Published in final edited form as:

Leuk Lymphoma. 2016 February ; 57(2): 320–327. doi:10.3109/10428194.2015.1065978.

Early-Stage Nodular Lymphocyte-Predominant Hodgkin Lymphoma: The Impact of Radiotherapy on Overall Survival

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Abstract

The purpose of this study was to use the National Cancer Database to examine the association between radiation therapy (RT) and overall survival (OS) in early-stage nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) using standard and propensity score (PS)-adjusted Cox proportional hazards models. From 1998-2011, 1,915 patients with stage I/II NLPHL were studied, with a median follow-up of 6.6 years (median age=44). Of the cohort, 1,224 (64%) received RT (alone or with chemotherapy) to a median dose of 30.6 Gy. Patients were more likely to receive RT if male, younger age, lower stage, no “B”-symptoms, favorably insured, and treatment at comprehensive centers (all $p < 0.05$). Patients administered RT had an improved 5-year OS (HR=0.62; 95% CI, 0.43-0.89, $p=0.01$). After PS-matching ($n=868$) based on all known co-variables, RT use trended towards improved OS (HR=0.49; 95% CI, 0.23-1.05, $p=0.06$). This study represents one of the largest prospective datasets examining the role of RT for stage I/II NLPHL and inclusion of RT may be considered.

Keywords

Lymphocyte-predominant Hodgkin Lymphoma; Radiotherapy; Overall Survival; National Cancer Database

INTRODUCTION

As a variant of Hodgkin lymphoma (HL), nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) represents approximately 5% of HL.[1] Traditionally, patients with NLPHL present with localized, early-stage peripheral lymphadenopathy, and are less likely to present with “B” symptoms, bulky disease, or mediastinal involvement.[2-6] Thus the

behavior of this disease entity contrasts favorably to classical HL (cHL), and its clinical behavior is more comparable to that of an indolent non-Hodgkin's lymphoma.[7-12] A retrospective matched-pair analysis from the German Hodgkin Study Group (GHSg) of 394 patients with NLPHL (compared to 7,904 patients with cHL) confirmed these findings and validated the improved prognosis (tumor control and overall survival) of this disease entity. [8]

Historically, excellent survival rates for NLPHL were attributed to the efficacy of definitive large-field radiation therapy (RT).[13-15] Given the localized nature of most cases of NLPHL, national guidelines currently recommend involved-site radiation therapy (ISRT) as standard treatment for clinical stage I/II NLPHL.[16] However, as per these guidelines, first-line treatment for stage I/II patients with "B" symptoms may include chemotherapy with consideration given to ISRT and/or immunotherapy with Rituximab.[16] Exploiting the universal expression of CD20 by malignant cells in NLPHL, recent studies have found promising, but non-durable response rates with Rituximab.[17] Hence, controversy exists in the oncology community regarding the survival benefits of administering RT to patients with early-stage NLPHL.

The rarity of this condition has prompted many groups to evaluate population-based observational cohorts, such as the Surveillance Epidemiology and End Results(SEER) database, to determine the role of definitive RT in the treatment program for early-stage NLPHL.[10,18,19] These studies have consistently found an increased risk of death with the omission of RT, and despite current NCCN recommendations, they have found a dramatic decrease in utilization of RT in adolescent and adult patients.[10,18,19] However, these studies may suffer from inherent treatment selection bias, related to numerous patient and clinical factors affecting treatment decisions. We suggest that more rigorous statistical methodology may remove potential confounding biases, inherent in large, observational datasets [20]. Additionally, there are limitations of the SEER database; it does not contain information regarding type of systemic chemotherapy regimens for upfront or salvage purposes, nor does it provide rationale for cases in which RT was omitted in the initial treatment strategy.

Therefore, we used the National Cancer Database (NCDB) data on early-stage NLPHL to evaluate contemporary treatment trends, adherence to national guidelines, and subsequent impact on survival. The primary endpoint of this study was to determine whether use of RT impacted overall survival. As secondary endpoints, we explored the relationship between clinicopathologic and socioeconomic parameters and overall survival. We also examined the RT utilization trends from 1998 to 2011. Our hypothesis was that the inclusion of RT improves overall survival in patients with early-stage (clinical stage I/II) NLPHL.

METHODS AND MATERIALS

Data Source

The NCDB, a nationwide hospital-based oncology database, was used to conduct a cohort study of patients with Hodgkin lymphoma diagnosed from 1998 through 2011. As a joint project of the American College of Surgeons, the Commission on Cancer (CoC) and the

American Cancer Society, the NCDB is a prospectively collected, hospital-based registry representing roughly 75% of all cancers diagnosed in the U.S. from 1,500 hospitals and has accumulated data on approximately 29 million cancer cases.

