

Survival of patients with CD20-negative variants of large B-cell lymphoma: an analysis of the National Cancer Data Base

Lindor Qunaj, Jorge J. Castillo & Adam J. Olszewski

To cite this article: Lindor Qunaj, Jorge J. Castillo & Adam J. Olszewski (2017): Survival of patients with CD20-negative variants of large B-cell lymphoma: an analysis of the National Cancer Data Base, Leukemia & Lymphoma

To link to this article: <http://dx.doi.org/10.1080/10428194.2017.1387912>

 View supplementary material 

 Published online: 11 Oct 2017.

 Submit your article to this journal 

 View related articles 

 View Crossmark data 

ORIGINAL ARTICLE: CLINICAL



Survival of patients with CD20-negative variants of large B-cell lymphoma: an analysis of the National Cancer Data Base

Lindor Qunaj^a , Jorge J. Castillo^b  and Adam J. Olszewski^{a,c} 

^aDepartment of Medicine, Alpert Medical School of Brown University, Providence, RI, USA; ^bDivision of Hematologic Malignancies, Dana Farber Cancer Institute, Boston, MA, USA; ^cDivision of Hematology–Oncology, Rhode Island Hospital, Providence, RI, USA

ABSTRACT

Using records from the National Cancer Data Base, we studied overall survival of CD20-negative variants of diffuse large B-cell lymphoma (DLBCL): primary effusion (PEL, $N=228$), plasmablastic (PBL, $N=481$), ALK-positive large B-cell (ALK+LBCL, $N=15$), and human herpesvirus-8-positive DLBCL (HHV8+DLBCL, $N=77$). Three-year survival was 27% for PEL, 40% for PBL, 34% for ALK+LBCL, and 63% for HHV8+DLBCL. Compared with unspecified DLBCL, and adjusting for clinical characteristics (including the HIV status), survival was significantly worse for PEL (hazard ratio [HR], 1.58; 95% confidence interval [CI], 1.31–1.90), PBL (HR 1.66; 95% CI, 1.41–1.95), and ALK+LBCL (HR, 2.70; 95% CI, 1.27–5.75), but not for HHV8+DLBCL (HR, 0.89; 95% CI, 0.54–1.45). The HIV status was not an independent prognostic factor in PEL, PBL, or HHV8+DLBCL. Advanced stage was prognostic for PBL ($p=.0002$), but not for ALK+LBCL ($p=.96$), or HHV8+DLBCL ($p=.28$). In PEL and PBL survival significantly differed according to primary site. Novel therapeutic approaches are urgently needed for these rare diseases.

ARTICLE HISTORY

Received 27 August 2017
Revised 19 September 2017
Accepted 22 September 2017

KEYWORDS

Diffuse large B-cell lymphoma; epidemiology; plasmablastic lymphoma; primary effusion lymphoma; ALK-positive large B-cell lymphoma; multicentric Castleman disease

Introduction

CD20-negative variants of diffuse large B-cell lymphomas (DLBCL) represent a diverse group of aggressive non-Hodgkin lymphomas characterized by extranodal involvement, association with viral infections, and relatively poor prognosis [1–3]. Their rarity, variable clinical presentation, and unique pathological features have historically posed a challenge for accurate and consistent diagnosis. These obstacles have also precluded design of large-scale studies which could identify important epidemiological considerations and optimize therapeutic modalities. As a result, our current understanding of these malignancies relies primarily on case reports, small case series, and systematic reviews of data in four distinct types of CD20-negative DLBCL: primary effusion lymphoma (PEL) [4], plasmablastic lymphoma (PBL) [5], anaplastic lymphoma kinase-positive large B-cell lymphoma (ALK+LBCL) [6], and human herpesvirus-8-positive DLBCL (HHV8+DLBCL, usually arising from multicentric Castleman's disease) [7,8]. Case series have demonstrated a strong relationship between PEL, PBL, HHV8+DLBCL, and infections with HIV, Epstein–Barr virus (EBV), and/or HHV8 (also known as Kaposi sarcoma herpesvirus) [5,7,9–11].

Beginning in 2010, cancer registries in the United States (US) began to explicitly distinguish the CD20-negative DLBCL subtypes (except for PEL, which was identified since 2004), allowing for a larger and more diverse sampling of patients. This addition followed the World Health Organization's (WHO) formal recognition of PEL, PBL, ALK+LBCL, and HHV8+DLBCL in the 2008 classification of lymphoid neoplasms [12]. The objective of our study was to use these newly available data to describe demographic and clinical characteristics, use of chemotherapy, and survival outcomes in patients with CD20-negative DLBCL subtypes in a large nationwide sample.

Methods

Data source

We obtained data from the National Cancer Data Base (NCDB), a joint project of the Commission on Cancer of the American College of Surgeons and the American College of Surgeons, which has collected information on patients receiving care at hospitals accredited by the Commission on Cancer since 1998 [13]. Across a variety of clinical settings, the NCDB

CONTACT Adam J. Olszewski  adam_olszewski@brown.edu  Department of Medicine, Alpert Medical School of Brown University, Division of Hematology–Oncology, Rhode Island Hospital, 593 Eddy St., Providence, RI 02903, USA

© 2017 Informa UK Limited, trading as Taylor & Francis Group

accounts for about 84% of all lymphomas diagnosed in the US [14]. Researchers can apply for access to data subsets, which include variables related to demographics, patient's baseline health status, staging, and treatment. Information on chemotherapy is limited to record of any administration of chemotherapy, without information on doses, route of administration, number of cycles, specific drugs, or response to treatment [15]. The NCDB uses electronic data checks as well as regular audits of participating programs to assure high quality and completeness of records. We used the 2008 WHO histology codes to select patients with histologically confirmed diagnosis of PEL (histology code 9678/3), PBL (9735/3), ALK+LBCL (9737/3), or HHV8+DLBCL (9738/3). Data on PEL were available beginning in 2004, and on PBL, ALK+LBCL, and HHV8+DLBCL beginning in 2010. We compared those cases to matched cases of DLBCL, not otherwise specified (DLBCL-NOS, codes 9680/3 and 9684/3) diagnosed in 2010–2013. This study was approved by the Institutional Review Board at Rhode Island Hospital.

