

Original article

Stage-modified international prognostic index effectively predicts clinical outcome of localized primary gastric diffuse large B-cell lymphoma

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Summary

Background: The definition of prognostic parameters in early stages of gastric lymphoma is still controversial. The aim of this retrospective analysis was to assess the value of the stage-modified international prognostic index (IPI) in predicting the outcome of a large, consecutive series of patients with PGL of diffuse large B-cell histology (DLCL).

Patients and methods: Three hundred twelve consecutive, newly-diagnosed, patients with localized PGL (stages I–III according to the 'Lugano staging system for GI lymphomas') referred from April 1972 to December 1997 to eight Italian and one Swiss centers were reviewed and their outcomes updated to June 1998. One hundred three patients were treated with single-modality therapy, while two hundred four received combined-modality treatment, most of which included surgery and short-term chemotherapy.

Results: After a median follow-up of 66 months (range 0.6–300 months), 195 (64%) were alive in first continuous complete remission (CCR). The five-year estimates of overall survival (OS) and event-free survival (EFS) were 75% and 67%, respectively. OS and EFS varied according to IPI, from, respectively, 90% and 82% for patients with 0–1 risk factors, to 40% and 35% for patients with ≥ 3 risk factors ($P = 0.00001$). Cox regression analysis showed that IPI was the strongest predictor of survival.

Conclusions: This study shows that stage-modified IPI is an effective predictive model in patients with primary DLCL of the stomach, enabling identification of patients with significantly different outcomes.

Key words: combined-modality treatment, DLCL, PGL, stage-modified IPI

Introduction

Non-Hodgkin's lymphomas (NHL) arising from extranodal sites represent approximately one-half of all NHL and have significantly different morphologies, presentations and natural histories than those of their nodal counterparts [1]. It may be that these tumors present specific problems requiring different treatment strategies.

Primary gastric lymphoma (PGL) is the most common extranodal NHL, accounting for approximately 30% of all extranodal cases, and it remains the subject of much debate and controversy with regard to the appropriate treatment. The two more common histologic subtypes in the stomach are the clinically-indolent mucosa-associated lymphoid tissue (MALT) low-grade lymphoma and the more aggressive diffuse large B-cell lymphoma (DLCL). The historical indication for surgery in the initial treatment of gastric MALT lymphoma has recently been questioned and most patients with low-grade histology confined to the stomach are currently treated with antibiotics for *Helicobacter pylori* infection

[2, 3], and subsequently by chemotherapy or radiotherapy when the disease persists [4–6]. In contrast, the management of patients with aggressive PGL is even more controversial [7, 8]. In this setting evaluation of factors that might influence prognosis, such as the international prognostic index (IPI), together with the role of different treatment strategies could be of great utility for a more coherent approach to the management of these patients. The international prognostic index was shown to be an effective prognostic model for advanced DLCL [9] and a model of IPI, including Stage II within adverse features, was recently used successfully in predicting the clinical outcome of patients with early-stage aggressive NHL of both nodal and extranodal origin [10]. However, in this analysis, no clear-cut information about the prognostic factors of DLCL of the stomach is offered. Thus, we decided to contribute to this field by investigating the role of IPI in predicting relevant clinical outcomes such as response to therapy and survival in a large and unselected series of patients with aggressive PGL.

Table 1. Clinical characteristics of 312 patients with PGL.

Characteristics	Number of assessable patients	Number of patients (%)
Age (in years)	312	
Median	61	
Range	14–85	
Sex		
Male	312	161 (52) 151 (48)
Main symptoms ^a	307	
Epigastric pain		234 (76)
Nausea/vomiting		64 (21)
Weight loss		62 (20)
Haemorrhage		26 (8)
Perforation		7 (2)
Ileus		2 (0.6)
B symptoms	307	31 (10)
Localization within the stomach ^b	297	
Cardia		16 (5)
Fundus		42 (14)
Corpus		146 (49)
Antrum		128 (43)
Pylorus		11 (4)
Stump		6 (2)
Endoscopic findings ^c	286	
Ulceration		193 (67)
Diffuse infiltration/polypoid		68 (24)
Gastritis		30 (10)
Histology	312	
Diffuse large cell		265 (85)
Diffuse large cell with low-grade component		47 (15)
Bulky disease ≥ 10 cm	310	58 (19)
Lugano staging	312	
I		163 (52)
II1		56 (18)
II2		50 (16)
IIE		43 (14)
Previous or concomitant malignancies	312	13 (4)

^a Numbers total > 307, as > 1 symptom can be found in the same patient.

