A retrospective multicenter analysis of elderly Hodgkin lymphoma: outcomes and prognostic factors in the modern era

Andrew M. Evens, DO, MSc¹, Irene Helenowski, PhD², Erika Ramsdale, MD³, Chadi Nabhan, MD⁴, Reem Karmali, MD⁵, Britt Hanson, DO⁶, Benjamin Parsons, DO⁴, Scott Smith, MD, PhD⁶, Annette Larsen, RN¹, June M. McKoy, MD, MPH, MBA⁷, Borko Jovanovic, PhD², Stephanie Gregory, MD⁶, Leo I. Gordon, MD,⁸ Sonali M. Smith, MD³

¹ Division of Hematology/Oncology, The University of Massachusetts Medical School, Worcester, MA; ²Department of Preventive Medicine, Northwestern University, Chicago, IL; ³Department of Medicine, Division of Hematology/Oncology, University of Chicago Hospitals, Chicago, IL; ⁴Department of Medicine, Division of Hematology/Oncology, Advocate Lutheran General Hospital, Park Ridge, IL; ⁵Division of Hematology, Rush University Medical Center, Chicago, IL; ⁶Division of Hematology/Oncology, Loyola University Medical Center, Maywood, IL; ⁷Division of Geriatric Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL; ⁸Division of Hematology/Oncology, Northwestern University, Chicago, IL;

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Correspondence to: Andrew M. Evens, D.O., M.Sc.
Division of Hematology/Oncology
The University of Massachusetts Medical School
55 Lake Avenue North
Worcester, MA 01655
Andrew.Evens@umassmed.edu
ABSTRACT

We investigated a recent (1/99-12/09) cohort of 95 elderly Hodgkin lymphoma subjects. At diagnosis, median age was 67 years (60-89), while 61% had significant co-morbidity, 17% had a geriatric syndrome, 26% were unfit, and 13% had loss of activities of daily living (ADL). Response rate to therapy was 85%, while incidence of bleomycin lung toxicity was 32% (associated mortality rate: 25%). With 66-month median follow-up, 2-year and 5-year overall survival (OS) were 73% and 58%, respectively (advanced-stage: 63% and 46%, respectively). Most IPS factors were not prognostic on univariate analyses, while multivariate regression identified 2 risk factors associated with inferior OS: 1) Age >70 years (2.24 (95%CI 1.16-4.33), p=0.02) and 2) Loss of ADLs (2.71 (95%CI 1.07-6.84), p=0.04). Furthermore, a novel survival model based on number of risk factors (0, 1, or 2) showed differential 2-year OS 83%, 70%, 13%, respectively (p<0.0001), and 5-year OS 73%, 51%, 0%, respectively (p<0.0001).
Introduction

Survival rates for elderly Hodgkin lymphoma (eHL), typically defined as ≥60 years of age, are disproportionately inferior compared with younger patients. Studies in the 1970s-1990s established five-year progression-free survival (PFS) or freedom from treatment failure (FFTF) rates for advanced-stage eHL of 30%-45% with 5-year overall survival (OS) rates of 40%-55%. There are limited data examining eHL outcomes in the modern era.

Additionally, a paucity of prognostic data exists for eHL, while the potential impact of functional status on survival is largely unexplored, including recent reports. The most established prognostic tool in HL is the International Prognostic Score (IPS), which utilizes 7 adverse clinical prognostic factors, including age >45 years, to predict outcome. However, only 9% of patients in that analysis were age >55 years, while none >65 years were included (personal communication, Volker Diehl).

Methods

We conducted a multicenter retrospective analysis of patients consecutively diagnosed and treated with eHL at 5 medical centers between January 1999 and December 2009; the study was approved by each institution’s IRB. All cases were pathologically confirmed by expert hematopathologists. Staging and therapy were at the treating physician’s discretion. Of 111 cases, 95 had complete data and were entered into a centralized database.

Functional status

Functional status was obtained retrospectively. Co-morbidity was determined using the Cumulative Illness Rating Scale (CIRS), which assesses basic chronic medical illnesses taking into account the severity of each and has been revised and validated to reflect common geriatric problems (CIRS-G). The presence of geriatric syndromes at diagnosis (dementia, delirium, depression, osteoporosis, incontinence, falls, failure to thrive, and/or neglect/abuse) and loss of activities of daily living (ADL) (i.e., loss in: activity of bathing, dressing, toileting, transferring,
feeding, and/or continence) were also documented. "Fit" was defined as no loss of ADLs, <3 grade 3 CIRS-G co-morbidities, no grade 4 CIRS-G, and no geriatric syndrome at diagnosis.14,15

