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ORIGINAL ARTICLE

Early-stage diffuse large B cell lymphoma of the head and neck: clinico-biological characterization and 18 year follow-up of 488 patients (IELSG 23 study)

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Abstract It is known that extranodal head and neck diffuse large B cell lymphomas (eHN-DLBCL) can affect various anatomical structures what is not well-known, however, is whether they differ in terms of clinical presentation and outcome. Clinical data of the multi-institutional series, the largest of its kind as yet, has been analysed with the aim of answering these open questions and providing long-term follow-up information. Data from 488 patients affected by stage I/II eHN-DLBCL was collected: 300 of the Waldeyer's Ring (WR), 38 of the parotid and salivary glands (PSG), 48 of the thyroid gland (TG), 53 of the nasal cavity and paranasal sinuses (NPS), 24 of the palate and oral cavity (POC) and 25 with more than one

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involved site. Different eHN-DLBCL arising have distinct characteristics at presentation. The intermediate high risk-modified IPI was 67 % in TG, 44 % in WR, 38 % in PSG and POC and 20 % in MS. The worst 5-year survival rate had TG-DLBCL (61 %) due to the 61 % of patients with a mIPI >1. The addition of radiotherapy (cRT) to remitters did not translate into a survival advantage (5-year disease-free survival of 67 % in the cRT group vs. 70 % in the other). Three of four central nervous system recurrences occurred in NPS-DLBCL. Survival of HN-DLBCL was inferior to nodal DLBCL. This study showed that eHN-DLBCL remitters have an inferior survival when compared to nodal DLBCL, and that the addition of cRT does not provide a survival advantage. Since the standard of care nowadays is chemo-immunotherapy, survival of these patients might have been improved.

Keywords DLBCL · Lymphoma · Extranodal · Head · Neck

Introduction

The head and neck region (HN) includes some of the most common sites of presentation of extranodal lymphomas, being mainly represented by diffuse large B cell lymphomas (DLBCL) [1]. Due to the various anatomical structures, the HN can be subdivided into different subregions, namely Waldeyer's Ring (WR), parotid and salivary glands (PSG), thyroid gland (TG), nasal cavity and paranasal sinuses (NPS), and palate and oral cavity (POC). WR is the most frequently involved site [2]. Different anatomical sites of the HN region consist of diverse tissues and some of them do not contain primary lymphoid tissue, suggesting different mechanisms of lymphomagenesis. It is well-known that lymphomas can arise in extranodal sites as a result of chronic infections [3] or autoimmune diseases such as Sjögren disease [4] and Hashimoto's thyroiditis [5]. Therefore, lymphoid neoplasia arising in the different HN organs might also have peculiar clinical characteristics and outcome. For instance, an increased risk of CNS relapse has been reported for DLBCL of the paranasal sinuses but not for other extranodal HN-DLBCL (eHN-DLBCL) [6, 7]. There are studies exploring the clinical characteristics and outcome of DLBCL arising in the different eHN anatomical subregions, but they are often limited by a small patient number, heterogeneous histology, and the inclusion of cases with advanced stage disease [8–18]. To the best of our knowledge, no study has provided a direct comparison between DLBCL arising in the different eHN regions. Another important open question is whether these specific extranodal lymphomas should be considered different from nodal DLBCL (nDLBCL) in terms of clinical behaviour, implying a diverse therapeutic approach. In order to shed some light on these open questions, the largest international database of eHN-DLBCL so far was established under the sponsorship of the International Extranodal Lymphoma Study Group. Herein, clinical data of this multi-institutional series were analysed and discussed with the aim of elucidating whether the primary site of eHN might have different prognostic role. Moreover, we provided a direct comparison between eHN-DLBCL and nDLBCL in order to give a long-term follow-up comparison.

Patients and methods

Study population

From 1985 to 2006, 17 international cancer centres referring to the IELSG collected clinical and therapeutic data retrospectively from 488 patients affected by stage I/II eHN-DLBCL. The histologic diagnosis was performed according to the WHO classification of 2001 [19], and therefore, histologic specimens of cases assessed before 2001 were revised by the respective centres. The most common site of disease was the WR ($n=300$), followed by PSG in 38 cases, TG in 48, NPS in 53 and POC in 24. Two of these sites were contemporaneously affected (multiple sites; MS) in 25 patients. Primary DLBCL of the HN was defined as DLBCL which primarily affected an eHN region with (stage II) or without (stage I) involvement of regional lymph nodes (cervical and supraclavicular areas) [20]. Patients with stage II and mediastinal and/or axillary lymphadenopathies were excluded. Staging procedures included at least complete physical examination, bone marrow biopsy and enhanced computed tomography. As not all centres were equipped with a computed tomography device in the early 1980s, ultrasonography was used in some cases. The modified International Prognostic Index (mIPI) for localised DLBCL [21] was assessed at the time of diagnosis in order to evaluate its prognostic significance in eHN-DLBCL. Two subgroup analyses of this IELSG eHN-lymphoma database were previously published [22, 23]. A historical cohort of 231 patients affected by stage I/II nDLBCL who received a CHOP or CHOP-like chemotherapy regimen (CHT) [24] with or without involved field radiotherapy consolidation (cRT) were compared to the eHN-DLBCL in terms of survival in order to provide a direct comparison between the two different disease presentations. This

