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Diffuse large B-cell lymphoma of Waldeyer's ring has distinct clinicopathologic features: a GELA study

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Background: Diffuse large B-cell lymphomas (DLBCLs) arising in specific extranodal sites have peculiar clinicopathologic features.

Patients and methods: We analyzed a cohort of 187 primary Waldeyer's ring (WR) DLBCLs retrieved from GELA protocols using anthracyclin-based polychemotherapy.

Results: Most patients (92%) had stage I–II disease. A germinal center B-cell-like (GCB) immunophenotype was observed in 61%, and BCL2 expression in 55%, of WR DLBCLs. *BCL2*, *BCL6*, *IRF4* and *MYC* breakpoints were observed in, respectively, 3 of 42 (7%), 9 of 36 (25%), 2 of 26 (8%) and 4 of 40 (10%) contributive cases. A variable follicular pattern was evidenced in 30 of 68 (44%) large biopsy specimens. The 5-year progression-free survival (PFS)

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and the overall survival (OS) of 153 WR DLBCL patients with survival information were 69.5% and 77.8%, respectively. The GCB immunophenotype correlated with a better OS ($P = 0.0015$), while BCL2 expression predicted a worse OS ($P = 0.037$), an effect overcome by the GCB/non-GCB classification. Compared with matched nodal DLBCLs, WR DLBCLs with no age-adjusted international prognostic index factor disclosed a better 5-year PFS rate (77.5% versus 70.7%; $P = 0.03$).

Conclusions: WR DLBCLs display distinct clinicopathologic features compared with conventional DLBCLs, with usual localized-stage disease, common follicular features and a high frequency of GCB immunophenotype contrasting with a low rate of *BCL2* rearrangements. In addition, they seem to be associated with a better outcome than their nodal counterpart.

Key words: clinicopathologic features, diffuse large B-cell lymphomas, outcome, Waldeyer's ring

introduction

About one-third of diffuse large B-cell lymphomas (DLBCLs) manifest primarily in non-nodal locations [1]. In the recent WHO classification, subsets of DLBCLs arising in peculiar extranodal sites have been individualized as distinct disease subgroups (primary DLBCLs of the central nervous system, primary cutaneous DLBCLs, leg-type) or as distinct disease entities (primary mediastinal large B-cell lymphoma), based on specific clinical and/or pathologic features [2–4]. Yet, the majority of extranodal DLBCLs remain categorized as DLBCLs, not otherwise specified (NOS).

Waldeyer's ring (WR) represents one of the most common extranodal sites for DLBCL development [5], comprising up to 20% of the cases [6]. Peculiar features have been suggested for WR DLBCLs. Clinically, a relationship to gastrointestinal tract involvement has been mentioned, either concurrent with diagnosis or at subsequent relapse [7–9]. Pathologically, the presence of focal follicular features has been reported in a subset of tonsillar DLBCLs, suggesting a morphologic subgroup distinct from *de novo* nodal DLBCLs, possibly corresponding to either transformed follicular lymphomas, or transformed marginal zone lymphomas with follicular colonization [10]. Genetically, translocations affecting the *IRF4* locus in 6p25 have recently observed in a subtype of germinal center-derived B-cell lymphomas frequently manifesting in the cervical region including the WR and particularly affecting children and young adults [11]. Several clinical comparative studies of nodal versus WR DLBCLs have variably suggested differences in response to therapy and outcome, or similar features [9, 12–14]. However, published series are based on rather limited cohorts of patients, oftentimes heterogeneous with respect to histopathology, and rarely correlated clinical and pathologic features [9, 14–20].

The purpose of this work was to study the pathologic features of primary WR DLBCLs, and to compare their clinical outcome with that of nodal DLBCLs, based on the analysis of a retrospective series of well-characterized patients with a long follow-up treated in GELA protocols.

patients and methods

patient selection

WR DLBCL patients

The GELA files were searched for patients diagnosed with primary DLBCLs of the WR (coded as palatine tonsil, lingual tonsil or nasopharynx). Of 208 with pathologic documentation of a WR DLBCL consecutively enrolled into the protocols LNH93, LNH98, LNH01 and LNH03 between 1993 and 2003, 187 qualified for primary WR DLBCLs. Outcome analysis and clinicopathologic correlations were restricted to a subset of 153 patients with available updated survival information, corresponding to the protocols LNH 93-1 to 93-5, LNH 98-2 and LNH 98-5 (summarized in supplementary Table S1, available at *Annals of Oncology* online) [6, 21–25]. All patients had received anthracyclin-based polychemotherapy without immunotherapy, except for two patients treated with R-CHOP in the LNH 98.5 trial.

