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Prognostic impact of abdominal lymph node involvement in diffuse large B-cell lymphoma

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Abstract

Objective: The prognostic value of site of nodal involvement in diffuse large B-cell lymphomas (DLBCL) is mainly unknown. We aimed to determine the prognostic significance of nodal abdominal involvement in relation to tumour cell markers and clinical characteristics of 249 DLBCL patients in a retrospective single-centre study.

Methods: Contrast-enhanced computed tomography (CT) of the abdomen and thorax revealed pathologically enlarged abdominal lymph nodes in 156 patients, while in 93 patients there were no pathologically enlarged lymph nodes in the abdomen. In 81 cases, the diagnosis of DLBCL was verified by histopathological biopsy obtained from abdominal lymph node.

Results: Patients with abdominal nodal disease had inferior lymphoma-specific survival ($P = .04$) and presented with higher age-adjusted IPI ($P < .001$), lactate dehydrogenase ($P < .001$) and more often advanced stage ($P < .001$), bulky disease ($P < .001$), B symptoms ($P < .001$), and double expression of MYC and BCL2 ($P = .02$) compared to patients without nodal abdominal involvement, but less often extranodal involvement ($P < .02$). The worst outcome was observed in those where the abdominal nodal involvement was verified by histopathological biopsy.

Conclusion: Diffuse large B-cell lymphomas patients with abdominal nodal disease had inferior outcome and more aggressive behaviour, reflected both in clinical and biological characteristics.

KEYWORDS

abdominal lymph node, BCL2, DLBCL, MYC, survival

1 | INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common high-grade lymphoma and is a heterogeneous disease with different clinical, biological and genetic characteristics. The clinical presentation of DLBCL is often nodal, but a large proportion of patients have extranodal disease.

Distinct sites of extranodal DLBCL have been studied extensively and revealed immunophenotypic and genetic differences as well as diverse outcomes.[1] However, the prognostic impact of site of nodal involvement remains to be clarified.[2] Infradiaphragmatic site of lymph node involvement in classical Hodgkin lymphoma is associated with different histological presentations and inferior outcomes.[3,4]

The tumour cells in DLBCL are considered to be derived from activated B-cells (ABC) or germinal centre B-cells (GCB) based on gene expression profiling (GEP).[5] Several immunohistochemical algorithms have been developed as substitutes and applied with varying concordance with GEP.[6-8] The Hans algorithm is the most commonly used algorithm and has a reasonable correlation with GEP,[6] based on the immunohistochemical staining results of three proteins: CD10, BCL-6 and MUM1.

In addition, other tumour cell markers have prognostic impact in DLBCL. High expression of P53 and double expression of MYC and BCL2 are associated with inferior outcome in DLBCL.[10,11] Gene rearrangements of MYC and BCL2 and/or BCL6, referred to as "double-hit" lymphomas, are recognised as a separate entity with dismal outcome according to the 2016 WHO classification of Tumours of Haematopoietic and Lymphoid Tissues.[9]

In this study, we evaluated clinical characteristics and tumour cell markers in DLBCL patients with the aim to characterise particularly those with abdominal lymph node involvement taking into consideration the site of lymph nodes involved and study their association with clinical outcome.

2 | MATERIALS AND METHODS

2.1 | Patients

This study retrospectively retrieved 249 patients (age range 26-86 years) diagnosed with de novo DLBCL between 2002 and 2016 at the Department of Clinical Pathology, Uppsala University Hospital, which is a referral centre for the Uppsala Health Care region. Patients with immunodeficiency-associated lymphoproliferative disorders (PTLD) were excluded. Only patients treated with rituximab, cyclophosphamide, adriamycin, vincristine and prednisone (R-CHOP) or R-CHOP-like regimens (R-CHOP14, R-CHOP21 and R-CHOEP) were included in the study. All clinical data were retrieved from patient records. Age-adjusted international prognostic index (aa-IPI) was used to define the different risk groups with one point for each: (a) Ann Arbor stage III-IV; (b) elevated serum lactate dehydrogenase (LDH); and (c) ECOG performance status 2-3, where 0-1 is considered to be low risk and 2-3 is considered to be high risk, in accordance with National Swedish guidelines.

