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A diachronic-comparative analysis for the identification of the most powerful prognostic index for localized diffuse large B-cell lymphoma

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Background: In the rituximab era, the conventional International Prognostic index (IPI) lost at least in part its predictive power, while the National Comprehensive Cancer Network-IPI (NCCN-IPI) seems to be a new and valid prognosticator. However, it has not yet been evaluated in patients with localized disease and it has not been compared with the modified IPI (mIPI) of the pre-rituximab era. In order to evaluate the different prognosticators and to assess the importance of rituximab and radiotherapy (RT), we carried out the so far largest retrospective analysis of patients with localized diffuse large B-cell lymphoma (DLBCL).

Patients and methods: We retrospectively assessed clinical and therapeutical data of 1405 patients treated in from 1987 to 2012 in 10 cancer centers in Italy and 1 in Austria.

Results: All patients underwent an anthracycline containing polychemotherapy and 254 additional rituximab. The median follow-up was 5.7 years (range 0.1–23 years). The 5-year overall survival (OS) was 75%, being significantly superior in those who underwent additional rituximab, while RT consolidation did not improve the outcome of those who received immunochemotherapy. Patients with extranodal disease benefited from the addition of rituximab, while RT did not improve OS of the immunochemotherapy subgroup. In the pre-rituximab era, the mIPI showed a better performance than the others. In rituximab-treated patients, the NCCN-IPI had the highest discriminant value and the 5-years OS varied significantly ($P < 0.001$) between the three risk groups and was 98% in low-risk patients, 82% in those with a low-intermediate risk and 57% among high-intermediate and high-risk cases.

Conclusions: The NCCN-IPI is so far the best prognosticator for patients with localized DLBCL who underwent R-CHOP(-like). The addition of rituximab is indispensable regardless of the risk category and site of involvement, while the addition of RT should be reserved to those cases who are ineligible to rituximab.

Key words: lymphoma, rituximab, IPI, NCCN-IPI, localized

introduction

Diffuse large B-cell lymphoma (DLBCL) is an aggressive but potentially curable group of non-Hodgkin lymphomas accounting for ~30% of newly diagnosed cases [1]. The clinical course is heterogeneous and, while some patients after several treatment lines eventually die of the disease, others achieve an early complete remission and never relapse. Research regarding risk-adapted therapies for this neoplasia is still at the beginnings but new, targeted therapies are underway. Therefore, clinicians need easily applicable prognostic parameters to predict these patients' clinical course, especially since new molecular markers have not yet entered the clinical routine.

Up to now, the International Prognostic index (IPI) has proven to be the most important score for predicting the patient's clinical course and has been the gold standard for >20 years [2]. However, in clinical routine as well as in clinical trials, it might not be an optimal tool for stage I/II patients since they cannot have ≥2 involved extranodal sites, and the negative impact of stage II disease might be underestimated. Therefore,

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Miller et al. [3] proposed the stage-modified IPI (mIPI) for DLBCL patients for whom chemotherapy, according to the CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisone), with or without radiotherapy (RT), was planned. It proved to be a strong prognosticator but it was never validated in a population-based analysis. After the introduction of rituximab, Persky et al. [4] applied the mIPI to a study cohort who underwent R-CHOP with or without RT, but they did not evaluate explicitly its strength to discriminate between patients with different prognoses. Only recently, Zhou et al. [5] published a revised version of the IPI, namely the National Comprehensive Cancer Network-IPI (NCCN-IPI), for DLBCL patients treated in the rituximab era and again only stage III/IV disease was considered as a bad prognosticator, while the number of affected extranodal sites were not classified as a poor prognostic factor but only certain extranodal localizations. This revision was necessary since the introduction of rituximab reduced the discriminatory power of the IPI, especially in patients with a high-risk disease [6, 7]. Again, patients with stage I/II disease were not evaluated separately.