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study was performed following the principles of the declaration of Helsinki and was approved by the Institutional Review Board of Bergamo, Italy.

Statistical analyses

The aim of this retrospective study was to compare the clinical features and outcome of patients with DLBCL which had arisen at the different eHN sites and to provide a direct comparison to nDLBCL. A chi-square test was performed to assess the significance of differences between categorical variables. Medians were compared with the Mann–Whitney *U* test or the Kruskal–Wallis test. Overall survival (OS), event-free survival (EFS) and disease-free survival (DFS) were plotted as curves using the Kaplan–Meier method and were defined according to Cheson et al. [25]. Since our cohort consisted only of patients with stage I/II disease, the modified IPI (mIPI) [21] was applied. The mIPI was first published in 1998 and has proved to be a valid prognosticator for stage I/II nDLBCL. Risk was assigned according to the number of adverse prognostic features, including age greater than 60 years, stage II disease, increased serum lactate dehydrogenase (LDH) concentration and decreased performance status.

The log-rank test was employed to assess the impact on survival of categorical variables. Cox's proportional hazard model [26] was applied to evaluate the impact on the survival of prognostic factors, namely, mIPI >1, male gender, B symptoms, bulky disease and the different anatomical primary sites. In order to provide a more homogeneous population for the analysis of outcome, patients treated without chemotherapy were excluded from the analysis of response, relapse and outcome (EFS, OS and OS)

A p value of <0.05 was considered as statistically significant. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) software v.17.0.1 (SPSS, Chicago, IL, USA).

Results

Patient characteristics

The main patient characteristics according to the different HN regions are summarised in Table 1. Age distribution varied according to the site of presentation, the oldest patients being more frequent in TG and the youngest in the POC subgroup. Male gender prevailed in all subgroups, except in PSG and TG in which the percentage of female patients was 58 and 77 % (p < 0.001), respectively. When compared to all other sites of primary disease at the time of diagnosis, the TG group presented with the highest rate of adverse prognostic factors such as age >60 years (p <0.001), male sex (p <0.001), poor ECOG performance status (p <0.001), mIPI >1 (p =0.002) and bulky disease (≥10 cm) (p <0.001). Only stage II was more frequent in WR-DLBCL (p <0.001). Overall clinical characteristics were similar between eHN-DLBCL and nDLBCL, and larger differences were observed only regarding the percentage of stage II disease and age >60 years. Importantly, the mIPI distribution was comparable between both groups (mIPI >1 in 42 % of eHN-DLBCL and 47 % in nDLBCL).

Treatment

Patients were treated according to the therapeutic guidelines for localised DLBCL of the participating centres. The majority of them received an anthracycline containing chemotherapy with (n =259; 53 %) or without subsequent involved field radiotherapy (n =142; 29 %) or prior surgery (n =22; 4.5 %), while only a minority of cases were given other therapies such as cRT or surgical excision alone (n =33; 6.4 %) or in combination (n =5; 1 %) or the combination of all the three aforementioned treatment modalities (n =23; 5 %). Patients who were given chemotherapy received a median of 6 cycles (1–12 cycles), consisting of a CHOP or a CHOP-like chemotherapy regimen [24] in nearly 95 % of cases. Rituximab was added to CHT in seven cases, while only one patient received this antibody as the sole treatment. There were no differences in treatment modalities distribution among studied patients divided by anatomical regions (Supplementary Table 1). Intrathecal chemotherapy (methotrexate 12.5 mg) as central nervous system (CNS) prophylaxis was administered in 29/439 (7 %) patients. The clinical features at the time of diagnosis of these patients are summarised in Supplementary Table 2. cRT consisted of 4–9 MV photons with a median planned dose of 4,000 cGy (range 3,000–7,000). Eight patients (2 %) interrupted cRT because of toxicity after a maximum dose of 2,800 cGy.

