Extranodal Diffuse Large B-Cell Lymphoma: Molecular Features, Prognosis, and Risk of Central Nervous System Recurrence

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Opinion statement

Diffuse large B-cell lymphoma (DLBCL) arises from extranodal organs in about 30% of cases. Its prognosis and risk of recurrence in the central nervous system (CNS) vary according to the primary site of origin. Recent studies begin to clarify these differences using molecular classification. Testicular, breast, and uterine DLBCL (as well as possibly primary cutaneous DLBCL, leg-type) share a high prevalence of the non-germinal center B-cell (non-GCB) phenotype and the *MYD88/CD79B*-mutated (MCD) genotype. These biologic features, which resemble primary CNS lymphoma, may underlie their stage-independent propensity for CNS involvement. Management of these lymphomas should involve CNS prophylaxis, preferably using systemic high-dose methotrexate to prevent intraparenchymal recurrence. Involvement of the kidneys, adrenal glands, ovary, bone marrow, lung, or pleura usually indicates disseminated disease, conferring worse prognosis. Involvement of these sites is often associated with high CNS-International Prognostic Index (IPI), concurrent *MYC* and *BCL2* or *BCL6* rearrangements, or intravascular lymphoma—risk factors warranting CNS prophylaxis. In contrast, craniofacial, thyroid, localized bone, or gastric lymphomas have a variable prevalence of the non-GCB phenotype and lack *MYD88* mutations. Their outcomes with standard immunochemotherapy are excellent, and the risk of CNS recurrence is low. We recommend individualized consideration of CNS prophylaxis based on the CNS-IPI score and anatomical proximity in cases of epidural, orbital, or skull involvement. Rituximab-containing immunochemotherapy is a standard approach for all extranodal DLBCLs. Surgery is no longer required for any primary site, but routine consolidative radiation therapy is recommended for testicular lymphoma. Radiation therapy also appears to be associated with better progression-free survival in primary bone DLBCL. Future studies should better distinguish primary from secondary sites of extranodal involvement, and investigate the association of newly identified genotypes with the risk of CNS or systemic recurrence.

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous entity comprising intermediate- and high-grade B-cell lymphomas with diverse molecular backgrounds, clinical course, and response to therapy. Up to a third of DLBCLs may arise from extranodal sites, most commonly gastrointestinal tract, skin and soft tissues, bone, or genitourinary tract [1–4]. Additionally, advanced DLBCL can spread to extranodal organs, particularly bone marrow, pleura, peritoneum, liver, and central nervous system (CNS), sometimes obscuring the primary site of origin. Primary extranodal DLBCL is thus more often recognized at early stage (IE/IIE), except when it originates from organs that define stage IV disease. The distinction between primary and secondary involvement makes many studies difficult to interpret, particularly because clinical trials usually report only the number of involved extranodal sites, rather than individual sites of origin [5–8]. The recognition that occurrence of DLBCL in specific organs may be associated with distinct clinical or molecular features, as well as consistent patterns of recurrence, raised interest in examining both extranodal origin and secondary involvement as prognostic factors [3, 2, 4, 9, 10]. Moreover, the risk of CNS recurrence, one of the most devastating complications of DLBCL, appears to be significantly tied to specific extranodal sites [11].

In this review we survey recent evidence regarding prognostic significance, molecular characteristics, and therapeutic implications of extranodal origin in DLBCL. We emphasize the divergent survival outcomes, risk of CNS recurrence, prevalence of subtypes defined by cell of origin or genomic alterations, as well as indications for radiation therapy (RT) for lymphomas arising from specific extranodal sites.

Assessment of prognosis in DLBCL

Prognosis in DLBCL has been historically assessed using clinical features comprising the International Prognostic Index (IPI), but in the era of rituximab-based immunochemotherapy the IPI explains less than 25% of variation in overall survival (OS) and poorly separates the highest-risk subgroups [9, 12]. The enhanced IPI (which improved on the specification of age and lactate dehydrogenase [LDH] as non-binary variables) has identified involvement of CNS, liver/gastrointestinal (GI) tract, lung, or marrow as additional unfavorable prognostic factors [9]. The Spanish Lymphoma Study Group evaluated extranodal origin in addition to the IPI, and found no additive prognostic value, but specific anatomic sites were not distinguished [13]. In contrast, a Danish-Canadian series of 443 patients staged with positron emission tomography (PET) found that 67% had extranodal involvement, that PET uptake in bone/bone marrow, pleura, or female reproductive organs was independently associated with worse progression-free survival (PFS) and OS, and that >2 or >3 involved sites conferred progressively worse prognosis [3]. Another series of 1,221 patients from Japan showed inferior OS with involvement of pleura, peritoneum, small intestine, adrenal

