Leukemia Research 38 (2014) 866–873

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Improved survival with rituximab-based chemoimmunotherapy in older patients with extranodal diffuse large B-cell lymphoma

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ARTICLE INFO

Article history:
Received 17 February 2014
Received in revised form 28 March 2014
Accepted 14 April 2014
Available online 1 May 2014

Keywords:
Diffuse large B-cell lymphoma
R-CHOP chemotherapy
Rituximab
SEER program
Comparative effectiveness research

ABSTRACT

Using the Surveillance, Epidemiology, and End Results (SEER)–Medicare database, we investigated the relative benefits of adding rituximab to CHOP chemotherapy in diffuse large B-cell lymphoma (DLBCL) of extranodal origin, and found similar advantage for nodal and extranodal lymphomas. Hazard ratio for overall survival was 0.64 for nodal, and 0.70 for extranodal DLBCL. Hazard ratios for lymphoma-related death were 0.62 and 0.57, respectively. The advantage was largest for DLBCL of the spleen, liver and lung. Conversely, it was not evident for thyroid or testicular lymphomas. Compared with nodal DLBCL, spleen was the only site with significantly better prognosis after R-CHOP.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma subtype with approximately 22,000 new cases each year in the United States (US) [1]. Its prognosis has substantially improved with the addition of rituximab to standard chemotherapy [2–4]. In a third of cases DLBCL arises from extranodal sites, and these lymphomas differ in clinical characteristics [5]. Previous studies of prognosis in primary extranodal DLBCL showed varying results, and whether the benefits of rituximab-based chemoimmunotherapy are the same for nodal and extranodal disease is controversial.

Advanced nodal lymphoma may also involve extranodal sites by direct invasion or diffuse spread. Rituximab appears to improved outcomes in advanced DLBCL with extranodal extension, but some studies found no such benefit in primary extranodal DLBCL [6,7]. Worse outcomes in early-stage DLBCL with extranodal involvement were suggested, while the opposite was reported in advanced stage [6,8]. Finally, specific extranodal sites of involvement were prognostic in patients with DLBCL in some studies, but not in others, and this issue has not been analyzed in the context of treatment effects [5,9–11].

We conducted a retrospective analysis of DLBCL cases from the Surveillance Epidemiology and End Results (SEER)–Medicare database. Our primary objective was to assess the relative benefits of adding rituximab to chemotherapy for primary nodal and extranodal DLBCL. The secondary objective was to identify specific extranodal sites associated with better or worse outcomes after rituximab-based chemotherapy.

2. Methods

2.1. Data source and variables

The study was approved by the Institutional Review Board and conducted in accordance with the Helsinki Declaration. We extracted data on all DLBCL cases diagnosed between 1996 and 2009 from the SEER–Medicare database curated by the National Cancer Institute (NCI). SEER collects cancer registry data (demographic, clinicopathologic and survival variables) from 18 geographic areas currently covering 26% of the US population. Medicare provides medical insurance to all Americans who are ≥65 years old or disabled, and the linked database captures inpatient and outpatient medical services rendered to patients [12]. This database has been validated for identification and analysis of intravenous chemotherapy in lymphomas [4,13,14]. The available SEER-Medicare submission contained Medicare claims until December 31, 2010 and survival data until December 31, 2011.

We identified DLBCL cases using the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) histology codes (9680, 9684), excluding transformed indolent B-cell lymphomas, primary intravascular, effusion, mediastinal or central nervous system DLBCL (Fig. 1). Extranodal sites were categorized using the ICD-O-3 topography codes. Waldeyer's ring and spleen were included as separate