Response and relapses

In patients who underwent chemotherapy alone or in combination, the overall response rate was 91 %: 481 patients achieved a CR (86 %) and 26 achieved a PR (6 %). Thirty-eight patients (8 %) were resistant to treatment. The CR rate was similar between the different anatomical subregions and ranged from 78 % in MS to 91 % in POC (Table 2). Eventually, 20 % of remitters relapsed and the rate of recurrent disease varied according to the different sites of presentation, but the difference did not achieve statistical significance because of the limited number of cases. The lowest recurrence rate was observed in POC (9 %) and the highest in PSG group (29 %). Except for TG, where 4 of the 5 relapses were local failures (two of them had received CHT and three combined therapy), distant recurrences prevailed in the other subregions. Overall, only four patients (1 %) experienced CNS relapse. None of them had received CNS prophylaxis and three were affected by NPS-DLBCL (p =0.004). None of the other

Table 1 Clinical characteristics of 488 patients registered at the time of diagnosis

Parameter	WR ($n=300$)		PSG ($n=38$)		TG ($n=48$)		NPS ($n=53$)		POC ($n=24$)		MS ($n=25$)		p value	HN-DLBCL ($n=488$)		nDLBCL ($n=328$)	
	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%					
Age >60 years	134/300	45	25/38	66	36/48	75	27/53	51	10/24	42	14/25	56	0.001	246/488	50	117/328	36
Median age, years (range)	58 (14–91)		64 (31–82)		71 (34–90)		61 (21–91)		54 (31–75)		63 (21–93)		<0.001	61 (14–93)			
Gender (m:f)	173:127	58:42	17:21	45:55	11:37	23:77	28:25	53:47	14:10	58:42	15:10	60:40	<0.001	158:230	53:47	178:150	54:46
Performance Status >1	25/293	8	4/37	11	15/47	32	2/52	4	0/24	0	0/25	0	<0.001	46/478	10	8/287	3
Stage													<0.001				
IE	82/300	25	21/38	55	23/48	48	39/53	74	11/24	46	13/25	52		189/488	39	322/328	98
IIE	218/300	73	17/38	45	25/48	52	14/53	26	13/24	54	12/25	48		299/488	61	6/328	2
B symptoms	37/288	13	1/36	3	2/47	4	5/53	9	2/24	8	2/25	8	0.275	49/473	10	n.a.	n.a.
LDH>UNL	28/233	12	4/33	12	8/37	22	5/40	12	3/20	15	0/18	0	0.356	48/381	13	52/306	17
Bulky disease >10 cm	22/276	8	6/38	16	12/43	28	2/47	4	1/21	5	1/21	5	0.001	44/446	10	40/279	14
IPI													0.002				
0–1	192/297	65	26/37	70	17/46	37	34/50	68	18/24	75	12/35	48		299/479	62	n.a.	n.a.
>1	105/297	35	11/37	30	29/46	63	16/50	32	6/24	25	13/35	52		180/479	38		
mIPI													0.004				
0–1	145/257	56	21/34	62	16/44	36	33/45	73	13/21	62	16/20	80		244/421	58	145/274	53
>1	112/257	44	13/34	38	28/44	67	12/45	27	8/21	38	4/20	20		177/421	42	129/274	47
Hashimoto Thyroiditis	0/195	0	0/25	0	11/35	31	0/42	0	0/17	0	0/19	0	<0.001	11/368	3	n.a.	n.a.

The p value refers to the comparison of all HN disease localizations (excluding nDLBCL)

WR Waldeyer's Ring; *PSG* parotid and salivary glands; *TG* thyroid gland; *NPS* nasal cavity and paranasal sinuses; *POC* palate and oral cavity; *nDLBCL* nodal diffuse large B cell lymphoma; *m* male; *f* female; *IPI* International Prognostic Index; *mIPI* modified International Prognostic Index; *n.a.* not available

Table 2 Response rate, relapses, status at last follow-up and 5-year survival rates according to the different anatomical subregions