glands, testis, bone marrow, or blood [14], while a smaller study from Taiwan listed lung/ pleura, liver, lower urinary tract, and bone marrow as high-risk sites [15]. In contrast, a US registry-based analysis of 25,992 cases classified according to the primary site of origin found independently worse OS in DLBCL arising from the GI tract, respiratory system, and liver/pancreas, whereas extranodal lymphomas of head and neck, skin/soft tissue, and bone fared better than nodal disease [2]. Adjusting for stage, there was no significant difference in OS between DLBCL arising from the nodes, genitourinary tract, thyroid gland, or breast.

Considering limited prognostic power of clinical characteristics, recent attention has turned to molecular factors. Gene expression profiling (GEP) can distinguish the prognostically favorable germinal center B-cell (GCB), unfavorable activated B-cell (ABC), and intermediate unclassifiable signatures in DLBCL [16, 17]. Because GEP is not routinely available in clinical practice, the World Health Organization (WHO) allows distinction between GCB and ABC using immunohistochemistry for CD10, BCL2, and BCL6 (Hans algorithm), or similar schemas, despite their limited accuracy [1]. This cell-of-origin designation does not generally correlate with extranodal involvement [17], but the ABC signature is enriched in lymphomas originating from specific extranodal sites (Table 1). Furthermore, next-generation sequencing (NGS) has recently identified subtypes characterized by co-occurring point mutations or rearrangements in *MYD/CD79B* (MCD subtype), *BCL6/NOTCH2* (BN2 subtype), *NOTCH1* (N1 subtype), or *EZH2/BCL2* (EZB subtype) [18]. The MCD and N1 subtypes showed significantly worse PFS and OS compared with other ABC lymphomas, while the BN2 subtype (mostly of ABC origin) was prognostically favorable. In addition, multiple studies have reported poor prognosis in high-grade B-cell lymphoma with concurrent rearrangements of *MYC* and *BCL2* and/or *BCL6* genes ("double-hit" or "triple-hit" lymphoma), characterized by only 25–30% long-term survival after standard chemotherapy using rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP) [19–21]. Double-hit lymphomas (predominantly GCB) are separated from DLBCL in the 2016 WHO classification, but remain intermixed in published clinicopathologic observational series [1]. They involve extranodal sites in >60% of cases, predominantly through secondary spread to blood, bone marrow, CNS, or stomach/ intestine, whereas their prevalence among primary extranodal lymphomas has not been comprehensively described [22–24]. Additionally, DLBCL expressing both MYC and BCL2 by immunohistochemistry (termed "dual-expresser") has been associated with worse prognosis [25–29]. More recently, *TP53* mutations are increasingly recognized as a characteristic associated with chemotherapy resistance and poor survival, independent of the IPI or cell of origin, and other genomic biomarkers are being investigated [30–33].

CNS recurrence: risk assessment and prophylaxis

The overall risk of CNS recurrence in DLBCL is 2–5%, and has decreased after introduction of rituximab-based immunochemotherapy [34–36, 11]. Historically, CNS recurrence has been associated with highly proliferative tumors, stage IV or high-IPI disease, involvement of 2, or certain specific extranodal sites like the bone marrow, testicle, and paranasal sinuses, though without a clear consensus about who should receive CNS-directed prophylaxis [37–39]. A pooled analysis of 2,164 patients who immunochemotherapy on trials conducted by the German High-Grade Non-Hodgkin Lymphoma Study Group found

