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# The modified International Prognostic Index can predict the outcome of localized primary intestinal lymphoma of both extranodal marginal zone B-cell and diffuse large B-cell histologies

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**Summary.** We have previously reported on the efficacy of a modified International Prognostic Index (MIPI) in predicting the outcome of patients with primary gastric lymphoma. This prompted the retrospective analysis of a large series of patients with primary intestinal lymphoma (PIL) of both diffuse large B-cell (DLCL) and low-grade (extranodal marginal zone B-cell lymphoma, MZL) histology. Clinical records of 122 patients with localized primary intestinal lymphoma of MZL ($n = 35$) and DLCL ($n = 87$) histology, confirmed by an *ad hoc* expert panel of pathologists, were reviewed. Forty-nine patients were treated with single therapy, while 72 received combined-modality treatment, which included surgery followed by a short-term chemotherapy. MIPI was included in a multivariate prognostic analysis for overall survival (OS) and event-free survival (EFS). Sixty-five patients (75%) with DLCL and 22 with MZL (65%) achieved complete remission. After a median follow-up of 42 months (range 6–163 months), 5-year estimates of OS and EFS were 68% and 50% for DLCL and 65% and 26% for MZL. OS varied according to MIPI, from, respectively, 86% and 87% for DLCL and MZL patients with 0–1 risk factor to 50% and 32% for patients with > 1 risk factor ($P = 0{\cdot}01$ and $P = 0{\cdot}02$). Similar results were obtained for EFS. Cox regression analysis showed an unfavourable MIPI to be the only independent predictor of shorter EFS. This retrospective study shows that stage-MIPI can be a reliable prognostic indicator for PIL of both low-grade MZL and diffuse large B-cell histology, enabling the early identification of patients at higher risk of failure.

**Keywords:** modified international prognostic index (MIPI), primary intestinal lymphoma (PIL), extranodal marginal zone B-cell lymphoma (MZL), diffuse large B-cell lymphoma (DLCL).

The gastrointestinal tract (GI) is the commonest site for extranodal non-Hodgkin's lymphoma (NHL) (Zucca *et al*, 1997), and primary gastric NHL is more frequent than intestinal NHL. Primary intestinal non-Hodgkin's lymphoma is characterized by younger age at presentation, less localized stage of disease and more aggressive histological type, mainly diffuse large B-cell type (DLCL) (Gospodarowicz *et al*, 1990; Radaszkiewicz *et al*, 1992; D'Amore *et al*, 1994; Kocher *et al*, 1997). The other most frequent histological subtype in the bowel is extranodal marginal zone B-cell lymphoma (MZL) low-grade lymphoma. MZL arising in the stomach has been shown to have a better outcome than

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DLCL and to be related to *Helicobacter pylori* infection (Roggero *et al*, 1995). Treatment of primary intestinal lymphoma remains controversial. Surgery has an important role in local control of the disease and related complications such as bowel obstruction, bleeding or perforation. However, resection rarely eradicates lymphoma and many patients require further treatment either with chemotherapy (Salles *et al*, 1991; Shepherd *et al*, 1998) or radiotherapy (Herrmann *et al*, 1980; Gospodarowicz *et al*, 1983; Geara, 1999). This continues to be a matter of debate.

In this setting, the evaluation of factors that influence prognosis, such as those considered by the International Prognostic Index (IPI), could be useful for a more coherent management approach. The IPI is an effective prognostic model for advanced DLCL (Shipp & Harrington, 1993). Recently, a modified IPI (MIPI), including stage II within adverse features, was successfully used to predict the outcome of patients with early stage aggressive nodal and extranodal NHL (Miller *et al*, 1998) as well as primary gastric DLCL (Cortelazzo *et al*, 1999). Thus, we extended the analysis to patients with primary intestinal lymphoma of MZL and more cases with DLCL histology to investigate the role of the MIPI in predicting response to different treatments and patient survival.

## PATIENTS AND METHODS

*Patients.* Between September 1982 and January 2000, the clinical records of 287 consecutive newly diagnosed patients with primary intestinal lymphoma were filed at 16 participating centres. The original histology slides were available for 161 patients and were centrally reviewed by an *ad hoc* expert panel according to the World Health Organization (WHO) Classification of Tumors (2001). The 161 cases were reclassified as Burkitt lymphoma (10 cases, 6%), anaplastic large cell lymphoma (8 cases, 5%), mantle-cell lymphoma (5 cases, 3%), peripheral T-cell lymphoma (3 cases, 2%), other unspecified histology (13 cases, 8%) and low-grade MZL or DLCL (122 cases, 76%). The latter group was selected for the current retrospective study because of the large patient number and a greater clinico-diagnostic and therapeutic homogeneity. All cases satisfied the criteria for primary gastrointestinal lymphoma (GIL) as previously defined (Lewin *et al*, 1978; Herrmann *et al*, 1980). Detailed disease history and prior therapy records were reviewed.

