**Cardiovascular Diseases after Hodgkin Lymphoma Treatment; 35-year Disease Risk and Sequence of Events**


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**Purpose/Objective(s):** Survival following Hodgkin lymphoma (HL) has improved significantly over time due to development of effective radio- and chemotherapy regimens. HL survivors, however, are known to be at increased risk of cardiovascular disease (CVD), causing excess morbidity and mortality. The aims of this study are to evaluate whether the increased risk persists after 35 years and whether there are specific patterns in the sequence of CVDs in individual patients.

**Materials/Methods:** A cohort study was performed including 2,528 5-year HL survivors, diagnosed before age 51 and treated between 1965 and 1995. We assessed CVD endpoints (ischemic heart disease [IHD], cardiomyopathy and congestive heart failure [HF] and valvular heart disease [VHD]) up to October 2013 through questionnaires to general practitioners and cardiologists. Cumulative incidences of CVDs were estimated accounting for death as a competing risk. Risk factors were evaluated using Cox regression. Standardized Incidence Ratios (SIRs) were estimated to compare CVD risk with the general population.

**Results:** We identified 1419 CVDs in 752 patients, after a median follow-up of 20.6 years. Following mediastinal radiotherapy (RT), 35-year cumulative incidence of CVDs was 46.3% (95%CI: 43.5%-49.1%), compared to 18.6% in patients not treated with mediastinal RT (14.3%-23.4%). The most frequently diagnosed first cardiac event was IHD, followed by VHD. 49% of CVD patients developed multiple CVDs; 92% of these patients had received mediastinal RT; among patients with one CVD event and patients without any CVD events, this was 90% and 77% respectively (p<0.001). HF was mostly diagnosed as last CVD (84% of HF). Both mediastinal RT (Hazard Ratio (HR): 3.6, 95%CI: 2.8-4.7) and anthracycline-containing chemotherapy (HR: 1.6, 95%CI: 1.3-1.9) increased the risk of any CVD. There was no interaction between mediastinal RT and CT (p=0.292). At 35 years after HL diagnosis, our patients had a 2.4-fold increased SIR of primary IHD or HF (95%CI: 1.23-4.1), compared to the general population, corresponding to 135 excess cases per 10,000 person years. 9.4% of patients who died, died from CVDs. Median survival time after any CVD, IHD and HF (all as first events), was 5.1 years, 6.3 years and 1.2 years, respectively.

**Conclusions:** The risk of CVD is significantly increased for at least 35 years following HL treatment, especially after mediastinal RT. Multiple CVDs are observed in almost half of the patients. Physicians should be aware of the persistent increased risk of CVDs and the increased risk of developing subsequent CVDs.

RT utilization and overall survival gains over time in early-stage HD.

**Materials/Methods:** We evaluated clinical features and survival outcomes among patients diagnosed with stage I and II HD from 1998 to 2011 from a prospectively collected database - the National Cancer Data Base (NCDB), comprised of cases from 1,500 sites across the US. The association between RT use, co-variables, and outcome was assessed in a multivariate Cox proportional hazards model. Survival was estimated using the Kaplan-Meier method.

**Results:** Among the 76,672 patients with HD within the NCDB, a total of 41,502 patients with stage I or II disease were eligible for this study, with a median follow-up of 7.5 years. The median age was 37 years (range: 18-90). Multi-agent chemotherapy was given to 96% of the patients. Of the cohort, 20,441 (49%) received RT to a median dose of 30.6 Gy. The 10-year overall survival of the entire cohort was 80.8%. Patients who did not receive RT had a 10-year overall survival rate of 76.4% versus 84.4% for those who received RT (p<0.00001). When adjusting for age, stage, co-morbidity, transplant procedure, chemotherapy use, and socioeconomic status, RT use was associated with significantly improved overall survival (HR=0.51; 95% CI, 0.46-0.56, p<0.00001). Utilization of RT was associated with younger age (≤40 years), insured status, higher socioeconomic status, and treatment at comprehensive cancer centers (all p<0.0001). The use of RT decreased significantly from 56% to 41% between 1998 and 2011. The most common reason given for not administering RT was that it was not part of the planned initial treatment strategy (88.4%). The omission of RT was associated with higher rates of transplant procedures performed, a surrogate for persistent/relapsed disease (p=0.04). Initiating chemotherapy within 30 days after diagnosis was associated with improved overall survival at 10 years (84.5% vs. 78.3%, p<0.00001), even when adjusting for all co-variables (HR=0.86; 95% CI 0.77-0.95, p=0.005).