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http://dx.doi.org/10.1016/j.leukres.2014.04.009
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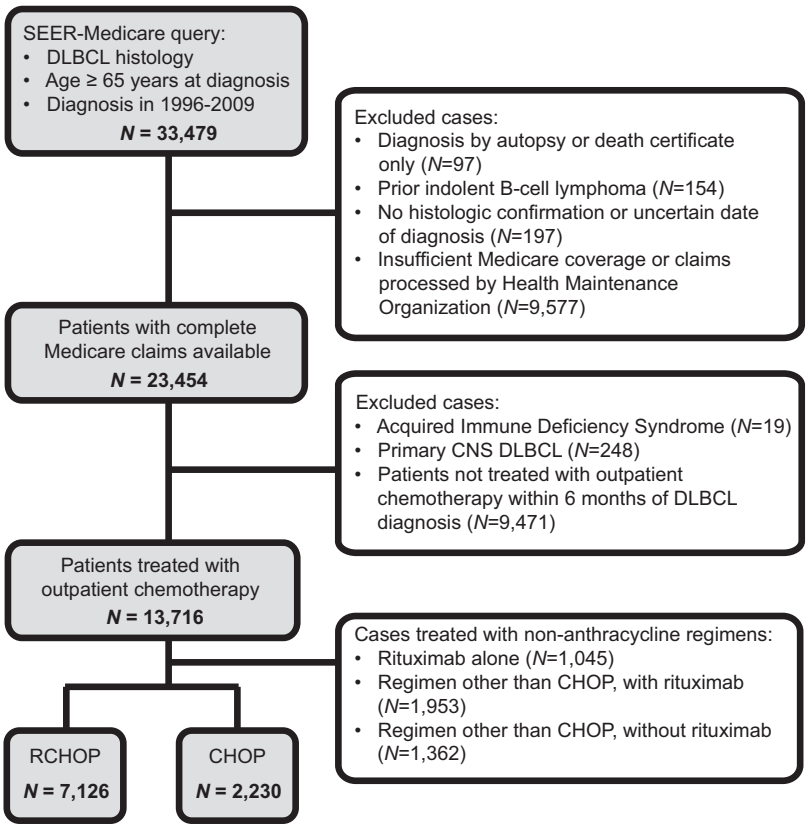

Fig. 1. CONSORT diagram for cohort selection.

sites because of potential prognostic significance [11]. The SEER manual contains specific modules for ascertainment of the primary site of DLBCL, enabling consistent distinction of the primary extranodal involvement from secondary dissemination of nodal lymphoma [15]. All lymphomas originating from liver, lung or bone marrow were recoded as stage IV in concordance with the Ann Arbor staging system. We excluded about 29% of cases (primarily Health Maintenance Organization enrollees) who did not have complete Medicare claims available in the period from 12 months before to 6 months after the DLBCL diagnosis. Additionally, 40% of patients did not receive outpatient chemotherapy—a group characterized by extremely short survival (median 3 months) suggestive of palliative approaches or early inpatient mortality (Fig. S1, online supporting information).

Specific intravenous chemotherapy agents were identified using Healthcare Common Procedure Coding System codes. Patients were assumed to receive CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or an equivalent regimen if all intravenous drugs were given within 60 days of treatment initiation, although specific doses, detailed schedules and relative intensity could not be discerned from the data. Oral prednisone was not recorded. Rituximab could be delivered within 180 days of treatment initiation, accommodating post-CHOP maintenance strategies [16]. Patients treated with non-anthracycline regimens had a markedly shorter survival indicating prohibitive comorbidities (Fig. S2, online supporting information). We used claims from the 12-month period before treatment to construct correlates of the unavailable components of the International Prognostic Index (IPI)—lactate dehydrogenase levels and performance status. These included number of comorbid conditions (using the NCI modification of the Charlson Comorbidity Index), poor functional status indicator (based on utilization of home care, durable medical equipment and other medical services) and anemia (using claims for related medical services, blood transfusions and erythropoietin administration) [13,17]. These variables strongly correlated with survival outcomes (Fig. S3, online supporting information). The receipt of radiotherapy (within 1 year of DLBCL diagnosis) was ascertained from the Medicare claims, but not included in the regression models, because we could not discern treatments given as part of initial course, at progression or as a palliative modality.

2.2. Endpoints

We used overall survival (OS) and cumulative incidence of lymphoma-related death (LRD) as the endpoints for comparative analysis. LRD was differentiated from other causes of death using death certificates and analyzed by competing risk methodology. Accounting for competing risks is of particular importance for older patients, in whom non-cancer mortality is substantial [18]. LRD was defined by standard SEER algorithms, additionally including all events attributed to a "lymphoma" or "leukemia" on death certificates. Death certificates were only available until December 31, 2009. Later events were censored for LRD analysis.

2.3. Statistical analysis

Basic group characteristic were compared using chi-square or rank-sum tests. Kaplan–Meier OS curves were compared using log-rank test, and the cumulative incidence curves using Gray's test. Missing values of race, stage and B symptoms were accounted for by multiple imputation using chained equations, with 40 imputed datasets [19]. OS and LRD were studied in multivariate proportional hazard Cox and Fine-Gray models, respectively. The proportional hazard assumption was evaluated using time-interaction tests, but the inclusion of time-varying terms had no impact on the coefficients of interest. All analyses were performed using two-sided tests, 95% confidence intervals (CI), and alpha level 0.05, using Stata version 13.1 (StataCorp LP, College Station, TX).