*Methods.* Staging procedures were performed with standard methods available at time of first diagnosis and were considered adequate only when they included: patients' history and physical examination, radiological and endoscopic evaluation with multiple biopsies of upper and lower GI tract, computerized tomography of chest, abdomen and pelvis, abdominal ultrasound evaluation, bone marrow biopsy, examination of Waldeyer's ring and routine biochemistry including measurement of serum lactate dehydrogenase (LDH) and full blood counts. Patients undergoing surgery had additional pathological staging. Bulky disease was defined as any mass 10 cm or more in maximal diameter. Weight loss was not considered a systemic B symptom because a consequence of disease localization was anorexia and ache (Bellesi *et al*, 1989; Maor *et al*, 1990). Clinical stage was evaluated in accordance with the Lugano-modified Ann Arbor classification for gastrointestinal lymphomas (Rohatiner *et al*, 1994). This staging system was chosen because it was designed for lymphoma of the gastrointestinal tract and included the main modifications to the Ann Arbor system adopted in previous staging classifications (Mushoff, 1977; Blackledge *et al*, 1979). Stage I included patients with lymphoma confined to the gastrointestinal tract as single primary site or multiple, non-contiguous lesions diagnosed simultaneously at several gastrointestinal sites. In stage II, lymphoma was extended into the abdomen involving local (paraintestinal) (stage II1) or distant (coeliac or retroperitoneal) (stage II2) lymph nodes, or penetrating into the serosa to involve adjacent organs (stage IIE). Finally, stage IV patients had disseminated extranodal involvement or supradiaphragmatic nodal involvement. The present analysis excluded those with stage IV.

*Treatments.* The study covered a long period of time in which the surgery, chemotherapy and radiation therapy choices were not predefined. However, in most of the institutions the initial therapy included surgery. After an initial surgical approach, patients were managed with observation, chemotherapy, radiation therapy or combined therapy. Treatment was based upon age, performance status, symptoms, stage, histological grade and size of lymphoma.

*Assessment of response.* Response to treatment and end-points were assessed according to published guidelines (Cheson *et al*, 1999). Complete remission (CR) was defined as the disappearance of all clinical and radiographic evidence of disease, disease-related symptoms, and normalization of any abnormal laboratory test related to NHL for a minimum of four weeks. A decrease by at least 50% in tumour volume was defined as partial remission (PR) and anything less than PR was a non-response (NR), including an early death. Progressive disease (PD) was defined as a 50% or greater increase in tumour size or the appearance of any new lesion during or at the end of therapy. Patients not in CR at the end of the treatment programme were considered as treatment failure. After completion of treatment, patients were seen every 3–4 months for the first 2 years and every 6–12 months thereafter.

*Statistical analysis.* Study end-points were CR rate, overall survival (OS), event-free survival (EFS) and disease-free survival (DFS). Survival data were computed using the life-table method (Kaplan & Meier, 1958). OS was the interval from diagnosis to death, whatever its cause or last follow-up. Events accounting for EFS were NR, relapse, PD or death. The EFS interval was calculated from date of diagnosis to the event or last follow up. DFS was taken from the time of CR to relapse or last follow up. The clinical variables analysed in prognostic models were patient age, sex, histology, IPI risk class, B symptoms, bulky disease $> 10$ cm, anatomical involvement, number of involvement sites. As reported, we adopted a stage-modified IPI in which the original Ann Arbor stage II was substituted by the above-cited Lugano staging system for GI-NHL (Cortelazzo

*et al*, 1999). Because of the relatively small number of patients in high-risk categories (≥ 3 risk factors), subgroups with different IPI index were grouped together (low, consisting of 0–1 risk factors versus all other IPI categories) in outcome analysis.

Outcome of different clinical and prognostic groups were compared using the two-sided log-rank test (Mantel, 1966). All probability (*P*) values were two-sided and statistically significant when $< 0{\cdot}05$. A stepwise multivariate logistic regression model was used for detecting factors with independent prognostic value for response. The prognostic value of different variables for PD, relapse or death was assessed by multivariate analysis using the Cox multiple regression model (Cox & Snell, 1989). Risk ratios and 95% confidence intervals were used to compare groups with regard to established study end-points. All analyses were carried out using the INTERCOOLED STATA 4·0 statistical package (Stata Corporation, TX, USA).

## RESULTS

### *Patient characteristics*

One hundred and twenty-two patients satisfied the eligibility criteria and were thus evaluable. Eighty-seven were classified as DLCL and 35 were classified as MZL. Their median follow-up was 43 months (range 6–147 months) and 40 months (range 6–160 months) respectively. Pretreatment characteristics are listed in Table I. Median patient age was slightly higher in the MZL group, while other adverse clinical features such as advanced stage, poor Eastern Cooperative Oncology Group (ECOG) performance status (PS) (Oken *et al*, 1982), elevated LDH, extranodal disease, bulky disease and high-risk MIPI, were not statistically different into the two groups. The majority of patients were diagnosed by laparotomy ($n = 98$). The site of origin of the primary intestinal lymphoma is reported in Table II. The most frequently involved sites, in patients with DLCL, were the ileocaecal region, defined as involvement of terminal ileum, caecum, appendix and/or lower part of colon ascendens ($n = 45$) and small bowel ($n = 25$), while in the MZL group, lymphoma was equally distributed in the different parts of bowel. The tumour was confined to a single primary site in 77 cases with DLCL and 30 with MZL, while in 10 DLCL and 5 MZL patients, multiple non-contiguous lesions were simultaneously documented. Symptoms at diagnosis are given in Table III. The most frequent symptoms were abdominal pain (DLCL = 71%, MZL = 60%), nausea and vomiting (DLCL = 20%, MZL = 9%), and weight