Variables

We collapsed all race and ethnicity options to five categories: white non-Hispanic, white Hispanic, black, Asian/other, and unknown. HIV status was explicitly recorded in the data. Stage was classified as early (I/II) or advanced (III/IV), and assigned according to the American Joint Committee on Cancer system. All cases of PEL were classified as advanced stage regardless of recorded stage, given that PEL is formally defined as stage IV malignancy [16].

The anatomic origin (or primary site) for each lymphoma was categorized as nodal or extranodal. Extranodal sites were further classified based on typical primary locations: heart/mediastinum/pleural cavity, peritoneal cavity, and other sites for PEL; and head and neck, gastrointestinal, skin/connective tissue, bone marrow, and other sites for PBL.

Overall survival (OS) was the only available survival endpoint, and was calculated from the date of diagnosis until death or last recorded follow-up. As a quality measure, the NCDB requires complete follow-up from at least 90% of analytic cases within 5 years from diagnosis. Progression-free survival or cause of death was not recorded in the data.

Statistical analysis

We compared clinical characteristics between groups using chi-squared (for categorical variables) or Kruskal–Wallis test (for continuous variables).

Unadjusted OS estimates were calculated using the Kaplan–Meier method, and compared by log-rank test, where indicated, stratified by age (grouped into 18–50, 51–60, 61–70, 71–80, and >80 years) and HIV status. Survival of DLBCL-NOS and CD20-negative subtypes was compared in a single multivariable proportional hazard model stratified by age group, sex, race/ethnicity, HIV status, and stage of lymphoma. The model thus reported hazard ratios (HR) for each CD20-negative DLBCL subtype (compared with DLBCL-NOS) with 95% confidence intervals (CI). We then generated adjusted survival curves graphically representing the expected survival of DLBCL-NOS patients with the same distribution of covariates as among patients with each CD20-negative DLBCL subtype, using previously described methods [17]. Briefly, OS of DLBCL-NOS patients was modeled in a flexible parametric survival model including age, sex, race, HIV status, lymphoma stage, and B symptoms [18]. We included B symptoms, because they correlated with the International Prognostic Index (IPI) in a subset of NCDB records (~11%) that had explicit IPI data [19]. This model was then used for out-of-sample prediction in the population of patients with each CD20-negative subtype to generate the 'expected survival' if these patients had DLBCL-NOS histology instead. All statistical analyses were conducted in Stata/MP version 14.2 (StataCorp, LLC, College Station, TX). Associations with p value < .05 were considered statistically significant. Additionally, all cell sizes < 11 were suppressed in the results to protect patients' privacy, according the NCDB Data Use Agreement.

Results

Patient characteristics

We identified 801 patients with the four subtypes of CD20-negative DLBCL recorded in the NCDB, and a comparative cohort of 68,402 cases of DLBCL-NOS. PEL constituted 0.2%, PBL 0.7%, ALK+LBCL 0.02%, and HHV8+DLBCL 0.11% of all DLBCL cases. Median age at diagnosis was significantly lower in CD20-negative subtypes ($p < .0001$ for comparison with DLBCL-NOS), with HHV8+DLBCL representing the youngest group (Table 1). Compared with DLBCL-NOS, patients with CD20-negative subtypes were also significantly more likely to be male ($p < .0001$) and Hispanic or black ($p < .0001$), with the male to female ratio ranging from 2.0 in ALK+LBCL to 5.7 in PEL.

Except for ALK+LBCL, CD20-negative DLBCL patients were significantly more likely to be HIV-positive (overall, 48%) compared with those with DLBCL-NOS (3%, $p < .0001$). Similarly to known associations in

Table 1. Characteristics of patients with CD20-negative DLBCL, compared with DLBCL-NOS.

	DLBCL-NOS	PEL	PBL	ALK + LBCL	HHV8 + DLBCL
N	68,402	228	481	15	77
Age, median (IQR)	68 (57–78)	54 (41–78)	55 (45–69)	57 (33–76)	47 (39–66)
Sex, N (%)					
Male	37,061 (54.2)	194 (85.1)	367 (76.3)	^a –	59 (76.6)
Female	31,341 (45.8)	34 (14.9)	114 (23.7)	^a –	18 (23.4)
Male: female ratio	1.2	5.7	3.2	2.0	3.3
Race, N (%)					
White non-Hispanic	54,948 (80.3)	141 (61.8)	301 (62.6)	^a –	48 (62.3)
White Hispanic	4456 (6.5)	29 (12.7)	77 (16.0)	^a –	^a –
Black	5313 (7.8)	50 (21.9)	83 (17.3)	^a –	19 (24.7)
Asian/other	2971 (4.3)	^a –	^a –	^a –	^a –
Unknown	714 (1.0)	^a –	^a –	^a –	^a –
HIV Status, N (%)					
HIV-negative	66,233 (96.8)	98 (43.0)	268 (55.7)	^a –	36 (46.8)
HIV-positive	2169 (3.2)	130 (57.0)	213 (44.3)	^a –	41 (53.2)
Stage, N (%)					
Early (I/II)	30,502 (44.6)	–	207 (43.0)	^a –	26 (33.8)
Advanced (III/IV) ^b	37,900 (55.4)	228 (100.0)	274 (57.0)	^a –	51 (66.2)
B symptoms, N (%)					
Absent	41,219 (60.3)	107 (46.9)	280 (58.2)	^a –	38 (49.4)
Present	18,332 (26.8)	90 (39.5)	137 (28.5)	^a –	29 (37.7)
Unrecorded	8851 (12.9)	31 (13.6)	64 (13.3)	^a –	10 (13.0)
Primary site, N (%)					
Nodal	45,492 (66.5)	98 (43.0)	226 (47.0)	^a –	61 (79.2)
Extranodal	22,910 (33.5)	130 (57.0)	255 (53.0)	^a –	16 (20.8)

ALK + LBCL: ALK-positive large B-cell lymphoma; DLBCL-NOS: diffuse large B-cell lymphoma, not otherwise specified; HHV8 + DLBCL: human herpesvirus-8-positive diffuse large B-cell lymphoma; IQR: interquartile range; PBL: plasmablastic lymphoma; PEL: primary effusion lymphoma

^aExact value is <15 and was suppressed according to the NCDB policy to protect patients' privacy.