**Conclusions:** Our study reveals that patients with early stage HD who received consolidation RT was associated with improved survival. Omitting RT within the CMT program was associated with higher rates of salvage transplant procedures. Despite this data, from 1998 to 2011, there appears to be a significant nationwide decrease in the utilization of RT. To our knowledge, this study represents the largest prospective dataset examining the role of RT for stage I and II HD. The data suggests that CMT contributes significantly to the cure rate for early stage HD, and that RT should remain standard practice.


**Presentation Number:** 338

**Comparison Between the German Hodgkin Study Group (GHSG) Involved Field Radiotherapy (IF-RT) versus the International Lymphoma Radiation Oncology Group (ILROG) Involved Site Radiotherapy (IS-RT) for Patients with Hodgkin’s Lymphoma- Is ISRT the New Standard?**

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**Purpose/Objective(s):** The present study addresses the role of IS-RT defined by the ILROG in comparison to the GHSG standard treatment IF-RT for patients with Hodgkin’s Lymphoma (HL). Further we compared intensity-modulated radiotherapy (IMRT) in contrast to standard RT (APPA).

**Materials/Methods:** For 44 patients with de novo HL treated with combined modality approach consisting of chemotherapy followed by 30 Gy IF-RT comparisons between the standard GHSG RT-volume IF-RT and the newly by the ILROG defined IS-RT were made. Further 60 treatment plans from 10 selected patients with APPA-treatment planning and virtually simulated IMRT-plans were evaluated. For the virtually simulated IMRT we used a sliding-window technique with 5 (IMRT-5F) and 7 (IMRT-7F) beam angles. For every patient 3 plans (APPA, IMRT-5F and IMRT7F) were calculated for the IF-RT and the IS-RT respectively. Following organs at risk (OAR) were analysed: lung, heart, spinal cord, female breast and skin. We compared the different values with regard to dose volume histograms (DVH), conformity and homogeneity indices.

**Results:** The average volume using IF-RT was 1642.53 cm$^3$ and 919.24 cm$^3$ for the IS-RT. With respect to the coverage of the planning target volume (PTV) the IMRT achieves a better conformity (CI: 0.95±0.02 APPA; 0.97±0.03 IMRT-5F; 0.97±0.02 IMRT-7F) and homogeneity (HI: 0.24±0.05 APPA; 0.24±0.07 IMRT-5F; 0.26±0.05 IMRT-7F) compared to the APPA. Regarding the Dmean for the lung the IMRT shows increased doses in
contrast to the APPA. The IMRT (IMRT-5F>IMRT-7F) shows improved values for the Dmax concerning the
dose applied to the spinal cord and to the heart. Due to the large amount of calculated values only the values
regarding the heart are named exemplary in this abstract: ISRT: Dmean: (6.57Gy APPA; 5.14Gy IMRT-5F;
5.28Gy IMRT-7F) IFRT: Dmean (17.6Gy APPA; 15.3Gy IMRT-5F; 15.62Gy IMRT-7F). Regarding the Dmean of
the female breast the APPA shows improved values. The ISRT spares significantly dose applied to the heart
and the lungs as well as to the female breast.

Conclusions: The IS-RT reduces significantly the treated volumes. IMRT shows advantages in the conformity
of covering the PTV. The APPA shows reduction of dose applied to female breast and the lungs and the IMRT
spares dose applied to the heart. We would recommend using IMRT or conventional APPA field arrangement
on an individual patient adapted basis.


Presentation Number: 145

The Role of Radiation Therapy in the Treatment of Primary Mediastinal B Cell Lymphoma Treated with
Rituximab containing Regimens

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Background: The role of radiation therapy in the initial treatment of patients with primary mediastinal B cell
lymphoma (PMBCL) is controversial. The goal of this study is to evaluate the outcome of patients treated with
Rituximab (R) containing regimens with and without thoracic radiation at a single institution.