Parameter	WR %	PSG %	TG %	NPS %	POC %	MS %	All HN-DLBCL %
Patients who underwent chemotherapy alone or in association with local treatments (n=446)							
Response rate							
CR	86	84	86	83	92	78	86
PR	5	3	2	13	4	13	6
NR	9	13	12	4	4	9	8
Relapses	21	29	13	26	9	11	20
Status at last follow-up							
Alive in CR	72	65	64	69	88	70	70
Alive with disease	1	11	4	8	4	9	4
Death in CR	21	21	18	21	4	17	20
Death with disease	6	3	14	2	4	4	6
5 year OS	74	75	61	78	90	74	74
5 year EFS	65	59	55	69	77	68	65
4 year DFS	70	46	74	56	90	87	70
Cause of death							
Disease	19	19	16	19	4	17	18
Other	7	3	16	4	4	4	7
Patients who underwent local treatments only (n=38)							
Response rate							
CR	86		75	100	100		87
PR	7		0	0	0		5
NR	7		25	0	0		8
Relapses	42		0	40	0		36
Status at last follow-up							
Alive in CR	39		0	40	100		37
Alive with disease	7		0	0	0		5
Death in CR	29		25	20	0		26
Death with disease	25		75	40	0		32
5 year OS	66		0	60	n.a.		58
5 year EFS	55		100	50	n.a.		47
4 year DFS	44		n.a.	50	n.a.		62
Cause of death							
Disease	18		25	0	0		16
Other	36		75	60	0		42

n.a. not available

features assessed at the time of diagnosis were predictive for a CNS relapse. In the whole cohort, the relapse rate was highest in patients with mIPI >3 (43 %; p=0.004), while it was less frequent in cases with mIPI 0–1 and 2 (17 %).

Survival and follow-up

After a median follow-up of 4 years (range, 1 month–18 years), 314 patients (71 %) were alive in CR, 17 were alive with disease (4 %), 87 had died with disease (20 %) and 27 had died in CR (6 %). The highest death rate was observed in TG (32 %) and the lowest in POC, where at the last follow-up visit more than 91 % of the patients had been still alive (p=n.s.). Death due to lymphoma occurred in 16–19 % of the patients in all subgroups except in POC-DLBCL where only one patient died of disease.

Event-free survival

The median EFS was 11 years with a 5 and 10-year estimated EFS of 65 and 57 %, respectively (Supplementary Table 3; Supplementary Figure 1). EFS varied according to the different primary disease localizations (Fig. 1) with the worst 5 and 10-year survival rates being among patients with TG (55 and