^b Numbers total > 297, as > 1 localization can be observed in the same stomach.

^c Numbers total > 286, as > 1 finding can be observed in the same case.

Patients and methods

Staging

Three hundred twelve consecutive newly-diagnosed patients with diffuse large B-cell histology (DLCL) of the stomach referred from April 1972 to December 1997 to eight Italian and one Swiss centers were reviewed and their outcomes updated to June 1998. The pathologists of each of the institutions reviewed all of the original histology slides. Patients with a minor low-grade histology component within a prominent DLCL in their biopsy specimens were not excluded from the study. Cases were defined as primary gastric lymphoma (PGL) if the stomach was the most probable site of origin of NHL, despite limited or extensive dissemination within the abdominal cavity [11, 12]. The diagnostic workup included patient history and physical examination, radiological and endoscopic evaluation with multiple biopsies of the stomach completed by computer-assisted tomography of chest, abdomen and pelvis, bone marrow biopsy, examination of Waldeyer's ring and routine chemistry tests including measurement of serum lactate

dehydrogenase (LDH) and peripheral-blood counts. Bulky disease was defined as any mass 10 cm or more in maximal diameter. Weight loss was not considered a B symptom because it usually depended on gastric localization. Patients were staged according to a Blackledge [13] modified classification for lymphomas of the gastrointestinal tract (Lugano staging system for gastrointestinal NHL) [14]. Briefly, stage I included patients with lymphoma confined to stomach as single primary site or multiple, non-contiguous lesions. In stage II lymphoma was extended into abdomen involving local (paragastric) (stage II1) or distant (celiac or retroperitoneal) (stage II2) lymph nodes or penetrated into serosa involving adjacent organs or tissues (stage IIE). Finally, stage IV patients had a disseminated extranodal involvement of lymphoma or a gastric lesion with supradiaphragmatic nodal involvement. In the present analysis we included only patients with localized disease, thereby excluding those with stage IV.

Stage-modified international prognostic index (IPI)

IPI [9, 10] was modified by substituting the above-cited Lugano staging system for GI-NHL for the Ann Arbor stage II. The following adverse prognostic variables were considered: age > 60 years, stage \geq II2, increased LDH, ECOG performance status (PS) ≥ 2 and more than one extranodal site (EN) of disease, excluding stomach. Age, clinical stage, performance status and number of extranodal sites were available for all patients, while serum LDH was reported in 259 of 312 patients (83%). The IPI of initial diagnosis was thus available in 259 patients. Three risk categories were defined according to the number of adverse prognostic features: 0 or 1 variable, low-risk category; 2 variables, intermediate-risk category (low- intermediate category of IPI); ≥ 3 variables, high-risk category (high-intermediate and high of IPI).

Response evaluation

The study covers a long period of time in which the chemotherapy, surgery, and radiotherapy choices were not predefined. However, in most of the institutions the prevailing strategy was surgery followed by adjuvant chemotherapy. Some patients had surgery only either because of a very limited disease or because post-surgery complications did not allow the administration of further therapy. Other patients were judged as inoperable and were given only chemotherapy.

Patients were considered in complete remission (CR) when all physical and radiological signs of disease had disappeared for a minimum of four weeks. Patients not in CR at the end of the treatment program were considered as treatment failures. After completion of treatment, patients were seen every 3 to 4 months for the first two years and every 6 to 12 months thereafter.

Statistical analysis

The end-points were the rate of patients alive in first continuous complete remission (CCR), overall survival (OS) and event-free survival (EFS). The follow-up of patients in CCR was calculated from the achievement of CR to relapse, last follow-up alive or death regardless of cause. Overall survival was computed by the life-table method starting from diagnosis to date of death, whatever the cause, or last follow-up alive. Events were treatment failure, relapse, evidence of disease progression or death, whatever the cause and EFS was calculated from the date of diagnosis. The statistical significance of observed differences was assessed by the log-rank test and all probability values were two-sided. The prognostic value of different variables for clinical outcome (sex, IPI, residual low-grade component, B symptoms, bulky disease) was assessed by multivariate analysis using the Cox multiple regression model. Risk ratios (RR) and 95% confidence intervals (95% CI) were used to compare groups with regard to major clinical outcomes. All analyses were done using the Intercooled Stata 4.0 statistical package (Stata Corporation, 702 University Drive East College Station, TX 77840, USA).

