Benefit from the Inclusion of Radiation Therapy in the Treatment of Patients with Stage III Classical Hodgkin Lymphoma: A Propensity Matched Analysis of the Surveillance, Epidemiology, and End Results Database

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Manuscript pages: 20

Tables/Figures: 3/3

Running head: RT for Stage 3 Classical Hodgkin Lymphoma

Key words: radiotherapy, classical Hodgkin lymphoma, SEER

ABSTRACT

Background: While stage III and IV classical Hodgkin lymphoma (HL) patients are often combined and defined as "advanced stage," there are significant differences in disease distribution and burden between the two stages. This may obscure advantages of radiotherapy (RT) in a combined modality therapy strategy in stage III disease due to the relative lack of benefit in stage IV patients.

Methods: We queried the Surveillance, Epidemiology, and End Results (SEER) database, restricting our search to patients with stage III classical HL diagnosed from 2004 – 2012, to examine the difference in overall and cause-specific survival (OS and CSS) between patients who did or did not receive RT.

Results: Patients treated with RT had improved OS and CSS relative to those treated without RT (5-year OS 91.6% with RT compared to 71.4% without RT, HR = 0.34, $p < 0.001$) and CSS (5-year OS 95.4% with RT compared to 84.7% without RT, HR = 0.32, $p < 0.001$). A benefit in OS and/or CSS was seen in all patient subgroups except for older adults (>64 years).

Conclusion: These data support at least a cautionary approach to omitting RT from treatment strategies for patients with advanced stage HL.

BACKGROUND

The role of radiation therapy (RT) in the treatment of Hodgkin lymphoma (HL) continues to be defined and refined, as does its technical application. In early-stage (stage I or II) classical HL, multiple studies have shown that combined modality therapy improves progression free survival (PFS), which can translate into a benefit in overall survival (OS) [1-5]. However, the use of RT has declined over the last two decades as shown in recent population-based studies of SEER and the National Cancer Database among patients with early-stage disease [6, 7]. Contemporary studies (RAPID and EORTC H10) have also shown that RT is associated with an improvement in PFS in patients with PET-negative disease after initial chemotherapy, though the RAPID trial did not show any change in overall survival (OS) among patients who received RT with PET-negative disease after upfront chemotherapy [8, 9].

Among patients with advanced-stage (AS, stage III or IV) classical HL (cHL), data regarding the use of adjuvant RT are less clear. Evidence regarding any potential OS benefit of adjuvant RT is mixed [10-16]. The clearest benefit is seen in the use of RT in the treatment of residual masses, particularly if PET-avid, after chemotherapy [11, 17, 18]. Retrospective evidence has suggested a disease-free survival (DFS) benefit to consolidative RT after complete response (CR) to sites of bulky disease [19]. However, recent retrospective analysis suggests RT may be omitted in some patients with bulky disease who have an especially favorable response to chemotherapy without any detriment to OS [20]. The variability of these results is likely due to the large heterogeneity in these studies regarding patient population, systemic therapies, length of follow up, and assessed outcomes. Additionally, a wide variety of RT techniques, treatment volumes, field designs, treatment schedules, and doses have been used and accepted as standard of care over the

past several decades, and provider-to-provider interpretation of these recommendations varies [21, 22]. Antiquated techniques and excessive RT doses may compromise survival due to late appearing adverse effects in a disease with a generally favorable long-term outcome.

Previous retrospective data suggests that nearly all patients with advanced-stage HL who eventually required autologous stem cell transplantation (ASCT) for disease relapse failed in a site of initial disease (97%), and the vast majority of those patients relapsed only in sites of initial disease (71%) [23]. Despite the fact that both stage III and IV HL clearly represent disseminated disease, stage III patients may have disease distributions and burdens more amenable to RT; additionally, they have improved survival outcomes relative to those with stage IV disease. Consequently, we postulated that adjuvant RT may be more beneficial to patients with stage III compared with stage IV disease, and this might be obscured in studies that combine both groups. We aimed to investigate this by querying a large, population-based database in a contemporary treatment era to assess both OS and cause-specific survival (CSS), recognizing that survival is impacted by late treatment sequelae.