matching with nodal DLBCL patients

For the comparison of outcome, WR DLBCL patients with clinical annotations were matched to DLBCL patients presenting with nodal involvement, on the basis of sex, age (<60 versus >60 years), age-adjusted international prognostic index (aaIPI) and randomization arm, leading to 135 pairs. Comparison of outcome was further restricted to a subset of 107 pairs of patients with no aaIPI factor.

pathologic studies

The archival slides that had been centrally reviewed at the time of enrollment into clinical trials, comprising 74 surgical specimens (large biopsies or excisions) (40%) and 113 sampling biopsies (60%), were re-examined by 2 hematopathologists (LdeL and PG) for cytologic characterization, according to the variants described in the WHO classification [2], and for the assessment of the pattern of growth. All cases by definition exhibited at least partially a diffuse pattern, and were categorized as: purely diffuse (D), predominantly diffuse (D > N) or predominantly nodular (N ≥ D). A tissue microarray (TMA) comprising two 0.6 mm cores representative of 59 cases with available tissue blocks was constructed in duplicate.

immunohistochemistry

Immunohistochemistry was carried out using an indirect immunoperoxidase method. The following markers were used after appropriate antigen retrieval: BCL2, CD20, CD44, CNA.42, HLADR, MUM-1/IRF4 (DakoCytomation, Glostrup, Denmark); BCL6 (Ventana, Tucson, AZ); CD5, CD10, CD21, CD23, cyclin D1 (Novocastra, Newcastle, UK). The presence of Epstein-Barr virus (EBV) was detected by *in situ* hybridization with probes specific for EBV-encoded small RNA (EBER) sequences (DakoCytomation). Slides were evaluated semi-quantitatively by two independent observers (LdeL and PG). A positivity threshold was defined at 50% for BCL2 [26], and at 30% for BCL6, CD10 and MUM-1 [27]. CD21, CD23 and/or CNA.42 were used for the staining of follicular dendritic cell (FDC) meshworks. In case of negativity, only the cases with internal positive controls were recorded. Classification into germinal center B-cell-like (GCB) versus non-GCB immunophenotypes was based on the algorithm of Hans et al. [27].

FISH analysis

A subset of cases were studied by interphase FISH on TMA sections, using split-signal DNA probes targeting *MYC*/8q24, *BCL2*/18q21 and *BCL6*/3q27genes (probes Y5410, Y5407, Y5408; Dako, SA, Glostrup, Denmark) according to the manufacturer's recommendations (www.euro-fish.org) and analyzed and scored as recently reported [28]. For the detection of breakpoints affecting the *IRF4* locus, two different break-apart assays using differently labeled BAC/PAC clones were carried out [11].

statistical analyses

Results were expressed as means ± standard deviations, medians and ranges for continuous variables and as proportions for categorical variables. Associations between pathologic variables were tested using the chi-square test. End points of interest were complete response (CR), progression-free survival (PFS) (defined as the time interval between randomization to primary treatment failure, relapse and death from any cause or last follow-up) and overall survival (OS) (defined as the time interval between randomization to last follow-up or death from any cause). The OS and PFS were analyzed using a Cox regression model taking matching into account. The OS and PFS were displayed by Kaplan–Meier curves in each group. Within the WR DLBCL group, the OS and PFS were evaluated using univariate and multivariate Cox regression models. Results were considered significant at the 5% level ($P < 0.05$). Statistical analyses were carried out using the SAS (version 9.1 for Windows) statistical package.

results

clinical presentation of WR DLBCL patients

The 187 patients with primary WR DLBCLs comprised 169 patients with stage I–II disease, and 18 stage IV patients due to extensive local disease ($n = 7$) or dissemination limited to the bone marrow ($n = 11$). The population of patients with clinical follow-up comprised 106 men and 47 women at a median age of 57 years. Of these 153 patients, 141 had stage I or II disease and 12 patients (8%) had stage IV disease, due to locally invasive disease ($n = 5$) or bone marrow involvement ($n = 7$). The aaIPI, available for 144 patients, was 0 in 114 patients (79%), 1 in 27 patients (19%) and 2 in 3 patients (2%).