Herein, we present the first population-based validation of the prognostic power of the IPI, the mIPI and the NCCN-IPI in stage I/II DLBCL patients who underwent in first line a CHOP or CHOP-like chemotherapy with or without rituximab or RT.

patients and methods

study population

From 1987 to 2012, 10 cancer centers in Italy and 1 in Austria retrospectively collected clinical and therapeutic data from 1405 consecutive patients affected by stage I/II DLBCL. The histologic diagnosis was carried out according to the 2001 [8] and 2008 [9] WHO classifications and, therefore, histologic specimens of cases assessed before 2001 were reviewed by local specialists in lymphoma diagnosis. Staging included, in all cases, bone marrow biopsy in order to exclude stage IV disease as well as a whole-body imaging. At time of diagnosis all IPI parameters (age, lactate dehydrogenase levels (LDH), performance status, stage, number and localization of extranodal sites) were assessed. The mIPI was calculated as proposed by Miller et al., [3] while the NCCN-IPI was calculated according to Zhou et al. [5]. The CHOP(-like) [10] group consisted of 1151 patients who underwent a median of four cycles (range 2–8 cycles) of chemotherapy followed by RT in 523 cases (45%). The remaining 254 patients underwent a median of six cycles of R-CHOP(-like) (range 1–10 cycles) with additional RT in 115 cases (45%). Clinical characteristics assessed at time of diagnosis are summarized in the supplementary Table, available at *Annals of Oncology* online. This study was carried out following the principles of the Helsinki declaration and was approved by the institutional review board of Bolzano, Italy.

statistical analysis

The primary end point of this analysis was overall survival (OS), defined as the time from diagnosis of DLBCL until death from any cause, or date of last follow-up for censored patients [11]. OS was calculated by the Kaplan–Meier method; survival curves were compared using the log-rank test. A Cox proportional hazards (PH) model was used to estimate the hazard ratio (HR) and its confidence interval at 95% (95% CI), with the low-risk group as the reference group. Univariate and multivariate analyses were carried out by means of Cox PH regression. Continuous biologic covariates were dichotomized according to usual clinical thresholds and the χ^2 test or Fisher's exact test was used to compare categorical variables. Since this is an observational, retrospective and multicenter study, a sample size was not planned. The performance of the different prognostic scores (IPI, mIPI and NCCN-IPI) were checked graphically by the Kaplan–Meier curves and analytically by means of the HRs and discriminating power, expressed as c-Harrell [12] and explained variation (R^2, as defined by Royston) [13]. The c-Harrel and R^2 standard error and 95% CI were estimated by means of 250 bootstrap resamples. We compared all three scores (IPI, mIPI, NCCN-IPI) for patients who underwent a CHOP(-like) chemotherapy with or without rituximab. All carried out tests were two sided.

results

overall outcome

Overall, the median follow-up was 5.7 years (range 0.1–23 years), varying from 6.2 years (range 0.1–23 years) in the pre-rituximab cohort ($n = 1151$, 82%) to 4.6 years (range 0.1–12 years) in those patients who underwent immunochemotherapy ($n = 254$, 18%). The actual number of patients for each of the prognostic index is shown in Table 1. The 5-year OS was 75% (95% CI 73% to 78%) for all 1405 patients, being significantly superior in those who underwent additional rituximab (85%, 95% CI 80% to 89%) compared with the remaining ones who did not (73%, 95% CI 70% to 76%; $P < 0.001$).

pre-rituximab era

We evaluated the impact of all prognostic factors contributing to one of the evaluated scores regarding their impact on OS. They all proved to be strong prognosticators for OS (Table 2). Also, all three scores were strong predictors for OS (Table 2 and Figure 1). However, in the pre-rituximab era, the mIPI showed a better performance by allocating 15% of patients in the high-risk group (compared with 2% by the IPI and 5% by the NCCN-IPI) with a c-Harrell of 64.0 (59.9 for IPI and 61.3 for NCCN-IPI).

