Cure, Late Effects and Prevention in Hodgkin Lymphoma

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University of Toronto
Toronto, Canada

Objectives/Outline

• review progress in treatment of HL
• outline consequences of successful therapy
  - late effects
• demonstrate how prospect for late effects may be improving
• summarize screening/prevention data & recommendations
### Canadian Cancer Incidence 2005

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin's</td>
<td>850*</td>
</tr>
<tr>
<td>Non-Hodgkin's</td>
<td>6400</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>1850</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4000</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>22,200</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>21,800</td>
</tr>
</tbody>
</table>

* PMH: 80-100/yr

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#### Decline in mortality rate from HL in North America

![Graph showing decline in mortality rate from HL](image)

Aisenberg, Blood, 1999; Reprinted from Ries; NIH Publ 97-2789, 1997
HL Outcomes – Continued Improvement


SEER database: >16,000 pts 1980-2004

Relative survival:

<table>
<thead>
<tr>
<th></th>
<th>1980-84</th>
<th>2000-04</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 y</td>
<td>73%</td>
<td>85%</td>
</tr>
<tr>
<td>10 y</td>
<td>62%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Hodgkin Lymphoma: Hodgkin Lymphoma:

Recent Therapeutic Observations

Limited Stage Disease:

- Abbreviated CTx + IF RT is superior to STNI
  - Noordjik E et al; JCO 2006
    - EBVP
  - Ferme C et al; NEJM 2007
    - MOPP/ABV
  - Bonadonna et al; JCO 2004
    - ABVD + STNI or IFRT
Hodgkin Lymphoma: Recent Therapeutic Observations

**Advanced Stage Disease:**

ABVD is equivalent to MOPP/ABV but has less serious/fatal toxicity

- Duggan D et al; JCO 2006

- Esc BEACOPP is superior to COPP-ABVD

**EORTC, GELA, NCIC-CTG**

Advanced Stage HD (3+ IPI risk factors)

- Randomization
  - ABVD x 6-8
  - escBEACOPP x 4 + stdBEACOPP x 4

Primary outcome = 3 yr FFTF

SS = 592 with alpha = .05; beta = .2;

delta = 10% (70-80%)

Secondary Outcomes: survival, QoL, economic
GISL HD 2000
BEACOPP v ABVD v CEC

Federico M, J Clin Oncol 2009

Advanced Hodgkin Lymphoma
ABVD vs MOPP/ABV Hybrid
Intergroup CALGB, ECOG, SWOG, NCIC

<table>
<thead>
<tr>
<th></th>
<th>ABVD</th>
<th>MOPP/ABV</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>433</td>
<td>419</td>
<td></td>
</tr>
<tr>
<td>CR%</td>
<td>76</td>
<td>80</td>
<td>0.16</td>
</tr>
<tr>
<td>Progression %</td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>5 y FFS%</td>
<td>63</td>
<td>66</td>
<td>0.42</td>
</tr>
<tr>
<td>5 y OS%</td>
<td>82</td>
<td>81</td>
<td>0.82</td>
</tr>
</tbody>
</table>
865 stage I - II HD patients treated at PMH between 1968 and 1986

Overall survival

Long-Term Cause-Specific Mortality of Patients Treated for Hodgkin’s Disease

*J Clin Oncol* 2003
Long-Term Cause-Specific Mortality of Patients Treated for Hodgkin’s Disease

J Clin Oncol 2003

Cause of death
- Hodgkin’s disease
- Other than HD
- Second cancer
- Cardiovascular disease

Numbers at risk
1032 918 766 513 272 100
GELA H89 Trial: Chemotherapy +/- radiation for advanced stage HL; Causes of Death

- N = 533, median f/u 10 yrs
- 129 deaths:
  - Hodgkin lymphoma PD/rel: 60 (46%)
    - treatment: 15
    - salvage treatment: 7
  - Second cancer: 24 (19%)
  - Cardiovascular: 1
  - Unknown/not spec.: 22

Ferme C, Blood 2006

Second Cancers Briefly

- leading cause of death for HL survivors
- majority are solid tumors/carcinomas
  - minimum latency 5-10 yrs
- related to treatment exposure (dose), age
- cancer risk reduction, screening, prevention must be explored
Some notes on risks
Relative risk (RR) or observed/expected

- limited value:
  - moderate ↑ RR for common cause of death vs large ↑ for rare cause

Absolute excess risk (x per 10,000 person years)

- better way to judge what specific diseases contribute to excess mortality in HL survivors

(takes into account general population risk)

Long-Term Cause-Specific Mortality of Patients Treated for Hodgkin’s Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>RR (per 10,000 person-years)</th>
<th>AER (per 10,000 person-years)</th>
<th>25-year actuarial risk of death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid tumors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia and MDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Second Cancers – Relative Risks
32,591 HL survivors

female breast 2.0 (1.8-2.3)
lung 2.9 (2.6-3.2)
colon 1.6 (1.4-1.9)
esophagus 2.8 (1.8-4.0)
stomach 1.9 (1.5-2.4)
leukemia 9.9 (8.7-11.2)