that age >60, elevated serum lactate dehydrogenase (LDH), poor performance status, advanced-stage disease, and involvement of kidneys or adrenals were independently associated with CNS recurrence [40]. Including involvement of 2 extranodal sites as an additional variable, the authors proposed the "CNS-IPI", with the 2-year risk of CNS recurrence varying from 0.8% (1 risk factor), to 2.9% (2–3 risk factors), and to 10.0% (4 risk factors). Of note, patients variably received intrathecal prophylaxis—most commonly those with marrow, testicular, epidural, or paranasal sinus involvement. Lack of molecular data and low number of specific extranodal cases limited more granular assessments. The CNS-IPI validation cohort from the British Columbia Cancer Agency (BCCA) additionally identified marrow, testes, orbit, or pericardium as high-risk sites. Importantly, 73% of CNS recurrences were intra-parenchymal, 26% leptomeningeal only, and 1% intraocular [41]. When applied to 984 participants from the randomized United Kingdom National Cancer Research Institute (UK NCRI) trial, the high-risk CNS-IPI group had 2-year CNS recurrence risk of 5.2%, with 81% of intra-parenchymal events [35]. Despite frequent CNS prophylaxis, relapses occurred in lymphomas involving paranasal sinuses (17%), breast (12%), kidneys/ adrenals (6%), and bone (5%), but not testis (0%). In the German RICOVER-60 trial, the incidence of CNS recurrence was 4.8%, with 65% of the events being intraparenchymal, 26% leptomeningeal, and 9% involving both compartments [34]. Another large international (UK, Australia, BCCA, Denmark) series of 1,532 patients staged with positron emission tomography (PET) confirmed that multiple extranodal sites and involvement of uterus or testis were associated with CNS recurrence [36]. Therefore, some experts offer CNS prophylaxis to all DLBCLs involving high-risk sites like testes, uterus, breast, or epidural bone lesions [42]. British guidelines recommend prophylaxis for those with elevated LDH and >1 extranodal site, or with testicular, breast, or epidural involvement [43], while the Spanish Lymphoma Group recommends it additionally for high CNS-IPI, double-hit lymphoma, and involvement of kidney or adrenal gland [44]. The US National Comprehensive Cancer Network (NCCN) guidelines acknowledge the uncertain efficacy of intrathecal or systemic prophylaxis, suggesting it in high CNS-IPI, HIV-associated, testicular, breast, or double-hit lymphoma [45].

Considering that high CNS-IPI identifies only 55% of patients who will experience CNS recurrence [40], there is an ongoing need to identify better biomarkers of risk. Two recognized high-risk populations are double-hit (13% risk) [20] and dual-expresser lymphomas (10% risk) [26]. Intrathecal prophylaxis is included in high-intensity protocols applied in double-hit lymphoma, like the dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R), but its value in preventing intraparenchymal recurrences is uncertain. In a multi-institutional retrospective series of 223 patients treated with DA-EPOCH-R, only 39% received CNS prophylaxis [46]. CNS relapses occurred in 5.8%, without any significant difference according to the administration of intrathecal therapy. Researchers from MD Anderson Cancer Center reported a higher rate of CNS recurrence after DA-EPOCH-R in CD5+ disease (33% versus 16%), which in 50% was associated with extranodal involvement at diagnosis, most commonly in the bone marrow (35%) [47]. CD5 positivity may thus be another marker of disseminated disease with high risk of CNS recurrence, reported as 8–11% in three other series [48–50]. Nevertheless, an unmet need persists to identify molecular mechanisms that drive

dissemination and homing of DLBCL cells to the CNS, and that could better define the population requiring prophylaxis. Some insight has emerged from the study of primary CNS lymphoma, which is characterized by predominance of the ABC subtype [51], presence of *MYD88/CD79B* mutations, as well as PD-1/PD-2 pathway alterations [52, 51, 53, 54]— features shared with testicular and certain other extranodal lymphomas. Preliminary data suggest that expression of molecules involved in B-cell adhesion and migration, including CXCR5/CXCL13 axis, CD44, and ITGA10, may also help predict the risk of CNS recurrence [55–57].

The optimal CNS prophylaxis approach remains to be prospectively delineated, and clinical practice largely relies on observational studies. Common strategies include intrathecal methotrexate (with or without cytarabine and/or hydrocortisone), or intravenous high-dose methotrexate [43]. Because of predominance of intra-parenchymal CNS recurrences, and lack of benefit to intrathecal treatment in several studies [34, 58–60], systemic approaches are increasingly favored [44, 61]. Published data suggest potential efficacy of methotrexate at 3–3.5 g/m^2 administered either concurrently with R-CHOP (on day 15 of cycles 2, 4, and 6) [62], or after its completion [63]. Some studies used sequential systemic methotrexate and cytarabine-based consolidation [64, 65]. However, further prospective evaluation is needed to determine the true risk/benefit ratio of these approaches.