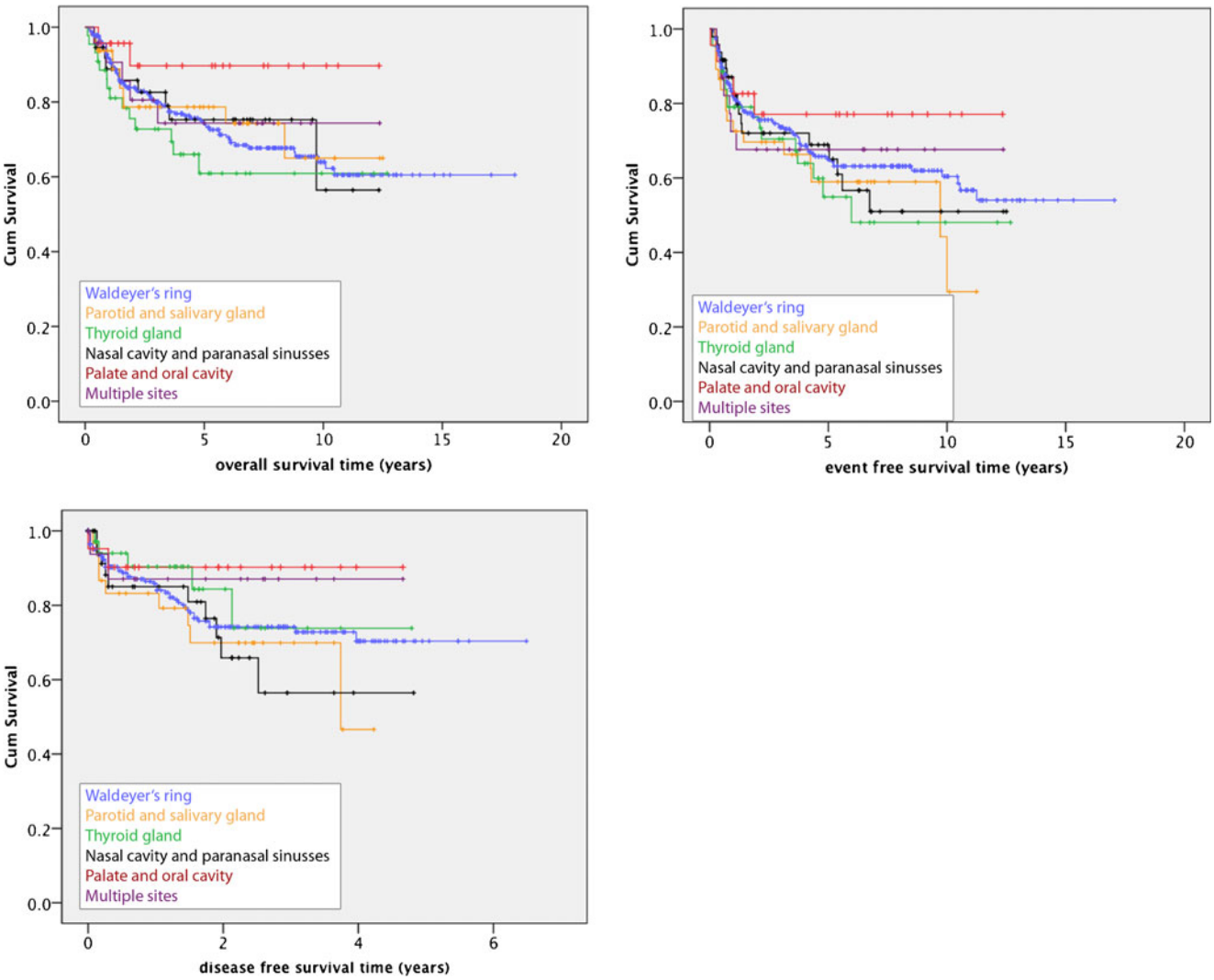

Fig. 1 Overall survival time, event-free survival and disease free survival according to the different primary disease localizations (**a**, **b**, **c**)

48 %) and the best in patients with POC (both 77 %; Table 2), without achieving statistical significance. The addition of cRT did not prolong EFS of patients who achieved a CR after an anthracycline-containing chemotherapy regimen (Supplementary Figure 2). When comparing eHN-DLBCL patients to 328 nDLBCL cases receiving similar treatment, the latter had a significantly better EFS ($p<0.001$; Fig. 2). This was still valid when the same analysis was performed for patients with mIPI 0–1 ($p=0.017$) and a mIPI ≥2 ($p<0.001$) as well as for patients with stage I ($p=0.006$) but not with stage II disease ($p=0.350$; supplementary figure 3). The survival difference between the three mIPI risk groups was highly significant ($p<0.001$), with a 10-year EFS ranging from 68 to 18 % (Fig. 3). In multivariate analysis, only mIPI >I ($p=0.001$) and the presence of systemic symptoms ($p=0.003$) were significant predictors for shorter EFS.

Overall survival

The median OS was 16 years with a 5 and 10-year OS of 74 and 65 %, respectively (Supplementary Table 4; Supplementary Figure 1). OS varied according to the different primary disease localizations (Fig. 1) with the worst survival rates among patients with TG (both 61 %) and the best in patients with POC (both 90 %; Table 2). However, due to the limited number of cases, the observed differences were not statistically significant. cRT influenced survival significantly with a 10-year OS ranging from 57 to 66 % ($p<0.001$; Supplementary Figure 2). When comparing eHN-DLBCL patients to nDLBCL cases, a statistically significant OS difference was observed ($p<0.001$; Fig. 2). This was still valid when the same analysis was performed for patients with mIPI 0–1 ($p=0.031$) and a mIPI ≥2 ($p<0.001$) but not for patients with stage I ($p=0.051$) or

