Variables affecting survival after second primary lung cancer: A population-based study of 187 Hodgkin's lymphoma patients

Michael T. Milano[1], Huilin Li[2], Louis S. Constine[1], Lois B. Travis[1]

[1]Department of Radiation Oncology and Rubin Center for Cancer Survivorship, University of Rochester School of Medicine, Rochester, NY 14642, USA; [2]Division of Biostatistics, Department of Environmental Medicine, New York University School of Medicine, New York, NY, 10016, USA

ABSTRACT

Background: Patients successfully treated for Hodgkin's lymphoma (HL) are at known risk for subsequent malignancies, the most common of which is lung cancer. To date, no population-based study has analyzed prognostic variables for overall survival (OS) among HL survivors who developed non-small cell lung cancer (NSCLC).

Methods: For 187 HL patients who developed NSCLC (among 22,648 HL survivors), we examined the impact of the following variables on OS after NSCLC diagnosis: gender, race, sociodemographic status (based upon county of residence), calendar year and age at NSCLC diagnosis, NSCLC histology and grade, HL stage and subtype, radiation for HL and latency between HL and NSCLC. Patients were grouped by NSCLC stage as follows: localized, regional or distant. All patients were reported to the population-based Surveillance, Epidemiology, and End Results program. For those variables significant on univariate analyses, hazard ratios (HR) were derived from Cox proportional hazards model.

Results: Sociodemogaphic status, gender and latency between NSCLC and HL did not significantly affect OS of any NSCLC stage group. For patients with localized NSCLC, a history of mixed celluarlity HL was associated with a 3-fold improved OS (P=0.006). For patients with regional NSCLC, prior radiotherapy for HL was associated with a 2-fold worse OS (P=0.025).

Conclusions: A history of mixed cellularity HL subtype and a history of no radiotherapy for HL are favorable prognostic factors among patients who develop NSCLC. Further research into clinicopathologic and treatment-associated variables potentially affecting OS after second primary NSCLC among HL survivors is warranted.

KEY WORDS Non-small cell lung cancer; Hodgkin's lymphoma; population-based; cancer survivorship

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Introduction

Hodgkin's lymphoma (HL) remains a largely curable disease (1), though the excellent life expectancy is offset by adverse late effects of treatment, including second malignancies (2-7). The 3- to 20-fold relative risks of lung cancer after HL (2,4,6-11) accounts for the largest absolute risk of second cancer (2,12), with lung cancer being the greatest contributor to overall mortality from second cancers. Beyond 15-30 years after therapy for HL, the cumulative mortality from all second primary cancers exceeds deaths due to HL (3,13-15). While HL treatment with radiotherapy (10,16-18) and/or alkylating-agent chemotherapy (10,18-19) both increase lung cancer risks in dose-dependent manner, smoking is implicated as the most important etiologic factor (10,17-18,20). We (21), and others (8,22-24), have analyzed survival after lung cancer diagnosis in HL survivors. In our recent U.S. population-based analysis (21), we compared the survival of 187 HL survivors who developed NSCLC versus 178,431 patients with first primary NSCLC, simultaneously accounting for demographic, clinicopathologic, and treatment-associated variables. We demonstrated a significantly inferior OS among HL survivors who develop NSCLC, compared to patients with *de novo* NSCLC (21), which we hypothesized may be attributable to host factors inherent to the development of HL, more aggressive tumor biology of therapy-associated cancers, or

No potential conflict of interest.

Corresponding to: Michael T. Milano, MD, PhD. Department of Radiation Oncology University of Rochester Medical Center 601 Elmwood Ave, Box 647 Rochester, NY 14642, USA. Tel: 585-273-4096; Fax: 585-275-1531. Email: Michael_milano@urmc.rochester.edu.

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a limitation in treatment options for NSCLC after HL.

We now investigate the impact of specific demographic, clinicopathologic, and treatment-associated variables on survival of HL survivors who developed NSCLC. We hypothesized that radiotherapy for HL and lower sociodemographic status would adversely affect survival after NSCLC. Within a cohort of 22,648 patients with a first primary HL reported to the population-based cancer registries of the Surveillance, Epidemiology, and End Results (SEER) program (http://seer.cancer.gov/), we identified all patients who developed NSCLC as a second primary cancer (HL-NSCLC). This cohort represents the same patient group for whom we previously compared their survival to patients with *de novo* NSCLC (21).