3. Results

3.1. Patient characteristics

Our analytical cohort included 9356 patients treated with either CHOP or R-CHOP regimens (Table 1). The proportion receiving R-CHOP increased from 1% in 1998 to 96% by 2004 (Fig. S4, online supporting information). Consequently, the median follow-up for patients receiving CHOP and R-CHOP was 11.7 years and 5.2 years, respectively. The median age was 75 years (range: 65–99 years), equal in both groups ($P = 0.53$). The R-CHOP cohort had an unfavorable distribution of stage, comorbidities, B symptoms and anemia. Extranodal primary site was present in 35%, with most common involvement of the gastrointestinal tract, head and neck (including Waldeyer's ring and paranasal sinuses) and skin/connective tissue (Table 2). Over 50% of DLBCLs of liver or lung origin had an incorrect assignment of Ann Arbor stage I or II instead of IV, which was corrected.

Table 1
Clinical characteristics of patients with DLBCL treated with CHOP or R-CHOP chemotherapy from the SEER–Medicare database, 1996–2009.

Parameter	All patients (*N* = 9356)		CHOP (*N* = 2230)		R-CHOP (*N* = 7126)		*P*
	N	%	*N*	%	*N*	%	
Age							
65–69 years	1879	20.1	452	20.3	1427	20.0	0.23
70–74 years	2582	27.6	624	28.0	1958	27.5	
75–79 years	2569	27.5	635	28.5	1934	27.1	
80+ years	2326	24.9	519	23.3	1807	25.4	
Sex							
Male	4636	49.6	1065	47.8	3571	50.1	0.052
Female	4720	50.4	1165	52.2	3555	49.9	
Race							
White[a]	8116	86.7	1957	87.8	6159	86.4	0.18
Hispanic	545	5.8	110	4.9	435	6.1	
Black	269	2.9	59	2.6	210	2.9	
Asian	426	4.6	104	4.7	322	4.5	
Stage							
I/II	4523	48.3	1226	55.0	3297	46.3	<0.001
III/IV	4339	46.4	888	39.8	3451	48.4	
Unrecorded	494	5.3	116	5.2	378	5.3	
B symptoms							
Absent	4219	45.1	729	32.7	3490	49.0	<0.001
Present	1840	19.7	400	17.9	1440	20.2	
Unrecorded	3297	35.2	1101	49.4	2196	30.8	
NCI comorbidity index							
0	5301	56.7	1332	59.7	3969	55.7	<0.001
1	2436	26.0	572	25.7	1864	26.2	
≥2	1619	17.3	326	14.6	1293	18.1	
Poor performance status							
Absent	6309	67.4	1494	67.0	4815	67.6	0.61
Present	3047	32.6	736	33.0	2311	32.4	
Anemia-related claims							
Absent	6391	68.3	1609	72.2	4782	67.1	<0.001
Present	2965	31.7	621	27.8	2344	32.9	
Primary site							
Nodal	6119	65.4	1442	64.7	4677	65.6	0.40
Extranodal	3237	34.6	788	35.3	2449	34.4	
Radiation therapy							
Administered	3086	33.0	899	40.3	2187	30.7	<0.001
Not administered	6270	67.0	1331	59.7	4939	69.1	

[a] Including 20 cases with unrecorded race, suppressed in the table according to NCI policy.

Table 2
Primary sites of DLBCL involvement in patients treated with CHOP or R-CHOP chemotherapy from the SEER–Medicare database, 1996–2009.

Primary site	*N*	% total	% extranodal
Lymph nodes	6119	65.4	–
Extranodal	3237	34.6	100.0
Gastrointestinal tract	1008	10.8	31.1
Head/neck	650	7.0	20.1
Skin/connective tissue	316	3.4	9.8
Testicular	181	1.9	5.6
Bone	172	1.8	5.3
Thyroid	155	1.7	4.8
Respiratory tract	151	1.6	4.7
Liver/pancreas	144	1.5	4.5
Other genitourinary tract	107	1.1	3.3
Spleen	105	1.1	3.2
Breast	97	1.0	3.0
Other specified/unspecified[a]	151	1.6	4.7

[a] Including mainly eye and orbit, bone marrow, peritoneum, adrenal gland and heart.

Extranodal involvement was significantly more common in Asians (odds ratio 1.53 compared with white non-Hispanic group, $P < 0.0001$). It was also associated with early stage, absence of B symptoms, presence of anemia and higher comorbidity index, but not with age, sex or performance status (Table S1, online supporting information).