Statistical analysis

PFS (time from date of eHL diagnosis to death or disease relapse/progression) and OS (time from date of eHL diagnosis to death or last follow-up) were per Kaplan-Meier method. Survival differences were assessed using the log-rank test. For comparison to a healthy population, instantaneous survival statistics for each matched age from the U.S. Social Security Department database were used; the average of these weights were computed as determined by the proportion of men and women in our population. Univariate associations between clinical/laboratory factors and survival were derived using Cox proportional hazards model.16 Variables with a p-value ≤0.05 in univariate analyses were entered into the multivariate Cox proportional hazards model in a stepwise fashion. Significant factors in multivariate analysis were incorporated into a prognostic model for survival constructed by classification and regression tree (CART) analysis. All statistical analyses were via SAS v9.2 (SAS Institute Inc., Cary, NC).

Results/Discussion

Baseline characteristics

Among 95 eHL subjects, the median age was 67 years (range 60-89), with one-third ages 70-79 years and 7% age 80-89. At diagnosis, 21% had history of coronary artery disease and 16% had diabetes. Disease characteristics included 54% B symptoms, 27% PS 2-4, 4% bulky disease, 25% bone marrow involvement, and 20% had other/non-marrow extranodal disease (most common: bone and lung). The relatively high incidence of B symptoms and low rate of bulky disease are consistent with prior eHL series.1,3,7,8,17,18 Altogether, 64% of patients here had stage III/IV, of which 58% had an IPS of 4-7. Histology was nodular sclerosis in 47%, mixed cellularity 31%, NOS 16%, lymphocyte predominant 5%, and lymphocyte depleted 1%. These data confirm
prior studies showing eHL more commonly presents with mixed cellularity subtype,\textsuperscript{3-5} while younger patients more frequently have bulky disease at diagnosis possibly supporting that eHL is biologically distinct.

**Functional status**

We identified that 61% of patients had a CIRS-G grade 3 or 4 in at least 1 category, while 46% had a cumulative CIRS-G score >6. Further, at time of eHL diagnosis, 17% had presence of a geriatric syndrome, 26% were classified as 'not fit', and 13% had loss of ADLs. To our knowledge, this is the first study to examine the prevalence of geriatric syndrome and level of fitness (including ADLs) in eHL.

The presence of co-morbidity as a prognostic factor is particularly relevant for older patients. In a population-based study, van Spronsen et al. reported that among eHL, 56% had a serious co-morbid condition vs 13% in younger patients (p<0.0001). Levis et al. reported results of eHL patients who received lower intensity chemotherapy;\textsuperscript{19} multivariate analysis found that the presence of co-morbidity independently correlated with disease-specific survival (DSS) and OS. Furthermore, DSS was identical to OS, suggesting ineffective treatment and/or different biology rather than death from other causes.

**Treatment**

Intensive regimens such as BEACOPP (escalated or baseline) are too toxic for eHL,\textsuperscript{20} while bleomycin-containing regimens such as ABVD are often not tolerated.\textsuperscript{3-5,21-23} Levis et al analyzed outcomes of patients ≥65 years receiving a registry-recommended protocol of ABVD, MOPP or ABVD/MOPP therapy.\textsuperscript{4} The 8-year PFS and OS were 41% and 46%, respectively, both significantly inferior compared with patients <65 years; notably, 23% of eHL patients receiving ABVD-based therapy suffered treatment-related death.

Primary treatment here consisted of: ABVD-based (n=67), MOPP-based (n=6), BCVPP (n=6), ChlVPP (n=5), radiation alone (n=4), CHOP (n=3), hospice (n=2), BEACOPP (n=1), and
watchful waiting (n=1). 78% of patients received granulocyte-colony stimulating factor (G-CSF), the majority (63%) of which was pegfilgrastim. Landgren et al showed previously that relative dose intensity (RDI) ≥65% was associated with improved survival with MOPP or ABVD-based therapy. The RDI here was 71%; RDI did not correlate with survival, however data was not available for all subjects. The overall response rate (ORR) among the 92 treated patients was 85% (73% CR). The incidence of bleomycin lung toxicity (BLT) was 32%, which had an associated mortality rate of 25%. Moreover, the incidence of BLT was 38% vs 0% among patients receiving G-CSF vs not, respectively (p=0.0001).

Risk factors for BLT include older age, cumulative bleomycin dose, renal insufficiency, pulmonary radiation, underlying lung disease, and tobacco history. G-CSF may increase the incidence of BLT; others have shown an increased incidence of BLT when G-CSF is used during bleomycin-containing chemotherapy with associated mortality rates >20%. Our data supports this association.

