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ORIGINAL ARTICLE

Stage I non-Hodgkin lymphoma: no plateau in disease-specific survival ?

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Abstract

Stage I non-Hodgkin lymphoma (NHL) is rare; prognostic impact of different histologic subtypes and treatment modality is still unclear. We used the Surveillance, Epidemiology and End Results (SEER) database to evaluate survival outcomes among adult patients (age ≥ 18 years, $N = 58{,}230$) diagnosed with stage I NHL of various histologic subtypes between 1998 and 2014. Five-year disease-specific survival of patients with stage I diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), Burkitt lymphoma (BL), mantle cell lymphoma (MCL), and peripheral T cell lymphoma (PTCL) was 82%, 92%, 95%, 89%, 78%, 77%, and 77%, respectively. The median disease-specific survival was not reached in all histologic subtypes analyzed; however, there does not appear to be a plateau in disease-specific survival of patients with stage I NHL irrespective of subtypes. Although lymphoma was the most common cause of death (40.7%), death from other cancer (17.4%) and cardiovascular disease (13.6%) were also frequent. Chemotherapy appeared favorably associated with OS in patients with DLBCL, BL, and MCL while patients with FL, MZL, SLL, and PTCL who require chemotherapy for initial treatment showed shorter OS. Patients with stage I NHL have favorable disease-specific survival; however, no plateau was seen regardless of histologic subtypes thus suggesting that patients may need attention and follow-up even in aggressive lymphomas after 5 years of remission.

Keywords Stage I lymphoma · Disease-specific survival · SEER · Radiation

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Introduction

Stage I non-Hodgkin lymphoma (NHL) is a rare condition. The percentage of patients presenting with localized disease (Ann Arbor stage I/II) differs by histologic subtype but patients with limited stage disease typically have fewer adverse prognostic factors and therefore, better outcomes than patients with advanced stage disease [1, 2]. Overall outcomes are favorable with a 5-year overall survival (OS) around 80% [3], but late recurrences were seen in trials and optimal follow-up duration is still unclear [4]. Currently, the National Comprehensive Cancer Network (NCCN) guideline recommends different treatment modalities such as radiation alone, chemoimmunotherapy, and combined modality (CMT chemotherapy followed by radiation) to different subtypes but evidences behind this recommendation are relatively scarce due to the rarity of condition [5]. We evaluated survival outcome of patients with stage I NHL focusing on evaluating the differences in survival outcome by histologic subtypes and treatment modalities.

Patients and methods

The Surveillance, Epidemiology and End Results (SEER) 18 database, which currently covers approximately 27.8% of the US population, was used to evaluate overall survival (OS) of patients with stage I NHL by different histologic subtypes in patients aged ≥ 18 years diagnosed between 1998 and 2014. We excluded PCNSL, lymphoma developed from adnexa and eye, primary mediastinal lymphoma, testicular lymphoma, extranodal NK cell lymphoma, and cutaneous T cell lymphoma due to unique biological and clinical features requiring different treatment strategies [6–9]. Also, enteropathy-associated T cell lymphoma (EATL) and hepatosplenic T cell lymphoma (HSTL) were excluded to focus primarily on nodal peripheral T cell lymphomas (PTCLs). Overall survival (OS) was calculated from diagnosis to death from any cause, disease-specific survival was calculated from diagnosis to death from lymphoma, using the Kaplan-Meier method. Differences in the survival function in different groups were analyzed using the log-rank test. Cox proportional hazard models were used to evaluate associations between patient characteristics and survival. All analyses were performed using STATA version 13.1 (StataCorp LP, College Station, TX), with significance set at the 5% level.