Methods

Patients

From the U.S. population-based SEER 13 (1973-2006) database, patients were identified who developed NSCLC as a first primary cancer after HL diagnosis (HL-NSCLC group). Of 22,648 patients registered with a first primary HL in the SEER-13 program, 238 developed a second primary NSCLC, with a minimum latency of 2 months, which is the standard adopted by the SEER program to exclude synchronous primary cancers. Because we made no a priori assumptions about NSCLC etiology (i.e. tobacco use, HL therapy, host susceptibility), we did not otherwise require a specific latency period between HL and NSCLC.

Patients were grouped into localized, regional or distant stage NSCLC, as described in SEER Staging Manuals (http://seer.cancer.gov/tools/codingmanuals/historical.html). Generally, localized NSCLC is confined to the ipsilateral lung or bronchus (≥2 cm from the carina), and/or with atelectasis that does not involve the entirety of the lung, regional NSCLC involves hilar or mediastinal nodes and/or direct extension to regional structures, and distant NSCLC implies metastatic spread beyond regional nodes or structures.

Because SEER did not record lung cancer stage before 1988, analyses grouped by stage are restricted to those reported from 1988 forward. One-hundred eighty-seven of 238 HL-NSCLC patients were assigned a NSCLC stage. The histologic types of NSCLC that were included are listed in our prior publication (21) and in Table 1.

HL stage and presence or absence of B symptoms were obtained from the SEER database extent of disease (EOD) fields. For 13 patients, the EOD data resulted in two possible HL stage assignments; the variable of HL stage was analyzed separately using both of these assignments as described previously (21).

The SEER database records sociodemographic parameters of the population residing in each patient's county of residence, determined from U.S. census data. As a surrogate for sociodemographic status, the proportion of adults residing within the patient's county who were age ≥25 years with less than a high-school education was used (21).

Statistical analysis

Actuarial OS was calculated using the Kaplan-Meier method. Survival times were measured from date of NSCLC diagnosis until date of death or last follow-up. All survival analyses were conducted using SAS 9.1.3 software (SAS Institute Inc). Kaplan–Meier curves were prepared using R 2.7.0. For univariate analysis, the log-rank test was used to test the significance of discrete variables, and Cox regression was used to test the significance of continuous variables.

For the multivariate analyses, Cox proportional hazards regression analyses were used; the initial Cox model included year of NSCLC diagnosis, age at NSCLC diagnosis and all variables with P values <0.2 in the univariate analyses. Year of NSCLC diagnosis and age at NSCLC diagnosis were excluded from the final Cox analysis (described in the results) if not significant with univariate and initial multivariate analyses. All P values are two-sided, with $P<0.05$ defined as statistically significant.

Results

Patient and tumor characteristics

Among 238 HL survivors who developed NSCLC, the lung cancer stage was available for 187. Table 1 outlines the previously described (21) demographic and clinicopathologic characteristics of these 187 patients at the time of HL and NSCLC diagnoses (grouped by NSCLC stage), as well as the latency between these diagnoses. The stage distribution of NSCLC after HL (20% localized, 29% regional, and 51% distant) was not appreciably different between the eras of 1988-1999 and 2000-2006 (P=0.92). The pertinent differences in demographic and clinicopathologic characteristics between NSCLC stage groups was also described previously (21). Eight of 38 (21%) of patients with localized NSCLC received radiation alone for NSCLC, 28 received surgical resection alone and 2 received no surgery or radiation. Twenty of 54 (37%) of those with regional NSCLC received radiation for NSCLC (of whom 6 also underwent surgical resection); twenty-three underwent surgical resection without radiation and 11 received no surgery or radiation.

Prognostic factors among HL survivors with NSCLC

NSCLC stage was highly significant ($P<0.001$) for OS for all stage comparisons (i.e. localized *vs.* regional, regional *vs.* distant

Table 1. Patient and tumor characteristics among 187 Hodgkin lymphoma patients who developed non-small cell lung cancer(NSCLC).