Variables captured included basic demographics, socioeconomic characteristics, cancer staging, course of treatment, co-morbid conditions, and vital status. This study period reflected a time during which RT was an accepted standard treatment course for early stage NLPHL. At the time of analysis, 2011 data were the most recent data available

Study Patients

The flow CONSORT diagram in Figure 1 shows the study exclusion criteria used to define the cohort. All patients (n=76,681) diagnosed with HL (classical and NLPHL) from 1998 to 2011 were initially included. Only patients within the age range of 18-90 with Stage I or II NLPHL were included. Patients with stage III or IV disease were excluded. Patients without a coded utilization of RT or missing variables were also excluded. For purposes of minimizing potential confounding effects from all known covariates, we also excluded patients with any missing data points in all clinicopathologic parameters of interest. As displayed in the flow CONSORT diagram (Figure 1), with the above inclusion criteria, the study cohort was limited to 1,915 patients. Furthermore, in accordance with NCDB participant user file data-use agreements, the survival analysis excluded patients (n=899) diagnosed from 2007-2011, to allow for at least 5 years of follow-up for all patients. Thus, the survival analysis cohort was a total of 1,016 patients.

Study Variables

Our variable of main interest was the use of radiation therapy (RT). Demographic and clinical data included gender, race/ethnicity (white, black, or other), age (≤ 40 vs. >40 , based on known prognostic value in NLPHL[13]), indicators of income and education based on area of residence derived from Census data (the proportion of adults without a high school diploma according to patients' zip code of residence was categorized as $<14\%$, from 14% to 19.9%, from 20% to 28.9%, and $>29\%$, based on national quartiles and used as proxies for patient socioeconomic status), median household income, insurance status (categorized as private, Medicare, Medicaid, or uninsured), treatment facility type (categorized as Community Cancer Program, Comprehensive Community Cancer Program, and Academic/Research Program [including NCI-designated Comprehensive Cancer Centers]), geographic region (categorized into 9 predefined regions), Charlson-Deyo co-morbidity Score(CDCS) (categorized 0, 1, and 2+), clinical stage (I vs. II), presence of "B" symptoms, histology, and vital status. As few patients have CDCS ≥ 2 , the NCDB reports only three categories (as above).

The outcome variable-overall survival was calculated from the date of diagnosis to December 31, 2011, the date of death, or the date of last contact, whichever occurred first.

Statistical Analysis

Categorical and continuous variable distributions were assessed by using standard descriptive statistics. Chi-square tests were used to compare the sociodemographic and

clinical characteristics of the study population by RT utilization status. Survival was calculated in months from date of diagnosis to date of last contact or confirmed death. Overall survival after planned intervention was the primary outcome. Kaplan-Meier survival curves were stratified by RT use, and Wilcoxon tests were performed. We assessed the association of RT utilization with age, gender, race, socioeconomic status (education level, household income), insurance status, facility type, stage (I vs. II), the presence of B-symptoms, and CDCS.

Propensity Score Analysis

Rather than traditional covariate adjustment via multivariate hazards modeling, propensity score(PS) adjustments to our Cox model may have significant advantages when analyzing large observational cohorts like SEER or NCDB.[21] As an observational cohort, use of RT was likely not random, and may have been influenced by patient and disease-related characteristics, potentially leading to biased survival estimates due to confounding. Thus, we used PS methods to account for imbalances between the two comparison groups on measured covariates. As the estimated probability of receiving RT versus not receiving RT was based on observed pretreatment covariates, we calculated PS using multivariate logistic regression with overall survival as the outcome of interest, with adjustment for age, stage, presence of B-symptoms, CDCS, insurance status, socioeconomic status indicators, facility type, and use of chemotherapy. The estimated PS was then used to match patients with similar propensity to receive RT based on nearest neighbor matching without replacement using calipers of width equal 0.2 SD of the logit of the propensity score (Mahalanobis matching). The success in achieving covariate balance was evaluated using standardized differences of means <0.05 ($<5\%$ difference between the arms) indicative of acceptable balance. After exclusion of patients diagnosed after 2006, in accordance to above NCDB data-use agreements, the propensity score analysis was restricted to 868 patients.