Prognosis of extranodal DLBCL arising from specific anatomical sites

Craniofacial sites

Historically, DLBCL located in the orbit or paranasal sinuses has been associated with poor prognosis and a high risk of CNS relapse, leading to a recommendation for intrathecal prophylaxis [66, 67]. However, a recent analysis of 290 patients enrolled in German High-Grade Non-Hodgkin Lymphoma Study Group trials (including all craniofacial sites—orbit, paranasal sinuses, and oral cavity, 70% stage IE/IIE) showed a significantly decreased risk of CNS recurrence after rituximab-based chemoimmunotherapy (1.6% versus 4.2%), which was not influenced by prophylaxis (4.2% with versus 2.3% without, P=.98) [68]. Still, 64% of patients with CNS recurrence had paranasal sinus, and 14% orbital involvement, possibly due to anatomic proximity that facilitated direct invasion. Administration of consolidative RT was not associated with better event-free or OS, and overall prognosis was excellent. Consistently, a Korean study showed only one CNS recurrence among 80 cases of in sinonasal DLBCL (with 30% rate of intrathecal prophylaxis), and no difference in survival with RT, confirming that in the rituximab era neither RT nor routine intrathecal therapy are necessary (Table 2) [69]. Little is known about specific molecular features of DLBCL of the head and neck, except that 80% are non-GCB, with frequent gain of 1q31 (containing *RGS1*, 55%) and loss of 9p21.3 (containing *CDKN2A*, 64%) [70]. Extranodal head/neck location was associated with a better prognosis than nodal DLBCL in population-derived data, but not in clinicopathologic series [2, 14, 4, 68]. Importantly, Waldeyer's ring is considered a primary nodal site and does not require special therapeutic considerations [71].

Thyroid gland

DLBCL constitutes 50% of primary thyroid lymphomas, and like the second common marginal zone (MZL) subtype, it is strongly associated with autoimmune (Hashimoto) thyroiditis [72, 73]. Ninety percent of thyroid DLBCLs present at stage IE/IIE. Consequently, they have favorable prognosis similar to stage-matched nodal DLBCL [2, 14, 10]. Specific molecular data are sparse, but most thyroid lymphomas are of the GCB subtype, with rare *MYC, BCL2*, or *BCL6* rearrangements, and no *MYD88* mutations [74]. Thyroid DLBCL can be treated with immunochemotherapy alone, or with the combination of chemotherapy and RT. Surgery is no longer used as a standard modality for thyroid lymphoma, and CNS recurrences are unusual. Historical series have suggested better outcomes after consolidative RT [75], but data from the R-CHOP era are lacking. Patients with thyroid DLBCL have received immunochemotherapy alone on contemporary clinical trials [8].

Lung and mediastinum

Primary pulmonary DLBCL is exceptionally rare, and may occur as transformation from extranodal MZL of the mucosa-associated lymphoid tissue (MALT), the predominant (up to 90%) lymphoma in this organ [76]. Pleural involvement is also typically encountered in disseminated disease. Primary mediastinal (thymic) large B-cell lymphoma (PMBCL) constitutes a separate WHO entity with unique clinical, epidemiologic and molecular features [1]. It is characterized by PD-1 overexpression, constitutional JAK-STAT activation, and subtype-specific GEP [77]. Historically treated with RCHOP and consolidative RT, PMBCL has now shown excellent outcomes after DA-EPOCH-R chemotherapy alone, obviating the need for RT in the predominantly young, female population affected by this disease [78–80]. The low risk of CNS recurrence does not warrant prophylaxis.

GI tract

One third of extranodal DLBCL cases occur in the GI tract, making it the most common primary extranodal site [2, 15]. The enhanced IPI considers it high risk, but does not differentiate primary from secondary involvement, or liver from stomach/intestine [9]. Careful histopathologic evaluation is needed to rule out Burkitt or mantle cell lymphoma, diseases often involving the intestine. The GI tract is also a common site of dissemination for double-hit lymphomas [22, 23]. Meanwhile, survival of localized gastric DLBCL appears to be excellent in recent series, independently of cell of origin or MYC/BCL2 dual-expresser status, with no reported CNS recurrences and no difference in outcomes with the use of surgery or RT [81, 82]. Some provocative studies have reported regression of gastric DLBCL after eradication of *Helicobacter pylori* (found in about 50% of cases), akin to gastric MALT lymphoma [83–85]. In one analysis, 33% of GI lymphomas were non-GCB, whereas *MYD88* or *CD79B* mutations were identified in only <5% [86]. In an examination of 49 cases from Japan, the non-GCB phenotype was seen in 50%, but *MYD88* mutation only in 6% [87]. Another series examining genetic profiles of GI DLBCL found only 3% rate of $EZH2^{Y641}$ mutation and 17% rate of *BCL2* rearrangements in the GCB subgroup (none in the ABC subgroup), suggesting a low prevalence of the EZB genotype [88, 18]. In contrast, liver involvement occurs usually in disseminated cases, thus contributing to poor

prognosis [9]. Primary hepatic DLBCL may be associated with hepatitis C infection (25–60%), and may have a better prognosis than in cases of secondary involvement, although data are too sparse to make confident conclusions [89–91].