	NSCLC			
	All Staged	Localized	Regional	Distant
Total	187	38	54	95
Age at HL diagnosis(years)				
<10-19	3(2%)	0	0	3(9%)
20-39	58(31%)	3(8%)	15(28%)	40(42%)
40-59	84(45%)	21(55%)	27(50%)	36(38%)
≥60	42(22%)	14(37%)	12(22%)	16(17%)
Race				
Black	11(6%)	3(8%)	5(9%)	3(3%)
White	171(91%)	34(89%)	48(89%)	89(94%)
Other/unknown	5(3%)	1(3%)	1(2%)	3(3%)
Gender				
Male	123(66%)	26(68%)	32(59%)	65(68%)
Female	64(34%)	12(32%)	22(31%)	30(32%)
Year of HL diagnosis				
1973-1979	39(21%)	3(8%)	11(20%)	25(26%)
1980-1989	76(41%)	13(34%)	22(41%)	41(43%)
1990-1999	55(29%)	15(39%)	14(26%)	26(27%)
2000-2006	17(9%)	7(18%)	7(13%)	3(3%)
HL Stage				
I	52(28%)	13(34%)	14(26%)	25(26%)
II	59(32%)	9(24%)	19(35%)	31(33%)
III-IV	66(35%)	16(42%)	20(37%)	30(32%)
Unknown	10(5%)	0	1(2%)	9(9%)
HL B symptoms				
Yes	44(24%)	12(32%)	17(31%)	25(26%)
No	77(42%)	14(37%)	21(39%)	42(44%)
Unknown	56(30%)	12(32%)	16(30%)	28(29%)
HL Subtype				
Nodular sclerosis	96(51%)	15(39%)	26(48%)	55(58%)
Mixed cellularity	45(24%)	18(47%)	11(20%)	16(17%)
Lymphocyte depleted	4(2%)	1(3%)	0	3(3%)
Nodular lymphocyte predominant	3(3%)	0	1(2%)	2(2%)
Lymphocyte rich	12(13%)	1(3%)	2(4%)	9(9%)
Classic, NOS	27(14%)	3(8%)	14(26%)	10(11%)
Radiation for HL				
Yes	110(59%)	19(50%)	33(61%)	58(61%)
No	69(37%)	18(47%)	21(39%)	30(32%)
Unknown	8(4%)	1(3%)	0	7(7%)
Latency between HL and NSCLC(years) ¶				
0 to 5	40(22%)	16(46%)	12(22%)	12(13%)
>5 to 10	42(22%)	8(23%)	14(26%)	20(21%)
>10 to 15	36(19%)	7(18%)	10(19%)	19(20%)
>15 to 20	37(20%)	5(13%)	11(20%)	21(22%)
>20	32(17%)	2(5%)	7(13%)	23(24%)

Table 1. ***(continued)***

Table 1. Patient and tumor characteristics among 187 Hodgkin lymphoma patients who developed non-small cell lung cancer(NSCLC) (continued).

	NSCLC			
	All Staged	Localized	Regional	Distant
Age at NSCLC diagnosis(years)				
≤39	7(4%)	1(3%)	0	6(6%)
40-59	86(46%)	11(29%)	25(46%)	50(53%)
60-69	55(29%)	13(34%)	18(33%)	24(25%)
≥70	39(21%)	13(34%)	11(20%)	15(16%)
Year of NSCLC diagnosis				
1988-1999	83(44%)	17(45%)	26(48%)	40(42%)
2000-2006	104(56%)	21(55%)	28(52%)	55(58%)
Sociodemographic status				
<U.S. average	35(19%)	10(30%)	7(13%)	18(19%)
≥U.S. average	152(81%)	28(70%)	47(87%)	77(81%)
NSCLC Grade				
Well differentiated	6(3%)	3(8%)	2(4%)	1(1%)
Moderately differentiated	35(19%)	16(42%)	11(20%)	8(8%)
Poorly differentiated	60(32%)	8(21%)	23(43%)	29(31%)
Undifferentiated; anaplastic	11(6%)	1(3%)	3(6%)	7(7%)
Unknown	75(40%)	10(26%)	15(28%)	50(53%)
NSCLC Histology [‡]				
Squamous cell carcinoma	68(36%)	23(61%)	28(52%)	17(18%)
Adenocarcinoma	69(37%)	10(26%)	14(26%)	45(47%)
Bronchiolo-alveolar carcinoma	8(4%)	4(11%)	2(4%)	2(2%)
Adenosquamous	1(0.5%)	0	0	1(1%)
Large cell carcinoma	12(6%)	0	3(6%)	9(10%)
Non-small cell carcinoma	29(16%)	1(3%)	7(13%)	21(22%)