Materials/Methods: We retrospectively identified patients treated for PMBCL between 1995 and 2013.
Baseline clinical characteristics, treatment modalities, overall patient outcomes, acute and long term toxicity
were assessed.

Results: We identified 274 patients with PMBCL, of which 198 were treated with rituximab (R) based
chemotherapy regimens. Of these, 88 had newly diagnosed stage I/II disease and were treated with three
main R containing regimens (R-CHOP=51, R-HyperCVAD=15, DA R-EPOCH=22), which are the primary focus of
this abstract. The median age at diagnosis was 36.3 years and 53% were female. At a median follow up of
4.17 years (range: 0.42 to -12.25y), the 5y OS rate is 98.8% for the entire cohort with 1 death due to disease.
Radiation therapy was given to 58 (72.5%) of 80 patients that achieved an initial CR/CRu to initial
chemotherapy with mean dose of 37.3 Gy (range 30-45 Gy). The 3y EFS and OS of those who achieved a
CR/CRu and received radiation was 98.3% and 100% respectively versus 100% and 100% for those who did
not. As recent data suggests omitting radiation in patients who receive intensified regimens may result in
similar outcomes, we analyzed the impact of radiation individually for the 3 main R based regimens (Table 1).
The DA R-EPOCH group had more primary refractory (4/22, 18.2%), however all were successfully salvaged
with radiation therapy +/- autologous stem cell transplant. The 18 patients who achieved a CR after DA R-
EPOCH all remain in remission at a median follow up of 1.67 years. There were two secondary malignancies:
gallbladder spindle tumor (1%) and myelodysplastic syndrome/AML (1%). Three patients treated with
combined modality therapy experienced an asymptomatic decrease in ejection fraction found on routine
surveillance (5.2%). One patient treated with chemotherapy alone experienced a cardiac arrest (4.5%). There
were no grade 3 or higher acute radiation related toxicity.

Conclusion: PMBCL patients treated with radiation therapy after a complete response to R-chemotherapy
regimens have an excellent outcome and limited long-term toxicity. Roughly 15-20% of patients who are
refractory to DA R-EPOCH may experience primary refractory disease that may be salvageable with radiation
therapy.
Table 1.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>R-CHOP (51)</th>
<th>R-HCVAD (15)</th>
<th>DA R-EPOCH (22)</th>
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<tr>
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<td>14</td>
<td>18</td>
</tr>
<tr>
<td>+ XRT</td>
<td>-XRT</td>
<td>+XRT</td>
<td>+XRT</td>
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<tr>
<td>N (%)</td>
<td>43 (90)</td>
<td>5 (10)</td>
<td>11 (79)</td>
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<tr>
<td>EFS%</td>
<td>97.7</td>
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Low Dose (12 GY) Total Skin Electron Beam Therapy (tsebt) for Mycosis Fungoides (mf): Results of Three Phase 2 Clinical Trials

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Purpose/Objective(s): To evaluate response rate (RR), time to response (TTR), time to progression (TTP), duration of clinical benefit (DoCB) and toxicity of 12 Gy TSEBT in patients with stage IB-III MF

Materials/Methods: Three prospective phase 2 clinical trials at 2 institutions were designed to evaluate the efficacy and toxicity of 12 Gy TSEBT (12 fractions/3 wks), with 12 Gy supplements to soles and perineum. Eligible pts had failed at least 1 prior standard therapy for MF and pts treated with prior TSEBT were excluded. Pts did not use topical or other therapies for MF during TSEBT or during the initial 8 wk observation period to evaluate response. Primary end point was RR. Clinical response in the skin was evaluated using a modified severity weighted assessment tool (mSWAT), with CR=100% clearance; PR>50% clearance; SD<50% clearance; and PD (for non-responders) = baseline mSWAT x 1.25. PD (for responders) = increase in mSWAT > [nadir+50% of baseline]. Secondary endpoints were TTR, TTP, and the DoCB. DoCB was defined as the time interval from initiation of TSEBT until any of the following occurred: progressive disease (PD), topical therapy to more than 50% of the body surface, initiation of another “total skin” equivalent therapy, or initiation of any systemic therapy.