Cox Proportional Hazards Model

Unadjusted associations of individual covariates with survival were described using univariate Cox proportional hazards model. A multivariate Cox proportional hazards model was then fitted to estimate the hazard ratios associated with RT-use and other covariates with respect to OS and their 95% confidence intervals (CI's), after adjustment for the propensity score. The criterion $P<0.05$ was used for retaining interactions in the model.

Sensitivity Analysis

The covariates, CDCS and "B" symptoms only were available starting in 2003 and 2004, respectively. In a sensitivity analysis, we included the CDCS and "B" symptoms parameters and repeated the multiple Cox regression analysis, so that the patients diagnosed prior to 2003 would be excluded in this analysis ($n=311$ patients). In this sensitivity analysis, we found little difference in the covariates predicting for RT use or survival. Thus, to maximize the follow-up time and number of patients in the study, we report the results from the PS model that excluded these prognostic variables (CDCS and B-symptoms; $n=868$).

All statistical analyses were performed using statistical software STATA version 12.1. For all statistical testing, we used a two-sided significance level of $p=0.05$. Institutional review board exemption was obtained from the hospital Institutional Review Board.

RESULTS

Descriptive statistics

The overall study cohort comprised of 1,915 total patients with stage I and II NLPHL, with 1,016 patients studied in the survival analysis, and 868 patients analyzed within the propensity score analysis. The median age was 44 years(range:18-90);67% were male and 33% were female. Table 1 summarizes patient demographic and clinical characteristics as well as the association with the use of RT. The majority of patients were white(73%), had stage I disease(60%), had no “B” symptoms(87%), had no co-morbidities(89%), and favorable insurance status(76%). Fifty-three percent of patients were treated at comprehensive community cancer programs and 34% were treated at academic/research program facilities (10% at community cancer programs, 3% at others). As depicted in Figure 2, 708(36.9%) of patients received RT alone to a median dose of 30.6Gy, 408(21.3%) received multi-agent chemotherapy alone, and 799(41.8%) received combined modality treatment (chemotherapy + RT).

Utilization of Radiation Therapy

In the bivariate analysis (Table 1), patients were more likely to receive RT if they were of male gender($p=0.02$), white race($p=0.004$), age ≥ 40 ($p=0.005$), stage I (vs. II)($p<0.0001$), no “B” symptoms($p<0.0001$), lower CDCS($p<0.0001$), favorably insured($p<0.0001$), and treatment at comprehensive cancer programs($p=0.02$).

Figure 3 displays the utilization of RT over time for the patients with NLPHL. The utilization rates have decreased significantly from 68.8% in 1998 to 60.8% in 2011. The most common physician-reported reason for not administering radiation therapy was that it was not part of the planned initial treatment strategy (88.0%). In a small proportion of patients (<10%), RT was recommended but not administered, refused, or unknown whether delivered.

Survival Analysis

The median follow-up for the entire cohort was 6.6 years. In the unadjusted univariate analysis of the cohort, the use of RT was associated with an improvement in overall survival (HR=0.62;95%CI,0.43-0.89, $p=0.01$).The use of chemotherapy was not associated with an improvement in OS. Also, younger age (<40) was associated with an increase in OS (HR=0.10;95%CI,0.05-0.19, $p<0.0001$). Within the univariate model, patients with Medicaid insurance or uninsured were found to have an inferior overall survival than patients with more favorable insurance status (HR=6.49;95%CI,4.48-9.41, $p<0.0001$). Patients with higher co-morbidity scores (CDCS=1) had an inferior overall survival (HR=3.92;95% CI, 1.97-7.79, $p<0.0001$).

Figure 4 displays the PS-matched cohort, stratified by RT. Five-year OS was 88.1% for patients who did not receive RT and 94.1% for those who received RT ($p=0.003$, Wilcoxon test).

Propensity Score Analysis

The propensity score adequately balanced all variables affecting treatment selection or OS. After the adjustment within the multivariate Cox proportional hazards model, the risk of death remained lower in patients receiving RT (HR 0.49, 95% CI 0.23–1.05, $p=0.06$) with a trend towards significance (Table 2). The overall survival was not significantly different amongst several measures of socioeconomic status, such as education and income (all $p>0.05$). Also, younger age (<40) and favorable insurance status remained significant predictors of decreased risk of death (all $p<0.01$, Table 2).

Sensitivity Analysis

Different inclusion decisions for adjusting covariates in the model, such as including CDCS and presence of “B” symptoms, produced results consistent with the primary analysis (data not shown). In additional sensitivity analysis, we excluded patients receiving combined modality therapy of chemotherapy and RT, thus restricting the comparable groups to chemotherapy alone versus RT alone, and consistent results were obtained (data not shown).