[‡]squamous cell carcinoma (ICD-O-3 8050-8084/3), adenocarcinoma (ICD-O-3 8140/3, 8255/3, 8260/3, 8310/3), bronchiolo-alveolar carcinoma (ICD-O-3 8250-8254/3), adenosquamous carcinoma (ICD-O-3 8560/3), large cell carcinoma (ICD-O-3 8012/3), non-small cell carcinoma (ICD-O-3 8046/3); [¶]Number of years between HL and NSCLC diagnosis.

and localized *vs.* distant), and thus all analyses were performed wth patients grouped by NSCLC stager. The actuarial survival, by NSCLC stage was described previously (21). Table 2 shows results from univariate analyses assessing the influence of various prognostic factors on OS of HL-NSCLC patients, grouped by NSCLC stage. For 13 (7%) patients, 2 different possible HL stages were assigned (see Methods); therefore separate univariate analyses were performed allowing for each stage assignment to be analyzed. HL stage (I-II or III-IV) was not significant for any NSCLC stage group. For regional NSCLC patients, P values for HL stage ranged from 0.11-0.16, though no HL stage grouping was consistently adverse or favorable among the separate analyses.

For patients with localized NSCLC, mixed cellularity HL subtype (P=0.035) was a significantly favorable prognostic factor, while older age at HL diagnosis (P=0.012), older age at NSCLC diagnosis (P=0.006) and radiotherapy for NSCLC (P=0.004) were significantly adverse prognostic factors. Radiotherapy for HL was an adverse (P=0.068) factor for patients with regional NSCLC; additionally, non-white race proved to be a significantly associated with worse OS. For distant NSCLC, no prognostic variable proved to be significant for OS.

Table 3 summarizes the multivariate analyses of potential prognostic variables affecting OS. For HL-NSCLC patients with localized NSCLC, increasing age at NSCLC diagnosis was associated with a non-significantly (P=0.15) increased risk of death, while HL subtype other than mixed cellularity was associated with a significantly greater risk of death (HR=3.45; P=0.006). For patients with regional NSCLC, prior radiation for HL (HR=2.08, P=0.025), non-white race (HR=3.70, P=0.019) and earlier calendar year of NSCLC diagnosis (HR=1.08, P=0.021) were adverse predictors of OS. The

Table 2. Univariate analyses of variables which affect survival in patients with Hodgkin lymphoma (HL) who developed non-small cell lung cancer (NSCLC).

	Localized NSCLC	Regional NSCLC	Distant NSCLC
	P value	P value	P value
Univariate analysis			
Age at HL diagnosis (*older*) [$]	0.012 *	0.48	0.99
HL stage [†]	0.62-0.84	0.11-0.16 *	0.63-0.78
HL subtype (*mixed cellularity: no*) [‡]	0.035 *	0.94	0.95
Radiation for HL (*radiation: yes*)	0.86	0.068 *	0.29
Latency of NSCLC [$]	0.91	0.89	0.43
Age at NSCLC diagnosis (*older*) [$]	0.006 *	0.38	0.59
Calendar year of NSCLC diagnosis (*earlier*) [$]	0.098 *	0.25	0.15 *
Radiation for NSCLC (*radiation: yes*)	0.004 *	0.45	0.54
NSCLC histology [¤]	0.63	0.86	0.29
NSCLC grade	0.76	0.42	0.21
Sociodemographic status [$]	0.54	0.71	0.72
Race (*non-white*)	0.32	0.036 *	0.61
Gender	0.96	0.81	0.92