rituximab era

The impact of all prognostic factors contributing to one of the evaluated scores regarding their impact on OS is listed in Table 2. Also, for patients treated with additional rituximab, IPI, mIPI and NCCN-IPI proved prognostic ability (Table 2 and Figure 2). However, intermediate- and high-risk groups of the mIPI tend to overlap (HR 1.50, $P = 0.260$). Instead, IPI and NCCN-IPI segregated the cohort in three well-separated risk groups but the IPI allocated 5% of patients to the high-risk group while the NCCN-IPI assigned 12% to it. Overall, NCCN-IPI showed better performances than the other prognostic scores, with the highest discriminant value in terms of c-Harrell (75.2 versus 69.8 and 73.4 for IPI and mIPI, respectively) and explained variation R^2 (49.7% versus 36.7% and 35.9% for IPI and mIPI, respectively). When considering stage II disease as a negative prognosticator instead of stage III/IV as in the mIPI, the discriminatory power of the NCCN-IPI did not improve (data not shown).

comparison of treatment modalities

Due to the large number of assessed patients, we compared the OS according to the addition of rituximab and RT (Figure 3). Patients who underwent both rituximab and RT had a superior

Table 1. Actual number of patients in each of the three risk groups for each of the prognostic indices

Factor	No rituximab		Rituximab		Total			Missing
	N	*n* (%)	*N*	*n* (%)	*N*	%	*P*-value	*N* (%)
IPI								
	1151		254		1405			–
0–1		936 (81)		188 (74)		1124 (80)	0.014	
2		186 (16)		53 (21)		239 (17)		
3		29 (2)		13 (5)		42 (3)		
mIPI								
	1151		254		1405			–
0–1		690 (60)		127 (50)		817 (58)	0.013	
2		292 (25)		78 (31)		370 (26)		
3–4		169 (15)		49 (19)		218 (16)		
NCCN-IPI[a]								
	905		234		1139			266 (19)
0–1		385 (42)		88 (38)		473 (41)	0.004	
2–3		472 (52)		119 (51)		591 (52)		
4–6		48 (5)		27 (11)		75 (4)		

[a]Only one patients had score of 6.

OS when compared with all the others. However, RT consolidation improved OS significantly only in those patients who underwent sole chemotherapy ($P < 0.001$) while it did not influence the survival of cases treated with additional rituximab ($P = 0.216$). Among the latter, survival curves were even overlapping in the NCCN-IPI 0-1 group ($P = 0.778$; Figure 4) but also cases with an NCCN-IPI of 2–3 ($P = 0.507$) and 4–6 ($P = 0.243$) did not profit from RT.

When analyzed separately, patients with or without extranodal disease and an NCCN-IPI of 0-1 had a significant survival benefit when rituximab was added to standard therapy ($P = 0.007$ and $P = 0.040$). Instead, while in patients with extranodal disease who underwent only chemotherapy, the addition of RT lead to a survival benefit ($P = 0.003$), this was not the case for immunochemotherapy-treated patients ($P = 0.820$).

discussion

Herein, in the first population-based validation of the prognostic power of the IPI, the mIPI and the NCCN-IPI in stage I/II DLBCL patients who underwent in first line a R+/−CHOP or CHOP-like chemotherapy regimen with or without RT, we provide evidence that the new NCCN-IPI is the best available Clinical Prognostic index for patients with localized disease. Moreover, rituximab has changed the clinical course of this neoplasia in patients with localized disease as well and, therefore, immunochemotherapy should also be considered as the standard of care for patients with localized DLBCL, while RT should be reserved for those patients in whom rituximab is contraindicated.

In the pre-rituximab era, the mIPI, proposed more than 15 years ago [3], proved to be the best prognosticator for OS. This could be in part explained by the important survival difference between stage I and stage II patients which we also confirmed in the present analysis and was not considered in the conventional IPI. However, since up to now almost all patients undergo immunochemotherapy consisting of an anthracycline-containing chemotherapy regimen associated with rituximab with or without RT the mIPI has become obsolete. Furthermore, rituximab completely changed the clinical course of patients with DLBCL [14], so the discriminatory power of the IPI is reduced for both those patients with advanced stage disease [6, 7] and for those with localized disease, as shown in the present analysis. For the former, the NCCN-IPI was assessed in an independent evaluation set, while the current study analyzed its discriminatory power for the latter and ascertained that the NCCN-IPI had the highest discriminant value in terms of c-Harrell and explained R^2 variation. When considering stage II disease as a negative prognosticator instead of stage III/IV, as in the mIPI, the discriminatory power of the NCCN-IPI did not improve. Therefore, the NCCN-IPI can also be applied to patients with localized DLBCL without the necessity for modifications as was the case in the pre-rituximab era [3].