Results

Patient characteristics

Patient clinical characteristics at presentation are reported in Table 1. Three hundred twelve consecutive patients with a median age of 61 years (range 14–85 years), 161 of them male and 151 female, were diagnosed as having a PGL by endoscopy (286 cases) or laparotomy (26 cases) and followed for a median of 66 months (range 0.6–300 months). The most common complaint at presentation was abdominal pain (76%) associated with nausea and vomiting (21%) and weight loss (20%). Upper gastrointestinal tract bleeding, such as hematemesis or melena, was documented in only 8% of patients and a minority of cases (3%) presented with perforation or occlusion. B symptoms were present in only 31 patients (10%). The body and pyloric antrum were the most common sites of involvement and ulceration was found in the majority of patients (67%). Two hundred sixty-five patients (85%) were classified as having a DLCL, while in forty-seven (15%) cases there was evidence of residual MALT low-grade component. Bulky disease was present in 58 patients (19%).

According to the 'Lugano staging system for GI NHL' 163 patients (52%) had a limited disease (stage I). In 56 (18%) patients PGL was detected in paragastric lymph nodes (stage III). In 93 patients (30%) the disease was extended above the stomach region: in 50 cases in distant abdominal lymph nodes such as celiac or retroperitoneal (stage II2), while in the remaining 43 cases the disease penetrated serosa and involved adjacent organs (liver, pancreas, duodenum, spleen, kidney) (stage IIE).

Eleven patients (3.5%) had had a previous malignancy (four hematological and seven epithelial malignancies) at a median time of four years (range 1–19 years) prior to the PGL diagnosis. In a further two cases gastric carcinoma, in addition to lymphoma, was diagnosed in the same sample obtained by gastrectomy.

Table 2 reports the frequency of parameters considered for the assignment of IPI score in 259 patients in whom all the risk factor data, including LDH, were available. One hundred twenty-two patients (47%) were older than sixty years and eighty-four (32%) presented an extended disease (stage > II2). The rate of other risk factors (poor ECOG-PS, elevated LDH, extranodal sites ≥ 2) ranged from 3%–23%. According to stage-modified IPI 167 patients (65%) were in the low-risk category, 52 (20%) in the intermediate category, and 40 (15%) in the high-risk category.

Treatment

In five cases (2%) no treatment was administered due to either poor performance status or advanced patient age: four died of the disease and one is alive with lymphoma 15.6 months after diagnosis. Treatment modalities are detailed in Table 3.

Table 2. Characteristics of 259 patients with PGL according to IPI.

Characteristics	Number of patients (%)
Age > 60 years	122 (47)
Lugano staging \geq II2	84 (32)
ECOG performance status ≥ 2	60 (23)
Increased LDH	52 (20)
Extranodal sites ≥ 2	7 (3)
Number of risk factors	
0–1	167 (65)
2	52 (20)
≥ 3	40 (15)

Table 3. First treatment of 312 patients with PGL.

Treatment	Number of patients
Single therapy	103
Chemotherapy	54
Surgery	46
Radiotherapy	3
Combined therapy	204
Surgery + chemotherapy	147
Surgery + chemotherapy + radiotherapy	39
Chemotherapy + radiotherapy	11
Surgery + radiotherapy	7
No treatment	5

Surgery

Two hundred thirty-nine patients (77%) underwent partial (139 cases) or total (100 cases) resection of stomach. Of this group, 46 (19%) with localized disease were treated by surgery alone, while adjuvant treatment was generally reserved for patients with advanced disease. Surgical morbidity including post-operative abscess, bleeding, anastomosis dehiscence, occlusion, fistula and deep-vein thrombosis or pulmonary embolism was 15% and was prevalent in patients older than 70 years. Mortality from surgery was 0.4%. However, the rate of peri-operative fatalities could have been underestimated, since most cases were referred after surgery, though delay of adjuvant therapy caused by postoperative complications was generally noticed.