^bIncluding <5% of cases with unrecorded stage.

DLBCL-NOS [11], HIV-positive patients with PBL, PEL, ALK + LBCL, or HHV8 + DLBCL were significantly younger on average (median age 45 versus [vs.] 70 years, $p < .0001$), more often male (88 vs. 70%, $p < .0001$), and less often white non-Hispanic (49 vs. 75%, $p < .0001$). HIV-positive patients had more often B symptoms (44 vs. 22%, $p < .0001$) or advanced-stage lymphomas (74 vs. 67%, $p = .021$).

In the HIV-negative population, median age was 68 years for DLBCL-NOS, 80 years for PEL, 67 years for PBL, 55 years for ALK + LBCL, and 65 years for HHV8 + DLBCL. The proportion of women was 47, 29, 29, 36, and 42%, respectively, and the proportion of patients who were black or Hispanic was 13, 21, 18, 14, and 30%, respectively.

Although PEL by definition is an extranodal lymphoma, in a number of cases the registry recorded its site of origin as 'unspecified lymph nodes'. Among those with a specified extranodal origin, 75% had pleural or pericardial location, 19% originated from peritoneum, and 6% in other or unknown sites. The most common recorded extranodal PBL sites were gastrointestinal tract (34%), head and neck (27%), skin or connective tissue (16%), and bone marrow (7%), with 16% other or unspecified sites.

Chemotherapy use

The use of chemotherapy varied considerably by lymphoma subtype, as well as by HIV status.

Compared with DLBCL-NOS (81%), application of chemotherapy was less frequent among patients with PEL (54%), PBL (66%), HHV8 + DLBCL (60%, all $p < .0001$), but not ALK + LBCL (>75%, $p = .96$). In contrast to DLBCL-NOS, HIV-positive patients were more likely to receive chemotherapy than HIV-negative ones in PEL (60 and 46%, respectively) and in PBL (75 and 59%, respectively). However, HIV-negative patients were significantly older, and differences in chemotherapy application were not significant after adjustment for age (Mantel-Haenszel estimates stratified by age group, $p = .98$ and $.87$, respectively).

Survival outcomes

With a median follow-up time of 2.6 years, median OS was 56 months (95% CI, 55–58) for DLBCL-NOS, 5 months for PEL (95% CI, 3–8), 15 months for PBL (95% CI, 12–23), 13 months for ALK + LBCL (95% CI, 7 to not reached), and it was not reached for HHV8 + DLBCL (Figure 1). Compared with DLBCL-NOS, unadjusted 3-year OS was significantly lower for PEL, PBL, but not significantly different for ALK + LBCL or HHV8 + DLBCL (Table 2). In a multivariable model stratified by age, sex, race, stage, and HIV status, OS was significantly worse for PEL (HR, 1.58; 95% CI, 1.31–1.90), PBL (HR 1.66; 95% CI, 1.41–1.95), and ALK + LBCL (HR, 2.70; 95% CI, 1.27–5.75) compared with DLBCL-NOS. In contrast, in this dataset there was

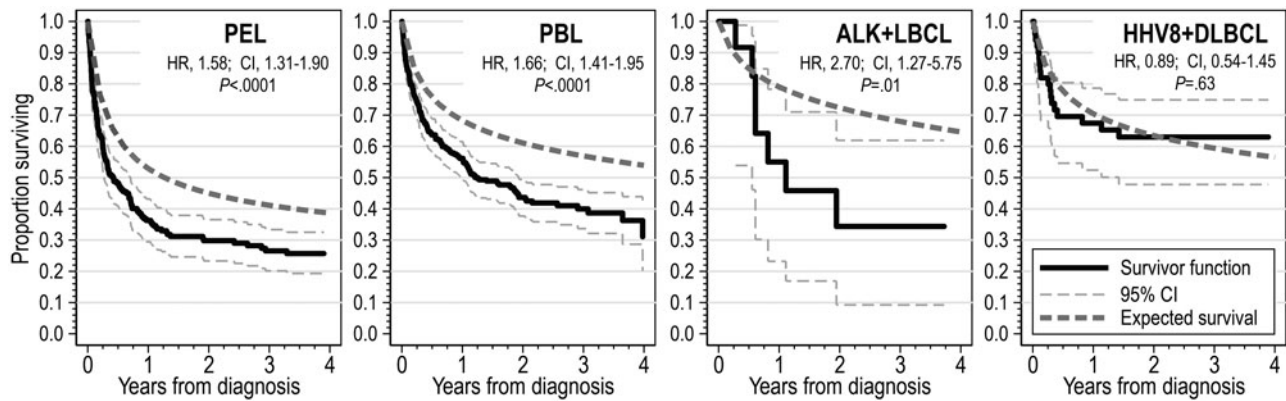


Figure 1. Survival of patients with primary effusion lymphoma (PEL), plasmablastic lymphoma (PBL), ALK-positive large B-cell lymphoma (ALK + LBCL) and human herpesvirus-8-positive diffuse large B-cell lymphoma (HHV8 + DLBCL), compared with DLBCL-NOS cases matched by age, sex, race, HIV status, and stage. Hazard ratios (HR) and 95% confidence intervals (CI) are derived from a proportional hazard model stratified by age group, sex, race/ethnicity, stage, and HIV status.