3.2. Overall survival

The median OS for the entire cohort was 5.6 years (CI, 5.3–5.9 years) with a 5-year OS of 53% (95% CI 52–54%). Patients receiving CHOP had a median OS of 3.7 years with a 5-year rate of 43% (95% CI 41–45%). The R-CHOP group had a median OS of 6.4 years and a 5-year rate of 56% (95% CI 55–57%, $P < 0.0001$). Patients with nodal DLBCL had a median OS of 5.0 years and a 5-year rate of 50% (95% CI 49–51%) while the extranodal group had a median OS of 6.5 years and a 5-year OS of 57% (95% CI 55–59%, $P < 0.0001$).

The 5-year OS for patients of all stages increased with the addition of rituximab to CHOP from 37% to 54% in nodal, and from 53% to 59% in extranodal DLBCL (Fig. 2a). In the analysis limited to stage I/II disease, R-CHOP was also associated with improved outcome (Fig. 2b); the 5-year OS improved from 49% to 63% in nodal, and from 57% to 62% in extranodal early-stage DLBCL. The OS difference between primary nodal and extranodal sites was thus nullified in early-stage DLBCL in patients treated with R-CHOP.

The impact of R-CHOP on OS was further studied in multivariate models adjusting for the available confounders: age, sex, race, marital status, stage, presence of B symptoms and anemia, number of