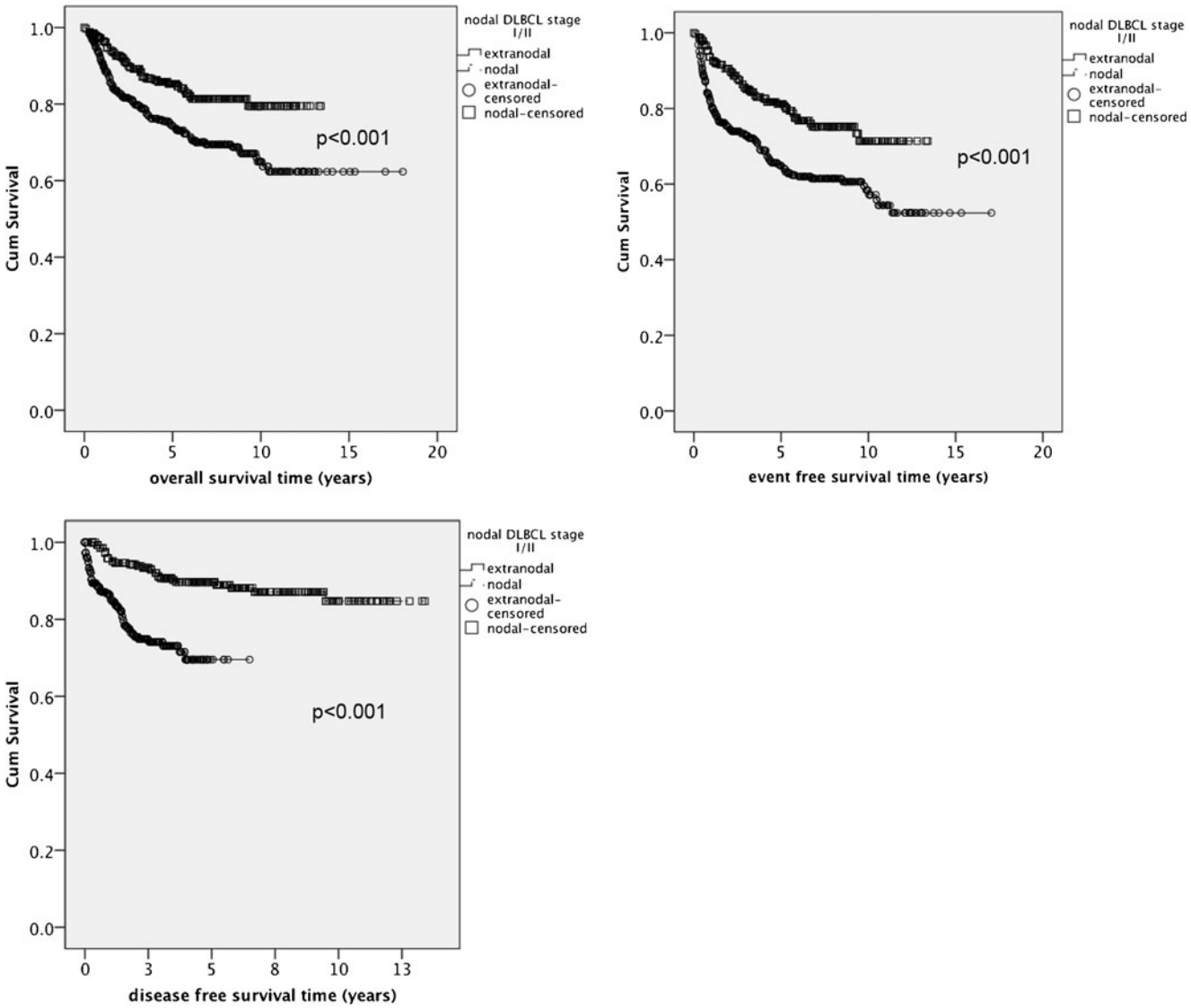

Fig. 2 OS, EFS and DFS for nDLBCL and eHN-DLBCL

stage II disease ($p=0.091$; Supplementary Figure 3). The survival difference between the three mIPI risk groups was highly significant ($p<0.001$), with a 10-year OS ranging from 79 % (low risk) to 23 % (high risk; Fig. 3). In multivariate analysis, mIPI ≥2 ($p<0.001$) and B symptoms ($p=0.001$) emerged as independent prognosticators for OS.

Disease-free survival

The estimated DFS for the whole study cohort was 70 % at 5 years (Supplementary Table 5), reaching a plateau after 4 years (Supplementary Figure 1). The best 4-year DFS was observed among POC and MS-DLBCL (>87 %) and the worst among NPS-DLBCL (56 %; $p=0.488$; Fig. 1). In contrary to EFS and OS, cRT did not prolong DFS. In particular, the curves were overlapping (Supplementary Figure 2). Again, the DFS difference between eHN-DLBCL and nDLBCL was statistically significant ($p\leq0.001$; Fig. 2). This was still valid when the same analysis was performed for patients with mIPI 0–1 ($p=0.001$) and a mIPI≥2 ($p<0.001$) as well as for patients with stage I ($p<0.001$) but not with stage II disease ($p=0.828$; Supplementary Figure 3). The survival difference between the three mIPI risk groups was highly significant ($p<0.001$), with a 4-year DFS ranging from 77 to 23 % (Fig. 3). However, no DFS differences between low- and intermediate-risk patients were observed, while it was clearly inferior for those with mIPI >3. In multivariate analysis, the most important prognosticator for DFS was mIPI >I ($p=0.041$).