Results

After excluding diseases as described above, a total of 58,230 patients were diagnosed with stage I disease during the study period (Table 1). The median age of the patients was 67 years (range 18–104). Diffuse large B cell lymphoma (DLBCL) was the most common histology ($N = 21{,}411$, 36.8%), followed by follicular lymphoma (FL, $N = 12{,}964$, 22.3%), marginal zone lymphoma (MZL, $N = 9773$, 16.8%), small lymphocytic lymphoma (SLL, $N = 2821$, 4.9%), peripheral T cell lymphoma (PTCL, $N = 2007$, 3.5%; includes PTCL not otherwise specified [$N = 1148$], anaplastic large cell lymphoma [$N = 737$] and angioimmunoblastic T cell lymphoma [$N = 122$]), mantle cell lymphoma (MCL, $N = 944$, 1.6%), Burkitt lymphoma (BL, $N = 673$, 1.2%), and lymphoma not otherwise specified ($N = 7542$, 13.0%). Significant improvements in OS were seen by the time of diagnosis (1998–2004 vs 2005–2010, 2005–2009 vs 2010–2014) in DLBCL, FL, MZL, and SLL (Supplemental figure).

Forty-one percent of patients received neither radiation therapy (RT) nor chemotherapy (40% of them received just surgical resection), 14% of patients received RT alone, 28% of patients received chemotherapy alone, and 16% of patients received CMT. With a median follow-up of 68 months, the median OS of patients with DLBCL, FL, MZL, SLL, BL, MCL, and PTCL was 120, 179, 165, 101, not reached, 70, and 109 months, respectively (Fig. 1a). Five and 10-year OS and disease-specific survival of each histologic subtype are summarized in Table 2. The most common cause of death was lymphoma in 8993 patients (40.7%) followed by other cancer in 3838 patients (17.4%) and cardiovascular disease in 2998 patients (13.6%), and the median disease-specific survival was not reached in any of the histologic subtypes analyzed (Fig. 1b).

Chemotherapy appeared favorably associated with OS in patients with DLBCL, BL, and MCL while RT alone was associated with comparable or even superior OS in patients with FL, MZL, and PTCL (Fig. 2). Combined modality therapy (CMT) was associated with the best outcomes in patients with stage I DLBCL and MCL. Since the primary site of disease can affect treatment options and outcomes, we performed multivariate analysis for OS adjusted by age, sex, ethnicity, and primary site of involvement (Table 3). Surgical resection prior to treatment was also associated with significantly longer survival in DLBCL, FL, MZL, BL, and PTCL; hazard ratio for surgical resection was 0.81 (95% confidence interval [CI]; 0.77–0.85, $p < 0.001$) in DLBCL, 0.83 (95%CI; 0.77–0.89, $p < 0.001$) in FL, 0.87 (95%CI; 0.79–0.95, $p = 0.002$) in MZL, 0.74 (95%CI; 0.55–1.00, $p = 0.053$) in BL, and 0.85 (95%CI; 0.73–0.99, $p = 0.033$) in PTCL.

Discussion

The study showed that survival outcomes among patients with stage I NHL are influenced by both histologic subtype and treatment modality. Disease-specific survival was favorable and about three-quarters of patients were alive from

Table 1 Patient characteristics

		All	DLBCL	FL	SLL	MZL	BL	MCL	*PTCL
N		58,230	21,411	12,964	2821	9773	673	944	2007
Median age	(range)	67 (18–104)	68 (18–104)	65 (18–102)	71 (22–99)	67 (18–101)	50 (18–99)	71 (24–98)	62 (18–98)
Male (%)		29,946 (51)	11,508 (54)	6388 (49)	1490 (53)	4358 (45)	484 (72)	622 (66)	1155 (58)
Ethnicity (%)	White	44,567 (77)	15,992 (75)	10,682 (82)	2382 (84)	7085 (73)	452 (67)	787 (83)	1433 (71)
	Black	3871 (7)	1329 (6)	545 (4)	235 (8)	739 (8)	47 (7)	46 (5)	239 (12)
	Hispanic	5478 (9)	2307 (11)	1046 (8)	109 (4)	993 (10)	109 (16)	64 (7)	185 (9)
	Asian/Pacific	3474 (6)	1523 (7)	521 (4)	61 (2)	771 (8)	59 (9)	39 (4)	114 (6)
	Others	840 (1)	260 (1)	170 (1)	34 (1)	185 (2)	6 (1)	8 (1)	36 (2)
Treatment (%)	None	23,905 (41)	5305 (25)	5978 (47)	2174 (77)	5465 (56)	97 (15)	402 (43)	784 (39)
	Radiation alone	8309 (14)	1246 (6)	2918 (23)	193 (7)	2566 (26)	5 (1)	80 (9)	304 (15)
	Chemotherapy alone	16,264 (28)	8454 (40)	2733 (21)	378 (13)	1290 (13)	471 (71)	356 (38)	557 (28)
	Chemo-radiation	9158 (16)	6103 (29)	1219 (9)	67 (2)	374 (4)	94 (14)	100 (11)	344 (17)