Chemotherapy

Two hundred fifty-one patients (80%) were treated with chemotherapy, of whom 186 received chemotherapy after PGL resection. The details of the chemotherapy regimens varied according to protocols in use at the time in different centers, but 217 of 251 (86%) patients received an adriamycin-containing regimen, 173 patients standard CHOP, 44 second- or third-generation treatment programs such as m-BACOD, ProMaCE-CytaBOM and MACOP-B and 34 patients (14%) non-adriamycin-containing regimens such as COP or CVP. In patients who were given chemotherapy alone, treatment-associated morbidity including perforation and acute bleeding (2%), intestinal obstruction, intestinal infarction, infec-

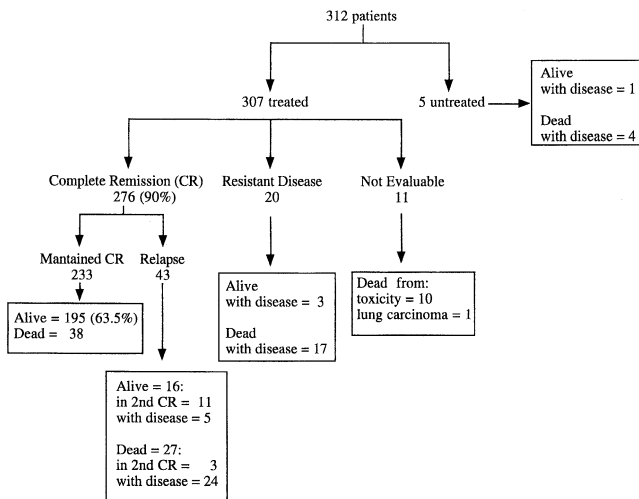


Figure 1. Flow diagram of clinical outcome of the 312 PGL patients.

tion, worsening of performance status and peripheral neuropathy was 35% and mortality 11%, while in those who received chemotherapy after surgery, morbidity and mortality were 32% and 2%, respectively.

Radiotherapy

Sixty patients (19%) received radiation therapy, usually as adjuvant treatment following surgery (7 cases), surgery and chemotherapy (above-cited 39 cases) or chemotherapy alone (11 cases). Three elderly patients with lymphoma limited to the gastric wall were selectively treated with radiation therapy alone because of high surgical and chemotherapy risk due to poor performance status.

Second tumors

Fourteen patients (5%) developed an additional solid tumor (four lung carcinomas, two breast carcinomas, one cutaneous squamous cell carcinoma, one distal esophageal carcinoma, one leiomyosarcoma, one pancreatic carcinoma, one melanoma, one bladder carcinoma, one glioblastoma, one hepato-cellular carcinoma) at a median of 5 years (range 2–21 years) after PGL diagnosis. The rate of second tumor in 3 of 46 patients (7%) who only underwent surgery was comparable to that of 11 of 251 (4%) patients treated with chemotherapy or combined therapy including chemotherapy ($P = 0.42$).

Response to treatments

One hundred ninety-five of three hundred seven treated patients (64%) are alive and in complete remission (CCR) with a median follow-up of seventy-seven months (range 4–285 months) (Figure 1), while twenty (7%) showed resistance to treatment and forty-three of two hundred seventy-six (16%) achieving CR, eventually relapsed. Eighteen patients (42%) relapsed in the site of prior disease after surgery (11%) or chemotherapy alone

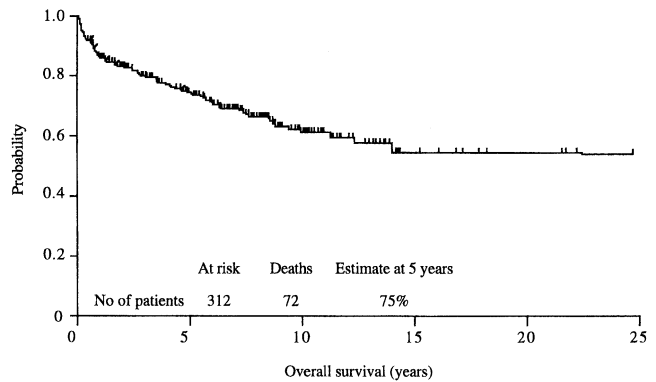


Figure 2. Overall survival of the 312 PGL patients.

Table 4. Response rate of 255 treated patients with PGL according to IPI.