METHODS

Demographic, clinical, pathologic, treatment, and survival data were extracted from the Surveillance, Epidemiology, and End Results (SEER) of the United States National Cancer Institute [24]. Data are reported in this registry from eighteen population-based registries that represent approximately 27.8% of the U.S. population including San Francisco-Oakland, Connecticut, metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle (Puget Sound), Utah, metropolitan Atlanta, San Jose-Monterey, Los Angeles, Alaska Natives, rural Georgia,

California (excluding San Francisco, San Jose-Monterey, Los Angeles), Kentucky, Louisiana, New Jersey, and greater Georgia [25].

The SEER-18 database was queried to identify patients at least 20 years of age diagnosed with stage III classical HL between 2004 and 2012 when the American Joint Committee on Cancer (AJCC) 6^{th} and 7^{th} editions were coded. A variety of demographic and treatment-related characteristics were investigated, including cause of death. Treatment-related variables coded in SEER reflect initial treatment only. No information regarding chemotherapy could be ascertained. Extranodal status was also determined; however no consistent information regarding the location or size of extranodal disease can be ascertained from the SEER database. We defined older adult patients as those greater than 65 years old, and adults as those between 20 – 65 years old. Regions used were defined by the Contract Health Services Delivery Areas (CHSDA): East represents Connecticut, Georgia, Kentucky, Louisiana, and New Jersey; Northern Plains represents Michigan and Iowa; Pacific Coast/Alaska represents Alaska, California, Hawaii and Washington; and Southwest represents New Mexico and Utah.

Overall survival (OS) was defined as time from diagnosis to death of any cause; patients who were marked as alive in the SEER-18 database were censored at the time of their last follow-up. Cause specific survival was defined as time from diagnosis to death that was coded as being related to Hodgkin lymphoma. Patients with any other cause of death or who were marked as alive were censored at time of death or last follow up. The Kaplan-Meier method was used for survival statistics and the Cox proportional hazards model was used for comparisons of survival between groups. Categorical data are described with absolute frequency counts and percentages;

continuous data are described with median and ranges. Chi-squared analysis was used for determinations of between-group differences. A 3:1 propensity score matched analysis was additionally performed to further investigate the relationship between RT and survival; propensity scores were calculated based on race, gender, age (as a continuous variable), histologic subtype, presence of B symptoms, and the presence of extranodal disease. All statistics were performed on StataMP Version 13 (College Station, TX).

RESULTS

Patient Characteristics

A total of 3600 patients were identified in the SEER database with stage III HL. Table 1 summarizes patient demographics and treatment characteristics. Median age of the population was 47 (range 20 – 94). The majority of patients were under the age of 65 (73.8%), male (58.5%) and Caucasian (81.7%). Nodular sclerosis was the most common histologic subtype (54.7%), followed by classical HL NOS (24.4%), and mixed cellularity (16.1%). Other histologic subtypes were seen in less than 5% of patients. Data was available regarding B symptoms for 3,185 patients; more patients exhibited B symptoms (56.5%) at diagnosis than those who did not (43.5%). A small minority of patients (8.2%) had extranodal disease at time of diagnosis; a larger minority (25.1%) had splenic involvement at time of diagnosis. In total, 13.2% of patients received RT. The proportion of patients receiving RT varied by age group with 16.0% of adults receiving RT compared with 5.4% of older adults.