Abbreviations: *DLBCL* diffuse large B cell lymphoma, *FL* follicular lymphoma, *SLL* small lymphocytic lymphoma, *MZL* marginal zone lymphoma, *BL* Burkitt lymphoma, *MCL* mantle cell lymphoma, *PTCL* peripheral T cell lymphoma

*PTCL includes peripheral T cell lymphoma—not otherwise specified, angioimmuoblastic T cell lymphoma, anaplastic large cell lymphoma

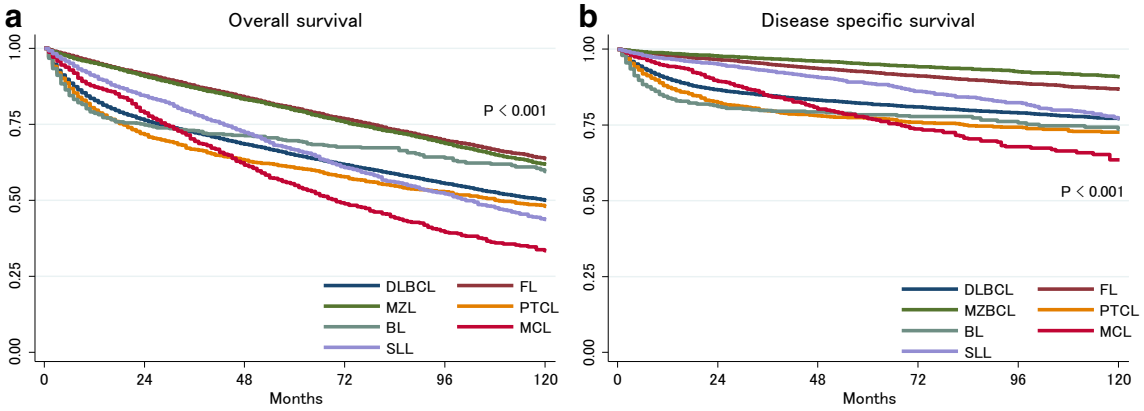

Fig. 1 Overall survival (**a**) and disease-specific survival (**b**) by different histologic subtypes

lymphoma at 10 years (except patients with MCL). However, FL, MZL, and BL were the only subtypes in which the median OS exceeded 10 years since about 60% of death in patients with stage I NHL was not due to disease progression. Second primary malignancies and cardiovascular death were the next most common causes.

Aside from particular site of involvement such as PCNSL, primary testicular lymphoma, and primary mediastinal lymphoma [7–9], the prognostic and treatment implications of primary site and extranodal disease have been controversial. We evaluated the difference in OS by primary site of involvement in patients with stage I disease and found that extranodal stage I disease was generally associated with longer OS in FL and MZL but shorter OS in PTCL [10]. Further studies are needed to investigate biological differences among nodal and extranodal sites and to evaluate whether site-specific treatment strategies can improve patient outcomes.