Risk factors	Number of patients		P value
	Total	First CCR (%)	
0–1	166	132 (79.5)	–
2	51	21 (41)	< 0.00005
≥ 3	38	14 (37)	< 0.00005
Total	255	167 (65)	

(13%) or combined treatment (3%). In 25 (58%) patients relapses were in new sites. Following relapse 11 patients (25%) achieved and maintained complete remission, while 5 are alive with lymphoma. In the group of 20 patients resistant to first-line treatment only 3 are alive with disease. The remaining 11 patients were not evaluable because 10 died of treatment-related toxicity and one of lung carcinoma. The CCR depended on IPI (Table 4) and was significantly better in patients with 0–1 than in those with high risk factors, ranging from 80% to 37%, respectively ($P < 0.00005$).

Overall survival analysis

Ninety-seven patients (31%) had died at the time of the analysis. Forty patients died of lymphoma, eleven of other malignancies (10 of metachronous tumor, 1 of previously diagnosed cancer and 1 of synchronous cancer), fifteen of heart disease, ten of treatment-related toxicity. In 21 patients the cause of death was unknown. The median follow-up times for surviving patients were 65 months (range 4–296 months). As shown in Figure 2 the actuarial estimate of overall survival at five years was 75%. Actuarial analysis of survival at 5 years showed a long-term success rate of 71% for patients with stage I–III and of 55% for patients with stage II2–III ($P = 0.022$). In contrast, no statistically significant difference in terms of survival was found between patients with stage I and those with stage III ($P = 0.464$) (data not shown). Therefore, stage ≥ II2 and not III was used to calculate the risk factors of stage-modified IPI. Moreover, overall survival varied according to the risk categories estab-

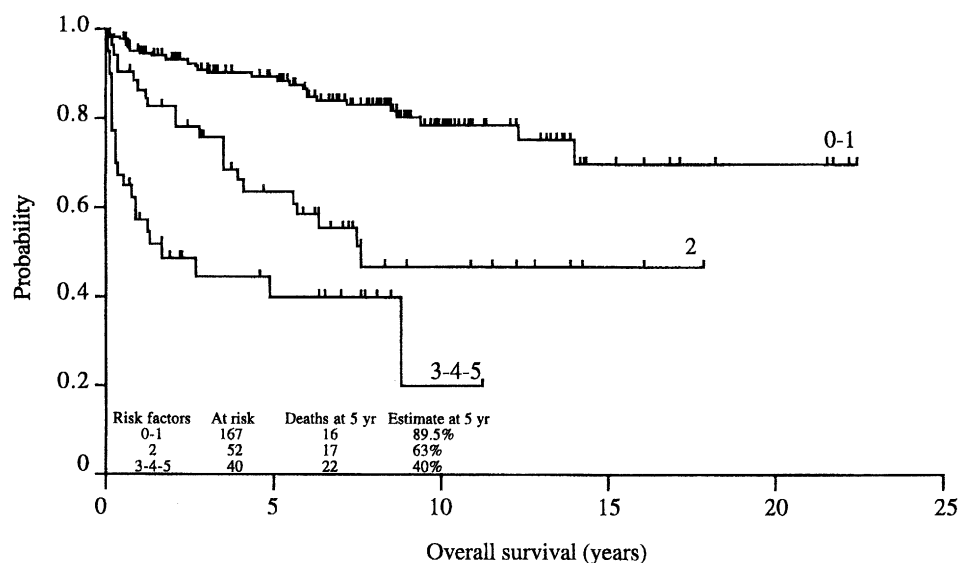


Figure 3. Overall survival of the 259 PGL patients according to the number of IPI risk factors: 0–1 vs. 2 risk factors ($P < 0.00001$); 0–1 vs. ≥ 3 risk factors ($P < 0.00001$); 2 vs. ≥ 3 risk factors ($P = 0.0063$).

Table 5. Risk factors for OS in 259 patients with PGL.

Variable	Analysis	Analysis			
		Univariate		Multivariate	
		Death rate (%)	P value	RR (95% CI)	P value
IPI ^a = 2	Yes	22/52 (42)	0.018	2.60 (1.46–4.66)	0.001
	No	53/207 (26)			
IPI ^a ≥ 3	Yes	24/40 (60)	< 0.0001	6.27 (3.51–11.19)	0.0001
	No	51/219 (23)			
Bulky disease ≥ 10 cm	Yes	20/45 (44)	0.012	1.49 (0.88–2.52)	0.140
	No	55/214 (26)			
Diffuse large cell with low-grade component	Yes	3/31 (10)	0.012	0.41 (0.13–1.30)	0.130
	No	72/228 (32)			
B symptoms	Yes	13/31 (42)	0.096	1.14 (0.62–2.10)	0.677
	No	62/226 (27)			
Sex = male	Yes	42/138 (30)	0.576	1.17 (0.74–1.86)	0.498
	No	33/121 (27)			