Dores, et al. JCO, 2002

Female Breast Cancer in HD Survivors

Dores et al, JCO, 2002
Features of Secondary Breast Cancer in Women Treated for Hodgkin Lymphoma

- average age $\sim$40 (vs 65 in general population)
- latency from HL treatment $\sim$17 y (13-28)
- more often bilateral ($\sim$10-15% vs 3%)
- Family Hx usually negative
  - no excess BRCA1/2, p53, ATM mutations
- risk increases with duration of menstruation post-therapy (young age at Rx vs early menopause)

- often located in the upper outer quadrant
  -- in or at edge of radiation field
Clinical Features of Breast Cancer After XRT for HL

<table>
<thead>
<tr>
<th>Series</th>
<th>Women Studied</th>
<th>Cancers Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Dana Farber</td>
<td>79</td>
<td>12</td>
</tr>
<tr>
<td>PMH</td>
<td>100</td>
<td>12</td>
</tr>
</tbody>
</table>


Breast Cancer After HL

Screening
- radiation to chest (age 10-30) - start 8 yrs after RT
  mammography + MRI annual (together? or in sequence q 6 mos?)

Clin Radiology, 2004
Ca: Cancer J Clin, 2007
Mammographic Breast Density in HL Survivors

<table>
<thead>
<tr>
<th>BiRADs</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>7</td>
<td>42</td>
<td>43</td>
<td>7</td>
</tr>
</tbody>
</table>

Breast Cancer After HL

Screening
- radiation to chest (age 10-30) - start 8 yrs after RT
- mammography + MRI annual (together ? or in sequence q 6 mos?)

Primary Prevention
- ? hormonal manipulation during treatment
  - theoretical

Secondary Prevention
- tamoxifen, raloxifene recommended "for discussion" by ASCO, USP-STF
- no reference to radiation-associated risk
Childhood Cancer Survivor Study

- women treated with chest RT age 25-39 less likely to have screening mammogram in post 2 yrs than those age 40-50 (36.5% vs 76.5%)

  - regular: 18.6% vs 52.6%
  - never: 47% vs 8%
  - BSE: 38% vs 39%

- rates of screening for those age 40-50 similar to general population, even though risk is higher

- women who had physician recommendation were 3x more likely to have a mammogram

  Oeffinger K, JAMA 2009

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Barriers and Misconceptions

- avoidance, insurance issues, lack of physician support

- education of risk in context of health promotion (vs disease detection)

  Bober SL. J Cancer Educ, 2007
Dilemma for the Clinician

“What are the long-term risks of my treatment?”

- data re: late effects are from treatments no longer in use
- need “long-term” follow-up from patients treated with current treatment strategies

Evidence That Less Radiation Lowers Risk of Complications

1. Dose reductions decrease excess relative risk:

   35 Gy mantle → 35 Gy IFRT → 20 Gy IFRT

   breast ca ERR ↓ 65% ↓ 40%
   male lung ca ERR ↓ 35% ↓ 40%

Koh ES, Radiat Oncol 2007
Hodgson D, Cancer 2007
2. Relative risk depends on field size:
   Cohort analysis: 1150 women:
   EFRT (mantle) v IFRT (mediastinum)

   → 20% absolute reduction in 30 yr cumulative incidence of breast ca
   
   De Bruin. J Clin Oncol, in press

3. Meta-analysis of trials involving RT ± chemo:
   Reduction in field EF → IF
   → ↓ second breast cancer
   odds ratio 3.25 (p = 0.04)

   Franklin J, Ann Oncol, 2006

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Change in Systemic Chemotherapy?

Example of secondary AML (JNCI, 2006)

- >35,000 1 yr HL survivors
- 14 cancer registries (Nordic, N America)
- pts treated 1970-2001

1. Excess absolute risk higher in 1st 10 yrs of follow-up
2. Decline in AML incidence for pts treated after 1985, esp among those getting chemotherapy
Causes of death after treatment of early stage HL - Recent Data

<table>
<thead>
<tr>
<th></th>
<th>GHSG HD8*</th>
<th>NCIC-CTG HD6**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median F/U (mos)</td>
<td>54</td>
<td>50</td>
</tr>
<tr>
<td># of patients</td>
<td>1064</td>
<td>399</td>
</tr>
<tr>
<td># of deaths</td>
<td>77</td>
<td>15</td>
</tr>
<tr>
<td># deaths - HL (%)**</td>
<td>31 (40)</td>
<td>6 (40)</td>
</tr>
<tr>
<td># deaths - other (%)</td>
<td>46 (60)</td>
<td>9 (60)</td>
</tr>
</tbody>
</table>