Due to the higher discriminatory power of the NCCN-IPI localized DLBCL, it might be possible to identify a subgroup which does not benefit from the association of all three treatment modalities therefore a comparison of the outcome of patients with an NCCN-IPI of 0-1 according to the addition of rituximab and RT was carried out. As expected, and in line with the SWOG 0014 study [4], the addition of rituximab improved OS substantially. On the other hand, RT consolidation seems to be questionable in patients who underwent immunochemotherapy. This is also valid for patients with extranodal disease. In the past, some study protocols considered extranodal disease in DLBCL as an indication for RT regardless of the presence of bulky disease [15, 16]. Therefore, prospective trials confirming the data of the current analysis are needed, since the omission of RT consolidation would reduce the risk of treatment-related toxicity. Indeed, the German UNFOLDER trial (NCT00278408) is currently evaluating the impact of RT on patients with bulky

Table 2. Impact of the single IPI/NCCN-IPI factors and the three analyzed prognostic indices (IPI, mIPI, NCCN-IPI) on overall survival in univariate analysis

	Without rituximab			With rituximab		
	HR	95% CI	*P*	HR	95% CI	*P*
Age 60+ years	1.83	1.47–2.28	<0.001	4.36	1.91–9.97	<0.001
Age (years)[a]						
≤40	1.00			1.00		
41–60	1.46	1.01–2.12	0.042	8.37	0.44–161[a]	0.159
61–75	2.20	1.54–3.15	<0.001	18.6	1.03–336[a]	0.047
>75	3.85	2.40–6.17	<0.001	42.5	2.34–770[a]	0.011
LDH > UNL	2.18	1.74–2.73	<0.001	2.71	1.41–5.21	0.003
LDH						
Normal	1.00			1.00		
>1–3 UNL	2.26	1.76–2.90	<0.001	2.70	1.35–5.41	0.005
>3 UNL	2.77	1.60–4.80	<0.001	4.97	1.14–21.6	0.033
PS >1	2.32	1.75–3.07	<0.001	3.43	1.73–6.77	<0.001
Stage II	2.01	1.59–2.54	<0.001	2.25	1.06–4.78	0.035
Male gender	0.99	0.79–1.23	0.913	1.50	0.75–3.01	0.248
RT	0.58	0.45–0.73	<0.001	0.64	0.32–1.26	0.197
IPI						
0–1	1.00			1.00		
2	2.51	1.95–3.23	<0.001	2.49	1.16–5.31	0.019
3	4.34	2.71–6.94	<0.001	12.3	5.21–28.5	<0.001
mIPI						
0–1	1.00			1.00		
2	2.14	1.65–2.78	<0.001	6.04	2.20–16.5	0.001
3–4	3.54	2.69–4.65	<0.001	9.08	3.30–25.0	<0.001
NCCN-IPI						
0–1	1.00			1.00		
2–3	2.02	1.54–2.65	<0.001	8.17	1.91–34.9	0.005
4–6	5.82	3.87–8.75	<0.001	31.4	6.98–141	<0.001

NCCN-IPI available in 905 cases treated without rituximab and 234 treated with rituximab.
[a]Since in the group of patients with age ≤40 no events were observed leading to a complete separation of events, the Firth's penalized likelihood Cox regression analysis was applied.