WR DLBCLs disclose a predominantly centroblastic morphology and a high prevalence of GCB-like immunophenotype

Of the 187 cases, 175 were classified as centroblastic (CB), 7 as immunoblastic (IB) and 5 were unclassifiable (Table 1). The prevalence of differentiation antigen expression was the following: CD10, 68 of 158 (43%), BCL6, 35 of 69 (51%), MUM-1, 36 of 99 (36%). The global immunophenotypic profile was GCB in 74 of 122 cases (61%) and non-GCB in 39%. The GCB immunophenotype was associated with CB morphology ($P = 0.012$). BCL2 expression in 93 of 168 cases (55%) correlated with a non-GCB immunophenotype ($P < 0.0001$). CD5 positivity was observed in 9 of 60 cases (15%) (all negative for cyclin D1). Positivity for CD44 (in 8 of 59 cases, 14%) correlated with a non-GCB immunophenotype ($P = 0.003$). Loss of HLA-DR expression was detected in 6 of 55 cases (11%) and correlated with BCL2 positivity ($P = 0.04$). EBER *in situ* hybridization was positive in lymphoma cells in 2 of 59 cases.

infrequent *BCL2* breaks in WR DLBCLs

Evaluable FISH results of at least two loci were obtained for 42 cases sampled in the TMA (Table 2). Only three cases of 42 (7%) harbored a *BCL2* rearrangement, one as the sole chromosomal break, and one each in association with *BCL6* or *MYC* rearrangement. All three were positive for BCL2 by immunohistochemistry, two had a GCB immunophenotype and one was non-GCB. Nine cases of 36 assessable (25%) (5 GCB and 4 non-GCB) harbored a *BCL6* rearrangement, of which 3 were positive for BCL6 expression. An *MYC*

Table 1. Morphologic and immunophenotypical features of primary WR DLBCLs

	All WR DLBCL patients ($n = 187$)	WR DLBCL patients with clinical follow-up ($n = 153$)[a]	Correlation with outcome
Morphology			
Centroblastic	175/187 (93%)	142/153 (93%)	NS
Immunoblastic	7/187 (4%)	6/153 (4%)	NS
Unclassifiable	5/187 (3%)	5/153 (3%)	NS
Immunophenotype			
CD10 positivity	68/158 (43%)	58/131 (44%)	Correlates with a better PFS ($P = 0.0055$) and OS ($P = 0.014$)
BCL6 positivity	35/69 (51%)	26/50 (52%)	Correlates with a better OS ($P = 0.048$)
MUM-1 positivity	36/99 (36%)	30/78 (38%)	Adversely affects the PFS ($P = 0.0046$)
GCB immunophenotype	74/122 (61%)	62/100 (62%)	Correlates with a better PFS ($P = 0.0003$) and OS ($P = 0.001$)
BCL2 positivity	93/168 (55%)	76/136 (56%)	Adversely affects the PFS ($P = 0.017$) and OS ($P = 0.037$)
CD5 positivity[b]	9/60 (15%)	7/44 (16%)	NS
CD44 positivity[b]	8/59 (14%)	7/43 (16%)	NS
HLA-DR positivity[b]	49/55 (89%)	35/40 (88%)	Correlates with a better PFS ($P = 0.04$) and OS ($P = 0.017$)

GCB, germinal center B-cell-like immunophenotype; OS, overall survival; PFS, progression-free survival; WR DLBCL, Waldeyer's ring diffuse large B-cell lymphoma; NS, non-significant.

[a]The results obtained for this subset of the population did not differ significantly from those obtained for the 187 patients.

[b]Carried out on TMAs.

rearrangement was detected in 4 of 40 assessable cases (10%) (one GCB and 3 non-GCB), as the sole chromosomal break in one case, in addition to a *BCL6* rearrangement in two cases, and in conjunction with a *BCL2* break in one case. None had immunomorphologic features of Burkitt lymphoma. A breakpoint affecting the *IRF4* locus was observed in 2 of 26 (8%) assessable cases. Both cases had a partly nodular architecture and both cases had a GCB immunophenotype (CD10+); one case occurred in a 79-year-old woman who was treated without anthracyclin-containing polychemotherapy. The other one occurred in a 32-year-old man who was treated by CHOP (cyclophosphamide, adriamycin, vincristine and prednisone) followed by IFRT (involved-field radiotherapy). The two patients achieved a complete remission.

Table 2. FISH results in primary WR DLBCLs

		BCL2 break	*BCL6* break	*MYC* break	*IRF4* break
All cases	42	3/42 (7%)	9/36 (25%)	4/40 (10%)	2/26 (8%)
GCB	25	2/26	5/22	1/24	2/16
Non-GCB	17	1/16	4/14	3/16	0/10

GCB, germinal center B-cell-like immunophenotype; WR DLBCL, Waldeyer's ring diffuse large B-cell lymphoma.