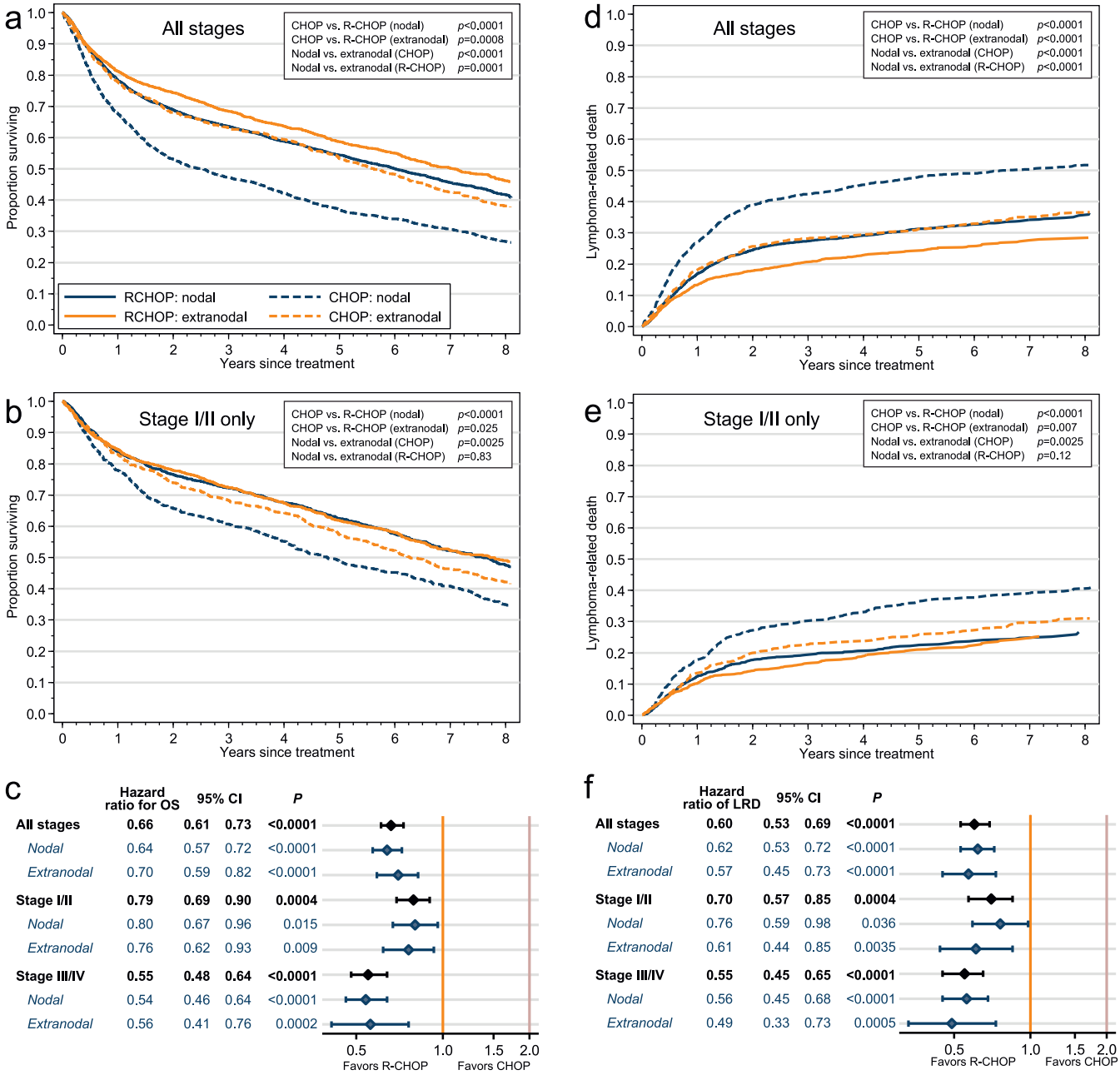

Fig. 2. Overall survival (OS) and cumulative incidence of lymphoma-related death (LRD) curves for patients with nodal and extranodal DLBCL treated with CHOP or R-CHOP chemotherapy. (a) OS, all stages; (b) OS, stage I and II only; (c) forest plots of hazard ratios for the effect of R-CHOP on OS in subsets, derived from multivariate Cox models; (d) LRD, all stages; (e) LRD, stage I and II only; (f) forest plots of hazard ratios for the effect of R-CHOP on LRD in subsets, derived from multivariate competing risk models.

comorbidities, performance status, epoch of diagnosis and specific primary sites. In the entire cohort, R-CHOP was associated with an improved OS over CHOP (hazard ratio, HR 0.66, CI 0.61–0.73). The HR for R-CHOP was similar for nodal and extranodal DLBCL in strata of early and advanced disease (Fig. 2c) and was not sensitive to inclusion of radiotherapy as a confounder. We did not detect significant heterogeneity of treatment effect by gender ($P = 0.88$ in the interaction test).

3.3. Lymphoma-related death (LRD)

Based on death certificates, 65% of events were ascribed to DLBCL. Cardiovascular disease (14%) and solid tumors (6%) were the most frequent competing causes. The cumulative incidence of LRD at 5 years in the entire cohort was 33% (95% CI 32–34%) and the risk of a competing event was 15% (95% CI 14–16%). The risk of LRD was significantly higher in the CHOP group (42%, CI 40–44%) than in the R-CHOP group (29%, CI 28–30%, $P < 0.00001$). The LRD rates for nodal and extranodal DLBCL were respectively 36% (95% CI 35–37%) and 26% (95% CI 24–28%, $P < 0.00001$). Conversely, the risk of death from competing causes was identical after R-CHOP or CHOP (15% for both, $P = 0.52$, Fig. S5, online supporting information) and slightly higher in extranodal (17%) than in nodal disease (15%, $P = 0.009$).

The addition of rituximab to chemotherapy decreased the 5-year incidence of LRD in both nodal (from 48% with CHOP to 31% with R-CHOP) and extranodal DLBCL (31% to 24%, respectively, Fig. 2d). In early-stage disease (Fig. 2e), the addition of rituximab significantly lowered the risk of LRD from 36% to 23% in nodal, and from 26% to 21% in extranodal DLBCL. The difference in LRD between