Formalin-fixed, paraffin-embedded (FFPE) diagnostic biopsies were reviewed by two haematopathologists (RMA, AAM). Tumours were classified as DLBCL according to the 2008 WHO classification.[9]

This study was approved by the Regional Ethical Review Board in Uppsala, Sweden (EPN 233/2014).

2.2 | Radiological evaluation

All patients were investigated using a contrast-enhanced computed tomography (CT) of the thorax and abdomen. PET was not performed in the majority of patients included. The images were independently reviewed by a radiologist (PG) with 6 years of experience, on a picture archiving and communication system (PACS). On axial images, the long axis and short axis of abdominal lymph nodes were measured. They were defined as pathological abdominal lymphadenopathy if two or more of them had a long axis ≥ 15 mm[12] and a short axis >10 mm,[13] and as "bulky" if the single lymph node or the conglomerate mass of lymph nodes was greater than 75 mm in diameter.[14,15] According to the localisation of the bulky mass, the involvement was defined as "abdominal" if the bulky disease was situated below the diaphragm.

2.3 | Immunohistochemistry

Immunohistochemical stainings were performed on FFPE tissue using fully automated protocols (DAKO Autostainer Link 48). Staining protocols with antibodies to MYC (clone Y69; Abcam), BCL-2 (clone 124; DAKO), BCL-6 (clone PG-B6p; DAKO), Ki-67 (MIB-1; DAKO), MUM-1(clone MUM1p; DAKO), CD10 (clone 56C6; DAKO) and p53 (DO-7; DAKO) were performed. The estimation of positive staining for CD10, BCL-6 and MUM-1 was based on the Hans algorithm. Cut-off values of 70% and 40% were used for BCL2 and MYC, respectively, as previously described.[16]

2.4 | Statistical analyses

Overall survival (OS) was calculated from the date of diagnosis to the date of death as a result of any cause or to the date of last follow-up. Lymphoma-specific survival (LSS) was calculated from the date of diagnosis to the date of death as a result of lymphoma or to the date of last follow-up, and patients who died of other causes than lymphoma were censored. Progression-free survival (PFS) was calculated from the date of diagnosis to the date of disease progression, death due to any cause or date of last follow-up. Survival outcomes were estimated by the Kaplan-Meier method and compared using the log-rank test and Cox proportional hazards regression. Univariate and multivariate Cox proportional hazards regression models that included biological and clinical variables of prognostic impact were conducted. Cases with missing information on at least one variable were omitted from the multivariate analyses. Clinical characteristics were compared between subgroups using the chi-square test. A P-value < .05 was considered to be statistically significant. Statistical analyses were performed using R Studio 1.1.383 (www.r-project.org).

3 | RESULTS

3.1 | Descriptive data

Radiological examination revealed pathologically enlarged lymph nodes in the abdomen in 156/249 (63%) of the patients. Patients with abdominal lymph node involvement (n = 156) more often had

TABLE 1 Clinical characteristics and tumour cell markers in 249 DLBCL patients who were reviewed radiologically and divided into patients with abdominal lymph node involvement and patients with no abdominal lymph node involvement