Kidney and adrenal glands

Kidney involvement is associated with stage IV disease in over 90% and a very poor survival in two recent series [92, 93]. The CNS-IPI designates kidney or adrenal involvement as singularly high-risk [40]. Even when studied as an additional factor in otherwise high-risk subtypes, secondary kidney/adrenal involvement conveys a higher rate of CNS recurrence. For example, in a cohort of testicular lymphomas, the HR for CNS relapse was 17.9 (95% confidence interval [CI], 3.8–84.1) when kidney/adrenal spread was present [94]. Primary adrenal lymphomas are mostly described by case reports owing to their exceptional rarity [95]. They exhibit an aggressive course, with salient features of adrenal insufficiency and frequent CNS involvement [96]. Many cases of adrenal lymphomatous tumors reveal presence of intravascular lymphoma, which has a predilection for dissemination into CNS, skin, or endocrine organs, and often has *MYD88* and *CD79B* mutations [97, 98, 1].

Testis

Primary testicular DLBCL develops in an immune-privileged site behind the blood-testis barrier and has a molecular profile very similar to primary CNS lymphoma, including $MYD88^{L265P}$ (70–80%), *CD79B* and *CDKN2A* (88%) mutations, as well as alterations in the *PD-1/PD-2* loci (50%) [53, 99, 100]. Most cases exhibit the ABC phenotype, and likely high prevalence of the newly recognized MCD genomic subtype [18, 101]. Because of the inherent risk of CNS or contralateral testicular (20%) relapse, the current standard of care for testicular DLBCL includes routine CNS prophylaxis and contralateral testicular RT, although only about half of patients receive RT in clinical practice [102, 101, 103, 104]. Rituximab has improved survival, yet it has not reduced the rates of CNS recurrence [94, 10]. A recent international retrospective of 280 primary testicular lymphomas found that 77% were stage IE or IIE [101]. Only 34% of patients received CNS prophylaxis, which did not decrease the incidence of CNS recurrence (21% at 10 years). A BCCA cohort reported 25% rate of CNS recurrence at median time of 2.3 years, with half of all relapses involving the CNS [94]. This risk appears independent of clinical stage. Interestingly, patients with early stage were more likely to experience an intra-parenchymal recurrence (90%), whereas those with advanced stage had more leptomeningeal recurrences (83%, of which 42% had concurrent parenchymal involvement) [94].

Breast

Primary breast lymphoma accounts for only 2% of extranodal lymphomas, and presents with a MALT component in 5% of cases [105]. Both clinical retrospectives and population-based studies report >90% prevalence of stage IE/IIE disease, and 5-year OS of 75–80% [106–108]. Clinicopathologic series consistently show predominance of the non-GCB phenotype (60–90%) [109, 107], as well as high prevalence of *MYD88* (58–70%) and *CD79B* (36–40%) mutations [110, 111]. Interestingly, these features resemble testicular lymphoma, and breast lymphomas have recently been also recognized to have a notable predilection for CNS recurrence [107, 108]. These data are highlighted in the current NCCN guidelines and may

support CNS prophylaxis [45]. Whether the risk of CNS recurrence correlates with the non-GCB phenotype or the *MYD88/CD79B*-mutated genotype remains to be investigated.

Uterus

A recent large international study found that 4% (27 of 678) of DLBCLs in women involve the uterus or ovary [112]. All cases of ovarian involvement occurred in the context of disseminated lymphoma, whereas 18% of those with uterine involvement were early-stage. Accounting for the IPI, ovarian involvement was not prognostic for PFS or OS outcomes, whereas uterine DLBCL showed worse PFS (HR, 2.28; 95%CI, 1.23–4.22) and OS (HR, 2.34; 95%CI, 1.21–4.52) than other lymphomas. Moreover, a 44% cumulative incidence of CNS relapse at 4 years was reported in uterine DLBCL (and no recurrences in ovarian lymphoma), which would classify it as a high-risk site. Similarly, in a series of 6 Chinese patients with DLBCL of the female genital tract, 4 (including 3 uterine/cervical) relapsed in the CNS [113]. Five of the 7 studied uterine lymphomas had the non-GCB phenotype and 4 had the $MYD88^{L265P}$ mutation [110]. Although confirmatory research is needed, DLBCL of the uterus may be genetically and clinically similar to breast and testicular lymphoma, including the risk of CNS recurrence.