There does not appear to be a plateau in disease-specific survival of patients with stage I NHL irrespective of subtypes. Even in DLBCL, continuous death from lymphoma was seen after 5 years which is consistent with long-term follow-up from the Southwest Oncology Group (SWOG) 8376 study [4]. Patients with stage I MCL appeared to have the most unfavorable outcome, with greater probability of death (from any cause or lymphoma progression) compared to other histologic subtypes. A Japanese multicenter retrospective study analyzed 633 patients with MCL and showed that survival outcome of patients with limited stage disease was similar to stage III disease [11]. Extranodal disease such as gastrointestinal involvement is very common in patients with MCL and rarely has clinical significance. Romaguera et al. showed that 88% of patients with MCL had lower GI tract involvement when colonoscopy with random biopsies was performed, although only 26% of patients had GI symptoms [12]. Although we are unaware of the rigor of staging in this cohort, outside of a clinical trial, most guidelines only recommend colonoscopy if there are symptoms suggestive of GI involvement present. Thus, it is possible that many patients with "stage I" MCL

Table 2 Survival outcome by histologic subtypes

	Median OS (months) [95% CI]	5-year OS (%) [95% CI]	10-year OS (%) [95% CI]	5-year DSS (%) [95% CI]	10-year DSS (%) [95% CI]
Diffuse large B cell lymphoma	120 [116–125]	64.9 [64.2–65.6]	50.0 49.1–50.8]	82.0 [81.4–82.5]	77.2 [76.4–77.9]
Follicular lymphoma	179 [171–190]	80.3 79.5–81.0]	63.7 [62.6–64.8]	92.4 [91.9–92.9]	86.8 [86.0–87.6]
Marginal zone lymphoma	165 [159–172]	79.5 [78.6–80.4]	61.9 [60.5–63.2]	95.1 [94.5–95.6]	90.9 [90.0–91.8]
Small lymphocytic lymphoma	101 [96–108]	66.6 64.6–68.6]	43.8 [41.3–46.2]	88.9 [87.2–90.0]	77.3 [74.7–79.6]
Burkitt lymphoma	Not reached [151-not reached]	69.6 [65.7–73.2]	59.5 [54.6–64.1]	78.4 [74.7–81.6]	73.6 [69.1–77.6]
Mantle cell lymphoma	70 [63–79]	54.9 [51.2–58.4]	33.5 [29.4–37.6]	77.1 [73.6–80.2]	63.5 [58.4–68.2]
Peripheral T cell lymphoma	109 [97–126]	60.7 [58.2–63.0]	48.1 [45.2–50.8]	77.3 [75.1–79.3]	72.6 [70.0–75.1]

Abbreviations: *OS* overall survival, *DSS* disease-specific survival, *CI* confidence interval