*P value <0.2 in univariate analysis. Variables associated with more adverse survival are shown in italics; [†]The range of P-values reflects analyses accounting for 2 possible HL stage assignments in 13 (7%) of the 187 HL-NSCLC patients (see text). No HL stage group was consistently adverse or favorable among the separate analyses. Consequently, HL stage was omitted from Cox proportional hazards multivariate analyses for regional stage NSCLC. Notably, the inclusion of HL stage did not appreciably change the HR or P values of the other variables in the Cox model; [‡]Mixed cellularity subtype versus all others; [$]Variables analyzed with a Cox model, using the single variable of interest; all others were analyzed using the log-rank method; [¤]Grouped into adenocarcinoma (including bronchiolo-alveolar) versus squamous cell carcinoma.

median survival of HL-NSCLC patients with regional disease who received radiation for HL versus those who did not receive radiation for HL was 6 *vs.* 14 months, and the corresponding 1-year OS was 27% *vs.* 55%. Of note, the percentage of HL-NSCLC patients undergoing radiation for regional NSCLC was similar (P=0.48) for patients previously irradiated for HL (22 of 33, 67%) versus patients who did not undergo radiation for HL (12 of 21, 55%).

Discussion

Important new findings in our study, based on 187 HL-NSCLC patients include a 3-fold improved OS among localized NSCLC patients with a history of mixed celluarlity HL (versus other subtypes), and a 2-fold worse OS among regional NSCLC patients treated with radiation (versus no radiation) for HL.

We are not aware of other investigations that analyze demographic, clinicopathologic, and treatment-associated prognostic factors for survival after NSCLC among HL survivors. Moreover, our study was conducted within the large, population-based registries that comprise the U.S. SEER Program.

Overall survival

We previously showed that overall, only 4% of all HL-NSCLC patients died of HL; for regional and distant NSCLC, 85% percent of deaths were from NSCLC, versus 48% for localized NSCLC (21). For localized NSCLC, deaths from heart disease occurred in 20% and deaths from other cancers (not HL or NSCLC) occurred in 16%, causes of mortality known to be increased among HL survivors (3,13,14).

Variables affecting survival of HL-NSCLC patients

Among HL-NSCLC patients, variables significantly affecting OS, based on multivariate analyses, included HL subtype, radiotherapy for HL, calendar year of NSCLC diagnosis and race. Older age was a non-significant adverse factor among those with localized NSCLC (Table 3), though we previously showed that the discrepancy in median survival between older and younger HL-NSCLC patients with localized disease was less pronounced compared to the *de novo* NSCLC population (21), partially attributable to increased deaths from other-cancers.

In the current study, mixed cellularity HL subtype was associated with a significantly (P=0.006) >3-fold reduced

Table 3. Multivariate analyses of variables which affect survival in patients with Hodgkin lymphoma (HL) who developed non-small cell lung cancer (NSCLC).

	Localized NSCLC	Regional NSCLC	Distant NSCLC
Multivariate analysis			
Age at HL diagnosis		ND	ND
P value	0.68		
Hazard ratio	0.98/year		
95% confidence interval	0.91-1.06		
HL subtype (*mixed cellularity: no*)[‡]		ND	ND
P value	0.006**		
Hazard ratio	3.63		
95% confidence interval	1.44-9.18		
Radiation for HL (*radiation: yes*)	ND		ND
P value		0.025**	
Hazard ratio		2.08	
95% confidence interval		1.09-3.94	
Age at NSCLC diagnosis (*older*)		ND	ND
P value	0.15		
Hazard ratio	1.07/year		
95% confidence interval	0.98-1.17		
Calendar year of NSCLC diagnosis (*earlier*)			
P value	0.21	0.021**	0.16
Hazard ratio	1.06/year	1.08/year	1.03/year
95% confidence interval	0.96-1.19	1.01-1.15	1.01-1.08
Radiation for NSCLC		ND	ND
P value	0.14		
Hazard ratio	2.38		
95% confidence interval	0.75-7.50		
Race (*non-white*)	ND		ND
P value		0.019**	
Hazard ratio		3.70	
95% confidence interval		1.23-11.1	