Skin

Unlike the indolent cutaneous MZL and follicle center lymphomas, primary cutaneous DLBCL, leg-type (PCDLBCL-LT) is aggressive, although rituximab has significantly improved survival outcomes [114, 115]. It classically, though not exclusively, presents as rapidly growing tumors on the legs of women over age 60 [1]. PCDLBCL-LT has a strong IRF4/MUM1 expression, ABC phenotype by GEP, and high prevalence of the $MYD88^{L265P}$ mutation [116–119]. In a French series of 13 patients who had a PCDLBCL-LT that relapsed in the CNS, 5 out of 6 tested cases had the *MYD88* mutation [120]. However, the overall reported incidence of CNS recurrence in PCDLBCL-LT varies between 4 and 13%, limiting the ability to recommend prophylaxis without more data [121, 120, 119]. The unique histopathologic and molecular features can help distinguish PCDLBCL-LT from DLBCL with secondary skin involvement, which is disseminated and may also have an unfavorable clinical course.

Bone

DLBCL involving bones as the only site of disease has a different prognosis from cases with a secondary bone or bone marrow dissemination. In a series of 161 patients with stage I/II primary bone DLBCL from the International Extranodal Lymphoma Study Group (IELSG), predating the use of PET or rituximab, 87% had stage I disease, and outcomes were similar with or without consolidative RT after chemotherapy (5-year PFS 74% versus 67%, *P*=.47) [122]. The risk of CNS relapse was low (2.5%), despite only 6 patients receiving prophylaxis. A separate analysis of multifocal (polyostotic) bone lymphoma showed better PFS (56% versus 34%) and OS (74% versus 36%) compared with stage IV DLBCL with secondary skeletal dissemination, and suggested better survival with the use of RT [123]. Researchers from MD Anderson described 102 patients with primary bone DLBCL (56% stage I/II), who had 5-year PFS of 80% after RCHOP chemotherapy, also improved by consolidative RT, at least in stage I/II disease [124]. Similarly, an analysis of prospective

trials from Germany suggested better PFS with RT [125]. The overall favorable prognosis of bone lymphoma can be partly ascribed to a GCB, centrocyte-like GEP signature [126]. Of note, *MYD88* mutations are absent in primary bone lymphoma [127]. French investigators reported 80% OS at 4 years in bone lymphoma, classifying 65% of cases as GCB [128]. In contrast, a series from the Moffitt Cancer Center reported 5-year PFS of 75% for unifocal, but only 14% for multifocal bone DLBCL (*P*=.002), with OS of 92% and 47% (*P*<.001), respectively [45]. Four out of 53 patients (3 with multifocal lesions, 2 with spinal involvement) experienced a CNS recurrence, highlighting the need for further research distinguishing unifocal, multifocal, and secondary bone DLBCL, as well as the differential CNS risk associated with craniospinal or long-bone lesions.

Summary

Primary extranodal large B-cell lymphomas are common and very heterogeneous in their features and outcomes. Recent molecular data have begun to clarify their divergent clinical behavior (Figure 1). The peculiar, stage-independent risk of CNS spread in testicular, breast, uterine, and possibly PCDBLCL-LT, may be related to prevalent MCD (*MYD88/CD79B*-mutated) genomic subtype in these lymphomas. It remains to be seen how this genotype might facilitate invasion of the CNS parenchyma, and whether therapies targeting the B-cell receptor or NF-κB signaling pathways could lower the risk. Some sites of extranodal involvement, like kidney/adrenals, lung/pleura, or ovary, almost always indicate disseminated disease with a high propensity to invade the bone marrow and leptomeningeal compartments, particularly in double-hit lymphoma. Conversely, unifocal bone, craniofacial, thyroid, or gastric DLBCL show a relatively favorable prognosis with standard immunochemotherapy. Their risk of CNS recurrence might be largely driven by potential local invasion due to anatomic proximity when epidural, orbital, or skull involvement is present, thus requiring a case-by-case approach to prophylaxis. Future studies can help clarify the relationship between extranodal DLBCLs and their indolent MALT counterparts, and whether the favorable behavior of some ABC-like lymphomas (e.g. in the stomach or craniofacial sites) might be hypothetically explained by less aggressive genotypes (e.g. the *BCL6/NOTCH2* subtype). Finally, prospective clinical studies are needed to establish consistent, biologically-driven strategy for CNS prophylaxis in DLBCL that could effectively prevent parenchymal recurrences.