Table 2. Unadjusted estimates of overall survival of patients with CD20-negative DLBCL, subtypes, compared with DLBCL-NOS.

Lymphoma	All cases OS (95% CI)	HIV-negative OS (95% CI)	HIV-positive OS (95% CI)	<i>p</i> *
DLBCL-NOS	59.3% (58.8–59.8)	59.6% (59.1–60.1)	50.5% (47.9–53.1)	<.0001
PEL	26.6% (20.2–33.4)	14.4% (6.8–24.6)	34.5% (25.6–43.6)	.21
PBL	40.0% (33.7–46.2)	34.7% (26.8–42.7)	47.6% (37.6–56.9)	.39
ALK + LBCL	34.4% (9.2–62.0)	37.9% (10.1–66.3)	^a	^a
HHV8 + DLBCL	63.0% (47.8–74.9)	62.9% (39.2–79.5)	63.1% (42.3–78.2)	.56

^aValue could not be calculated because of small sample size.

**p* value from log-rank stratified by age group.

ALK + LBCL: ALK-positive large B-cell lymphoma; CI: confidence interval; DLBCL-NOS: diffuse large B-cell lymphoma, not otherwise specified; HHV8 + DLBCL: human herpesvirus-8-positive diffuse large B-cell lymphoma; PBL: plasmablastic lymphoma; PEL: primary effusion lymphoma; OS: overall survival

no statistically significant difference between cases diagnosed as HHV8 + DLBCL or DLBCL, NOS (HR, 0.89; 95% CI, 0.54–1.45).

We then evaluated the prognostic significance of HIV infection status, stage, and primary site in the CD20-negative DLBCL subtypes. Unadjusted OS of HIV-positive PEL and PBL patients appeared paradoxically better, but HIV-negative patients were significantly older and less likely to receive chemotherapy. When survival was compared using a log-rank test stratified by age group, the HIV status was not associated with worse prognosis in any subtype (Figure 2). Advanced stage was associated with a significantly worse survival only among patients with PBL ($p < .0001$). This association was not observed in ALK + LBCL or HHV8 + DLBCL (Figure 3).

OS of PEL patients was significantly better (log-rank stratified by age and HIV status, $p = .0019$) for cases with intrathoracic origin (1-year OS, 50%) than for peritoneal (6%) or extracavitary origin (31%; Figure 4(A)). In PBL, 1-year OS was best for the head and neck, skin, bone, and connective tissue origin (75%), intermediate for gastrointestinal or other sites (50%), and worst for bone marrow disease (30%, log-rank stratified by age and HIV status, $p = .0002$, Figure 4(B)).

Discussion

By conducting this large-scale analysis of CD20-negative DLBCL subtypes recognized in the WHO classification, we have identified key differences between these rare lymphomas and DLBCL-NOS, and further defined the prognostic role of HIV status and clinical stage. Patients with CD20-negative subtypes are on average younger, more often male, nonwhite, and HIV-positive – with the exception of ALK + LBCL. They are also less likely to receive chemotherapy, and (with the exception of HHV8 + DLBCL), have significantly reduced survival compared to DLBCL-NOS. Despite higher prevalence of HIV among PEL, PBL, and HHV8 + DLBCL, we found no differences in OS by HIV status. We also found that traditional staging may not provide prognostic value in HHV8 + DLBCL, whereas advanced stage is strongly prognostic in PBL.

Compared with literature based on anecdotal reports and case series, our data confirm and more precisely quantify the prognosis of the CD20-negative DLBCL subtypes treated in the community. In PEL, single- and multi-institutional series of HIV-positive patients reported median OS of about 6 months, with only poor performance status and absence of antiviral

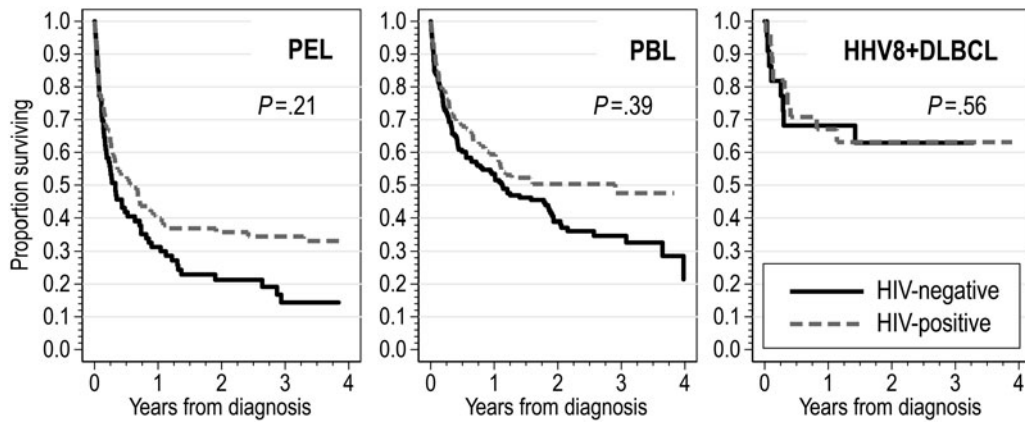


Figure 2. Survival of patients with primary effusion lymphoma (PEL), plasmablastic lymphoma (PBL), or human herpesvirus-8-positive diffuse large B-cell lymphoma (HHV8 + DLBCL), stratified by HIV status. p values are derived from a log-rank test stratified by age.