DISCUSSION

In the current study, representing contemporary treatment programs in the U.S., we found that the 5-year OS for patients with early-stage NPLHL who did not receive RT was 88.1%, significantly inferior when compared to those who received RT obtaining a 5-year OS of 94.1% ($p=0.003$). When adjusting the hazard ratio for the propensity score, the patients receiving RT experienced an improved overall when compared to patients who did not receive RT (HR 0.49, $p=0.06$), but did not reach statistical significance. In addition to these findings, the utilization rates have decreased by approximately 8%—a lesser degree than other studies (range 8–40%). [10,19] Similar to data on early-stage cHL patients [22], the most common physician-reported reason for not administering radiation therapy in this study was that it was not part of the planned initial treatment strategy (88%).

As one of the largest cohorts in the literature, this study utilized the NCDB to identify 1,915 patients, representing >75% of all nationwide diagnoses of early-stage NPLHL. The previously reported SEER data showed similar results of a decrease in the use of RT and a highly statistical survival benefit of this treatment. [10,18] The current study found underutilization of RT based on race, older age, presence of “B” symptoms, unfavorable insurance status, and treatment facility type. In contrast to previous studies [19], patients with stage I disease were more likely to receive RT than higher staged patients, perhaps reflecting the notion of sparing “low-risk” patients systemic therapy and treating these patients in a similar fashion as patients with indolent NHL. In addition, patients with stage II disease may have more extensive, and less contiguous disease, perhaps requiring undesirably larger fields of radiotherapy. Unadjusted and PS-adjusted survival analysis also found younger age, favorable insurance status, and CDCS associated with OS. The use of chemotherapy did not

affect OS in either univariate or PS-adjusted models. Contrary to the implicit prognostic value of “B” symptoms in the current NCCN guidelines guiding practitioners to more aggressive treatment options with multi-agent chemotherapy[16], the presence “B” symptoms did not portend a worse OS in the current, large dataset.

Because national guidelines suggest that definitive RT or chemotherapy +/- RT may be reasonable first-line treatment options for early-stage NLP HL, imbalances in treatment preferences would be expected in this observational cohort, and thus, it is important to eliminate confounding bias by performing the propensity score analysis. The advantage of this method over multivariable regression is that it closely mimics the design of a randomized trial. In the current study, maximum similarity of groups (by RT use) was delineated and tested prior to analyzing the outcomes. In the current study, the degree of survival benefit is consistent with much of the available data in the literature for HL. [19,22-24] Within HL, controversy exists regarding the omission of radiotherapy as randomized studies have shown improved disease control but similar OS rates with or without RT [25-28]. With the low incidence (5%) of NLP HL histology within HL, randomized studies may not be powered to detect survival differences based on RT use. Similar to the improvements in OS described by the meta-analysis by Herbst et. al[24] (HR=0.40) long-term follow-up and large patient numbers are necessary to best assess this outcome highlighting the strength of the NCDB.

This study captured a population of patients in the U.S. that have received high level of cancer care reflecting contemporary treatment programs with adherence to accreditation standards by the CoC. We discovered that patients treated at comprehensive community cancer programs were more likely to receive RT than patients treated at academic/research programs (including NCI-designated comprehensive cancer centers). This finding may be supported by various explanations: 1) academic/research programs have greater access to salvage programs such as chemotherapy, or immunotherapy-an option in event of relapse/persistent disease; 2) academic centers may have more rapidly increased the use of Rituxmab as part of therapy for NLP HL while decreasing the use of RT; 3) institutional bias against radiation therapy for fears of late-term morbidities; and 4) greater access to state-of-the art radiation therapy equipment in comprehensive centers.

Nevertheless, there are several limitations to this study. First, data were lacking to control for potential unknown confounders that are specific to the prognosis of HL, such as number of nodal sites, bulk of disease, and serum ESR. The loss of statistical significance for RT use in the PS-adjusted model may be attributed to a potential imbalance of unfavorable characteristics in favor of omitting RT. Accounting for these additional variables may have provided a more balanced interpretation of the benefits of radiotherapy. Second, the natural history of early-stage NLP HL is characterized by indolent late relapses outside of the treatment field(s)[13,14,29]and this dataset does not provide information regarding sites of local or regional relapse. Third, the risk of secondary malignancies, such as non-Hodgkin lymphoma, may be increased by 2-fold in patients with NLP HL[30] and the median follow-up is likely too short to detect survival differences accounting for this outcome.