Parameters	Whole cohort	Abdominal lymph node involvement n (%)	No abdominal lymph node involvement n (%)	*P*-value[b]
All patients	249 (100)	156 (100)	93 (100)	
Age				
<60 years	67 (27)	35 (22)	32 (34)	.056
≥60 years	182 (73)	121 (78)	61 (66)	
Gender				
Male	150 (60)	95 (61)	55 (59)	.89
Female	99 (40)	61 (39)	38 (41)	
Bulky				
Yes	60 (24)	51 (33)	9 (10)	**<.001**
No	186 (75)	102 (65)	84 (90)	
Missing	3 (1)	3 (2)	0 (0)	
B symptoms				
Yes	102 (41)	78 (50)	24 (26)	**<.001**
No	120 (48)	60 (38)	60 (68)	
Missing	27 (11)	18 (12)	9 (6)	
Age-adjusted IPI				
0-1	111 (45)	46 (29)	65 (70)	**<.001**
2-3	126 (50)	101 (65)	25 (27)	
Missing	12 (5)	9 (6)	3 (3)	
Stage				
I-II	97 (39)	35 (22)	62 (67)	**<.001**
III-IV	142 (57)	113 (72)	29 (31)	
Missing	10 (4)	8 (5)	2 (2)	
LDH				
Normal	88 (35)	39 (25)	49 (53)	**<.001**
High	148 (60)	107 (69)	41 (44)	
Missing	13 (5)	10 (6)	3 (3)	
Immunophenotype				
GCB	114 (46)	78 (50)	36 (39)	.22
Non-GCB	80 (32)	47 (30)	33 (35)	
Missing	55 (22)	31 (20)	24 (26)	
Double expression of MYC and BCL2				
Negative	108 (43)	64 (41)	44 (47)	**.02**
Positive	47 (19)	38 (24)	9 (10)	
Missing	94 (38)	54 (35)	40 (43)	
Ki67				
<70%	69 (28)	38 (24)	31 (33)	.10
≥70%	146 (59)	99 (63)	47 (51)	
Missing	34 (13)	19 (12)	15 (16)	
P53				
<50	98 (40)	61 (39)	37 (40)	.90
≥50	21 (8)	14 (9)	7 (8)	
Missing	130 (52)	81 (52)	49 (52)	

(Continues)

TABLE 1 (Continued)

Parameters	Whole cohort	Abdominal lymph node involvement n (%)	No abdominal lymph node involvement n (%)	*P*-value[b]
Extranodal				
Yes	97 (39)	55 (35)	48 (52)	**.02**
No	152 (61)	101 (65)	45 (48)	
Extranodal abdominal				
Yes	37 (15)	27 (17)	10 (11)	.22
No	212 (85)	129 (83)	83 (89)	

[a]All significant *P*- values are in bold.

[b]Chi-square or Fisher's exact test for abdominal lymph node involvement (n = 156) versus no abdominal lymph node involvement (n = 93).

bulky disease, B symptoms, higher aa-IPI, higher stage and more frequently double expression of MYC and BCL2 compared to patients with no lymph node involvement in the abdomen (n = 93). There was abdominal extranodal involvement of lymphoma in the gastrointestinal tract (n = 21), liver (n = 5) and pancreas (n = 1) in patients for whom radiological examination revealed pathologically enlarged lymph nodes in the abdomen. Patients without abdominal lymph node involvement more often had extranodal disease (Table 1). There were no significant differences in rates of high age, GCB and non-GCB, high Ki67 or high P53 between patients with abdominal lymph node involvement and patients without abdominal lymph node involvement (Table 1).

In 81/156 patients, abdominal nodal disease was verified by histopathological biopsy and there were no differences between patients with histopathologically proven abdominal nodal disease and patients with only radiological abdominal nodal disease regarding age, bulky disease, B symptoms, aa-IPI, stage, GCB and non-GCB, high Ki67, high P53 and double expression of MYC and BCL2 (data not shown).

3.2 | Survival

Patients with abdominal lymph node involvement had significantly inferior LSS (HR of 1.79 (95% CI: 1.01-3.17), *P* = .04) compared to patients without abdominal lymph node involvement, while there were no significant differences in OS (HR of 1.47 (CI: 0.96-2.25), *P* = .08) or PFS (HR of 1.41 (CI: 0.93-2.14), *P* = .1) between these two groups (Table 2) (Figure 1).