** includes deaths due to acute treatment toxicities

*Engert, JCO 2003;  **Meyer, JCO: 2005

Why not just go without radiation? (unless it is really needed)

NCIC-CTG HD6:
Randomized trial to determine efficacy and long-term safety of strategy with no RT vs one that uses EF RT
NCIC–CTG HD-6: Treatment Arms

Randomize

Standard Arm: + RT
- Favourable
  EFRT (M+PA/spleen)
- Unfavourable
  CMT (ABVD x 2 + EFRT)

Experimental Arm
- Both Strata
  ABVD x 2
  If CR: x 2 more = 4
  If PR: x 4 more = 6

Assess Outcomes
Primary: 12 yr OS

FFP - All Patients

Δ = 7%
P = 0.006

Meyer, JCO 2005
Sites of Progression: extended field RT

<table>
<thead>
<tr>
<th></th>
<th>RT+/-ABVD</th>
<th>ABVD alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infield only</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Outfield only</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Both</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>


Overall Survival - All Patients

P = 0.4

Meyer, JCO 2005
Sites of Progression:
involved field RT
(hypothetical)

<table>
<thead>
<tr>
<th>RT +/-ABVD</th>
<th>ABVD alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infield only</td>
<td>2</td>
</tr>
<tr>
<td>Outfield only</td>
<td>6</td>
</tr>
<tr>
<td>Both</td>
<td>2</td>
</tr>
</tbody>
</table>


Salvage therapy + ASCT has its downsides too…
### Causes of Death post-ASCT

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Deaths</td>
<td>154</td>
<td>90</td>
<td>64</td>
</tr>
<tr>
<td>Progressive HD alone</td>
<td>104</td>
<td>56</td>
<td>48</td>
</tr>
<tr>
<td>Second Cancer</td>
<td>14</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Second Cancer &amp; Progressive HD</td>
<td>9</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Non-malignant treatment-related toxicity</td>
<td>23</td>
<td>22</td>
<td>1</td>
</tr>
</tbody>
</table>

### Competing Risks Analysis

<table>
<thead>
<tr>
<th></th>
<th>3 yrs</th>
<th>10 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>68 %</td>
<td>39 %</td>
</tr>
<tr>
<td>Failure Free Rate</td>
<td>50 %</td>
<td>40 %</td>
</tr>
<tr>
<td>Probability of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2\textsuperscript{nd} Cancer</td>
<td>5 %</td>
<td>12 %</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3 %</td>
<td>7 %</td>
</tr>
<tr>
<td>Solid Tumour</td>
<td>2 %</td>
<td>5 %</td>
</tr>
</tbody>
</table>
Why not just go without radiation? (unless it is really needed)

For example: Decisions aided by FDG-PET

Negative predictive value post chemo:
very high: 90-95% → “don’t need XRT”

Positive predictive value post chemo:
quite variable!

Gallamini A, J Clin Oncol 2007
RCT of Observation vs RT for Patients with Bulky HL and Negative Post Chemo PET Scan

Bulk: > 5 cm long axis*
Chemo: VEBEP 6 cycles
RT: 32 Gy

Negative PET: no uptake
Positive PET: “uptake in …abnormal area”

260 patients 2000-2006 n = 160 randomized
stage I, II ~ 2/3
B symptoms ~ ½

Radiation: mantle, inv Y, para-aortic


Relapse:

Chemo alone: 11/80 (14%)
Chemo + RT: 2/80 (2.5%)

**PET Scans and Early Progression in Advanced Hodgkin Lymphoma**

German HL Study Group Trial HD15

Patients: \( \text{II}_{\text{EB}} \) or \( \text{II}_B + \text{LMM}; \text{III} + \text{IV} \)

- esc BEACOPP x 8
- esc BEACOPP x 6
- BEACOPP-14 x 8

\( R \)

PET +, > 2.5 cm on CT → 30 Gy IFRT

Total n: 1788 For analysis: 817

*Blood 2008*

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**PET Scans and Early Progression in Advanced Hodgkin Lymphoma**

311 patients: <CR after chemo → PET scan

66 positive (21%) - 63 received XRT

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**Graph**

- CR
- PET-ve
- PET+ve
"Interim PET should remain at this time as a test to be evaluated as part of clinical research where treatment regimens and imaging conditions are standardized; thus it should not be employed in the routine setting.

"... outside of study protocols where treatment strategies are explicitly defined on the basis of scan results, biopsy should be considered for positive PET findings if they are used to prompt a change in patient management."

**RAPID – Trial Design**

**Initial treatment:** ABVD x 3

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

- **PET +ve** 20%
  - 4th cycle ABVD then IFRT

- **PET -ve** 80%
  - Randomization
  - IFRT
  - no further treatment
OK, make the radiation field very small…
Involved Node Irradiation

ABVD, XRT and the heart

- Doxorubicin-based chemotherapy improves the survival of Hodgkin lymphoma (HL) patients, and has become a standard component of initial treatment.