Overall Survival Analysis

The median overall follow-up for the entire cohort was 34 months (interquartile range 11 – 66 months). The median OS was not reached in this cohort. The 1-, 3-, and 5-year OS was 84.0%, 76.3%, and 72.1% respectively. Table 1 describes 5-year OS percentages and hazard ratios for demographic, geographic, and disease characteristics. Relative to adult patients older adult patients had significantly reduced OS (HR = 5.31, 95% CI = 4.61 – 6.11, $p < 0.001$). Neither race, gender, nor geographic region had a significant effect on OS. As shown in Table 1 and Figure 1A, patients with the nodular sclerosis subtype had a statistically significant improved OS compared with others, and this remained true when compared with all other subtypes grouped together (HR = 0.54, 95% CI = 0.47 – 0.62, $p < 0.001$). Patients who presented with B-symptoms had reduced OS (HR = 1.33, 95% CI = 1.14 – 1.56, $p = 0.001$). Those treated with RT had a statistically significant increase in OS (5-year OS = 87.5%, HR = 0.45, 95% CI = 0.35 – 0.59, $p <0.001$) compared to others (5-year OS = 69.6%) as shown in Figure 2A. With multivariable analysis including RT, nodular sclerosis subtype, presence of B symptoms, and age group, all variables maintained their statistical significance (Table 2).

Cause-Specific Survival Analysis

The median CSS was not reached in this cohort. The 1-, 3-, and 5-year CSS were 92.1%, 87.4%, and 85.0% respectively for the entire cohort. Table 1 describes the CSS for multiple demographic and treatment parameters. Relative to adult patients, older adult patients had decreased CSS (HR = 4.52, 95% CI = 3.70 – 5.54, $p < 0.001$). Neither race, gender, nor geographic region within the United States had any significant impact on CSS. As shown in Figure 1B, relative to the nodular sclerosis subtype, the mixed cellularity subtype (HR = 1.46, 95% CI = 1.10 – 1.93, $p = 0.009$) and classical HL NOS subtype (HR = 1.94, 95% CI = 1.54 –

2.45, $p < 0.001$) had decreased CSS. The lymphocyte-rich subtype and lymphocyte-deplete subtype showed no significant difference in CSS relative to the nodular sclerosis subtype. Compared to all other subtypes grouped together, patients with nodular sclerosis subtype had a significantly improved CSS (HR = 0.60, 95% CI = 0.49 – 0.73, $p < 0.001$). The presence of B symptoms was associated with reduced CSS (HR = 1.61, 95% CI = 1.28 – 2.02, $p < 0.001$). As shown in Figure 2B, those who received RT had significantly improved CSS (5-year CSS = 92.8%, HR = 0.46, 95% CI = 0.32 – 0.67, $p < 0.001$) relative to those who did not receive RT (5-year CSS = 83.7%). Table 2 describes a multivariate analysis including RT, nodular sclerosis subtype, presence of B symptoms, and age group. All these variables maintained their statistical significance on multivariate analysis for CSS.

Subgroup Analysis of the Effect of Radiation

Further univariate subgroup analysis was performed to generate a more complete picture of the effect of RT. The results are summarized in Table 3. Regarding OS, RT was associated with improved OS in adult patients (HR = 0.57, 95% CI = 0.41 – 0.79, $p = 0.001$); in older adult patients this benefit did not reach statistical significance (HR = 0.73, 95% CI = 0.48 – 1.11, $p = 0.14$). For CSS, a benefit associated with RT was seen in adult patients (HR = 0.63, 95% CI = 0.41 – 0.98, $p = 0.04$); in older adult patients the hazard ratio favored RT, but was not statistically significant (HR = 0.56, 95% CI = 0.28 – 1.14, $p = 0.12$). Table 3 further summarizes the effect of RT in other various subgroups.

Propensity Score Matched Analysis

Propensity scores were calculated based on the six variables mentioned previously. Patients were matched in a 3:1 fashion between those who did not receive RT and those who did receive RT. Patients for whom a match could not be identified were excluded. As such, 1,224 patients were used for this analysis. On propensity score matched analysis, RT was associated with improved OS (HR = 0.70, 95% CI = 0.51 – 0.95, p = 0.02). Regarding CSS, the HR favored RT; however, this was not statistically significant at a 95% confidence level (HR = 0.66, 95% CI = 0.42 – 1.02, p = 0.06).