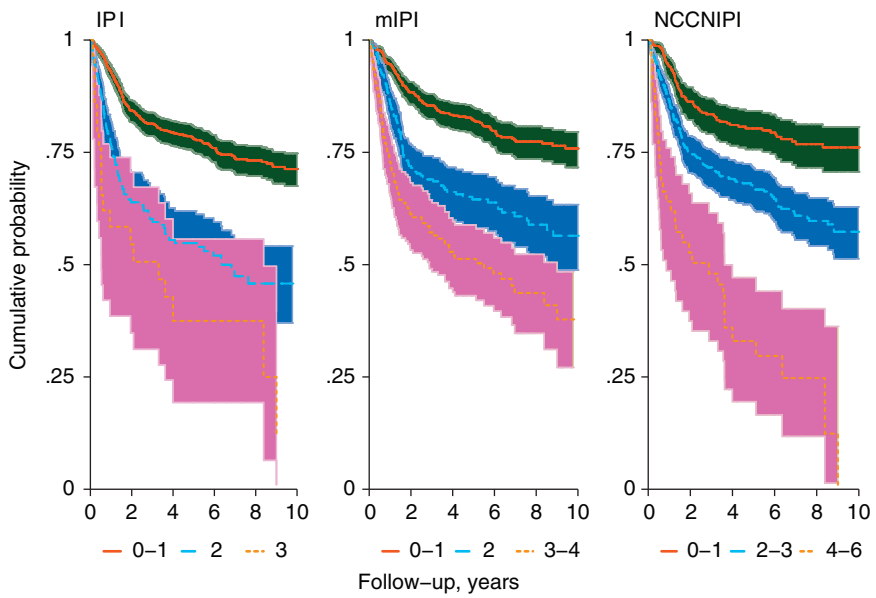


Figure 1. Overall survival according to IPI (A), mIPI (B) and NCCN-IPI (C) in patients who underwent a CHOP/CHOP-like regimen in first line.

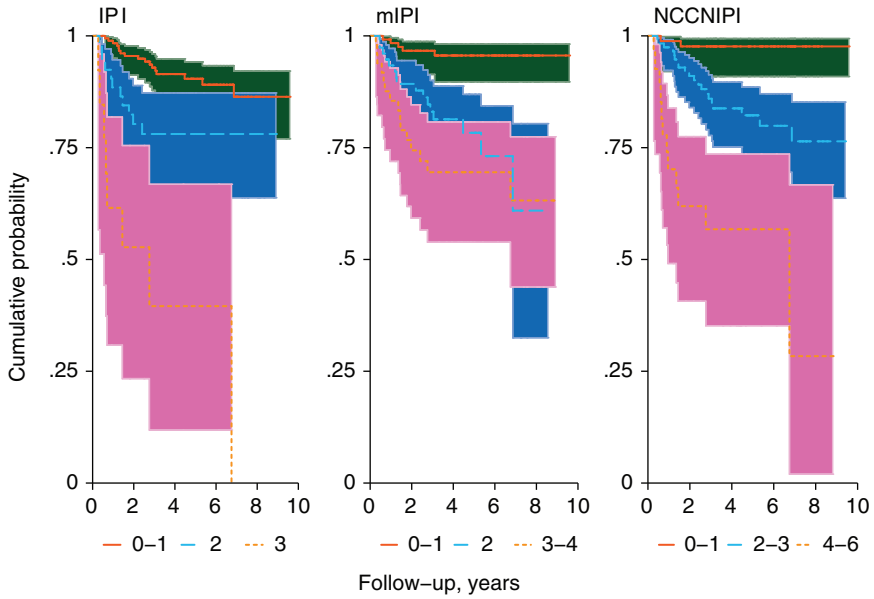
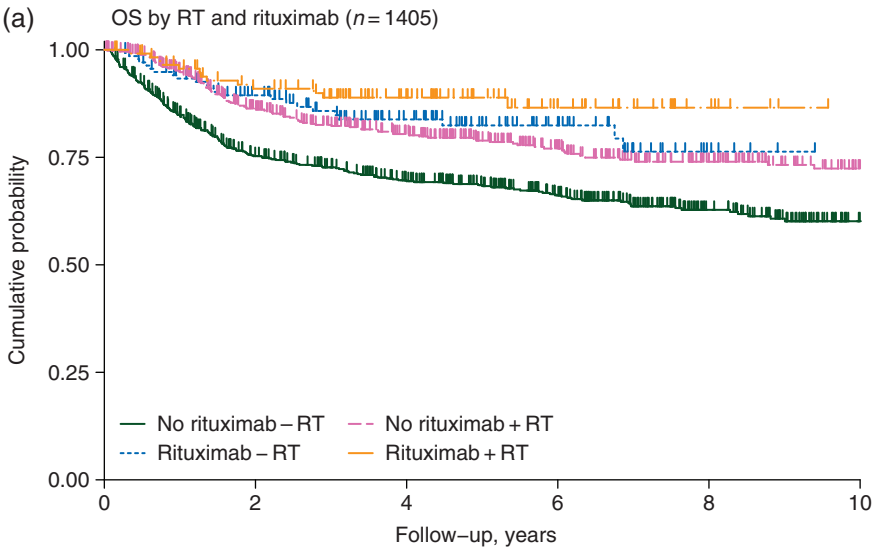