- Almost all studies of cardiac morbidity among HL patients precede the widespread use of this cardiotoxic drug.

- Most existing studies do not provide age and sex-adjusted estimates of absolute risk.

- Most focus on cardiac death, a blunt measure of treatment-related toxicity.
### 15-Year Incidence of Cardiac Hospitalization by Treatment

<table>
<thead>
<tr>
<th>Age at HL Dx</th>
<th>General Population (%)</th>
<th>Doxorubicin (%)</th>
<th>Chest RT (%)</th>
<th>Doxorubicin + Chest RT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>1.6</td>
<td>2.6</td>
<td>3.3</td>
<td>5.3</td>
</tr>
<tr>
<td>30</td>
<td>2.8</td>
<td>4.6</td>
<td>5.8</td>
<td>9.4</td>
</tr>
<tr>
<td>40</td>
<td>5.0</td>
<td>8.1</td>
<td>10.2</td>
<td>16.3</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>1.0</td>
<td>1.6</td>
<td>2.1</td>
<td>3.4</td>
</tr>
<tr>
<td>30</td>
<td>1.8</td>
<td>2.9</td>
<td>3.7</td>
<td>6.1</td>
</tr>
<tr>
<td>40</td>
<td>3.2</td>
<td>5.2</td>
<td>6.7</td>
<td>10.7</td>
</tr>
</tbody>
</table>

#### HD Subcohort and matched controls

40 years old men, no diabetes

- **Doxorubicin+Chest RT**
- **Doxorubicin only**
- **Chest RT only**
- **General population**

**Predicted probability of cardiac event**

**Time to cardiac event**
Conclusions

• Too soon to judge long-term toxicity/risks of modern Rx approaches
• Radiation and chemotherapy have been made safer…
  – smaller fields, limited alkylator exposure important
• Women need to be counseled re: value of breast Ca screening (mammography and MRI)
• Evaluation of prevention, screening strategies for other cancers, cardiovascular disease are important for thousands of HL survivors

Thank you to

• Mary Gospodarowicz, Richard Tsang, Woody Wells, Alex Sun
• Tracy Nagy, Norm Franke, John Kuruvilla, Armand Keating, Sahar Zadeh
• David Hodgson
• Melania Pintilie
• Ralph Meyer
## Lung Cancer – Dramatic Effects of Age, Treatment, Smoking History

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RT&gt;5 Gy</th>
<th>AA chemo</th>
<th>&gt;1 ppd smoker RR</th>
<th>others RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>no</td>
<td></td>
<td>1.0</td>
<td>6.0</td>
</tr>
<tr>
<td>yes</td>
<td>no</td>
<td></td>
<td>20.2</td>
<td>7.2</td>
</tr>
<tr>
<td>no</td>
<td>yes</td>
<td></td>
<td>16.8</td>
<td>4.3</td>
</tr>
<tr>
<td>yes</td>
<td>yes</td>
<td></td>
<td>49.1</td>
<td>7.2</td>
</tr>
</tbody>
</table>
Lung Cancer

Prevention?

Pharmacologic agents

“…subjects should only be encouraged to use chemo preventive agents in the context of a clinical trial”  
--- Proc ATS, 2009

Smoking cessation!

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Lung Cancer Screening:
Not ready for prime time

- no trials of CT scan vs observation
- high rate of non-calcified nodule detection (50%)
- costs of F/U CT: $$, radiation
- morbidity of biopsy/resection of benign nodules

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Jett, JR. Clin Cancer Res, 2005
Fertility

- most literature describes surrogate measures of fertility
  - FSH levels, azospermia
  - amenorrhea

Males: azospermic incidence
- ABVD/non-alkylator: 10%
- BEACOPP: 90%

Females: amenorrhea
- ABVD/non-alkylator: <5%
- BEACOPP: 50%

Time to pregnancy following ABVD

- median age at dx 25 y; age at pregnancy: 32y
- 2-6 cycles (med 4); 50% abd XRT
<table>
<thead>
<tr>
<th>Prevention?</th>
<th>Preservation!</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males:</strong></td>
<td>sperm cryopreservation</td>
</tr>
<tr>
<td></td>
<td>- even if “suboptimal”</td>
</tr>
<tr>
<td><strong>Females:</strong></td>
<td>ovarian suppression</td>
</tr>
<tr>
<td></td>
<td>- tissue/ovum cryopreservation</td>
</tr>
<tr>
<td></td>
<td>* data are poor</td>
</tr>
<tr>
<td></td>
<td>- IVF – expensive, need donor and takes time to perform</td>
</tr>
</tbody>
</table>