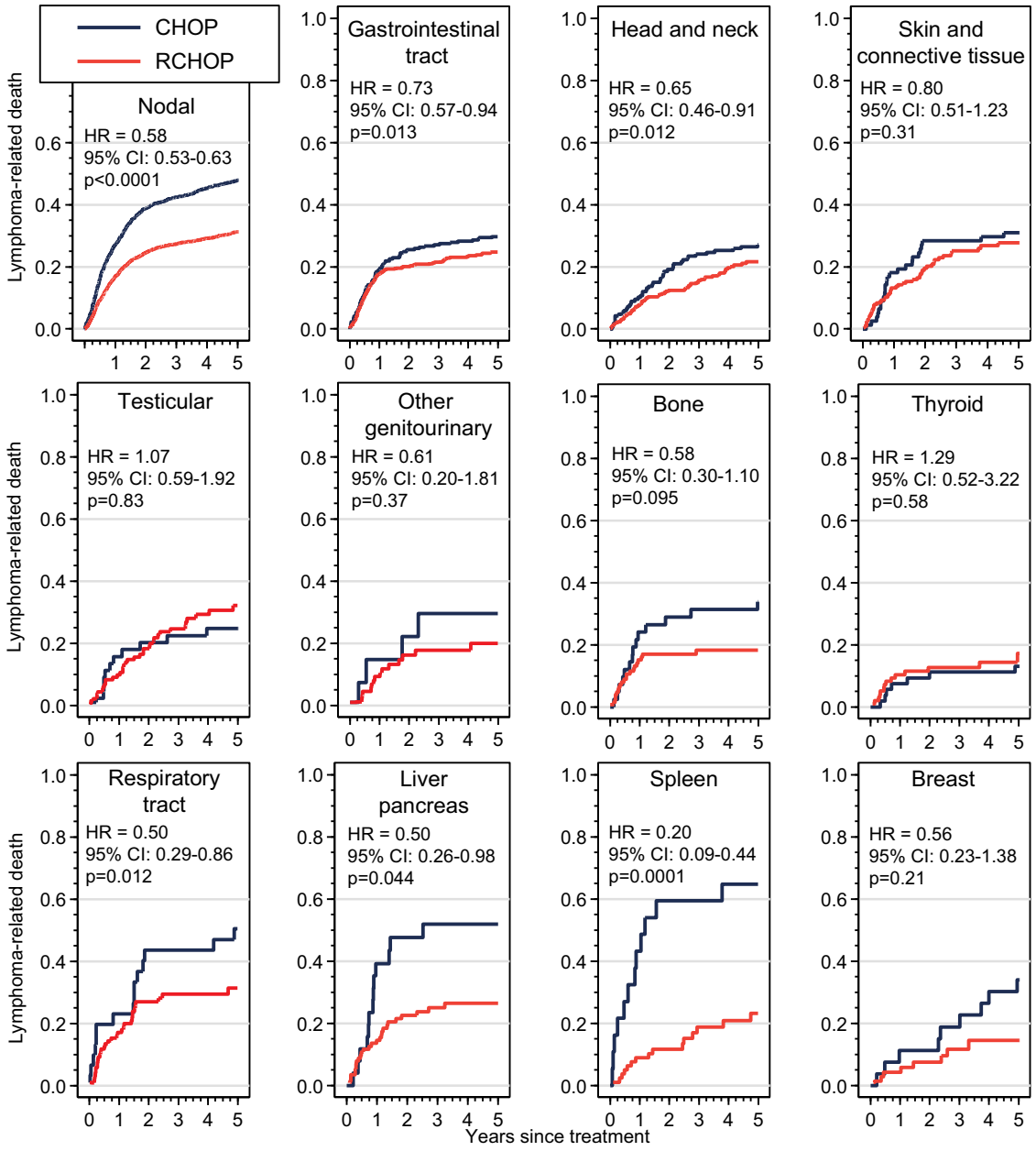

Fig. 3. Cumulative incidence of lymphoma-related death for DLBCL of specific primary sites after CHOP or R-CHOP chemotherapy. Hazard ratios (HR) are derived from univariate competing risk models.

early-stage nodal and extranodal disease was no longer significant after R-CHOP. In multivariate models, R-CHOP was associated with a significantly lower risk of LRD in all studied strata (Fig. 2f). There was no evident heterogeneity related to gender (*P* for interaction 0.98).

3.4. *Effect of R-CHOP in DLBCL of different extranodal sites*

We investigated potential heterogeneity of the effect of rituximab-based chemoimmunotherapy on survival in specific extranodal sites. The overall test for interaction was significant for OS (*P* for interaction test 0.032), but not for LRD (*P* = 0.10). In an exploratory subset analysis, which was univariate due to low number of events for some primary sites (Fig. 3), the largest impact of R-CHOP on LRD was evident for the DLBCL of the spleen, liver and lung, while testicular and thyroid lymphoma did not demonstrate a lower incidence of LRD with R-CHOP. Similar relationships were seen for OS and in multivariate models adjusting for essential confounders (Fig. S6, Table S2, online supporting information).

We additionally described survival in patients treated with R-CHOP according to the primary site of involvement, adjusting for other significant prognostic factors (Table 3). The sites associated with significantly better OS compared with nodal DLBCL were spleen, bone and respiratory tract, but only spleen had a significantly lower risk of LRD.

4. Discussion

In this population-based analysis, which according to SEER estimates should capture over 95% of DLBCL cases from the covered population, we demonstrated similar benefits of adding rituximab to CHOP chemotherapy for primary nodal and extranodal DLBCL. Despite theoretical pitfalls resulting from inferring treatments and certain variables from insurance claims rather than clinical records,

Table 3
Overall survival and risk of lymphoma-related death in patients with DLBCL of specific extranodal sites treated with R-CHOP chemotherapy. The hazard ratios are derived from multivariable proportional hazard models.