WR DLBCLs frequently exhibit a partially nodular growth pattern

Although all cases fulfilled the DLBCL diagnostic criteria and the majority of the cases (144 cases, 77%) exhibited a purely diffuse distribution of the neoplastic cells, a subset of cases (43 cases, 23%) had some nodular features. This observation was substantiated by immunohistochemistry carried out on surgical specimens, which demonstrated FDC meshworks in 31 of 69 (45%) assessable cases including 7 of 34 (20%) of those purely diffuse by morphology. The staining corresponded to either ill-defined FDC meshworks, suggestive of follicular colonization ($n = 15$), or to sharply delineated neoplastic follicles, suggestive of a truly follicular pattern ($n = 16$) (Figure 1). Among these cases comprising FDC meshworks, 14 of 25 assessable cases had a GCB immunophenotype and 11 were non-GC; at the genetic level, 8 had a normal hybridization pattern with the split probes tested and 6 had an abnormal pattern (2 cases with a *BCL6* break, 1 case with an *MYC* break, 1 case with an *IRF4* break, 2 cases with double rearrangements involving *BCL2* and either *MYC* or *BCL6*).

the overall good outcome of WR DLBCL patients correlates with the GCB-like immunophenotype

Response to therapy was known for 146 of 153 patients and CR was achieved in 135 of 146 of them (92%). Thirty

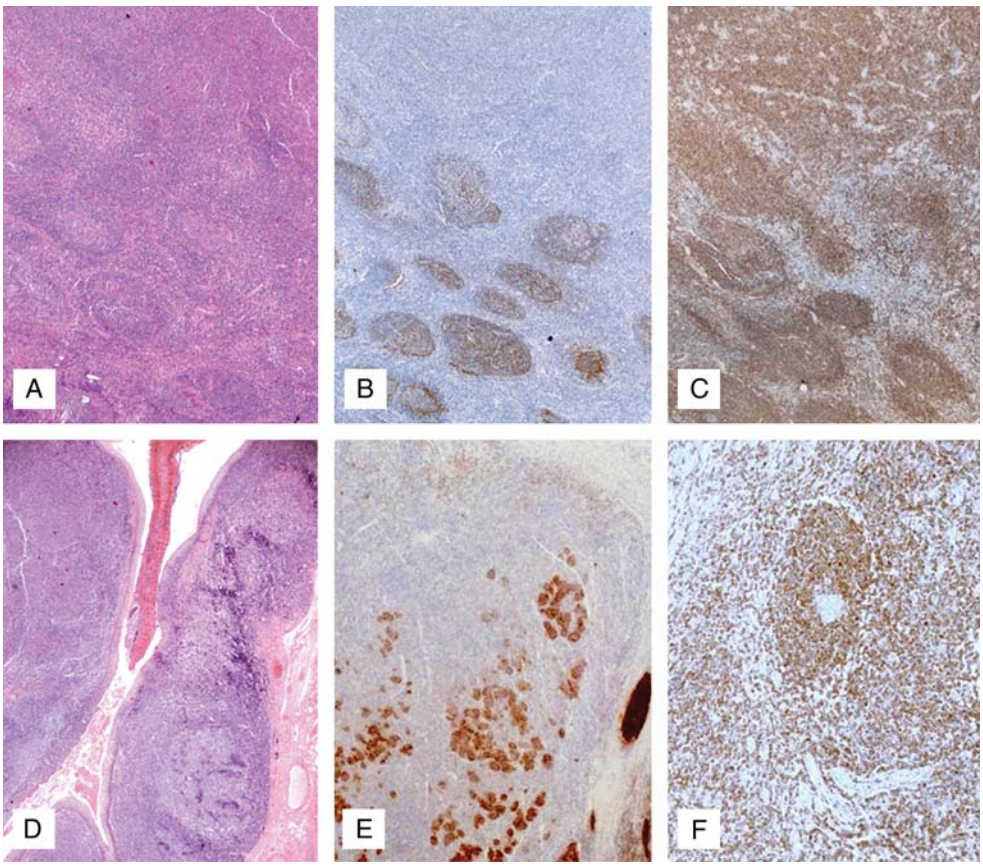

Figure 1 Follicular features in Waldeyer's ring diffuse large B-cell lymphomas (WR DLBCLs). (A–C) WR DLBCL displaying a partially follicular growth pattern (A: hematoxylin and eosin, ×100, B: CD21, immunoperoxidase, ×100; C: CD20, immunoperoxidase, ×100). (D–F): WR DLBCLs with large ill-defined follicular structures consistent with follicular colonization (D: hematoxylin and eosin, ×50; E: CD21, immunoperoxidase, ×100; F: BCL2, immunoperoxidase, ×200).