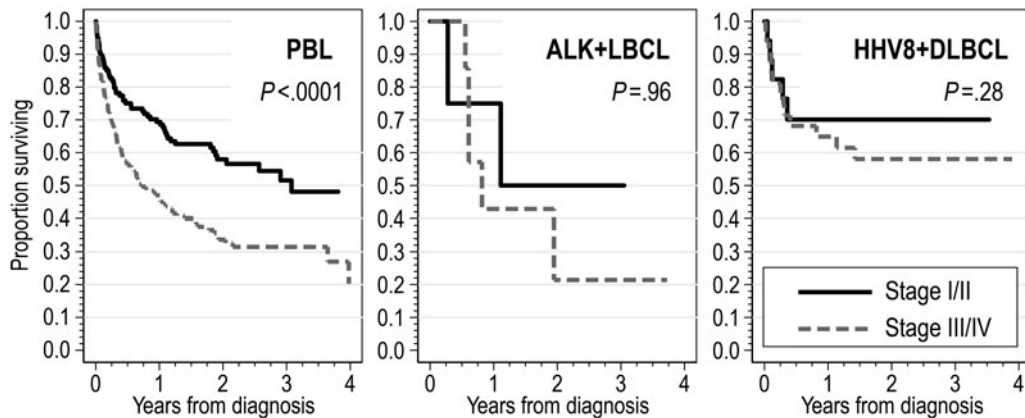


Figure 3. Survival of patients with plasmablastic lymphoma (PBL), ALK-positive large B-cell lymphoma (ALK + LBCL) or human herpesvirus-8-positive diffuse large B-cell lymphoma (HHV8 + DLBCL), stratified by Ann Arbor stage. p values are derived from a log-rank test stratified by age.

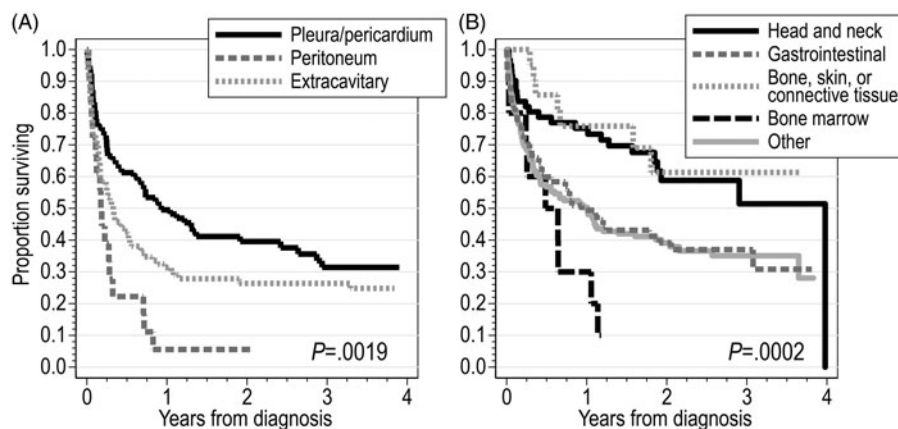


Figure 4. Survival of patients with primary effusion lymphoma (A), and plasmablastic lymphoma (B), stratified by primary site of origin. p values are derived from a log-rank test stratified by age and HIV status.

therapy recognized as significant prognostic factors [20,21]. The prognosis of HIV-associated PEL has not improved over time [11]. A collective review of 147 previously reported cases calculated median OS of

9 months, somewhat longer than our community-derived estimate of 5 months [22]. Interestingly, many PEL cases in the registries had unspecified lymph nodes recorded as the primary site, supporting the

anecdotal reports of extracavitary PEL [7,10]. We further demonstrated differential survival based on the primary site of PEL, although we could not discern the number of involved body cavities previously reported to carry a prognostic value [22]. We cannot rule out some degree of misclassification of HHV8 + DLBCL as 'nodal' PEL, because their differentiation requires expertise, including determination of co-infection with HHV8 and EBV [7,23]. Similarly, DLBCL associated with chronic inflammation, another rare WHO subtype associated with EBV infection, may involve pleural cavity ('pyothorax-associated lymphoma') leading to misclassification [12]. Recently, reports of HIV-negative PEL responding to immunomodulatory agents or intracavitary cidofovir have emerged [24–28]. Our data indicate that HIV-negative PEL is not infrequent, occurs in a much older population, and has prognosis as poor as in HIV-positive patients.

PBL has also been described as an HIV-associated subtype with poor prognosis. Castillo et al. reviewed 248 historically reported PBL cases, of which 63% were HIV-positive [29]. In this subgroup, median OS was 14 months, with 3-year estimate of 31%, and similar to our analysis, early stage carried a better prognosis. A subsequent review of 590 reported cases also showed 63% prevalence of HIV infection [5]. The lower (44%) HIV prevalence in the NCDB cohort may indicate under-reporting, or a higher incidence of HIV-negative PBL in the community. The NCDB data also show a higher proportion of gastrointestinal (34 vs. 14%) primary sites, and confirm that HIV status is not a poor prognostic factor in the contemporary era [30]. In a recent series of 135 cases from France, the prevalence of HIV infection was only 41%, and median OS was 32 months, supporting the notion that the epidemiology of PBL may be shifting [31]. The French series suggested better survival of HIV-positive patients, although our NCDB data indicate that there is no survival difference when age is accounted for, as younger HIV-positive patients are more likely to be treated with chemotherapy.

ALK + LBCL also had a poor prognosis in the NCDB data, with median OS of 13 months, regardless of stage, and despite chemotherapy application as frequent as in DLBCL-NOS. The survival estimate is lower than in the largest retrospective series of 38 cases with median OS of 20 months [6]. Similarly, a comprehensive retrospective review of 108 cases calculated median OS of 1.8 years and 5-year OS of 34% [32]. ALK + LBCL is distinct from other studied CD20-negative DLBCL subtypes in that it is defined by a specific molecular characteristic and lacks association with HIV or other viral infections [1]. The extremely low number

of cases of ALK + LBCL in the NCDB limits our interpretation and indicates poor recognition of this subtype, which requires detection of the t(2;17)(p23;q23) *CLTC-ALK* or t(2;5)(p23;q35) *NPM-ALK* translocations by fluorescence *in situ* hybridization. Raising awareness of this rare pathology is crucial, as specific targeted therapies for ALK-expressing lymphomas emerge [33]. So far, anecdotal use of ALK inhibitor crizotinib in ALK + LBCL appears less promising than in ALK-positive anaplastic large cell lymphoma, with only brief partial remissions [34,35].