First-line treatment options for early-stage NLP HL also includes chemotherapy and/or immunotherapy with Rituximab. Prospective studies of Rixtuximab have revealed tolerability with complete response rates of 41-85%. However, late relapses led to a median time to progression of 10-43 months.[31,32] In efforts to omit RT in pediatric patients, a study by van Grotel et al. revealed challenges in the diagnosis and treatment of this disease without local therapy.[33] The event-free survival was only 43%, and high doses of cytotoxic agents were necessary as salvage treatment in a high proportion of patients after relapse.[33]

Despite the OS benefit that has been demonstrated in the literature and the current study, the decrease in utilization rates of RT may be attributed to the concern of late-term side effects of treatment. Radiation oncologists have long abandoned STLI (subtotal lymphoid irradiation) fields, or EFRT (extended field radiation therapy) that were employed in studies such as the HD6.[26] More historical forms of mantle RT for NLP HL have been associated with late toxicities, including secondary malignancies, cardiovascular disease, hypothyroidism, cerebrovascular accidents, pulmonary problems, and muscle atrophy.[13] Investigators have reported an approximate 40% cumulative incidence of grade 3 to 5 chronic toxicity attributable to chemotherapy and RT among HL survivors 30 years following diagnosis and treatment.[34] Studies have found that the main cause of death among HL survivors 20 years after treatment was related to cardiovascular disease, rather than lymphoma.[35,36]

Data suggest that modern radiation therapy field reductions, which now include only the involved site and to much lower doses[37-41], appear to be safe and effective in NLP HL. [15] A multicenter study by Wirth et al. revealed no difference in FFTR when comparing EFRT versus IFRT in 202 patients with NLP HL.[15] The current study reflects a contemporary time period in which radiation with IFRT and ISRT had already begun. Thus, as an effective local, targeted therapy, radiotherapy provides an opportunity to reduce damage to normal tissues and provide durable cure rates.

In summary, inclusion of RT appears to improve long-term overall survival in patients with stage I/II NLP HL. The NCDB has proven to be a powerful tool to demonstrate this potential survival benefit in a relatively uncommon diagnosis in the U.S. We recommend that RT may be considered within the treatment program for patients with early-stage disease and for whom long-term disease control with first-line therapy is the primary goal.

Acknowledgments

The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society.

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Figure 1. CONSORT diagram

Figure 2. Percentage of NPLHL patients receiving chemotherapy alone, RT alone, or combined-modality therapy (CMT)

Figure 3. Percentage of NPLHL patients undergoing RT, between 1998 and 2011, by year of diagnosis

There was an absolute decrease from 68.8% to 60.8%.

Figure 4. Propensity Score Matched Cohort, Overall Survival (OS) by use of RT

The 5-year OS was 88.1% for patients who did not receive RT and 94.1% for those who received RT ($p=0.003$, Wilcoxon test).

Table 1

Patient characteristics according to use of RT.

Parameter	Patients (n)	RT		p-value
		No(%)	Yes (%)	
Overall	1,915	691 (36.1)	1,224 (63.9)	n/a
Gender				0.02 *
Male	1,281	63.7	68.7	
Female	634	36.3	31.3	
Race				0.04 *
White	1,413	70.5	75.7	
Black	429	25.2	20.8	
Other	73	4.3	3.5	
Age (years)				0.005 *
40	826	38.9	45.5	
>40	1,089	61.1	54.5	
Clinical Stage				<0.0001 *
I	1,148	50.8	65.1	
II	767	49.2	35.9	
Presence of "B" Symptoms				<0.0001 *
No	997	82.0	90.2	
Yes	146	18.0	9.8	
Charlson/Deyo co-morbidity score				0.005 *
0	1,241	85.3	91.0	
1	133	12.3	7.7	
2	24	2.4	1.3	
Insurance Status				0.001 *
Not Insured/Medicaid	366	23.9	17.6	
Insured (Medicare/Private Insurance/Managed Care)	1,480	76.1	82.4	
Education (% Not HS graduate in pt's zip code)				0.15
29%	303	19.1	15.6	
20-28.9%	412	24.0	22.3	