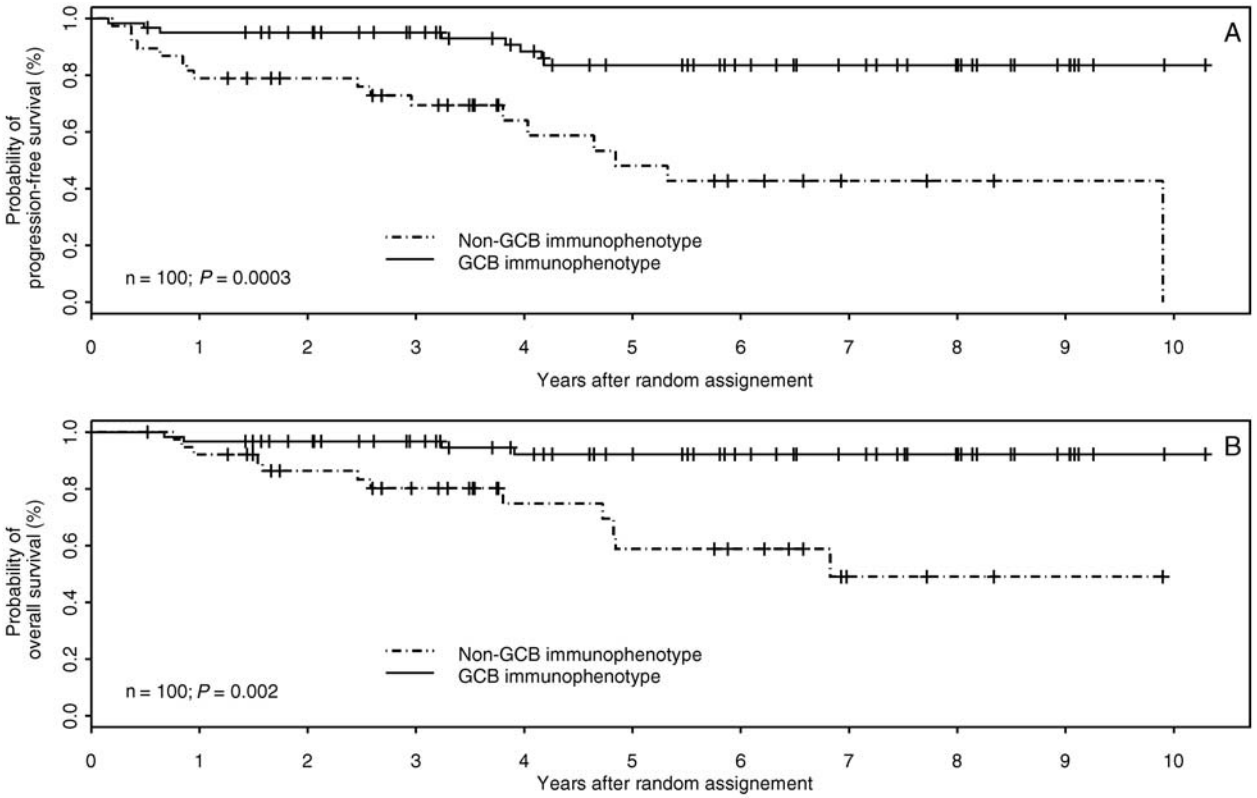

Figure 2 Progression-free (A) and overall survival (B) of Waldeyer's ring diffuse large B-cell lymphoma patients according to the germinal center B-cell-like (GCB)/non-GCB immunophenotype.