DISCUSSION

The radiosensitivity of HL has long been recognized, and the use of RT to cure HL predates the use of chemotherapy [26]. In recent decades, cure rates have significantly increased due to the systematic use of chemotherapy, with RT remaining an integral part of definitive therapy in early stage disease but still critical in select situations for advanced stage disease. More recently, drug-antibody conjugates in both the upfront and salvage settings have demonstrated effectiveness [27]. In view of these tremendous advances in the treatment of HL, an appropriate renewed focused has been placed on prognostic factors in order to decrease the morbidity of treatment.

Trials assessing the value of RT in patients with advanced stage HL report conflicting results [5, 10-16, 28]. Several randomized trials demonstrate an advantage in using combined modality therapy as compared to chemotherapy alone [16, 29, 30]. A study from Memorial Sloan-Kettering among patients with AS cHL treated with MOPP/ABVD showed improvements in relapse-free survival (RFS) and OS for patients treated with RT to all initially involved nodal

sites [16]. This is concordant with multiple patterns of relapse studies demonstrating that recurrences are in sites of initial disease in excess of 90% for patients with advanced stage HL [23, 31]. Similar improvements in OS and event-free survival (EFS) were seen in patients who achieved CR after ABVD treated with RT compared to those not treated with RT [15]. Final analysis of the HD12 trial of patients with advanced stage HL revealed that the 5-year freedom from treatment failure was inferior without RT in patients treated with BEACOPP [11].

Conflicting results were seen in the EORTC-GPMC H34 trial wherein patients who achieved CR after MOPP-ABV were randomized to receive RT to the involved-field (IFRT) or no RT; no improvement in EFS was seen in patients treated with RT [10]. The German Hodgkin Study Group compared consolidative treatment with an additional cycle of COPP plus ABVD versus 20 Gy of involved field RT in patients with AS cHL, and no significant difference was found [32].

Patients with stage III disease frequently have a disease distribution that is more amenable to a safe and clinically reasonable RT treatment plan than those with stage IV disease, since the volumes are generally smaller and organ irradiation is not included. Given this, we hypothesized that patients with stage III disease may represent a population of HL patients who may be more apt to receive a benefit from RT, and that this may contribute to conflicting results regarding the use of RT in patients with advanced stage HL. We conducted a population-based analysis using the SEER database to further explore this. These data suggest that the use of RT is associated with a significant benefit in both OS (5-year OS 87.5% with RT compared to 69.6% without RT, HR = 0.45, $p < 0.001$) and CSS (5-year OS 92.8% with RT compared to 83.7% without RT, HR

= 0.56, $p < 0.001$). The benefit associated with RT on OS was seen with both multivariate analysis and propensity score matched analysis; the benefit associated with CSS was only seen on multivariate analysis. On the propensity score matched analysis, RT was associated with numeric improvement in CSS (HR = 0.66), however, this did not reach statistical significance ($p = 0.06$). This is likely related to the decreased sample size in the propensity score matched analysis.

We additionally show that RT is associated with improved OS and CSS among a variety of subgroups including adult patients (ages 20-64 years), patients with and without B symptoms, patients without extranodal disease, and patients with and without splenic involvement. Patients with extranodal disease had a statistically significant correlation between RT and improved OS, but the improvement in CSS did not reach statistical significance ($p = 0.13$). Older adults had no statistically significant improvement in OS or CSS with RT, though the absolute value for the hazard ratio and shape of Kaplan-Meier curve trend towards favoring RT. This may be related to the extremely small number of older adult patients who were treated with RT (5.4% as compared to 16.0% in the adult population).