Results: 33 patients were included: 22 stage IB, 2 IIA, 7 IIB, 2 IIIA. 55% male; median age 63 (19-83). 4 pts (12%) had large cell transformation (LCT) and 8 (24%) had folliculotrophic MF (FMF). Median number of prior therapies = 4 (range 1-10) and prior systemic therapies = 1 (0-7). Median TTR was 7.6 weeks (3-12.4) and most significant response of disease was noted between wks 4 and 8. Overall RR (ORR) was 88% including 9 pts (27%) with complete response (CR). RR was independent of LCT or FMF. The median DoCB was 17.7 mos (range 1-38 mos) and DoCB was still apparent for 40% of patients 2 years following therapy. Adverse events (AEs) included temporary alopecia, distal extremity tenderness, fatigue, and temporary nail changes and generally were grade 1-2. Only 2 grade 3 AEs were recorded.

Conclusions: Low dose TSEBT provides reliable and rapid reduction of disease burden in pts with MF. With acceptable toxicity profile, low dose TSEBT could be administered safely multiple times during the course of a patient’s disease.

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R.T. Hoppe: A. Employee; Stanford University.  
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S. Leadership; Intl Society Cutaneous Lymphoma.
Favorable Outcome in Stage I-II Mantle Cell Lymphoma: A Report of 160 Patients from the International Lymphoma Radiation Oncology Group (ILROG)

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Purpose/Objective(s): Patients with Mantle cell lymphoma (MCL) often present with advanced-stage and have a poor prognosis. Stage I-II presentation is rare, and there are only limited data on treatment outcome for these patients. To assess the outcome of this group of patients, we retrospectively reviewed 160 patients seen in 13 ILROG institutions between 1990 and 2012. Of the 160 patients, 124 (77%) were males, 90 (56%) were > 60 years; 87 (54%) were stage I, 121 (76%) presented in the head and neck areas, 100 (63%) had extranodal presentation, 17 (14%) were bulky (>5 cm).

Materials/Methods: Treatment approaches consisted of combined modality (CM) with chemotherapy and consolidative radiation therapy (RT) in 95 (59%), chemotherapy alone in 37 (23%), and definitive RT alone in 28 (18%). The median radiation dose used was 35 Gy (range 12-45). Chemotherapy consisted of cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) or CHOP-like, regimens in 106 (80%). Rituximab was added to chemotherapy in 31/52 (60%) patients with available data. The median follow-up was 60 months (range 4-245). At last follow up, 60 (37%) patients relapsed and 40 (25%) died. The 5-and 10-years overall survivals (OS) were 76% and 64%, respectively. The 5-and 10-years disease free survivals (DFS) were 65% and 44%, respectively.

Results: On univariate analysis, the following characteristics were significantly associated with DFS and OS: age > 60 (HR=1.86, p=0.02 for DFS; HR=2.33, p=0.01 for OS), bulky disease (HR=1.93, p=0.06 for DFS; HR=3.28, p=0.002 for OS). On multivariate analysis while both DFS and OS were significantly influenced by age as a continuous variable (HR=1.06, p<0.001; HR=1.04, p=0.001) only OS was influenced by the presence of bulky disease (HR=3.4, p=0.001; HR=3.1).

Conclusions: Patients who presented with stage I-II MCL and were treated with programs that included consolidative local radiotherapy or even radiotherapy alone, demonstrated favorable disease control and relatively long survival.

<table>
<thead>
<tr>
<th>All Patients (%)</th>
<th>Chemotherapy alone (%)</th>
<th>Combined Modality (%)</th>
<th>RT Alone (%)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>5-year DFS</td>
<td>65</td>
<td>60</td>
<td>62</td>
<td>87</td>
</tr>
<tr>
<td>10-year DFS</td>
<td>44</td>
<td>40</td>
<td>44</td>
<td>54</td>
</tr>
<tr>
<td>5-year OS</td>
<td>76</td>
<td>82</td>
<td>71</td>
<td>88</td>
</tr>
<tr>
<td>10-year OS</td>
<td>63</td>
<td>70</td>
<td>61</td>
<td>56</td>
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</table>