td>
<td>4-yr: 95</td>
</tr>
<tr>
<td>BEACOPP x 4 + 30 Gy IRFT</td>
<td>255</td>
<td>NR</td>
<td>84</td>
<td>4-yr FFS: 91</td>
<td>4-yr: 93</td>
<td></td>
</tr>
<tr>
<td>GHSG HD11[25] (17% to 22%)</td>
<td>ABVD x 4 + 30 Gy IRFT</td>
<td>356</td>
<td>7.6</td>
<td>94.7</td>
<td>5-yr FFS: 87.2</td>
<td>5-yr: 94.3</td>
</tr>
<tr>
<td>ABVD x 4 + 20 Gy IRFT</td>
<td>347</td>
<td>7.6</td>
<td>92.8</td>
<td>5-yr FFS: 82.1</td>
<td>5-yr: 93.8</td>
<td></td>
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<tr>
<td>BEACOPP x 4 + 30 Gy IRFT</td>
<td>341</td>
<td>7.6</td>
<td>94.4</td>
<td>5-yr FFS: 87.9</td>
<td>5-yr OS: 94.6</td>
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<tr>
<td>BEACOPP x 4 + 20 Gy IRFT</td>
<td>351</td>
<td>7.6</td>
<td>94.6</td>
<td>5-yr FFS: 87.0</td>
<td>5-yr OS: 95.1</td>
<td></td>
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<tr>
<td>GHSG HD14[19] (18.7%)</td>
<td>ABVD x 4 + 30 Gy IRFT</td>
<td>765</td>
<td>3.6</td>
<td>95.0</td>
<td>5-yr FFS estimate: 89.1</td>
<td>5-yr estimate: 96.8</td>
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<tr>
<td>Escalated BEACOPP x 2 + ABVD x 2 + 30 Gy IRFT</td>
<td>763</td>
<td>3.6</td>
<td>95.7</td>
<td>5-yr FFS estimate: 95.4</td>
<td>5-yr estimate: 97.2</td>
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<tr>
<td>GHSG Advanced-Disease Protocols (Includes patients with stage I-IX plus extranodal sites or B symptoms. Bulky subsets were not separately reported.)</td>
<td>GHSG HD9[39] (bulky disease in 58% to 69% of pts; stage IIB in 9% to 16%)</td>
<td>COPP/ABVD x 8</td>
<td>261</td>
<td>10.2</td>
<td>85</td>
<td>10-yr FFTT: 64</td>
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<tr>
<td>Escalated BEACOPP x 8</td>
<td>466</td>
<td>9.3</td>
<td>88</td>
<td>10-yr FFTT: 70</td>
<td>10-yr: 80</td>
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<tr>
<td>GHSG HD12[40] (large mediastinal mass in 27.5% to 29.2%; stage IIB in 12.7% to 17.1%)</td>
<td>Escalated BEACOPP x 8</td>
<td>787</td>
<td>6.5</td>
<td>93.0</td>
<td>5-yr FFS: 86.4</td>
<td>5-yr: 92</td>
</tr>
<tr>
<td>Escalated BEACOPP x 4 followed by baseline BEACOPP x 4</td>
<td>787</td>
<td>6.5</td>
<td>91.1</td>
<td>5-yr FFS: 84.8</td>
<td>5-yr: 90.3</td>
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<tr>
<td>GHSG HD13[41] (large mediastinal mass in 29% to 30% stage III in 15% to 17%)</td>
<td>Escalated BEACOPP x 8</td>
<td>705</td>
<td>4.0</td>
<td>90.1</td>
<td>5-yr FFS: 84.4</td>
<td>5-yr: 91.9</td>
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<tr>
<td>Escalated BEACOPP x 6</td>
<td>711</td>
<td>4.0</td>
<td>94.2</td>
<td>5-yr FFS: 89.3</td>
<td>5-yr: 95.3</td>
<td></td>
</tr>
<tr>
<td>Baseline BEACOPP x 8</td>
<td>710</td>
<td>4.0</td>
<td>92.4</td>
<td>5-yr FFS: 85.4</td>
<td>5-yr: 94.5</td>
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</tr>
</tbody>
</table>

### Randomized Phase III Studies Which Included Stage I-II X CHL

#### Table: Results of Randomized Phase III Trials That Include Patients With Stage I-II Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Study (bulky mediastinal mass)</th>
<th>Treatment Arm</th>
<th>N</th>
<th>Median Follow-up (yrs)</th>
<th>Overall Response Rate (%)</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>North American Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG 2496 (subset with stage I-EX mediastinal HL) [33] (100%)</td>
<td>ABVD × 6–8 + 36 Gy IFRT</td>
<td>136</td>
<td>5.47</td>
<td>82</td>
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<td>Stanford V</td>
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<td>EORTC H9-U[35,36] (N)</td>
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</tr>
<tr>
<td></td>
<td>BEACOPP × 4 + 30 Gy IFRT</td>
<td>235</td>
<td>NR</td>
<td>84</td>
<td>4-yr FFS: 91</td>
</tr>
</tbody>
</table>