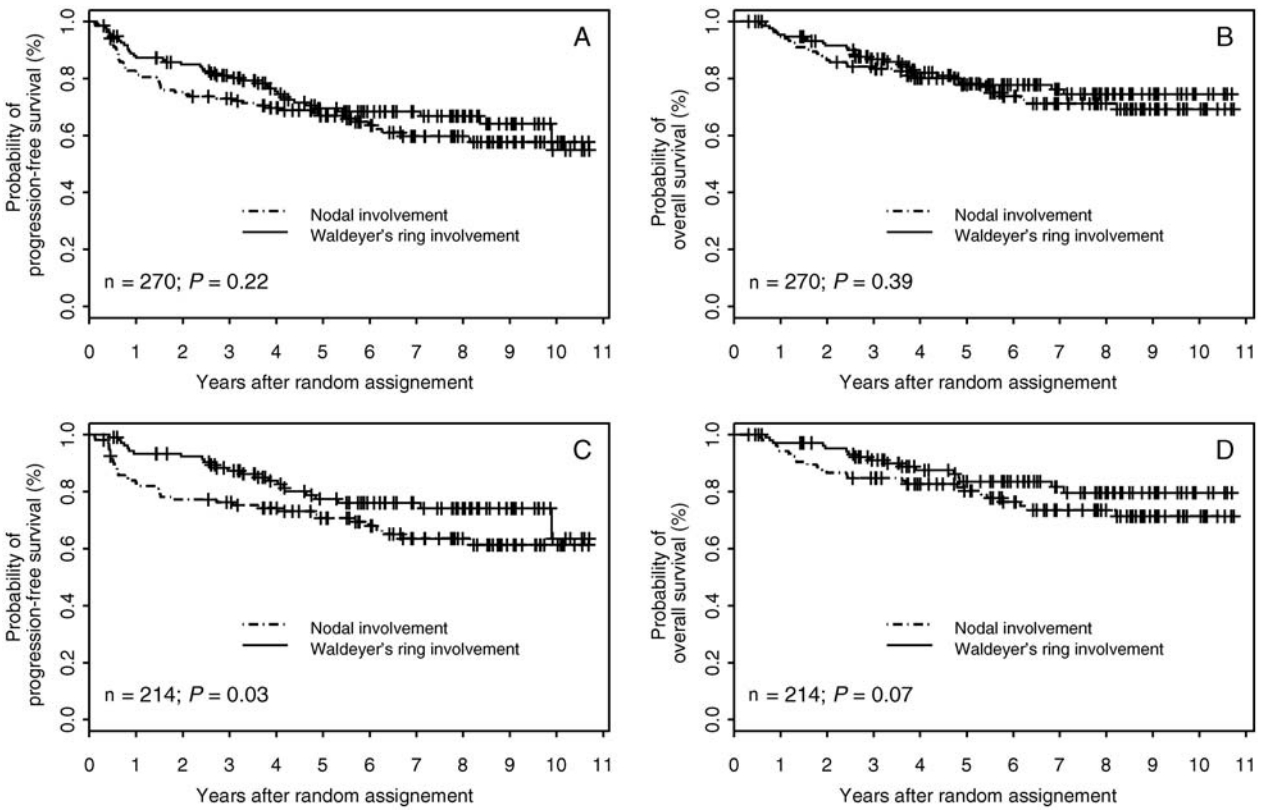

Figure 3 Comparison of the outcome of diffuse large B-cell lymphoma patients presenting with Waldeyer's ring (WR) versus nodal involvement. Panels A and C feature the 5-year progression-free survival, and panels B and D the 5-year overall survival of 135 pairs of matched WR and nodal patients (A and B) and of 107 pairs of matched patients with no age-adjusted international prognostic index factor (C and D).

Table 3. Clinical characteristics and outcome of 153 patients with primary WR DLBCLs

Clinical features		Correlation with outcome
Sex		
Male	106/153 (69%)	NS
Female	47/153 (31%)	
Age (years)		
>60	64/153 (42%)	Older age adversely
<60	89/153 (56%)	affects the PFS ($P = 0.0028$)
median (range)	57 (20–85)	and OS ($P = 0.0006$)
Ann Arbor stage		
Stage I–II	141/153 (92%)	Advanced-stage adversely
Stage IV	12/153 (8%)	affects CR ($P = 0.013$)
		and PFS ($P = 0.0036$)
LDH levels[a]		
Normal	123/144 (85%)	NS
Increased	21/144 (15%)	
Performance status (PS)[a]		
PS 0–1	143/144 (99%)	NA
PS>1	1/144 (1%)	
aaIPI[a]		
aa IPI 0	114/144 (75%)	Higher aaIPI adversely
aa IPI 1	27/144 (22%)	affects CR ($P = 0.0021$),
aa IPI 2–3	3/144 (3%)	OS ($P = 0.035$)
		and PFS ($P = 0.011$)
BM involvement	7/144 (5%)	NS

OS, overall survival; PFS, progression-free survival; WR DLBCL, Waldeyer's ring diffuse large B-cell lymphoma; aaIPI, age-adjusted International Prognostic Index; NS, non-significant; NA, not applicable.
[a]Available for 144 patients.

patients relapsed, at the initial site of presentation in 46% and in a novel site in 54%. Only one relapse occurred in the digestive tract. With a median follow-up of 66 months, the 5-year OS for the 153 patients was 77.8% (95% CI: 70.5% to 85.9%) and the 5-year PFS was 69.5% (95% CI: 61.6% to 78.4%).

The clinical features at the time of diagnosis were tested for their impact on outcome and response to treatment (Table 3). Age >60 years and higher aaIPI correlated with a shorter PFS and OS. The CR rate and the 5-year PFS were both adversely affected by a higher disease stage and a higher aaIPI.