Figure 2. Overall survival according to IPI (A), mIPI (B) and NCCN-IPI (C) in patients who underwent a R-CHOP/R-CHOP-like regimen in first line.



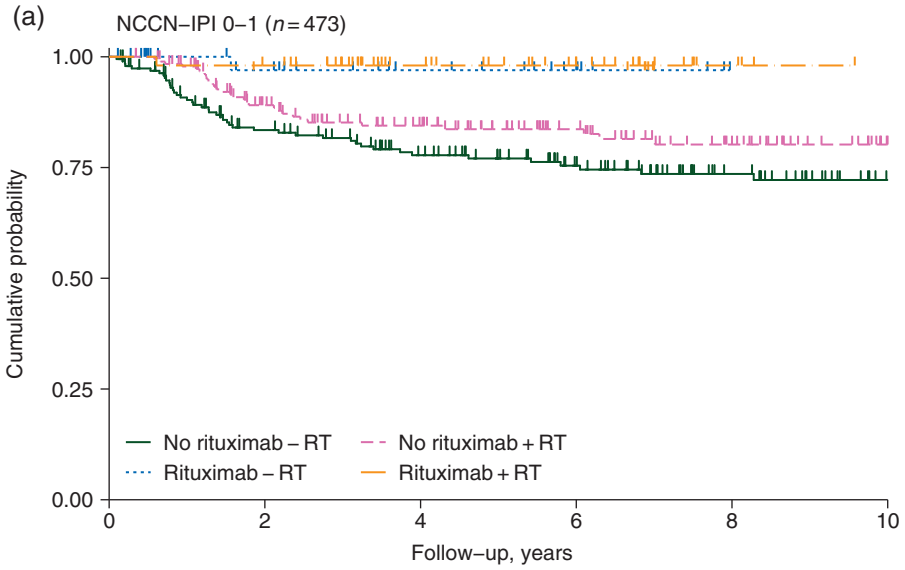
(b)

Group	*N*	*%*	*5-yrs OS% (CI95)*	*HR*	*CI95*	*P*
Without ritux –RT	628	45	68 (64–72)	1.00		
Without ritux +RT	523	37	79 (75–82)	0.61	0.48–0.76	<0.001
With ritux –RT	139	10	82 (74–88)	0.50	0.32–0.77	0.002
With ritux +RT	115	8	89 (81–94)	0.32	0.18–0.57	<0.001
Total	1405					

Figure 3. Overall survival according to rituximab administration and RT in the whole cohort (A: Graph; B: Analysis of significance). RT, radiotherapy.

and/or extranodal disease who undergo rituximab and CHOP. Overall, the NCCN-IPI is more complex than the conventional IPI but it seems to better weigh the impact of age, LDH and extranodal disease. Moreover, in contrast with the IPI, no adjustment of the scoring system for localized DLBCL is necessary since the attempt to consider stage II disease instead of stage III/IV as a poor prognosticator did not improve the discriminatory power.