In contrast, outcomes in HHV8 + DLBCL reported to the NCDB were essentially identical to DLBCL-NOS. The 63% 3-year OS is markedly higher than in prior case reports which defined this disease as a disseminated lymphoma in immunocompromised patients, characterized by aggressive course and dismal survival of 1–2 months [8,36,37]. While refined diagnostic criteria and advances in antiviral therapy might play a role in improved survival of HHV8 + DLBCL, this major discrepancy puts the reliability of this challenging diagnosis in the community under question. We note that the description of this lymphoma was changed from the 2008 WHO classification used by the NCDB ('large B-cell lymphoma' arising in HHV8-associated multicentric Castleman's disease) to 'HHV8 + DLBCL, NOS' in the 2016 revision [37,38]. Furthermore, HHV8 + DLBCL is difficult to distinguish from PBL, and existence of intermediate steps in the progression from multicentric Castleman's disease (including 'microlymphomas') to frank diffuse lymphoma may obfuscate the prognosis [7]. Nevertheless, the NCDB data reflect application of the current WHO classification of lymphomas in actual clinical practice, and uncovers the need for further research on the pathology, prognosis, and optimal management of this complex entity.

We found that a significant proportion of patients with CD20-negative subtypes (46% in PEL and 34% in PBL) did not receive chemotherapy at all. This surprising finding may hypothetically relate to the aggressiveness of clinical presentation, patients' poor functional status at diagnosis, advanced age, or complications of the HIV infection. Although no formal research confirmed the sensitivity of the NCDB variables indicating chemotherapy use, our results are consistent with prior studies showing that 23% of patients with DLBCL in the US, both HIV-positive and negative, receive no lymphoma-directed therapy [39,40]. We note that the unfavorable HR for OS of the CD20-negative subtypes compared with DLBCL-NOS (ranging from 1.58 for PEL to 2.70 in ALK + LBCL) is reminiscent of inverted HR for rituximab benefit in combination with CHOP (cyclophosphamide,

doxorubicin, vincristine, and prednisone) chemotherapy (1.56 in the Groupe d'Etude des Lymphomes de l'Adulte trial [41], and 2.04 in the MabThera International Trial [42]). This suggests that lack of efficacious monoclonal antibody may be one of the factors contributing to worse outcomes of the CD20-negative histologies, although aggressive biology related to viral oncogenesis and *MYC* rearrangements may play the pivotal role [9,43]. This observation has been reflected in the National Comprehensive Cancer Network guidelines, which state that CHOP is an inadequate therapy for PBL, and is reasonable but not preferred in PEL [44]. CD38, a marker of plasmacytic differentiation commonly expressed by PBL, PEL, ALK+LBCL, and HHV8+DLBCL, may be potentially targetable using the newly available monoclonal antibody daratumumab [1,7]. Other investigational approaches, so far only presented as case reports, include incorporating the proteasome inhibitor bortezomib into anthracycline-based regimens in PBL [45], use of brentuximab vedotin in CD30-expressing PEL [46], or ALK inhibitors in ALK+LBCL [34,35]. More recently, a few prospective interventional studies have been initiated in PBL and PEL (e.g. NCT02911142 and NCT01775475). Immune checkpoint inhibitors have shown activity in some lymphomas and solid tumors driven by viral infections, holding promise of an alternative therapeutic avenue [47–49].

Our results need be considered within the context of methodological limitations of cancer registry data, which do not include expert histopathologic review. Given the evolving classification of CD20-negative DLBCL and their relative rarity, the consistency of histologic code assignment in the community is uncertain. A substantial number of CD20-negative cases may be diagnosed as DLBCL-NOS in the absence of specialized immunohistochemistry or molecular analyses, as discrepancies in diagnosis upon expert review are not uncommon even in more straightforward lymphoma subtypes [50,51]. We used the grouping of DLBCL-NOS as a comparison – which is now recognized to be also heterogeneous. The emerging subcategories of 'double-expressor' and 'double-hit' lymphoma (defined by immunohistochemical expression or rearrangements in the *MYC*, *BCL2*, and/or *BCL6* genes) are now included in the WHO classification, but have not been yet distinguished in the cancer registry data. Along with the rarity of CD20-negative subtypes and the fact that the NCDB is not a population-based, but rather hospital-based resource [52], this lack of awareness and diagnostic expertise limits our sample size, precluding more nuanced analyses, in particular among ALK+LBCL patients. The narrow set of

variables collected by the NCDB represents another key limitation, as we lacked information about important pathologic features (expression of immunophenotypic markers like CD20, CD30, viral markers of EBV and HHV8, and molecular markers like *MYC* or *ALK* rearrangements), specific chemotherapy regimens, drugs, or doses. The observed differences in survival would be best explored while explicitly adjusting for the International Prognostic Index, but it was not available in the NCDB for a sufficient number of cases. However, previous research suggests that survival models based on registry data can provide OS discrimination similar to the IPI using sex, race/ethnicity, and B symptoms as surrogate variables [19]. Without data on response to therapy or subsequent lines of treatment, we could not study progression-free survival or the course of disease after recurrence/progression. We also cannot rule out an imbalance in the frequency of HIV testing between patients with DLBCL, NOS and with CD20-negative variants, although studies suggest that US registries collect the HIV status of lymphoma patients fairly accurately [53].