For the Cox proportional hazards multivariate regression analyses, the initial model included year of NSCLC diagnosis, age at NSCLC diagnosis and any variables with P value <0.2 in the univariate analyses. For patients with regional or distant NSCLC, the variable 'age at NSCLC diagnosis' was not significant with univariate or multivariate models (multivariate analysis not shown); therefore, the multivariate model was re-run without that variable (multivariate analysis shown). **P value <0.05 in multivariate analysis. Variables associated with more adverse survival are shown in italics; [‡]Mixed cellularity subtype versus all others; Abbreviations: HR=hazard ratio, ND=not done, since P value was >0.2 with univariate analysis, OS=overall survival.

mortality after localized NSCLC. Possible reasons for this association are unknown, but perhaps somehow relate to an increased likelihood of these patients having received chemotherapy for HL (25,26). We also previously showed that the distribution of HL subtypes among patients who developed NSCLC was significantly different between stage groups (P=0.005), with patients who developed localized NSCLC more likely to have had mixed cellularity HL, and less likely to have had nodular sclerosis HL (21).

The increased risk of death (albeit non-significant in multivariate analyses) among localized NSCLC patients treated with radiation for NSCLC may reflect the fact that historically radiation for early stage lung cancer was the preferred treatment for patients with relatively poor performance status and/or comorbidities that precluded surgical resection (27), though was based upon a small number (8 of 38) receiving radiation alone. The decreased risk of death among non-white HL patients with regional NSCLC (n=6) was based upon sparse numbers, and may represent a chance finding. The improved OS of HL survivors with more recent NSCLC diagnosis (significant for regional NSCLC) presumably reflects improved NSCLC outcomes following chemotherapy and radiotherapy advances over the past decades (28,29), a hypothesis confirmed by the highly significant (P<0.0001) effect of calendar year on OS in the general population (data not shown). However, improvements in lung cancer survival over time have been modest(28-30).

In the current analysis, a history of radiotherapy for HL was associated with a significantly (P=0.025) worse OS (HR=2.08)

among regional stage NSCLC patients. One possible reason accounting for the worse OS of regional NSCLC among those irradiated for HL is the potential limitation in treatment options for patients who were previously irradiated for HL. While our analysis did not demonstrate a lower likelihood of receiving radiation for regional NSCLC among patients who received radiation for HL versus those who did not, it is plausible that those with prior radiation did not receive full dose radiation and/or were treated with fields that compromised tumor coverage, though our analysis cannot address this hypothesis. Another possible explanation is that prior radiotherapy for HL may introduce radiation-induced genetic alterations potentially affecting the biologic behavior of treatment-induced NSCLC and its responsiveness to therapy. In an analytic population-based study of lung cancer following radiation for HL (31), archived paraffin-embedded tissues were evaluated for 15 patients who developed NSCLC and compared with *de novo* NSCLC. NSCLC after HL was characterized by a significant 5.9-fold increase (P=0.0002) in microsatellite alterations (31). The authors conclude that NSCLC developing in irradiated HL patients demonstrates widespread genomic instability, as manifested by increased numbers of microsatellite alterations. While the impact of miscrosatellite instability on the treatment response of NSCLC is speculative, the hypothesis of treatment-induced genetic instability affecting outcomes of second malignancies is compelling.

Comment

Strengths of the current study include the sizable number of patients (n=187) which allowed for analyses of outcomes by NSCLC stage, age, and other patient-related and tumor-related variables. Known limitations of SEER data include lack of detailed information about radiotherapy doses and fields, as well as the underreporting of radiotherapy use (32). Also, SEER does not report whether chemotherapy was administered, or information on tobacco use or tobacco history, factors, along with thoracic radiotherapy, which are linked to increased risks of NSCLC development, and which may also affect outcomes after NSCLC diagnosis (10,16,18-20,33). The SEER registries also do not collect data on known prognostic factors associated with NSCLC survival, such as weight loss and performance status (34-36). The SEER program also does not record presenting symptoms at diagnosis, which has been reported to be significant factor among patients who developed thoracic malignances after HL (24). Lastly, SEER only records the sociodemographic profile of the patient's county of residence, and thus individual sociodemographic parameters are not available. Nonetheless, we show that a history of mixed cellularity HL and prior radiotherapy for HL appear to impact survival after NSCLC.

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