In 2010, Gutiérrez-García et al. [17] compared the survival differences of patients with nodal and extranodal disease according to the addition of rituximab to standard chemotherapy. They concluded that immunochemotherapy significantly prolonged



(b)

Group	N	%	5-yrs OS% (CI95)	HR	CI95	P
Without ritux –RT	192	41	77 (70–83)	1.00		
Without ritux +RT	193	41	84 (77–88)	0.68	0.43–1.08	0.099
With ritux –RT	36	8	97 (80–99)	0.11	0.02–0.83	0.032
With ritux +RT	52	11	98 (87–99)	0.08	0.01–0.56	0.011
Total	473					

Figure 4. Overall survival according to rituximab administration and RT in patients with an NCCN-IPI of 0–1 (A: Graph, B: Analysis of significance). RT, radiotherapy.

survival of patients with nodal DLBCL while it did not in those with extranodal disease. In the cohort used for this study, this was not the case since all patients had a better OS regardless of the site of disease. Moreover, while in the pre-rituximab era RT consolidation improved the survival of patients with extranodal disease, nowadays it seems to be no longer necessary.

Despite the expected limitations of a retrospective analysis, the large number of cases, the long follow-up time and the homogeneity of selected patients according to stage and histotype all gave reliability to our results. A central pathology review was not carried out. However, all participating centers have extensive experience in lymphoma diagnosis and management, with the active involvement of hemopathology specialists. Since rituximab has entered the clinical routine around the year 2000, the follow-up time between the chemotherapy and immunochemotherapy group were different. However, the hazard function of survival reached its maximum around 12–24 months after diagnosis and tended to reach a plateau after around 60 months why in both groups most of the expected events were registered.

In conclusion, the NCCN-IPI is the best prognosticator for patients with localized DLBCL who undergo anthracycline-containing chemotherapy in association with rituximab since it has the best discriminating power. Therefore, with the arrival of new and risk-adapted treatment strategies, it might be helpful for clinical decision taking. The addition of rituximab is indispensable regardless of the risk category and site of involvement, while RT consolidation is questionable and should be reserved to those cases who are ineligible to rituximab. These results need to be evaluated in prospective trials.

disclosure

The authors have declared no conflicts of interest.

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Cognitive function and fatigue after diagnosis of colorectal cancer

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Background: Cognitive impairment and fatigue have been associated with cancer and its treatment. We present baseline data from a large longitudinal study that evaluates cognitive function, fatigue, and potential underlying mechanisms following diagnosis of colorectal cancer (CRC).

Patients and methods: We evaluated CRC patients with stage I–III disease before or after surgery, participants with limited metastatic disease and healthy controls (HC). Neuropsychological evaluation included clinical and computerised tests. Participants completed questionnaires for fatigue and quality of life (QOL)-(FACT-F), anxiety/depression, and cognitive symptoms (FACT-Cog). Ten cytokines, clotting factors, sex hormones, carcinoembryonic antigen (CEA), and apolipoprotein E genotype were evaluated. Primary end points were cognitive function on clinical tests evaluated by a Global Deficit score (GDS) and fatigue. Associations between test results, demographic, and disease related factors were explored.

Results: We assessed 291 participants with early-stage disease [median age 59 (23–75) years, 63% men], 72 with metastatic disease, and 72 HC. Using GDS, 45% (126/281) of participants with early-stage CRC had cognitive impairment versus 15% (11/72) of HC (odds ratio 4.51, 95% confidence interval 2.28–8.93; $P < 0.001$), with complex processing speed, attention/working memory, and verbal learning efficiency being most affected. Women with early-stage CRC had greater cognitive impairment than men [55/105 (52%) versus 71/176 (40%), $P < 0.050$]. Cognitive symptoms were self-reported by 21% (59/286) of early-stage patients versus 17% (12/72) of HC; fatigue by 52% (149/287) of early-stage patients and 26% (19/72) of HC ($P < 0.0001$). Women reported more fatigue than men ($P = 0.003$). Fatigue, QOL, anxiety/depression, and cognitive symptoms were associated with each other ($r = 0.43$–0.71), but not with neuropsychological performance. Most cytokines were elevated in cancer patients. Cognitive function was not associated with cytokines, sex hormones, clotting factors, CEA, or apolipoprotein E genotype.

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