TABLE 2 Relative risk of overall, lymphoma-specific and progression-free survival estimated as hazard ratio (HR) with 95% confidence interval (CI) and *P*-values among DLBCL patients by putative prognostic factors in DLBCL patients

	Number of patients[b]	Overall survival HR: 95% CI, *P*-value	Lymphoma-specific survival HR: 95% CI, *P*-value	Progression-free survival HR: 95% CI, *P*-value
DLBCL with abdominal lymph node involvement vs no abdominal lymph node involvement	248	1.47:0.96-2.25, 0.08	**1.79:1.01-3.17, 0.043**	1.41:0.93-2.14, 0.10
Age ≥ 60 years	248	**4.41:2.29-8.49, <0.001**	**2.51:1.23-5.09, 0.01**	**4.06:2.17-7.61, <0.001**
Male gender	248	1.16:0.77-1.73, 0.48	1.28:0.75-2.17, 0.36	1.28:0.85-1.90, 0.23
Bulky	245	1.11:0.70-1.77, 0.66	1.53:0.87-2.69, 0.14	1.04:0.66-1.65, 0.86
B symptoms	221	1.44, 0.95-2.20, 0.09	**1.67:0.96-2.90, 0.07**	1.41:0.93-2.13, 0.102
Age-adjusted IPI ≥ 2	236	**1.53:1.01-2.31, 0.046**	**1.95:1.12-3.40, 0.02**	1.33:0.90-1.99, 0.16
Stage ≥ III	238	1.26:0.83-1.91, 0.29	1.41:0.81-2.45, 0.22	1.17:0.78-1.76, 0.44
High LDH	235	**1.60:1.02-2.50, 0.04**	**2.72:1.41-5.26, 0.003**	1.43:0.93-2.19, 0.099
Activated B-cell phenotype non-GCB[c]	193	0.76:0.48-1.21, 0.25	0.74:0.40-1.40, 0.36	0.80:0.51-1.25, 0.32
Double expression of MYC and BCL2	154	**1.98:1.15-3.41, 0.01**	**3.69:1.69-8.05, 0.001**	**1.95:1.16-3.29, 0.01**
Ki67 ≥ 70%	214	1.55:0.97-2.49, 0.07	1.62:0.84-3.12, 0.15	1.58:0.996-2.51, 0.052
P53 ≥ 50%	119	**3.19:1.70-5.97, <0.001**	**3.96:1.69-9.31, 0.002**	**2.90:1.56-5.38, <0.001**
Extranodal	248	0.82:0.55-1.23, 0.34	0.66:0.38-1.13, 0.13	0.84:0.57-1.25, 0.39
Extranodal abdominal	248	1.02:0.59-1.74, 0.95	0.71:0.32-1.57, 0.40	0.94:0.55-1.60, 0.82

[a]All significant *P*- values are in bold.

[b]Number of cases with information enabling evaluation of survival, including cases with abdominal lymph node involvement verified by contrast-enhanced computed tomography, and in patients without abdominal lymph node involvement confirmed by contrast-enhanced computed tomography.

[c]According to the Hans algorithm.