Regarding associations with pathologic features (Table 1), no correlation was found with cytologic features, nor with a growth pattern. Expression of CD10 and a GCB-like immunophenotype strongly correlated with a better PFS ($P = 0.0055$ and $P = 0.0003$, respectively) and OS ($P = 0.014$ and $P = 0.001$, respectively) (Figure 2). MUM-1 expression adversely affected PFS ($P = 0.0046$), and BCL6 expression was associated with a better OS ($P = 0.048$). BCL2 expression was predictive of shorter PFS ($P = 0.017$). These correlations remained significant irrespective of the aaIPI. However, BCL2 expression did not retain its adverse effect in a bivariate model, considering the GCB versus non-GCB profile together with BCL2 expression, while the good prognostic value of the GCB immunophenotype remained significant for both the PFS ($P = 0.014$) and the OS ($P = 0.047$).

a better outcome for WR DLBCL patients compared with matched nodal DLBCL patients

The outcome of 135 matched pairs of DLBCL patients with either primary WR or nodal presentation was compared. CR was achieved in 123 of 134 (92%) versus 112 of 132 (85%) for WR versus nodal DLBCL patients ($P = 0.078$). With a median follow-up of 59 months, the 5-year PFS and OS estimates were 69% (95% CI: 61.6% to 78.4%) and 78% (95% CI: 71.4% to 85.7%) for WR lymphomas versus 67% (95% CI: 59.3% to 75.6%) and 78% (95% CI: 70.5% to 85.9%) for nodal lymphomas ($P = 0.22$ and 0.39 for the PFS and OS, respectively) (Figure 3A and B).

The same analysis was subsequently applied to the 107 pairs of patients with no aaIPI factor (from the LNH 93-1 and LNH 93-4 protocols; see supplementary Table S1, available at *Annals of Oncology* online) (Figure 3C and D). In this subgroup, the CR rate was 100% for WR DLBCL patients and 87% for nodal DLBCL patients ($P = 0.0001$). With a median follow-up of 79 months, the 5-year PFS was 77% (95% CI: 70.4% to 87.5%) for WR and 71% (95% CI: 62.9% to 80.5%) for nodal DLBCL patients ($P = 0.027$). WR DLBCL patients also tended to have a better OS, with 5-year estimates of 84% (95% CI: 77.5% to 92.5%) versus 80% (95% CI: 72.5% to 88.0%) for nodal lymphomas ($P = 0.07$).

discussion

In this report, we have investigated the clinical and pathologic characteristics of primary WR DLBCLs, with the aim of delineating the intrinsic features of DLBCLs in this anatomic site. Our study based on a cohort of 187 patients with primary WR DLBCLs, including 153 cases with updated survival information, represents the largest series of primary WR DLBCLs reported so far [9, 20, 29].

Our analysis has shed light on peculiar pathologic features of WR DLBCLs, somewhat different from those usually reported for DLBCLs, NOS. First, we show that WR DLBCLs comprise a majority of tumors (60%) with a GCB-like phenotypic profile. Most unselected series of nodal and extranodal DLBCLs categorized according to the Hans algorithm report a substantially higher proportion of lymphomas with a non-GCB-like immunophenotype [27, 28, 30–32]. In a way similar to us, although their series was rather small, Lopez-Guillermo et al. [13] also found a higher prevalence of tumors with a GCB phenotype among WR DLBCLs than in nodal cases [9 of 12 cases (75%) versus 36 of 77 cases (47%)]. Second, the frequency and distribution of genetic alterations explored by FISH differ from those reported in unselected series in respect of a low frequency of *BCL2* rearrangements (7%). This finding is particularly paradoxical since this alteration, reported in 20%–30% of DLBCLs, is strongly associated with a GCB immunophenotype [28, 33]. Conversely, the frequency of *BCL6* and *MYC* rearrangements in 25% and 10% of cases, respectively, is similar to those usually reported [34]. Finally, DLBCLs of the WR frequently exhibit, to variable extent, a follicular growth pattern, a feature better seen in surgical specimens. The presence of follicular features in tonsillar DLBCLs has been reported by Ree et al. [10], although at a

lower frequency. The significance of the follicular pattern, however, remains unclear. In about half of the cases, a minor nodular pattern with poorly delineated follicles was suggestive of follicular colonization by DLBCLs in a site naturally containing many hyperplastic follicles. In such cases, the possibility of transformed marginal zone lymphoma with follicular colonization was considered but could not be confirmed given the absence of a small cell component of these tumors, and the absence of a true marginal zone pattern. In the other half of cases, the presence of sharply delineated neoplastic follicles was rather suggestive of a truly follicular pattern. However, these cases appear to be heterogeneous at the genetic level with only a minority (two of eight cases with contributive FISH analysis) harboring a *BCL2* rearrangement of conventional follicular lymphoma, while conversely a subset harbor a *BCL6* break (two of eight cases), or an *IRF4* rearrangement (one of eight cases). Interestingly, *BCL6* rearrangements typically uncommon in grades 1–3A follicular lymphoma (FL) are detected in up to one-third of grade 3B cases, especially those associated with DLBCLs [35–38], and translocations activating *IRF4* identify a subtype of germinal center-derived B-cell lymphoma affecting predominantly children and young adults [11]. Thus, at least a small proportion of WR DLBCLs likely arise in association with grade 3B FLs harboring a *BCL6* or *IRF4* rearrangement. It is also noteworthy that the palatine tonsils and nasopharynx are among the most common sites of pediatric FL [39]. These, in contrast to the common adult type of FL, usually lack *BCL2* gene rearrangements, are grade 3B, usually present with localized disease and have an excellent prognosis. Thus, the possibility that a subset of transformed FL in the WR may be related to transformed FL is questionable.