^a IPI = 0–1: reference category.

lished by this prognostic system (Figure 3). The five-year estimate for OS was 89.5% for patients in the low-risk category, 63% for patients in the intermediate-risk category and 40% for patients in the high-risk category ($P = 0.00001$). Table 5 showed the results of univariate and multivariate analyses of parameters considered as predictors of OS. In the univariate analysis the following variables were related to short survival: the presence of two or more risk factors according to IPI, bulky disease and a large-cell histology without a low-grade component in biopsy specimens. In the multivariate analysis IPI ≥ 3 was the strongest factor predicting survival (RR = 6.27, 95% CI: 3.51–11.19, $P = 0.0001$). A multivariate analysis of prognostic factors for OS was performed using IPI [9] and the results were comparable to

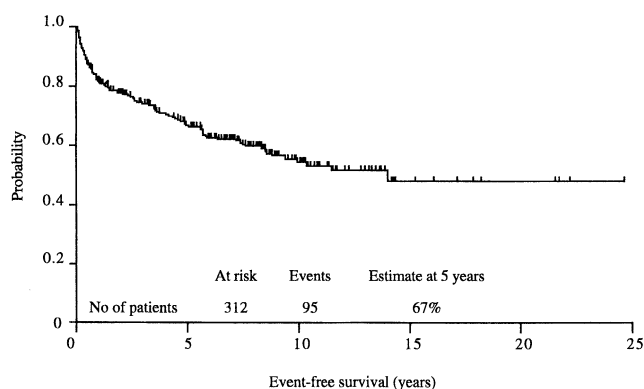


Figure 4. Event-free survival of the 312 PGL patients.

those obtained by the stage-modified IPI model (data not shown). Moreover, a multivariate analysis considering separately the single risk factors included in stage-modified IPI was done and PS ≥ 2 and age ≥ 60 years most effectively predicted OS (RR = 4.49, 95% CI: 2.68–7.53, $P = 0.0001$ and RR = 2.27, 95% CI: 1.35–3.81, $P = 0.002$, respectively).

Event-free survival

One hundred seventeen patients had events. Forty-eight died, twenty-six patients had resistant or progressive disease and forty-three relapsed. The median follow-up time for surviving patients without events was 80 months (range 6–295 months) and, as shown in Figure 4, the actuarial estimate of EFS at 5 years was 67%. The EFS of patients according to stage-modified IPI is shown in Figure 5. The five-year EFS was 82%, 48% and 35% for patients with 0 or 1, 2 or with 3 or more risk factors ($P = 0.00001$). The factors considered as predictors of EFS are shown in Table 6 together with the results of univariate and multivariate analysis. By univariate anal-

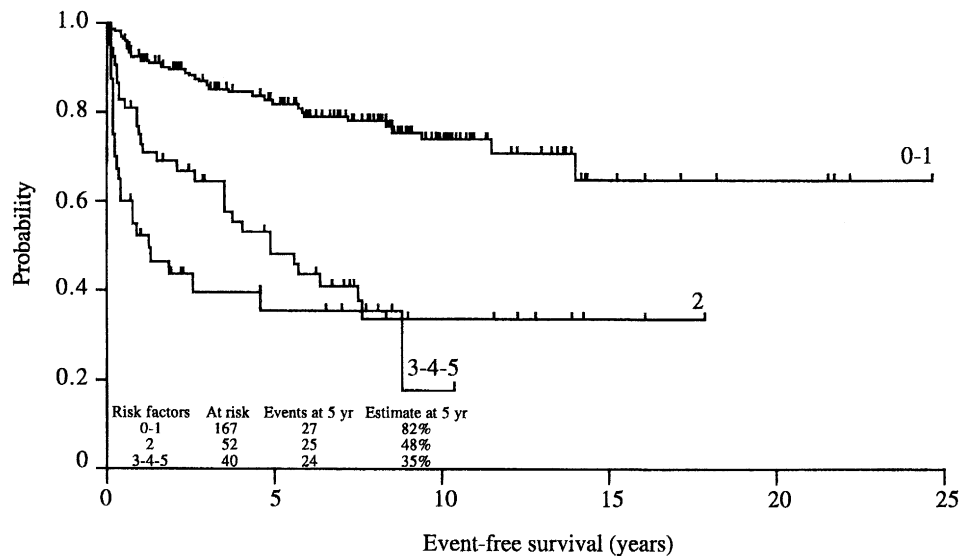


Figure 5. Event-free survival of the 259 PGL patients according to the number of IPI risk factors: 0–1 vs. 2 risk factors ($P < 0.00001$); 0–1 vs. ≥ 3 risk factors ($P < 0.00001$); 2 vs. ≥ 3 risk factors ($P = 0.06$).