Acknowledgements

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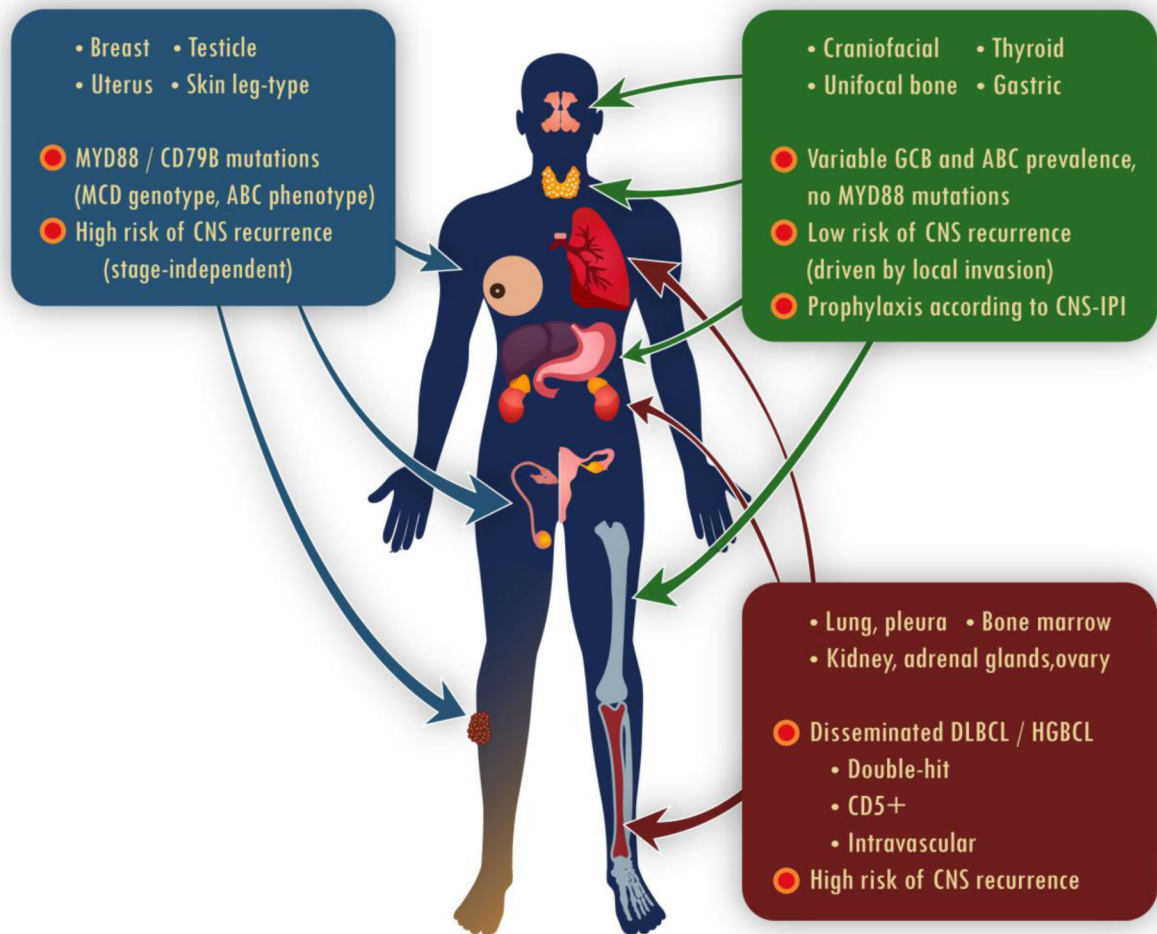
Figure 1.
Mechanisms associated with variable prognosis and risk of CNS recurrence in extranodal DLBCL of different anatomical origin.