This report suggests that nodular sclerosis subtype HL is associated with improved OS and CSS relative to other disease subtypes. This is concordant with previous results of large population-based databases and not unexpected given previous studies have suggested nodular sclerosis disease preferentially effects the young [7, 33]. We also reaffirm that the majority of patients (55.9%) with stage III HL exhibit B symptoms. This is similar to findings in the German HD-12 and EORTC H34 trials in which 56% and 55% of patients had B-symptoms, respectively. Our

study also confirmed other data that patients with B-symptoms have a significantly worse prognosis as compared to those without B-symptoms [34].

A contemporary approach to the treatment of advanced stage HL is the use of response-adapted therapy using interim PET imaging to guide treatment decisions after initial cycles of chemotherapy. Patients with advanced stage HL undergoing six cycles of ABVD who have PET-positive disease after two cycles of ABVD have markedly worse PFS than those with PET-negative disease after two cycles of ABVD [35]. A response-adapted model may be of particular value in identifying patients with advanced stage disease who may most benefit from RT and would be an ideal model to design future studies to further investigate the role of RT in these patients.

This analysis has limitations inherent to those in any analysis of the SEER database, the most significant being the limited amount of information that can be abstracted. As previously mentioned, chemotherapy data is not available in SEER and as such could not be included in this analysis. However, give the narrow and contemporary scope of this report (patients treated from 2004 – 2012), the vast majority likely received relatively similar chemotherapeutic regimens. PET/CT imaging is an important piece of the diagnostic workup in patients with Hodgkin lymphoma as it improves the sensitivity for detection of various sites of disease over CT alone [36]. The use of PET/CT imaging cannot be assessed in the SEER database and we cannot verify its use; this is an important limitation of this study as PET has the potential to upstage patients which could impact the population of Stage III patients analyzed herein. Furthermore, selection bias is possible given that patients were not randomized; the choice of therapy was based on the

oncologist's discretion regarding treatment with RT. However, this also may have "selected" higher risk patients to receive RT in order to maximize treatment intensity. Additionally, there is minimal information in SEER regarding RT treatment planning; we were unable to ascertain the clinical rationale/circumstances, sites treated, or doses used. Heterogeneity among RT treatment planning between patients is likely somewhat mitigated by the small, contemporary time period used for this study. Another potential limitation is error in coding for the receipt of RT within the SEER database; a study comparing SEER treatment data with data from Medicare claims indicated that the sensitivity of the SEER data to identify patients who received RT was 80%. Yet another limitation is the limited follow-up time (median 37 months); this is a direct consequence of using a modern treatment cohort.

CONCLUSION

This report provides a comprehensive population-based analysis of patients with stage III classic Hodgkin lymphoma, and the impact of several variables such as disease subtype, patient demographic, and presenting characteristics. RT is associated with a significantly improved OS and CSS in patients with stage III classical HL, based on the SEER database. This effect was seen across a wide variety of patient subgroups including adult patients, patients with and without B symptoms, and patients without extranodal disease. This data supports a cautionary approach to eliminating RT from treatment strategies for stage III classical HL. Prospective trials with attention to differences amongst patients with advanced stage disease are necessary to further define and refine the value of RT in these patient subsets.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ACKNOWLEDGEMENT

The authors thank Mrs. Laura Finger for editorial assistance.

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FIGURE LEGENDS

Figure 1. (A) Kaplan-Meier survival curve of overall survival in patients with stage III classical Hodgkin lymphoma sorted by subtype (B) Kaplan-Meier survival curve of cause-specific survival in patients with stage III classical Hodgkin lymphoma sorted by subtype (n = 4,108)