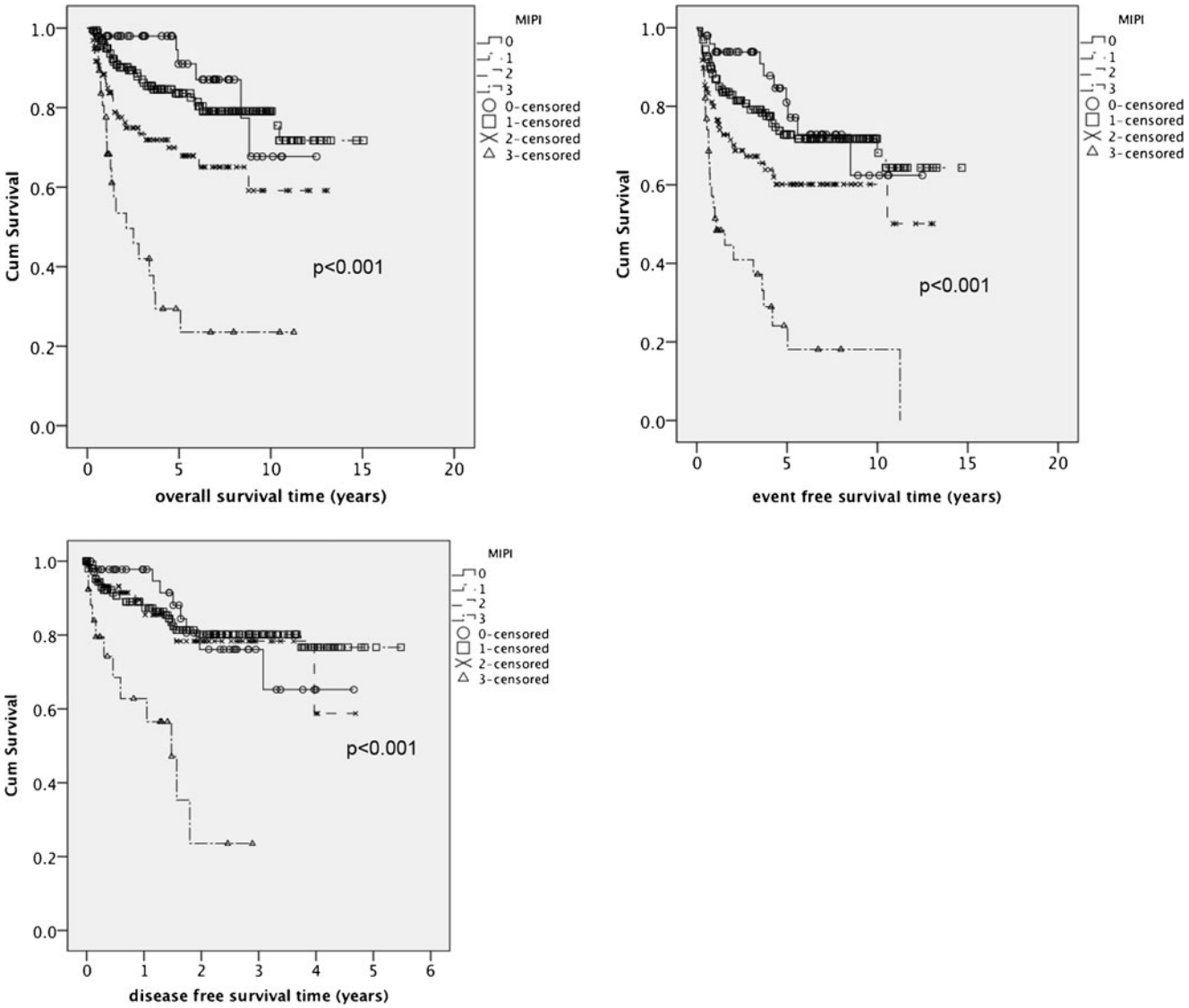

Fig. 3 Survival according to mIPI. According to the three different risk categories (low, intermediate and high risk), the 10-year OS was 78, 51 and 23 %, the 10-year EFS 67, 48 and 17 % and the 5-year DFS 80, 77 and 24 %

Discussion

The head and neck region is a relatively frequent site of presentation of extranodal DLBCL, which can arise in different anatomical HN subregions. The analyses of their clinical characteristics and survival as well as the possible therapeutic implications in comparison also with their nodal counterpart were subject of the present study.

Despite the expected limitations of a retrospective analysis such as a long accrual period, missing information and management heterogeneity, the large number of cases, the long follow-up time and the homogeneity of selected patients according to stage and histotype gave reliability to our results. The main limitation of the study was that the majority of analysed patients were treated with CHOP without the monoclonal anti-CD20 antibody rituximab. Nevertheless, the addition of rituximab could contribute to improve disease control in eHN-DLBCL as was the case for localised DLBCL in the SWOG trial [27]. As an additional limitation, a central pathology review was not performed and information regarding the cell of origin (ABC and GCB), which is a well-known important prognosticator [28], was not available. However, all participating centres have a lot of experience of lymphoma diagnosis and management, which also regards the active involvement of expert hemopathologists.