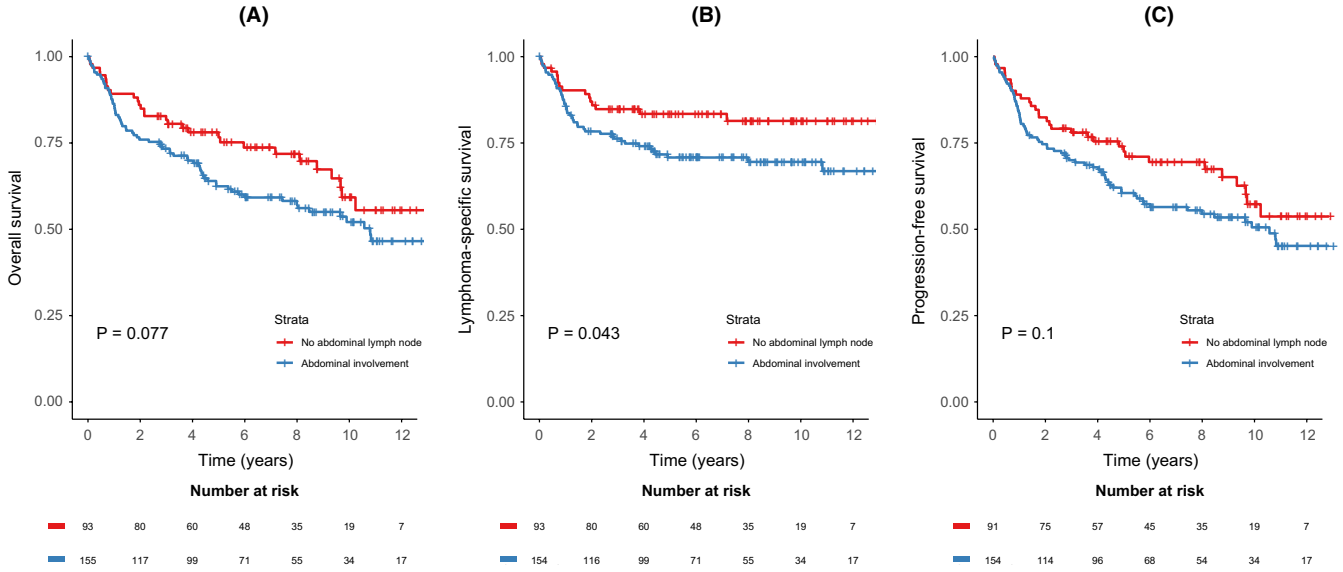

FIGURE 1 A, Overall survival, B, lymphoma-specific survival and C, progression-free survival in patients with abdominal lymph node involvement (n = 156) versus patients without abdominal lymph node involvement (n = 93)

Patients with histopathologically proven abdominal nodal disease had significantly inferior OS (HR of 1.79 (95% CI: 1.11-2.87), *P* = .02), LSS (HR of 2.43 (95% CI: 1.32-4.47), *P* = .004) and PFS (HR of 1.76 (95% CI: 1.11-2.78), *P* = .02) compared to patients with no abdominal lymph node involvement (Table S1).

In multivariate analyses, all significant and borderline significant variables from the univariate analyses were included and only high P53 remained to be statistically significantly associated with inferior OS (HR 3.08:95% CI: 1.45-6.55, *P* = .003) and LSS (HR: 3.66:95% CI: 1.29-10.43, *P* = .01), while high P53 (HR: 2.58:95% CI: 1.28-5.19, *P* = .008) and age ≥ 60 years (HR: 4.90:95% CI: 1.69-14.20, 0.003) remained as statistically significant prognostic factors associated with inferior PFS.

4 | DISCUSSION

We identified DLBCL patients with abdominal lymph node involvement as a group associated with more advanced disease and inferior survival outcome compared to patients without abdominal lymph node involvement. However, abdominal lymph node involvement did not remain as an independent prognostic factor in multivariate survival analyses. Thus, the inferior survival outcome (LSS) in DLBCL patients with abdominal lymph node involvement in our study might be explained by their association with clinical variables related to dismal outcome, including high age, high LDH, B symptoms, bulky disease, high aa-IPI and advanced stage.