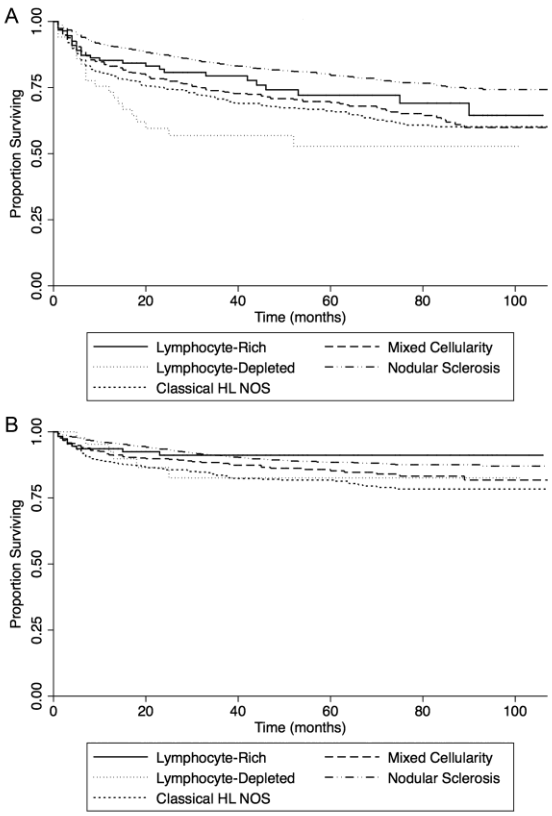
Note: Confidence intervals and number at risk not included for figure clarity

Figure 2. (A) Kaplan-Meier survival curve of overall survival in patients with stage III classical Hodgkin lymphoma sorted by receipt of radiation (B) Kaplan-Meier survival curve of cause-specific survival in patients with stage III classical Hodgkin lymphoma sorted by receipt of radiation (n = 4,108)

Key: RT = radiotherapy, CI = confidence interval

Figure 3. (A) Kaplan-Meier survival curve of overall survival in patients with stage III classical Hodgkin lymphoma sorted by age group and receipt of radiation (B) Kaplan-Meier survival curve of cause-specific survival in patients with stage III classical Hodgkin lymphoma sorted by age group and receipt of radiation (n = 4,108). Pediatric represents patients aged 0 – 19, adult represents patients age 20 – 64, and older adult represents patients 65 or older.

Key/Note: RT = radiotherapy, confidence intervals not included for figure clarity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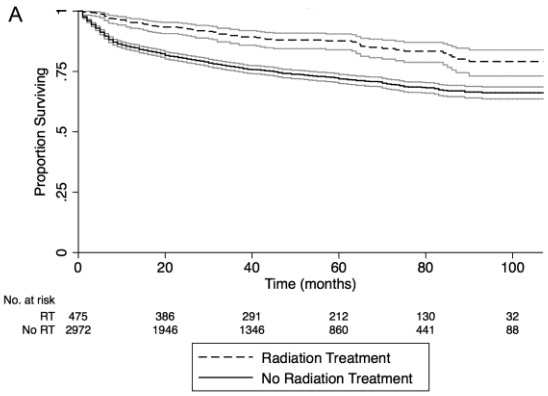
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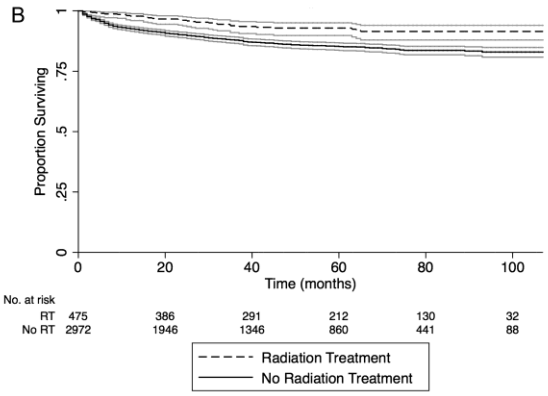
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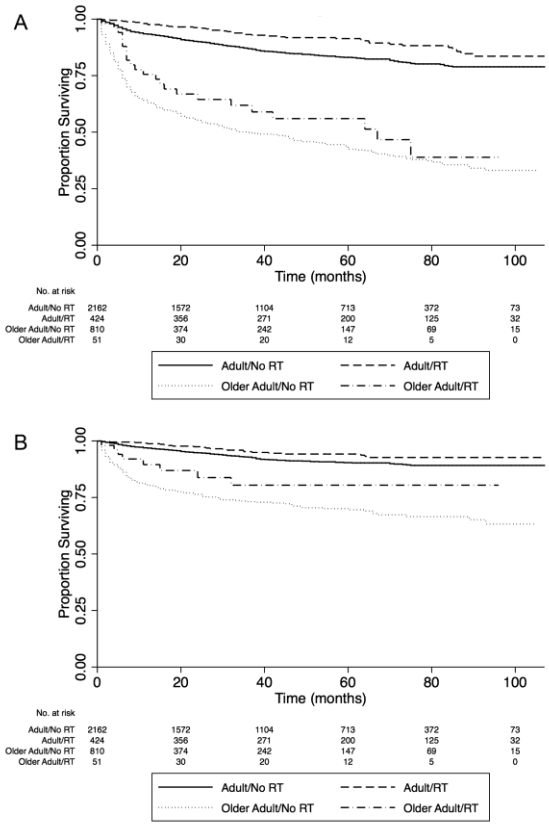
No. at risk
RT 475 386 291 212 130 32
No RT 2972 1946 1346 860 441 88
Radiation Treatment
No Radiation Treatment