Parameter	Patients (n)	RT		p-value
		No(%)	Yes (%)	
14-19.9%	421	22.1	24.2	
<14%	661	34.8	37.9	
Median Household Income (pt's zip code)				0.53
< \$30,000	266	16.3	14.0	
\$30,000-34,999	298	15.7	17.1	
\$35,000-45,999	485	27.3	26.8	
\$46,000	748	40.7	42.1	
Facility Type				0.02 *
Community Cancer Program	194	11.7	9.2	
Comprehensive Community Cancer Program	1,021	48.9	55.8	
Academic/Research Program	650	36.9	32.3	
Other	50	2.5	2.7	
Facility Location				0.001 *
New England	136	5.8	7.8	
Middle Atlantic	365	19.5	18.8	
South Atlantic	406	22.4	20.5	
East North Central	330	18.1	16.8	
East South Central	76	4.6	3.6	
West North Central	160	5.2	10.1	
West South Central	122	8.1	5.4	
Mountain	92	3.5	5.6	
Pacific	228	12.8	11.4	

* = Statistically significant.

Table 2

Unadjusted and Propensity Score-adjusted Analysis for Overall Survival (OS).

Prognostic Factor	Unadjusted Univariate Analysis (OS)		Propensity Score Adjusted, Analysis (OS)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
RT		0.01 *		0.06
No	1.00 (Ref.)		1.00 (Ref.)	
Yes	0.62 (0.43-0.89)		0.49 (0.23-1.05)	
Chemo		0.11		0.17
No	1.00 (Ref.)		1.00 (Ref.)	
Yes	0.74 (0.51-1.07)		0.58 (0.27-1.26)	
Age (years) at Diagnosis		<0.0001 *		0.001 *
40	0.10(0.05-0.19)		0.09(0.02-0.39)	
> 40	1.00 (Ref.)		1.00 (Ref.)	
Gender		0.11		0.92
Male	1.00 (Ref.)		1.00 (Ref.)	
Female	1.35 (0.93-1.96)		1.04 (0.47-2.32)	
Race				
White	1.00 (Ref.)		1.00 (Ref.)	
Black	0.93 (0.59-1.47)	0.77	1.64 (0.72-3.77)	0.24
Other	0.53 (0.13-2.16)	0.38	0.53 (0.13-2.16)	0.38
Education				
29%	1.00 (Ref.)		1.00 (Ref.)	
20-28.9%	0.66 (0.36-1.20)	0.17	1.28 (0.23-6.99)	0.77
14-19.9%	0.91 (0.53-1.55)	0.73	2.76 (0.60-12.61)	0.19
<14%	0.62 (0.37-1.04)	0.07	1.66 (0.37-7.48)	0.51
Median Household Income				
< \$30,000	1.00 (Ref.)		1.00 (Ref.)	
\$30,000-34,999	0.80 (0.42-1.53)	0.51	1.07 (0.22-5.30)	0.94
\$35,000-45,999	0.97 (0.57-1.67)	0.92	1.18 (0.32-4.36)	0.80
\$46,000	0.54 (0.31-0.93)	0.02 *	1.10 (0.31-3.90)	0.88
Insured Status		<0.0001 *		<0.0001 *
Insured	1.00 (Ref.)		1.00 (Ref.)	
(Medicare/Private Ins/Managed Care)				
Not Insured/Medicaid	6.49 (4.48-0.41)		3.97 (1.84-8.55)	
Facility Type				
Community Cancer Program	1.00 (Ref.)		1.00 (Ref.)	
Comprehensive Community Cancer Program	1.25 (0.66-2.36)	0.49	1.25 (0.66-2.36)	0.49
Academic/Research Program	0.91 (0.46-1.81)	0.79	0.91 (0.46-1.81)	0.79
Other	1.05 (0.23-4.76)	0.95	1.05 (0.23-4.76)	0.95
Stage		0.20		0.82
1	1.00 (Ref.)		1.00 (Ref.)	

Prognostic Factor	<u>Unadjusted Univariate Analysis (OS)</u>		<u>Propensity Score Adjusted, Analysis (OS)</u>	
	HR (95% CI)	p-value	HR (95% CI)	p-value
2	1.27 (0.99-1.84)		0.91 (0.42-1.97)	
Presence of "B" Symptoms		0.29		0.48
No	1.00 (Ref.)		1.00 (Ref.)	
Yes	1.66 (0.64-4.35)		1.46 (0.51-4.22)	
Charlson/Deyo co-morbidity score				
0	1.00 (Ref.)		1.00 (Ref.)	
1	3.92 (1.97-7.79)	<0.0001 *	4.27 (1.85-9.85)	0.001 *
2	4.23 (0.57-30.98)	0.16	4.23 (0.56-31.8)	0.16

HR = Hazard ratio; CI = confidence intervals; Ref. = reference group;

*
= Statistically significant.