Table 6. Risk factors for EFS in 259 patients with PGL.

Variable	Analysis	Analysis			
		Univariate		Multivariate	
		Event rate (%)	P -value	RR (95% CI)	P -value
IPI ^a = 2	Yes	30/52 (58)	0.0001	3.04 (1.84–5.04)	0.0001
	No	62/207 (30)			
IPI ^a ≥ 3	Yes	26/40 (65)	0.0001	5.38 (3.16–9.16)	0.0001
	No	66/219 (30)			
Diffuse large cell with low-grade component	Yes	3/31 (10)	0.001	0.29 (0.91–0.93)	0.037
	No	89/228 (39)			
B symptoms	Yes	16/31 (52)	0.044	1.18 (0.68–2.05)	0.553
	No	75/226 (33)			
Bulky disease ≥ 10 cm	Yes	21/45 (47)	0.086	1.14 (0.69–1.88)	0.613
	No	71/214 (33)			
Sex = male	Yes	46/138 (33)	0.432	0.84 (0.56–1.28)	0.422
	No	46/121 (38)			

^a IPI = 0–1: reference category.

ysis it appears that the presence of two or more risk factors according to IPI, a large cell histology without low-grade component in biopsy specimens and B symptoms were related to a poor outcome. However, by Cox multivariate analysis, IPI ≥ 3 was the strongest predictor of EFS (RR = 5.38, 95% CI: 3.16–9.16, $P = 0.0001$). Prognostic factors for EFS were also analyzed using the IPI model [9] and the results were comparable to those obtained by the stage-modified IPI system (data not shown). Moreover, single factors included in stage-modified IPI were examined by multivariate analysis and PS ≥ 2 , age ≥ 60 years and elevated LDH were the most effective variables in predicting EFS. (RR = 5.75, 95% CI: 2.49–6.44, $P = 0.0001$; RR = 2.92, 95% CI: 1.25–3.15,

$P = 0.003$ and RR = 1.95, 95% CI: 0.99–2.48, $P = 0.051$, respectively).

The analysis of EFS according to different treatments of 255 patients included in each of the three risk groups of stage-modified IPI showed that in 32 patients with 0–1 risk factors who were given single therapy, the clinical outcome was inferior to that obtained in 134 patients who received combined therapy (EFS at 5 years 72% vs. 85%, $P = 0.006$). The advantage of combined therapy over single treatment in terms of EFS was also confirmed in 51 patients with 2 risk factors (EFS at 5 years 58 vs. 37, $P = 0.04$) and in 38 patients with ≥ 3 risk factors (EFS at 5 years 62% vs. 19%, $P = 0.05$).

Discussion

This multicenter study was undertaken to assess the value of the IPI in predicting the clinical outcome of a wide and unselected series of patients with primary gastric lymphoma. With this aim, 312 patients with a histologically proven diagnosis of diffuse large B-cell lymphoma confined to stomach or limited to abdominal cavity were analyzed. The patients' clinical presentation and the diagnostic approach in this series are the same as those reported in previous studies [15–18]. In fact, the majority complained of abdominal pain, only a few of them presented surgical emergency, and diagnosis was mostly obtained by endoscopy. Regarding prognostic factors, IPI effectively predicts the response rate and survival of patients with advanced DLCL [9] and recently a model of IPI including stage II according to the Ann Arbor staging system within adverse factors was shown to be an effective prognostic model for patients with early-stage aggressive NHL of both nodal and extranodal origin [10]. In the present study the Ann Arbor staging system was replaced by the Lugano staging