Up to now, only few data regarding the clinical features of patients affected by eHN-DLBCL are available. Most is known about WR-DLBCL [14, 18, 29], which are mainly represented by males with an age lower than 60 years having a relatively low frequency of B symptoms, elevated LDH and

a high involvement of local lymph nodes. Similar features were also observed in our series. Due to the rarity of the other disease sites, only few cases have been described so far [8, 9, 12, 13]. In our series, age distribution significantly differed among the studied subgroups, male gender prevailed in all disease sites except in PSG and the highest rate of adverse prognostic factors such as poor performance status, elevated LDH and bulky disease was recorded in TG-DLBCL. Overall, clinical characteristics of eHN-DLBCL at the time of diagnosis differ from those reported for nodal localised DLBCL, which mainly present with advanced age, a higher rate of B symptoms and except for TG-DLBCL with a worse performance status [27]. However, this comparison is limited since half of the patients of the series published by Persky et al. were affected by extranodal DLBCL.

Most patients underwent an anthracycline-containing chemotherapy regimen with or without subsequent radiotherapy and/or prior surgery, while only a minority of cases was given an intrathecal CNS prophylactic chemotherapy. The overall response rate of 92 with 86 % of CRs was comparable to previously published studies of eHN-DLBCL [8, 9] and n-HN-DLBCL [21, 30] and did not differ in various anatomical subregions. Unexpectedly, the rate of CNS recurrences was very low (overall 1 %), prevailing in NPS (6 %) as previously reported in previous smaller retrospective series [6, 7]. After an OS time of 5 years, 75 % of patients in our series were still alive. These results compare favourably to previous studies [8, 9]. However, survival varied according to the different primary disease localizations, with the shortest 5 year OS among patients with TG (52 %) and the longest in patients with POC (90 %). As previously reported, the very short survival of TG-DLBCL has been attributed to the high rate of non-disease related deaths reflecting the higher rate of adverse prognostic factors at time of diagnosis [22]. Finally, the survival of remitters reached a plateau after 11 years, thus suggesting that eHN-DLBCL might be a curable disease. Another important observation of this analysis was that radiotherapy, given as a consolidation to patients who achieved CR after anthracycline-containing induction chemotherapy, did not improve DFS despite a significant impact on OS an EFS. This could be explained by the larger number of elderly patients in the non-cRT group leading to a higher non-disease related death rate. These data is in line to what previously published by us for patients affected solely by WR-DLBCL [31] and suggest that cRT could be omitted in remitters, sparing unnecessary toxicity which could seriously impair their quality of life [23, 32]. The analysis of the most important known prognosticator for stage I/II DLBCL, namely, the mIPI, proved to be a powerful predictor for OS and EFS subdividing the population into three risk categories [21]. This is in line with previous trials that have demonstrated its efficiency in other types of extranodal DLBCL [33]. However, in DFS, low- and intermediate-risk patients had overlapping survival curves (5-year DFS >77 % for both), suggesting that the applied treatment modalities provide sufficient disease control. Instead, high-risk patients had a clearly inferior DFS, implying that these cases need a more intensive upfront treatment. Of the other evaluated clinical parameters, only male sex and the presence of constitutional symptoms had an independent negative impact on survival, which is consistent with previous publications [8]. Finally, we provided a direct survival comparison between eHN-DLBCL who received an anthracycline-containing CHT with or without cRT and a historical cohort of stage I/II similarly treated nDLBCL. Survival of nDLBCL was clearly superior to eHN-DLBCL. In order to exclude a bias due to stage or mIPI differences observed between both groups (stage I disease was overrepresented in the nDLBCL group when compared to other series), we performed a mIPI and stage-matched analysis, which confirmed the results. However, due to the limits of such an analysis, we are not able to exclude the presence of other biases. Nevertheless, our results suggest that anthracycline-containing polychemotherapy alone is not sufficient for adequate tumour control. As previously shown for nDLBCL, the addition of immunotherapy [34] could lead to better survival in eHN-DLBCL.

In conclusion, eHN-DLBCL remitters have an inferior survival when compared to nDLBCL and that the addition of cRT does not provide a survival advantage. Since the standard of care nowadays is chemo-immunotherapy, the survival of these patients might have been improved. CNS prophylaxis should be reserved for cases with involvement of the paranasal sinuses. Finally, the mIPI is an important prognosticator, identifying patients who could profit from a more intensive therapeutic approach.

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