ABC: activated B-cell subtype; CNS: central nervous system; DLBCL: diffuse large B-cell lymphoma; GCB: germinal center B-cell subtype; HGBCL: high-grade B-cell lymphoma

Table 1.

Molecular and prognostic features of specific extranodal diffuse large B-cell lymphomas, based on recent observational studies of patients treated with immunochemotherapy.

Extranodal site	Non-GCB	EFS/PFS	OS	CNS recurrence	Other characteristics
Craniofacial[68–70]	82%	60–79%	65–87%	2%	• CNS prophylaxis no longer routinely recommended
Thyroid[74, 73]	22–33%	79%	85%	NR	• *MYD88* mutations are absent
Mediastinum (PMBLC)[79]	100%[a]	86%	95%	3%	• Outcomes after DA-EPOCH-R
GI tract[86, 85, 81, 82, 87]	33–50%	77–89%	83–90%	NR	• *MYD88 and CD79* mutations rare in non-GCB • *EZH2* mutations and *BCL2* translocations rare in GCB
Kidney[92, 93]	NR	40–44%	43–52%	36–41%	• 95% have stage III/IV disease • Intravascular lymphoma may be present
Testis[101, 94]	84%	51–56%	60–68%	19–25%	• *MYD88/CD79B* mutations in 70–80%
Breast[110, 107, 111, 108, 109]	60–90%	61–66%	75–82%	16–24%	• *MYD88* mutations present in 60–70% • *CD79B* mutation present in 36–57%
Uterus[112, 110]	63%	26%	33%	44%	• 82% have stage III/IV disease • 50% *MYD88* mutation in a small study
Skin, leg-type[118, 119]	100%	NR	52%	13%	• *MYD88* mutations in 60–80%
Bone[126, 45, 128, 124, 125]	10–35%	47–80%	80–93%	7%	• Multifocal disease has higher mortality and risk of CNS recurrence (particularly craniospinal) • *MYD88* mutations are absent

[a] PMBCL has a specific gene expression profile

DA-EPOCH-R: dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab; EFS: event-free survival; NR: not reported; OS: overall survival; PFS: progression-free survival; PMBCL: primary mediastinal large B-cell lymphoma; RT: radiation therapy; y: year.

Table 2.

Outcomes with or without consolidative radiation therapy in select extranodal diffuse large B-cell lymphomas.

Extranodal site/reference	N	Rituximab (%)	RT (%)	EFS/PFS		OS	
				Univariate	Adjusted HR(95%CI)	Univariate	Adjusted HR(95%CI)
Craniofacial							
Murawski, 2014[68]	202	29%	72%	3y EFS 79% w/o RT, 79% with RT, *P*=.84	1.0 (0.5–2.0)	3y 88% w/o RT, 86% with RT, *P*=.35	1.5 (0.7–3.3)
Lee, 2015[69]	80	100%	26%	5y PFS 56% w/o RT 65% with RT, *P*=.34		5y 65% w/o RT, 65% with RT, *P*=.98	
GI tract							
Sohn, 2012[82]	93	59%	15%	NR, NS		NR, NS	
Testis							
Deng, 2016[101]	252	64%	39%	NR, *P*=.012		NR, *P*=.027	
Ho, 2017[103]	120	53%	70%	5y PFS 30% w/o RT 65% with RT, P=.001	0.39 (0.24–0.64)	5y 52% w/o RT 73% with RT, P=.065	0.47 (0.28–0.83)
Breast							
Hosein, 2014[107]	76	69%	65%	NR, NS		NR, NS	
Bone							
Held, 2014[125]	161	21%	83%	3y EFS 36% w/o RT, 75% with RT, *P*<.001	0.3 (0.2–0.6)	3y71% w/oRT, 86% with RT, *P*=.06	0.5 (0.2–1.2)
Wu, 2014[45]	53	81%	49%	5y PFS 30% w/o RT, 80% with RT, *P*=.004	NS	5y71% w/oRT, 96% with RT, *P*=.021	NS
Tao, 2015[124]	102	72%	66%	5y PFS 63% w/o RT, 88% with RT, *P*=.007	0.14 (0.03–0.72)	5y 68% w/o RT, 91% with RT, *P*=.006	0.30 (0.09–1.01)
Pilorge, 2016[128]	76	100%	20%	NR, NS		NR, NS	

EFS: event-free survival; HR: hazard ratio; NR: not reported; NS: not significant; OS: overall survival; PFS: progression-free survival; RT: radiation therapy; w/o: without; y: year