system for GI-NHL so that we analyzed the clinical outcome of patients with advanced stage (\geq II2) in comparison with those with disease confined to stomach or paragastric lymph nodes (stages I–III1). Since the survival of patients with stage \geq II2 was significantly poorer than that of patients with more localized disease, the stage \geq II2 was included in the IPI model, with other adverse factors such as an age $>$ 60 years, increased LDH, ECOG performance status (PS) \geq 2 and more than one extranodal site (EN) of disease excluding stomach. This stage-modified IPI model enabled us to separate patients into three risk categories with very different survivals. In fact, patients in the low-risk category had a five-year estimate of event-free survival of 82%, while it was 48% and 35% for patients in the intermediate- and high-risk categories, respectively. Although these results could have been influenced by the therapy, the heterogeneity inherent in the variably treated groups and the retrospective nature of this study, prevented us from drawing firm conclusions as to the role of different therapeutic strategies. However, the analysis of treatments of patients in each of the three different risk groups showed that the number of IPI adverse features affected the efficacy and toxicity of different therapies.

The low-risk group mostly included patients with better presenting features such as age less than sixty years, a disease confined to the stomach, a good performance status and a low LDH value. The prevailing treatment given to these patients was surgery followed by a short-term course of adjuvant chemotherapy with adriamycin-containing regimens with or without radiotherapy. Nonetheless, selected cases underwent only surgery because of limited disease or were only given chemotherapy due to advanced age or poor performance status. Approximately 80% of patients are alive and still in first complete remission after a median follow-up of almost six years. This notable result is comparable with the best data reported by retrospective studies in smaller series treated with combined modality [19] and with those prospectively obtained by some authors who excluded surgery from their therapeutic strategy [20–22] or compared the clinical outcomes of resected and unresected PGL patients, without finding any significant difference between the two groups [23, 24]. In this low-risk category the chemotherapy-related morbidity (2.4%) and mortality (1.5%) were comparable to those reported in the literature [10, 20, 25, 26]. In particular, none of the patients immediately treated with chemotherapy at diagnosis had bleeding or perforation, which were previously reported as a major reason for preferring surgery in this setting [27–29]. On the other hand, surgical resection of the stomach presented very low morbidity (2.7%) and mortality (0.7%) in contrast to those reported in literature [30], even though we can not rule out the possibility that the rate of perioperative fatalities is underestimated since most cases were referred after surgery. Finally, our analysis is scarcely informative as to the toxicity associated with radiotherapy, but this

should not be ignored when considering the frequent involvement of the left kidney within the radiation field [21, 31–33].

The intermediate risk category accounted for 20% of patients and approximately half of them was free of adverse events at five years after surgery followed by a short-term course of adjuvant chemotherapy or chemotherapy alone, while those who underwent only surgery had a worse outcome.

In contrast to the relatively good results obtained in low- and intermediate-risk-category (IPI \geq 2) patients, only 35% of those with high IPI score experienced a long-term event-free survival. The best results were obtained by combining surgery and chemotherapy, while chemotherapy alone yielded the poorest results. This was not unexpected, since, in most institutions, chemotherapy alone was usually given to the inoperable patients with poor general condition and/or in locally advanced disease. Failures were due to chemotherapy resistance or relapse in the majority of cases (84%), while treatment-associated toxicity was responsible for death in 26% of patients. It is noteworthy that 9 of 26 (35%) high-risk patients who were given only chemotherapy did not complete the planned program because of toxicity during treatment. This indicates that intensive regimens of chemotherapy are hardly feasible in this group which primarily includes elderly patients. Obviously, the retrospective nature of our analysis prevented us from establishing the best treatment modality for the high-risk category of PGL patients, but it would seem reasonable that in patients in whom surgical resection is feasible, surgery followed by a short-term chemotherapy might be a valid up-front treatment. Patients who are considered unsuitable for surgery should be treated with chemotherapy and possibly adjuvant radiotherapy. Our analysis is not informative about this strategy because only a few patients were given this treatment, but the results of two prospective randomized trials [10, 34] showed that treatment with both chemotherapy and radiation therapy is clearly better and less toxic than chemotherapy alone in patients with early-stage NHL of both nodal and extranodal origin. However, the role of chemotherapy alone or combined with adjuvant radiotherapy in different risk categories of localized NHL, including stomach, and the best modality of radiotherapy administration was not clearly defined and remains a matter of investigation [10].

In conclusion, IPI seems capable of separating PGL patients in three subgroups with different clinical outcomes, suggesting a possible different treatment approach that, however, should be investigated by prospective randomized multicenter trials.

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