Outcomes

Among older patients entered onto German Hodgkin Study Group protocols, patients ≥60 years had significantly worse FFTF than younger patients. This difference remained significant with exclusion of events unrelated to HL. A US SEER data analysis by Brenner et al reported increasing survival of all ages of HL, including elderly patients, comparing outcomes in 1980-1984 with 2000-2004. Notably, the 1980-1984 survival rates for eHL were exceptionally low (~20-25%), while 2000-2004 survival rates remained markedly inferior compared with younger populations.

With a median follow-up of 66 months (range, 6-151 months), we documented the overall 5-year PFS and OS to be 44% and 58%, respectively. Stage I/II patients fared better compared with stage III/IV patients (5-year PFS and OS: 61% and 79% for stage I/II, vs 36% and 46% for stage III/IV; p=0.009 and p=0.001, respectively) (Figure 1). We also compared the OS of the eHL cohort with an age and gender-matched healthy population (Supplemental Figure 1). Among the 44 eHL
patients who died, 35 were as a result of HL (5 from BLT, 1 treatment-related sepsis, 2 cardiac
disease, and 1 prostate cancer). Univariate analyses of prognostic factors for survival are noted in
Table 1. Interestingly, 4 IPS factors (anemia, WBC, gender, lymphopenia) were not significant on
univariate or multivariate analysis.

**Multivariate analysis and survival model**

Few available reports have studied prognostic factors predictive of survival in eHL, and even
fewer have examined the relationship between functional status and outcome. Enblad et al,
analyzing registry data from 1985 through 1992 for eHL, showed that the IPS did not independently
predict outcome.\textsuperscript{17}

On multivariate regression analysis, only 2 factors here were associated with inferior
outcomes: 1) age $\geq 70$ years (PFS: HR 1.76 (95%CI 0.98-3.16), $p=0.06$; and OS: HR 2.24 (95%CI
1.16-4.33), $p=0.02$, and 2) Loss of ADLs (PFS: HR 2.47 (95%CI 0.98-6.21), $p=0.055$; and OS: HR
2.71 (95%CI 1.07-6.84), $p=0.04$ (Supplemental Table 1). Furthermore, these factors remained
significant with the 5 subjects with LP histology excluded (Supplemental Tables 2 and 3). A survival
model by CART analysis is illustrated in Figure 1. Collectively, these findings highlight the critical
impact of functional status on survival as well as continued modest outcomes of eHL over the past
decade; prospective trials validating these findings are warranted.

**Authorship (Brief Report):** AME: designed research, performed research, analyzed data, and
wrote the paper; IH: performed research, analyzed data, and wrote the paper; ER: performed
research, analyzed data, and wrote the paper; CN: performed research, analyzed data, and wrote
the paper; RK: performed research, BH: performed research; BP: performed research; SS:
performed research and wrote the paper; AL: performed research and wrote the paper; JM:
performed research and wrote the paper; AH: performed research and wrote the paper; SG:
performed research and wrote the paper; LIG: performed research and wrote the paper; SMS:
performed research, analyzed data, and wrote the paper.

**Conflict of interests:** None (all authors).
References


Table 1. Patient and disease characteristics with univariate analysis.