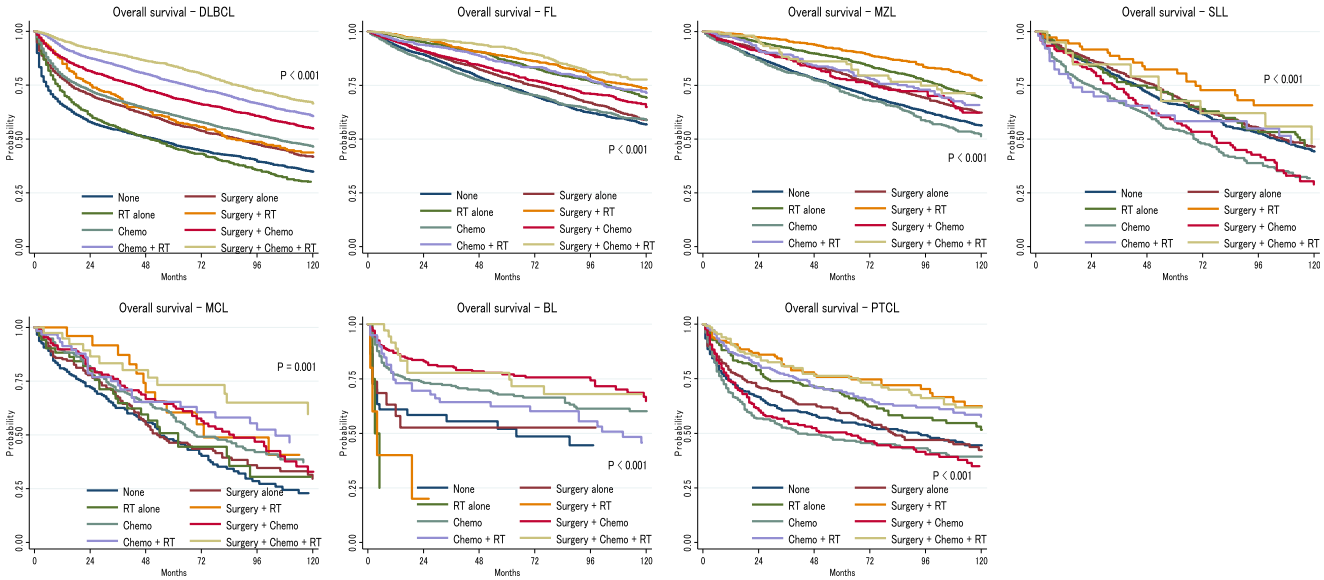

Fig. 2 Overall survival by treatment modality in different histologic subtypes

included in these analyses could have had advanced stage disease if adequately staged.

CMT in addition to surgical resection was associated with favorable outcomes in DLBCL and MCL. Since the initial report of landmark study of Southwest Oncology Group (SWOG 8739 showing survival improvement with less toxicity with 3 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by RT compared to 8 cycles of CHOP [2], CMT has been widely used and the CMT strategy has applied to rituximab era. Retrospective analysis from MD Anderson Cancer Center showed improved OS with consolidative RT compared to chemotherapy alone in limited stage disease with DLBCL [13]. However, long-term follow-up results of SWOG 8739 study have shown that the survival benefit from CMT disappeared after 7 to 9 years with continued late relapses [4]. In addition, a randomized study from the French group also recently confirmed that patients with a negative PET scan after 3 cycles of therapy and 4–6 cycles of R-CHOP are non-inferior to CMT [14]. These prospective trial results suggest selection bias in retrospective studies including this study, not supporting routine use of CMT in limited stage DLBCL. However, further studies may be warranted to evaluate if CMT has a role in specific condition, as is the case in PCNSL [15] and primary testicular lymphoma [16].

Unsurprisingly for FL and surprisingly for PTCL, outcomes from surgical resection with RT were similar to surgical resection with CMT. Prior studies for FL suggest that RT alone can results in long-term remission for stage I disease and thus would be a reasonable option [17]. However, MacManus et al. recently reported phase III study in which patients with stage I/II FL were randomized to receive either involved-field RT (IFRT) or IFRT and 6 cycles of R-CVP [18]. There was a marginal benefit in PFS but not in OS for patients who received CMT. Chemotherapy is considered standard of care for PTCL due to the aggressive nature of the disease; however, this study suggests the need for prospective evaluation of first line treatment of limited stage PTCL. RT alone was associated with favorable outcomes even compared to CMT in SLL and MZL. Interestingly, RT showed survival benefit even after surgical resection in indolent lymphomas. Although selection bias must be strongly considered, RT alone or RT even after surgical resection seems a reasonable option for patients with stage I indolent lymphoma.

Several limitations should be noted. As this study uses cancer registry data, there is no review of pathology and therefore the accuracy of diagnosis is unknown. Although we evaluated lymphoma subtypes encountered relatively frequently by pathologists in this study, Clarke et al. showed the accuracy of diagnoses particularly in rare subtypes such as T cell lymphomas in SEER registry data are suboptimal [19]. We analyzed patients diagnosed between 1998 and 2014 and staging of lymphoma at diagnosis dramatically changed during this period with the widespread introduction of ^{18}F-flurodeoxyglucose positron emission tomography scan resulting in a potential "stage migration" effect. Further, SEER data does not contain detailed information regarding disease-specific prognostic factors such as tumor bulk or treatment specifics such as use of rituximab or choice of chemotherapy regimen. There was significant improvement in OS from 1998–2004 to 2005–2009 in DLBCL, FL, and MZL which could be due to the introduction of rituximab but we are unable to thoroughly evaluate these important clinical questions. Also, response to treatment and information for relapse including transformation of indolent lymphoma are not available. The multivariate analysis for OS adjusting primary site of involvement showed that patients with FL, MZL, SLL, and PTCL who require chemotherapy have shorter survival compared to patients who initially were followed without treatment (likely watch and