In addition, DLBCL patients with abdominal lymph node involvement had a higher frequency of double expression of MYC and BCL2 compared to patients without lymph node involvement in the abdomen. DLBCL with double expression of MYC and BCL2; the so-called Double Expresser Lymphoma (DEL) has a distinct clinical phenotype with a dismal survival outcome, but it is not yet defined as a separate lymphoma entity.[9] Patients with DEL have higher median age and are more likely to have poor performance status, advanced stage, higher Ki67, intermediate/high risk IPI scores and an inferior complete response rate to R-CHOP chemotherapy compared to DLBCL patients without double expression of MYC and BCL2.[11] In the whole cohort, DEL and high expression of P53 were associated with inferior outcome. The negative prognostic impact of P53 and DEL has previously been confirmed by others.[10,11] In multivariate analysis, high expression of P53 was an independent negative prognostic indicator, which is in line with previous studies.[10,17] However, there was no difference in the expression of P53 in DLBCL patients with abdominal lymph node involvement compared to patients without lymph node involvement in the abdomen. Nor were there any differences in outcome regarding GCB or non-GCB phenotypes, which has also been shown by others.[18] However, other studies have found that patients with non-GCB have an inferior survival outcome compared to patients with GCB.[19] The prognostic impact of bulky disease in DLBCL has declined since the introduction of rituximab in the treatment of DLBCL.[20,21] In our study, DLBCL patients with abdominal lymph node involvement had a higher frequency of bulky disease than patients without lymph node involvement in the abdomen, but the bulky disease per se was not associated with worse prognosis in the whole cohort.

Interestingly, we found a group of patients where abdominal nodal involvement was verified by histopathological biopsy to have a significantly worse outcome (OS, LSS and PFS) compared to patients without abdominal lymph node involvement. The reason why patients underwent biopsy from abdominal lymph nodes might be clinical suspicion that the enlarged lymph nodes in the abdomen represented the most aggressive part of the disease.

However, there are many factors that determine the site of biopsy localisation in DLBCL patients, such as stage, anatomical region and presence of disease available for a surgical lymph node biopsy (or core needle biopsy only). Thus, it is difficult to evaluate the clinical decision for biopsy localisation in every patient. We believe that the biological characteristics of abdominal nodal engagement of DLBCL are not well investigated, supposedly due to difficulties performing biopsies of enlarged retroperitoneal lymph nodes localised close to large vessels. Further evaluation of biological and genetic alterations is required to explore the accurate explanation for their relation to clinical variables associated with poor prognosis of this group.

^{18}F-FDG PET-CT is recommended as the gold standard radiological examination for staging and assessment of treatment response in lymphoma.[22] However, abnormal uptake by causes other than lymphoma should be carefully excluded.[23,24] Furthermore, the size of lymph nodes does not appear to be a mandatory indicator of disease involvement.[25,26] ^{18}F-FDG PET was not performed routinely in our cohort, and consequently, it was only possible to re-evaluate CT images.[27] The reason why we did not include PET data or only patients with PET results was to avoid a selection bias, since younger patients were more often candidates for PET. Today, the national guidelines for high-grade B-cell lymphoma state that PET-CT should be done, although this is not always performed.

It is worth mentioning that a weakness of our study is that it was a single-centre retrospective study and is somewhat hampered by the rather low number of cases included. If abdominal lymph node involvement is an independent prognostic factor associated with dismal survival outcome in DLBCL, patients need to be investigated by more comprehensive studies. In addition, the insufficient tissue samples in cases where diagnosis was made on core needle biopsy made it not possible to perform all immunohistochemical stainings in these patients. Nor was further analysis, such as rearrangement analysis of MYC and BCL2 and other molecular analyses possible due to the sparse material. This emphasises the need of improved targeting and increased sampling volumes in percutaneous and endoscopic biopsies in order to study the supposed distinct biologic composition in nodal abdominal DLBCL.

In summary, we found that DLBCL patients with lymph node involvement in the abdomen had inferior prognosis (LSS) and more aggressive behaviour compared to patients without abdominal nodal involvement, reflected in both the clinical and the biological characteristics. Patients with histopathologically proven abdominal nodal disease have a more dismal outcome (OS, LSS and PFS). Thus, the site of lymph node involvement might have prognostic impact in DLBCL.

CONFLICTS OF INTEREST

The authors declare no relevant conflicts of interest, financial or otherwise.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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