		Overall survival			Lymphoma-related death		
	N	At 5 years, % (95% CI)	HR (95% CI)	*P*	At 5 years, % (95% CI)	HR (95% CI)	*P*
Nodal	4677	54 (53–56)	Reference		31 (30–33)	Reference	
Extranodal	2326						
Gastrointestinal tract	742	57 (53–61)	0.92 (0.82–1.03)	0.15	25 (21–28)	0.85 (0.71–1.01)	0.062
Head and neck	483	58 (53–63)	1.03 (0.89–1.19)	0.67	22 (17–26)	0.81 (0.65–1.02)	0.078
Skin and connective tissue	239	55 (48–61)	1.16 (0.96–1.41)	0.12	28 (21–35)	1.16 (0.88–1.54)	0.30
Testis	137	57 (48–65)	1.10 (0.86–1.41)	0.43	32 (24–42)	1.34 (0.97–1.85)	0.072
Bone	131	73 (64–80)	0.74 (0.55–0.98)	0.033	18 (12–26)	0.77 (0.50–1.19)	0.24
Respiratory tract	121	52 (42–61)	0.76 (0.58–0.99)	0.040	32 (23–41)	0.76 (0.53–1.10)	0.15
Liver and pancreas	119	58 (48–67)	0.82 (0.64–1.05)	0.12	27 (18–36)	0.79 (0.55–1.13)	0.20
Thyroid gland	102	69 (58–77)	0.80 (0.58–1.11)	0.18	17 (9–27)	0.63 (0.36–1.08)	0.094
Other genitourinary	94	59 (48–69)	0.97 (0.72–1.32)	0.86	20 (12–30)	0.66 (0.39–1.12)	0.12
Spleen	87	63 (51–73)	0.59 (0.41–0.83)	0.003	23 (14–35)	0.56 (0.33–0.94)	0.027
Breast	71	68 (54–78)	1.11 (0.76–1.61)	0.60	15 (7–26)	0.78 (0.43–1.41)	0.41

our estimates of survival are remarkably close to those from randomized trials in older patients. Feugier et al. [20] reported the 5-year OS of 45% (CHOP) and 58% (R-CHOP) in the Groupe d'Etude des Lymphomes de l'Adulte trial (43% and 56% in our dataset, respectively). The event-free survival endpoints could not be compared with our data, but in that study 63% of deaths were ascribed to DLBCL progression, 12% to treatment toxicity and 25% to other causes [3]. Similarly, the HR for R-CHOP versus CHOP in our study (0.66) is similar to one reported by the US Intergroup trial (HR 0.72, 95% CI 0.52–1.00) [16]. Our analysis thus validates these estimates in a real-life, comprehensive cohort, without the selection bias inherent to randomized trials. By the same token, we validated the SEER-Medicare dataset for observational analysis of treatments and outcomes in older Americans with DLBCL. However, our methodology based on outpatient chemotherapy records excluded patients with early inpatient mortality, so the estimates do not exactly reflect survival of all patients treated with anthracycline-based chemotherapy.

The subsets of primary nodal and extranodal lymphoma were not analyzed in either of the above randomized studies, nor in the MInT trial [2]. We provide comparative, even if only observational, evidence that addition of rituximab to CHOP improves survival outcomes in both nodal and extranodal DLBCL. Our results contradict findings from a prior study, which can be explained by the low statistical power ($N = 177$) and limited sampling of extranodal sites in that series [7]. There was no statistically significant heterogeneity of the benefit between the specific extranodal sites with respect to LRD, although the advantage appeared to be largest for primary sites associated with poor prognosis and defining stage IV lymphoma (liver, lung)—and most pronounced in DLBCL of the spleen. Conversely, no evident advantage was evident for testicular and thyroid lymphoma—possibly due to restricted chemotherapy penetration (testis) or curative locoregional management (thyroid) in those subtypes. In patients with testicular lymphoma a somatic mutation in the *MYD88* gene was recently described, with a 70% prevalence rate [21]. This mutation, first recognized in Waldenström's macroglobulinemia, seems to be prevalent in lymphomas of other immune-privileged sites such as central nervous system, whereas it is uncommon in nodal DLBCL [22,23]. Those "immune-privileged sites" of DLBCL may define a distinct group with shared molecular features and might need alternative strategies to improve their outcomes by targeting the *MYD88* signaling components such as the nuclear factor kappa B or Bruton tyrosine kinase [24].