Table 3 Hazard ratio for overall survival by treatment

	DLBCL			FL			MZL			SLL			BL			MCL			PTCL		
	HR	95%CI	*p* value	HR	95%CI	*p* value	HR	95%CI	*p* value	HR	95%CI	*p* value	HR	95%CI	*p* value	HR	95%CI	*p* value	HR	95%CI	*p* value
None	Ref			Ref			Ref			Ref			Ref			Ref			Ref		
Surgery alone	0.76	0.69–0.83	< 0.001	0.88	0.80–0.97	0.013	0.93	0.82–1.05	0.228	0.95	0.83–1.10	0.520	0.86	0.31–2.38	0.778	0.85	0.64–1.15	0.294	0.89	0.70–1.13	0.352
Radiation alone	0.79	0.71–0.88	< 0.001	0.73	0.64–0.82	< 0.001	0.75	0.66–0.86	< 0.001	1.08	0.81–1.45	0.608	1.26	0.29–5.52	0.759	1.06	0.66–1.68	0.816	0.78	0.57–1.07	0.124
Surgery + radiation	0.61	0.51–0.72	< 0.001	0.64	0.55–0.74	< 0.001	0.67	0.51–0.78	< 0.001	0.61	0.36–1.03	0.063	1.98	0.25–15.4	0.516	0.69	0.36–1.30	0.247	0.67	0.45–0.99	0.044
Chemotherapy	0.78	0.73–0.84	< 0.001	1.25	1.12–1.39	< 0.001	1.17	1.02–1.33	0.023	1.72	1.43–2.07	< 0.001	0.86	0.50–1.47	0.579	0.75	0.57–0.98	0.036	1.42	1.13–1.78	0.003
Surgery + chemotherapy	0.63	0.57–0.69	< 0.001	0.97	0.84–1.11	0.628	1.03	0.81–1.29	0.831	1.49	1.16–1.92	0.002	0.67	0.37–1.19	0.173	0.72	0.51–1.01	0.058	1.20	0.93–1.55	0.168
Chemotherapy + radiation	0.50	0.47–0.55	< 0.001	0.82	0.70–0.97	0.019	0.99	0.78–1.25	0.902	1.56	1.03–2.36	0.036	0.85	0.44–1.64	0.634	0.61	0.39–0.96	0.032	0.71	0.53–0.95	0.023
Surgery + chemotherapy + radiation	0.40	0.36–0.45	< 0.001	0.56	0.45–0.69	< 0.001	1.06	0.70–1.62	0.772	2.29	1.10–4.74	0.026	0.76	0.36–1.62	0.478	0.46	0.23–0.92	0.027	0.59	0.41–0.85	0.005

Adjusted by age, sex, race, site of primary disease

wait), suggesting the selection biases in the treatment performed for stage I disease. The analysis of impact of treatment is clear that it is a subject to selection bias and these findings should be viewed with caution.

In conclusion, patients with stage I NHL have favorable disease-specific survival; however, no plateau was seen regardless of histologic subtypes and thus suggesting that patients may need attention and follow-up even in aggressive lymphomas after 5 years of remission.

Authorship disclosure D.C. designed the study and performed the statistical analysis. D.C., Y.O., M.A.F., J.R.W., L.J.N., S.N., L.E.F., N.H.F., and C.Y.C interpreted the data and wrote the paper. All authors have read and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest Dr Fanale reports grants and personal consulting fees through 06/04/18 from Seattle Genetics and salary and stocks from 10/01/18 following the start of her employment with Seattle Genetics. Grants and personal fees from Takeda through 06/04/18, grants and personal fees from Celgene through 06/04/18, grants from ADC Therapeutics through 06/04/18, grants and personal fees from BMS through 06/04/18, grants and personal fees from Merck through 06/04/18, grants from Molecular Templates through 06/04/18, personal fees from Bayer through 06/04/18, personal fees from Spectrum through 06/04/18, grants from MedImmune through 06/04/18, grants from Gilead through 06/04/18, and grants from Genentech through 06/04/18.

Ethical approval SEER data is publically available de-identified database and thus deemed not needing approval from institutional review board.

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