In conclusion, the poor prognosis of CD20-negative DLBCL subtypes reflects an unmet need for new therapeutic approaches. Additional studies evaluating outcomes with specific chemotherapy regimens could inform the design of future clinical trials, and lead to more robust and evidence-driven treatment guidelines. Our study illustrates that comprehensive data collection by cancer registries might provide important insights into therapy and prognosis of rare lymphomas. Raising awareness of the rare DLBCL subtypes among community pathologists and clinicians should also be a priority, as our analysis uncovers discrepancies between clinical characteristics and outcomes in the registry data, compared with cases series complemented by expert hemopathology review. Further studies are needed to more accurately characterize the incidence of CD20-negative DLBCL and determine whether these lymphomas are being consistently recognized and optimally managed.

Acknowledgments

Presented in part at the 58th American Society of Hematology Annual Meeting & Exposition, December 3–6, 2016, San Diego, CA. A. J. O. is supported by the American Society of Hematology Scholar Award. 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.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article online at <http://dx.doi.org/10.1080/10428194.2017.1387912>.

Funding

This study was conducted using support from authors' academic departments only.

ORCID

Lindor Qunaj  <http://orcid.org/0000-0001-8461-8374>

Jorge J. Castillo  <http://orcid.org/0000-0001-9490-7532>

Adam J. Olszewski  <http://orcid.org/0000-0002-6472-6658>

References

- [1] Castillo JJ, Chavez JC, Hernandez-Ilizaliturri FJ, et al. CD20-negative diffuse large B-cell lymphomas: biology and emerging therapeutic options. *Expert Rev Hematol*. 2015;8:343–354.
- [2] Li J, Zhao S, Wang J, et al. CD20-negative diffuse large B cell lymphoma: a comprehensive analysis of 695 cases. *Tumour Biol*. 2016;37:3619–3637.
- [3] Montes-Moreno S, Montalban C, Piris MA. Large B-cell lymphomas with plasmablastic differentiation: a biological and therapeutic challenge. *Leuk Lymphoma*. 2012;53:185–194.
- [4] Chen YB, Rahemtullah A, Hochberg E. Primary effusion lymphoma. *Oncologist*. 2007;12:569–576.
- [5] Castillo JJ, Bibas M, Miranda RN. The biology and treatment of plasmablastic lymphoma. *Blood*. 2015;125:2323–2330.
- [6] Laurent C, Do C, Gascoyne RD, et al. Anaplastic lymphoma kinase-positive diffuse large B-cell lymphoma: a rare clinicopathologic entity with poor prognosis. *JCO*. 2009;27:4211–4216.
- [7] Chadburn A, Said J, Gratzinger D, et al. HHV8/KSHV-positive lymphoproliferative disorders and the spectrum of plasmablastic and plasma cell neoplasms: 2015 SH/EAHP workshop report-part. *Am J Clin Pathol*. 2017;147:171–187.
- [8] Dupin N, Diss TL, Kellam P, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. *Blood*. 2000;95:1406–1412.
- [9] Carbone A, Cesarman E, Spina M, et al. HIV-associated lymphomas and gamma-herpesviruses. *Blood*. 2009;113:1213–1224.
- [10] Guillet S, Gerard L, Meignin V, et al. Classic and extracavitary primary effusion lymphoma in 51 HIV-infected patients from a single institution. *Am J Hematol*. 2016;91:233–237.
- [11] Olszewski AJ, Fallah J, Castillo JJ. Human immunodeficiency virus-associated lymphomas in the antiretroviral therapy era: analysis of the National Cancer Data Base. *Cancer*. 2016;122:2689–2697.
- [12] Campo E, Swerdlow SH, Harris NL, et al. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. *Blood*. 2011;117:5019–5032.
- [13] Boffa DJ, Rosen JE, Mallin K, et al. Using the National Cancer Database for outcomes research: a review. *JAMA Oncol*. 2017 [Feb 23]. doi: 10.1001/jamaoncol.2016.6905
- [14] Bilimoria KY, Stewart AK, Winchester DP, et al. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol*. 2008;15:683–690.
- [15] Fallah J, Qunaj L, Olszewski AJ. Therapy and outcomes of primary central nervous system lymphoma in the United States: analysis of the National Cancer Database. *Blood Adv*. 2016;1:112–121.
- [16] Kaplan LD. Human herpesvirus-8: Kaposi sarcoma, multicentric Castleman disease, and primary effusion lymphoma. *Hematol Am Soc Hematol Educ Program*. 2013;2013:103–108.
- [17] Castillo JJ, Olszewski AJ, Kanan S, et al. Survival outcomes of secondary cancers in patients with Waldenstrom macroglobulinemia: an analysis of the SEER database. *Am J Hematol*. 2015; 90:696–701.
- [18] Royston P, Lambert PC. Flexible parametric survival analysis using Stata: beyond the Cox model. College Station (TX): Stata Press; 2011.
- [19] Olszewski AJ, Winer ES, Castillo JJ. Validation of clinical prognostic indices for diffuse large B-cell lymphoma in the National Cancer Data Base. *Cancer Causes Control*. 2015;26:1163–1172.
- [20] Simonelli C, Spina M, Cinelli R, et al. Clinical features and outcome of primary effusion lymphoma in HIV-infected patients: a single-institution study. *JCO*. 2003;21:3948–3954.
- [21] Boulanger E, Gerard L, Gabarre J, et al. Prognostic factors and outcome of human herpesvirus 8-associated primary effusion lymphoma in patients with AIDS. *JCO*. 2005;23:4372–4380.
- [22] Castillo JJ, Shum H, Lahijani M, et al. Prognosis in primary effusion lymphoma is associated with the number of body cavities involved. *Leuk Lymphoma*. 2012;53:2378–2382.
- [23] Chadburn A, Hyjek E, Mathew S, et al. KSHV-positive solid lymphomas represent an extra-cavitary variant of primary effusion lymphoma. *Am J Surg Pathol*. 2004;28:1401–1416.
- [24] Chan TSY, Mak V, Kwong YL. Complete radiologic and molecular response of HIV-negative primary effusion lymphoma with short-course lenalidomide. *Ann Hematol*. 2017;96:1211–1213.
- [25] Klepfish A, Zuckermann B, Schattner A. Primary effusion lymphoma in the absence of HIV infection-clinical presentation and management. *QJM*. 2015;108: 481–488.
- [26] Antar A, El Hajj H, Jabbour M, et al. Primary effusion lymphoma in an elderly patient effectively treated by lenalidomide: case report and review of literature. *Blood Cancer J*. 2014;4:e190.
- [27] Halfdanarson TR, Markovic SN, Kalokhe U, et al. A non-chemotherapy treatment of a primary effusion lymphoma: durable remission after intracavitary cidofovir in HIV negative PEL refractory to chemotherapy. *Ann Oncol*. 2006;17:1849–1850.