DLBCLs of the WR represent a group of extranodal DLBCLs associated with a favorable outcome with an estimated 5-year OS of 80% and a PFS of 72% in this retrospective cohort of 153 subjects treated with polychemotherapy alone before rituximab era (except for two patients). Among the clinical and pathologic factors tested for their association with survival, age >60 years, the non-GCB immunophenotype and positivity for BCL2 were identified as adverse prognostic factors.

Strikingly, the GC and non-GC immunophenotypic profile intended to reflect the cell-of-origin classification had a highly significant impact on both the PFS and the OS. Independent studies have established that, when defined by gene expression patterns, the cell-of-origin classification into GC and non-GC subgroups is a strong predictor of survival in patients treated by chemotherapy, as well as immunochemotherapy [40–46]. Conversely, the predictive value of cell-of-origin phenotyping on paraffin-embedded tissues by the combined immunostaining of CD10, BCL6 and MUM-1, using Hans algorithm [27], is more controversial [28, 30–32, 47–49]. Our study shows the strong prognostic value of the GC/non-GC classification in a retrospective multicentric series composed exclusively of extranodal DLBCLs in a single anatomic region (Figure 2). Although the actual correspondence of the phenotypic and transcriptomic categorizations cannot be assessed, the observed correlation between the GC phenotype and a CB morphology, on the one hand, and between a non-GC phenotype and CD44 and BCL2 expression, on the other hand, lends support to the reliability of the immunophenotypic classification.

Reports in the literature on BCL2 expression as a prognostic biomarker have been contradictory; although multiple large-scale trials have established an association between BCL2 expression and a decreased PFS or OS in DLBCLs [26, 30, 50, 51], recent studies have suggested that the prognostic value of BCL2 expression is overcome by the use of rituximab [52] and may be restricted to non-GCB tumors only [53]. In this clinically homogeneous cohort of patients treated before the era of rituximab, we confirm the results previously reported by our group on the prognostic value of BCL2expression on both the PFS and the OS, irrespective of the aaIPI [26]. However, in bivariate analysis, the adverse effect of BCL2 expression was overcome by the GCB/non-GCB immunophenotype.

In our study, WR DLBCLs appear to carry a better outcome compared with matched nodal DLBCLs, a difference that reached significance for the PFS of patients with localized disease and no adverse factor of the aaIPI in this retrospective series of patients treated with chemotherapy. Whether immunochemotherapy protocols would alleviate this difference and/or could still improve the outcome of patients with primary WR remains to be investigated. Nevertheless, the clinical characteristics of WR DLBCLs, together with distinctive pathologic features, reinforce the concept that the anatomic location is a major determinant of DLBCL heterogeneity, and might suggest that WR DLBCLs could constitute a biologically distinct DLBCL subgroup.

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disclosure

The authors have declared no conflicts of interest.

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International models of investigator-initiated trials: implications for Japan

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Background: Academic/institutional investigator-initiated clinical trials benefit individuals and society by supplementing gaps in industry-sponsored clinical trials.
Materials: In May 2010, experts from Japan, the Republic of Korea, the UK, and the United States, met at a symposium in Tokyo, Japan, to discuss how policies related to the conduct of clinical trials, which have been shown to be effective, may be applied to other regions of the world.
Results: In order to increase the availability of anticancer drugs world-wide, nations including Japan should examine the benefits of increasing the number of investigator-initiated clinical trials. These trials represent one of the most effective ways to translate basic scientific knowledge into clinical practice. These trials should be conducted under GCP guidelines and include Investigational New Drug application submissions with the ultimate goal of future drug approval.
Conclusions: To maximize the effectiveness of these trials, a policy to educate health care professionals, cancer patients and their families, and the public in general on the benefits of clinical trials should be strengthened. Finally, policies that expedite the clinical development of novel cancer drugs which have already been shown to be effective in other countries are needed in many nations including Japan to accelerate drug approval.
Key words: academic/institutional investigator-initiated clinical trials, anticancer drugs, good clinical practice, health care policy, international clinical trials, patient advocates

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introduction

In May 2010, representatives from the Health and Global Policy Institute (Tokyo, Japan), together with experts from the UK, the Republic of Korea (ROK), Japan, and the United