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<thead>
<tr>
<th>Prognostic factors</th>
<th>PFS</th>
<th>OS</th>
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<tr>
<td></td>
<td>HR^</td>
<td>95% CI</td>
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<tr>
<td>Age</td>
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</tr>
<tr>
<td>Continuous variable</td>
<td>1.05</td>
<td>(1.01, 1.09)</td>
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<tr>
<td>≥ 70 years vs 60-69</td>
<td>1.99</td>
<td>(1.16, 3.41)</td>
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<tr>
<td>Gender (female vs. male)</td>
<td>1.37</td>
<td>(0.74, 2.52)</td>
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<tr>
<td>History of CAD</td>
<td>1.94</td>
<td>(1.04, 3.63)</td>
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<td>Diabetes</td>
<td>0.28</td>
<td>(0.04, 2.31)</td>
</tr>
<tr>
<td>Prior Malignancy</td>
<td>1.51</td>
<td>(0.86, 2.67)</td>
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<td>Number of Medications (&gt; 5 vs. &lt; 5)</td>
<td>1.33</td>
<td>(0.73, 2.45)</td>
</tr>
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<td>Presence of B symptoms</td>
<td>2.32</td>
<td>(1.31, 4.11)</td>
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<td>Weight loss (&gt;10% baseline)</td>
<td>1.72</td>
<td>(0.99, 2.98)</td>
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<td>Performance status 3-4 (vs 0-2)*</td>
<td>2.40</td>
<td>(1.36, 4.26)</td>
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<td>CIRS-G</td>
<td></td>
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<tr>
<td>Any score 3 or 4</td>
<td>1.94</td>
<td>(1.09, 3.45)</td>
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<tr>
<td>&gt; 6 (cumulative)</td>
<td>1.28</td>
<td>(0.75, 2.18)</td>
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<tr>
<td>Loss of any ADLs</td>
<td>3.61</td>
<td>(1.79, 7.26)</td>
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<td>Presence of ‘geriatric’ syndrome</td>
<td>1.47</td>
<td>(0.77, 2.80)</td>
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<td>Patient fit (no vs. yes)</td>
<td>1.35</td>
<td>(0.76, 2.41)</td>
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<tr>
<td>Albumin &lt; 4.0 gram/dL</td>
<td>1.89</td>
<td>(0.94, 3.76)</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
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<td>--------------------------</td>
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<tr>
<td>WBC ≥ 15,000/mm³</td>
<td>1.89</td>
<td>(0.45, 7.93)</td>
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<tr>
<td>Lymphocyte count (&lt;600/mm³ or &lt; 8% of total WBC)</td>
<td>1.20</td>
<td>(0.57, 2.53)</td>
</tr>
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<td>Hemoglobin &lt;10.5 gram/dL</td>
<td>1.44</td>
<td>(0.80, 2.58)</td>
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<td>BM Involvement</td>
<td>2.07</td>
<td>(1.09, 3.93)</td>
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<tr>
<td>&gt;1 EN site</td>
<td>2.34</td>
<td>(1.21, 4.50)</td>
</tr>
<tr>
<td>Bulky disease &gt;7 cm</td>
<td>0.90</td>
<td>(0.29, 2.80)</td>
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<tr>
<td>Stage III/IV (vs I/II)</td>
<td>2.23</td>
<td>(1.19, 4.17)</td>
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<tr>
<td>MC</td>
<td>1.02</td>
<td>(0.51, 2.03)</td>
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<tr>
<td>NS</td>
<td>0.71</td>
<td>(0.34, 1.47)</td>
</tr>
<tr>
<td>LP</td>
<td>0.17</td>
<td>(0.02, 1.29)</td>
</tr>
</tbody>
</table>

*HRs >1 indicate a factor with poor prognosis, while HRs <1 indicate a factor with favorable prognosis.
*PS 2-4 vs 0-1 was not significant.
*Stage IV vs stages I-III portended similar prognostic importance as III/IV vs I/II.

Abbreviations: PFS, progression-free survival; OS, overall survival; CI, confidence interval; HR, hazard ratio; CI, confidence interval; CAD, coronary artery disease; CIRS-G, Cumulative Illness Rating Scale-Geriatric; ADL, activities of daily living; WBC, white blood cell count; BM, bone marrow; EN, extranodal; MC, mixed cellularity; NS, nodular sclerosis; LP, lymphocyte predominant.
Figure Legends.

Figure 1. Outcomes for eHL.

(A). Kaplan-Meier curves of PFS and OS for all eHL patients (n=95), (B) PFS and OS for early-stage patients, and (C) PFS and OS for advanced-stage eHL. Kaplan-Meier curves of (D) PFS and (E) OS for eHL patients based on number of the adverse prognostic factors present (age ≥70 years and loss of ADLs). The numbers of patients with 0, 1, or 2 factors at diagnosis were 48, 38, and 9, respectively; increasing number of risk factors portended an increasingly poor survival. A survival model based on number of adverse factors present (0, 1, or 2) was formed: 2-year PFS of 68% (95%CI 52%, 78%), 68% (95%CI 50%, 80%), and 13% (95%CI 0%, 42%), respectively (p<0.001); 2-year OS of 83% (95%CI 69%, 90%), 70% (95%CI 53%, 82%), and 13% (95%CI 0%, 42%), respectively (p<0.001); 5-year PFS of 55% (95%CI 39%, 68%), 39% (95%CI 21%, 55%), and 0%, respectively (p<0.0001); and 5-year OS of 73% (95%CI 58%, 84%), 51% (95%CI 32%, 67%), and 0%, respectively (p<0.0001).
Figure 1A-C.

A.

- Progression-Free
- Overall Survival

B.

- Early Stage PFS
- Early Stage OS

C.

- Advanced Stage PFS
- Advanced Stage OS
Figure 1D-E.

D.

- 0 Prognostic factor(s)
- 1 Prognostic factor(s)
- 2 Prognostic factor(s)

E.
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