A
Proportion Surviving
0.00
0.25
0.50
0.75
1.00
0
20
40
60
80
100
Time (months)
No. at risk
Adult/No RT 2162 1572 1104 713 372 73
Adult/RT 424 356 271 200 125 32
Older Adult/No RT 810 374 242 147 69 15
Older Adult/RT 51 30 20 12 5 0
Adult/No RT
Adult/RT
Older Adult/No RT
Older Adult/RT

B
Proportion Surviving
0.00
0.25
0.50
0.75
1.00
0
20
40
60
80
100
Time (months)
No. at risk
Adult/No RT 2162 1572 1104 713 372 73
Adult/RT 424 356 271 200 125 32
Older Adult/No RT 810 374 242 147 69 15
Older Adult/RT 51 30 20 12 5 0
Adult/No RT
Adult/RT
Older Adult/No RT
Older Adult/RT

Table 1. Patient Characteristics and Treatment Outcomes in those with Stage III Classical Hodgkin Lymphoma (n = 3,600)

			Overall Survival				Cause-Specific Survival			
Variable	**Number**	**Percentage**	**5-year OS**	**HR**	**95% CI**	**p-value**	**5-year CSS**	**HR**	**95% CI**	**p-value**
Age Group										
Adult (20 – 64 yrs)	2658	73.8%	83.1%	–	–	–	90.5%	–	–	–
Older Adult (>64 yrs)	942	26.2%	41.2%	5.31	4.61 – 6.11	<0.001	67.5%	4.52	3.70 – 5.54	<0.001
Race										
Caucasian	2941	81.7%	71.4%	–	–	–	84.4%	–	–	–
African American	463	12.9%	72.8%	0.88	0.71 – 1.09	0.26	86.4%	0.82	0.60 – 1.13	0.22

Other	196	5.4%	82.0%	0.75	0.53 – 1.06	0.10	91.5%	0.60	0.34 – 1.04	0.07
Gender										
Male	2105	58.5%	72.0%	1.01	0.87 – 1.16	0.94	85.5%	0.89	0.73 – 1.09	0.28
Female	1495	41.5%	72.3%	–	–	–	84.3%	–	–	–
Region										
East	1352	37.6%	71.4%	0.96	0.82 – 1.11	0.55	85.4%	0.84	0.67 – 1.04	0.11
Northern Plains	388	10.8%	75.4%	0.79	0.62 – 1.01	0.07	88.7%	0.67	0.46 – 0.97	0.03
Pacific Coast/Alaska	1700	47.2%	71.0%	–	–	–	83.3%	–	–	–