- [28] Luppi M, Trovato R, Barozzi P, et al. Treatment of herpesvirus associated primary effusion lymphoma with intracavity cidofovir. *Leukemia*. 2005;19:473–476.
- [29] Castillo JJ, Winer ES, Stachurski D, et al. Prognostic factors in chemotherapy-treated patients with HIV-associated Plasmablastic lymphoma. *Oncologist*. 2010;15:293–299.
- [30] Castillo JJ, Winer ES, Stachurski D, et al. Clinical and pathological differences between human immunodeficiency virus-positive and human immunodeficiency virus-negative patients with plasmablastic lymphoma. *Leuk Lymphoma*. 2010;51:2047–2053.
- [31] Tchernonog E, Faurie P, Coppo P, et al. Clinical characteristics and prognostic factors of plasmablastic lymphoma patients: analysis of 135 patients from the LYSA group. *Ann Oncol*. 2017;28:843–848.
- [32] Pan Z, Hu S, Li M, et al. ALK-positive large B-cell lymphoma: a clinicopathologic study of 26 cases with review of additional 108 cases in the literature. *Am J Surg Pathol*. 2017;41:25–38.
- [33] Werner MT, Zhao C, Zhang Q, et al. Nucleophosmin-anaplastic lymphoma kinase: the ultimate oncogene and therapeutic target. *Blood*. 2017;129:823–831.
- [34] Gambacorti Passerini C, Farina F, Stasia A, et al. Crizotinib in advanced, chemoresistant anaplastic lymphoma kissnase-positive lymphoma patients. *J Natl Cancer Inst*. 2014;106:djt378.
- [35] Wass M, Behlendorf T, Schadlich B, et al. Crizotinib in refractory ALK-positive diffuse large B-cell lymphoma: a case report with a short-term response. *Eur J Haematol*. 2014;92:268–270.
- [36] Oksenhendler E, Boulanger E, Galicier L, et al. High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. *Blood*. 2002;99:2331–2336.
- [37] Gonzalez-Farre B, Martinez D, Lopez-Guerra M, et al. HHV8-related lymphoid proliferations: a broad spectrum of lesions from reactive lymphoid hyperplasia to overt lymphoma. *Mod Pathol*. 2017;30:745–760.
- [38] Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127:2375–2390.
- [39] Hamlin PA, Satram-Hoang S, Reyes C, et al. Treatment patterns and comparative effectiveness in elderly diffuse large B-cell lymphoma patients: a surveillance, epidemiology, and end results-medicare analysis. *Oncologist*. 2014;19:1249–1257.
- [40] Suneja G, Shiels MS, Angulo R, et al. Cancer treatment disparities in HIV-infected individuals in the United States. *J Clin Oncol*. 2014;32:2344–2350.
- [41] Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346:235–242.
- [42] Pfreundschuh M, Kuhnt E, Trumper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncol*. 2011;12:1013–1022.
- [43] Taddesse-Heath L, Meloni-Ehrig A, Scheerle J, et al. Plasmablastic lymphoma with MYC translocation: evidence for a common pathway in the generation of plasmablastic features. *Mod Pathol*. 2010;23:991–999.
- [44] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): B-cell Lymphomas. Version 3.2017 – March 27, 2017.
- [45] Castillo JJ, Reagan JL, Sikov WM, et al. Bortezomib in combination with infusional dose-adjusted EPOCH for the treatment of plasmablastic lymphoma. *Br J Haematol*. 2015;169:352–355.
- [46] Bhatt S, Ashlock BM, Natkunam Y, et al. CD30 targeting with brentuximab vedotin: a novel therapeutic approach to primary effusion lymphoma. *Blood*. 2013;122:1233–1242.
- [47] Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372:311–319.
- [48] Laurent C, Fabiani B, Do C, et al. Immune-checkpoint expression in Epstein-Barr virus positive and negative plasmablastic lymphoma: a clinical and pathological study in 82 patients. *Haematologica*. 2016;101:976–984.
- [49] Goodman A, Patel SP, Kurzrock R. PD-1-PD-L1 immune-checkpoint blockade in B-cell lymphomas. *Nat Rev Clin Oncol*. 2017;14:203–220.
- [50] Laurent C, Baron M, Amara N, et al. Impact of expert pathologic review of lymphoma diagnosis: study of patients from the French Lymphopath Network. *JCO*. 2017;35:2008.
- [51] LaCasce AS, Kho ME, Friedberg JW, et al. Comparison of referring and final pathology for patients with non-Hodgkin's lymphoma in the National Comprehensive Cancer Network. *JCO*. 2008;26:5107–5112.
- [52] Bilimoria KY, Bentrem DJ, Stewart AK, et al. Comparison of commission on cancer-approved and -nonapproved hospitals in the United States: implications for studies that use the National Cancer Data Base. *JCO*. 2009;27:4177–4181.
- [53] Diamond C, Taylor TH, Im T, et al. How valid is using cancer registries' data to identify acquired immunodeficiency syndrome-related non-Hodgkin's lymphoma? *Cancer Causes Control*. 2007;18:135–142.