In early-stage DLBCL, the prognostic value of primary extranodal involvement present in the pre-rituximab era disappeared in patients treated with R-CHOP. When assessing DLBCL prognosis, the significance of primary extranodal origin should be distinguished from metastatic or contiguous invasion from a nodal site. The conventional IPI uses any involvement of ≥ 2 sites as a poor prognostic factor. Recently, two observational studies indicated that after R-CHOP chemotherapy it is rather the extranodal involvement of specific sites (liver, lung and bone marrow) that conveys poor prognosis [6,25]. We found, however, that primary DLBCL of liver and lung was often incorrectly staged as stage I or II in the community, reflecting clinicians' difficulty in interpreting the "diffuse extranodal" or "nodular lung" involvement directives from the staging manuals [26]. These primary sites, when appropriately assigned stage IV, in our data had in fact a favorable prognosis compared with stage IV nodal DLBCL. Thus, the poor prognosis of high-risk extranodal sites may be sufficiently encompassed in the difference between stage III and IV. This specific aspect is not distinguished in the original IPI, supporting the need for its proposed revision [25]. The favorable prognosis of splenic DLBCL after R-CHOP is a novel finding, and was not observed in the pre-rituximab era, although many series included spleen as a nodal site [6,8,10].

Our analysis has a few significant limitations. Firstly, we were not able to study progression-free survival, because recurrence or progression of lymphoma is not recorded by SEER. Therefore, we used LRD as a disease-specific endpoint. LRD reflects realistic cancer-specific survival outcomes, but it is subject to bias related to death certificate errors [27]. In particular, cardiovascular and septic events are increased after chemotherapy in older patients [14]. To mitigate this, we created an inclusive definition of LRD, and used competing risk regression, simultaneously modeling the effect of treatment on LRD and "other" causes. We saw a consistent decrease in LRD with no difference in competing events between R-CHOP and CHOP-treated groups. Secondly, our results derived from Medicare beneficiaries older than 65 years may not be applicable to younger patients, although the median age at DLBCL diagnosis in the US is 66 years. Advanced age correlates with unfavorable molecular features, including increased prevalence of the activated B-cell subtype [28]. Thirdly, because of the unavailability of IPI or other confounders (tumor bulk, lactate dehydrogenase level) we used proxy variables constructed from Medicare claims, and cannot rule out confounding related to unmeasured factors. Likewise, we could not differentiate CHOP from other regimens containing the same drugs, or adjust for differences in dose intensity and for inclusion of radiotherapy in the initial treatment plan. Any retrospective comparison of R-CHOP with CHOP is effectively a comparison with historical controls, although we saw a temporal overlap between the groups, and used the year of diagnosis as a covariate. Finally, inconsistent differentiation between DLBCL and high-grade marginal zone lymphoma in some organs (stomach,

thyroid, breast) may exist, and since the SEER data lack pathology review, misclassifications might have influenced prognosis for those sites.

5. Conclusions

In conclusion, addition of rituximab to anthracycline-based chemotherapy provides important survival advantage for older patients with DLBCL regardless of nodal or extranodal origin. The possible exceptions are primary thyroid and testicular locations, and future research should explore alternative strategies to improve outcomes in those subtypes. Chemoimmunotherapy nullifies the prognostic value of primary extranodal involvement in early-stage DLBCL, and primary involvement of liver and lung may not portend worse survival when appropriately compared with stage IV disease of nodal origin.

Conflict of interest

The authors have no conflict of interest to disclose.

Funding

This study was performed without any external funding.

Acknowledgements

The collection of the California cancer incidence data used in this study was supported by the California Department of Public Health; the NCI's SEER Program under contract N01-PC-35136 (Northern California Cancer Center), contract N01-PC-35139 (University of Southern California) and contract N02-PC-15105 (Public Health Institute); and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement #U55/CCR921930-02 (Public Health Institute). The ideas and opinions expressed herein are those of the authors and endorsement by the State of California, Department of Public Health, the NCI, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is not intended nor should be inferred. The authors acknowledge the efforts of the Applied Research Program, NCI; the Office of Research, Development and Information, CMS; Information Management Services (IMS), Inc.; and the SEER Program tumor registries in the creation of the SEER–Medicare database. All authors designed the research study, wrote, revised and approved the paper; AJO and JJC performed the statistical analysis.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.leukres.2014.04.009.

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