Southwest	160	4.4%	81.5%	0.69	0.47 – 1.02	0.06	90.8%	0.65	0.37 – 1.14	0.13
Subtype										
Lymphocyte-Rich	116	3.2%	71.2%	1.43	0.97 – 2.12	0.07	90.7%	0.94	0.48 – 1.84	0.87
Mixed Cellularity	578	16.1%	67.3%	1.72	1.42 – 2.07	<0.001	84.3%	1.46	1.10 – 1.93	0.009
Lymphocyte-Depleted	60	1.7%	45.0%	2.84	1.82 – 4.41	<0.001	73.9%	1.60	0.71 – 3.60	0.26
Nodular Sclerosis	1968	54.7%	78.5%	–	–	–	87.3%	–	–	–
Classical HL, NOS	878	24.4%	62.2%	1.94	1.65 – 2.29	<0.001	80.0%	1.94	1.54 – 2.45	<0.001

B Symptoms (n = 3,185)										
Present	1799	56.5%	69.0%	1.33	1.14 – 1.56	<0.001	81.6%	1.60	1.28 – 2.02	<0.001
Absent	1386	43.5%	76.6%	–	–	–	89.1%	–	–	–
Extranodal Disease										
Present	295	8.2%	69.3%	1.15	0.91 – 1.46	0.25	81.7%	1.37	0.99 – 1.88	0.057
Absent	3305	91.8%	72.3%	–	–	–	85.3%	–	–	–
Radiation										
Yes	475	13.2%	87.5%	0.45	0.35 – 0.59	<0.001	92.8%	0.46	0.32 – 0.67	<0.001
No	3125	86.8%	69.6%	–	–	–	83.7%	–	–	–

Table 2. Multivariate Analysis of Treatment Outcomes in Patients with Stage III Classical Hodgkin Lymphoma (n = 4,108)

	Overall Survival			Cause-Specific Survival		
Variable	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
			Age Group			
Adult (20 – 64 yrs)	–	–	–	–	–	–
Older Adult (>64 yrs)	4.83	4.13 – 5.64	<0.001	4.09	3.27 – 5.10	<0.001
			Subtype			
Nodular Sclerosis	0.73	0.62 – 0.85	<0.001	0.78	0.63 – 0.97	0.026
All Others	–	–	–	–	–	–
B Symptoms (n = 3,185)						
Present	1.44	1.24 – 1.69	<0.001	1.72	1.37 – 2.16	<0.001
Absent	–	–	–	–	–	–

Radiation						
Yes	0.66	0.50 – 0.86	0.002	0.62	0.42 – 0.92	0.016
No	–	–	–	–	–	–

Table 3. Univariate Subgroup Analysis of the Use of Radiotherapy (RT) in Patients with Stage III Classical Hodgkin Lymphoma (n = 4,108)

			Overall Survival			Cause-Specific Survival		
Variable	**n (%) with RT**	**n (%) without RT**	**HR for RT**	**95% CI**	**p-value**	**HR for RT**	**95% CI**	**p-value**
Age								
Adult (20 – 64 yrs)	424 (16.0%)	2,234 (84.0%)	0.57	0.41 – 0.79	0.001	0.63	0.41 – 0.98	0.04
Older Adult (>64 yrs)	51 (5.4%)	891 (94.6%)	0.73	0.48 – 1.11	0.14	0.56	0.28 – 1.14	0.11
B Symptoms (n = 3,185)								
Present	234 (13.0%)	1,565 (87.0%)	0.42	0.29 – 0.60	<0.001	0.46	0.28 – 0.74	0.002
Absent	202 (14.6%)	1,184 (85.4%)	0.53	0.35 – 0.79	0.002	0.46	0.24 – 0.88	0.019
Extranodal Disease								

Present	48 (16.3%)	247 (83.7%)	0.36	0.16 – 0.84	0.018	0.45	0.16 – 1.26	0.13
Absent	427 (12.9%)	2878 (87.1%)	0.46	0.35 – 0.61	<0.001	0.46	0.31 – 0.69	<0.001