**E2496:** reported outcomes specifically in patients with bulky disease

Other studies have included 9-25% of patients with bulky disease


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E2496: Results in Stage I-II Bulky Mediastinal CHL

By Treatment Arm

By International Prognostic Score (IPS)

North American Studies in Bulky CHL: Risk- and PET-Adapted

**Alliance**
- Bulky stage I and II
- ABVD x 2
- PET/CT
  - Pos
    - BEACOPP x 4 + IFRT
  - Neg
    - ABVD x 4 (total 6) No RT

**ECOG/SWOG**
- Bulky stage I and II
- ABVD x 2
- PET/CT
  - Pos
    - BEACOPP x 4 + IFRT
  - Neg
    - ABVD x 4 + IFRT
**HD 16**

**D.**

- Stage I/II without RF*
  - Standard Arm
    - 2x ABVD PET (+/-)
    - 20 Gy IFRT
  - Experimental Arms
    - 2x ABVD PET-
    - Follow-up
    - 20 Gy IFRT
    - 2x ABVD PET+

**HD 17**

**E.**

- Stage I/II with RF*
  - 2x BEACOPP esc + 2x ABVD
    - PET -
      - 30 Gy IFRT
      - No Rx
    - PET +
      - 30 Gy IFRT
      - 30 Gy INRT

**Risk Factors:**
- > 2 nodal areas, ESR ≥ 50 (no B symp)
- ESR ≥ 30 (B sympt), MMR > 0.33 (no B sympt/or EN sites)


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Early Stage CHL: Summary of Prospective Trials

• Prognosis of patients with early favorable and unfavorable CHL is excellent

• PET negative patients (Deauville 2) after 2-3 cycles of ABVD
  • Excellent outcome, but experience slightly more treatment failure than those receiving RT
  • INRT/ISRT appears adequate to prevent relapse and may have fewer long-term/late effects than previously seen with IFRT
  • No difference in OS, but follow-up of PET-adapted therapy is very short

• CALGB: Deauville 3
  • Avoids RT in more patients.
  • Esc BEACOPP does not improve outcomes in PET positive patients
  • Need better front line therapy

CRITICAL TO HAVE PET-CT REPORTS BASED ON DEAUVILLE CRITERIA IF RESPONSE ADAPTED THERAPY IS BASIS FOR TREATMENT DECISIONS
Audience Polling Results

Case 1: Therapy Choices for Stage IIA disease

1: ABVD x 2 + 20 Gy ISRT
2: ABVD x 4 + 30 Gy ISRT
3: Stanford V 8 weeks + 30 Gy ISRT
4: ABVD x 2 + Esc BEACOPP x 2 + ISRT
5: ABVD x 3-4
6: ABVD x 6

Case 1: Therapy Choices for 36 y female with Stage IIA disease

3 nodal sites (bil neck and upper mediastinum)
GHSG: unfavorable
NCCN and EORTC: favorable

1: ABVD x 2 + 20 Gy ISRT

2: ABVD x 4 + 30 Gy ISRT

3: Stanford V 8 weeks + 30 Gy ISRT

4: ABVD x 2 + Esc BEACOPP x 2 + ISRT

5: ABVD x 3-4 (If interim PET negative)

6: ABVD x 6
Early-stage CHL: Can We Eliminate Radiation Therapy for Most Patients?

Optimizing Therapy

<table>
<thead>
<tr>
<th>Considerations</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy Alone</td>
<td>Combined Modality Therapy</td>
</tr>
<tr>
<td>• Females &lt; age 35 yr</td>
<td>• Patients with favorable disease, especially when it is possible to limit the duration of chemotherapy</td>
</tr>
<tr>
<td>• Axillary and mediastinal involvement</td>
<td>• Patients with a positive interim PET scan (~ 25%)</td>
</tr>
<tr>
<td></td>
<td>• Patients with bulky mediastinal adenopathy</td>
</tr>
</tbody>
</table>
Early-stage CHL
Can We Eliminate Radiation Therapy for Most Patients?

Balancing Risk With Benefit for the Individual

Disease Control

Optimal Survivorship
Stage I-II CHL: Future Considerations

• Incorporation of novel agents

• Identification of biological subsets to guide therapy
Incorporation of Novel Agents

• Brentuximab Vedotin
• Check Point Inhibitors (Nivolumab, Pembrolizumab)
• Studies combining these agents with AVD (doxorubicin, vinblastine, and dacarbazine) are ongoing in the front line setting
Identification of biological subsets to guide therapy
Molecular markers to define risk

Frequency of 9p24.1 Genetic Alterations and Outcomes

GEP of micro dissected Hodgkin RS cells correlates with treatment outcome in CHL