**Table I.** Clinical features of 122 patients with primary intestinal lymphoma.

| | DLCL ($n = 87$) | | MZL ($n = 35$) | |
|---|---|---|---|---|
| Characteristics | Number of assessable patients | Number of patients (%) | Number of assessable patitents | Number of patients (%) |
| Age (years) | 87 | | 35 | |
| Median | | 56 | | 66 |
| Range | | 19–90 | | 24–89 |
| > 60 years | | 38 (44) | | 20 (57) |
| Sex, M/F | 87 | 42/45 | 35 | 17/18 |
| Lugano staging ≥ II2 | 87 | 47 (54) | 35 | 14 (40) |
| ECOG-PS ≥ 2 | 87 | 32 (37) | 35 | 10 (29) |
| Increased LDH | 76 | 19 (25) | 29 | 3 (10) |
| Extranodal sites ≥ 2 | 87 | 1 (1) | 35 | 0 |
| Bulky disease ≥ 10 cm | 73 | 32 (44) | 24 | 6 (25) |
| IPI ≥ 2 | 76 | 38 (50) | 29 | 11 (38) |

**Table II.** Sites of origin of primary intestinal lymphoma in 122 patients.

| Primary site | Total Number of patients (%) ($n = 122$) | DLCL Number of patients (%) ($n = 87$) | MZL Number of patients (%) ($n = 35$) |
|---|---|---|---|
| Small bowel | 25 (21) | 19 (22) | 6 (17) |
| Ileo-caecal origin | 47 (39) | 40 (46) | 7 (20) |
| Involvement of more than one intestinal site | 15 (12) | 10 (12) | 5 (15) |
| Other sites: | | | |
| Duodenum | 6 (5) | 1 (1) | 5 (14) |
| Colon | 20 (16) | 14 (16) | 6 (17) |
| Rectum | 9 (7) | 3 (3) | 6 (17) |

**Table III.** Symptoms at diagnosis of 122 patients with primary intestinal lymphoma.

| Symptoms* | Total Number of patients (%) ($n = 122$) | DLCL Number of patients (%) ($n = 87$) | MZL Number of patients (%) ($n = 35$) |
|---|---|---|---|
| Abdominal pain | 83 (68) | 62 (71) | 21 (60) |
| B symptoms (fever, night sweats) | 28 (23) | 23 (26) | 5 (14) |
| Nausea and vomiting | 20 (16) | 17 (20) | 3 (9) |
| Loss of weight† | 15 (12) | 12 (14) | 3 (9) |
| Bleeding | 14 (11) | 8 (9) | 6 (17) |
| Ileus | 4 (3) | 4 (5) | 0 |
| Constipation | 4 (3) | 4 (5) | 0 |
| Diarrhoea | 4 (3) | 3 (3) | 1 (3) |
| Perforation | 1 (1) | 1 (1) | 0 |

*More than one possible.
†Not considered as B symptoms, because caused by NHL.

loss (DLCL = 14%, MZL = 9%). Intestinal bleeding was observed in 9% of DLCL and 17% of MZL. Perforation or bowel obstruction developed in 6% of patients with DLCL. Fever and night sweats occurred in 26% of patients with DLCL and 14% of those with MZL.

Four patients had had a previous carcinoma, at a median 6 years prior to NHL. In two cases with DLCL, a cerebellar astrocytoma and an ovary carcinoma were diagnosed 30 and 45 d before intestinal lymphoma respectively.

*Treatments*

One patient with MZL lymphoma did not receive any treatment due to poor performance status and advanced age and died from disease 21 months after diagnosis.

Front-line therapy of the other 121 patients is reported in Table IV. Ninety-six patients (79%) underwent partial ($n = 91$) or extended ($n = 5$) resection. Twenty-eight cases (29%) had emergency surgery, while 68 had an elective laparotomy. Twenty-seven patients (22%), 13 with MZL and 14 with DLCL, who had a localized disease, were treated by surgery alone. Post-surgical, adjuvant treatment was generally reserved for patients with advanced disease and/or aggressive histology ($P = 0{\cdot}0001$). Ninety-two patients (76%), 20 with MZL and 72 with DLCL, were treated with chemotherapy. The majority (68 cases) received chemotherapy after resection, of which 64 patients with DLCL received an adriamycin-containing regimen. Thirty-three patients were given CHOP (cyclophosphamide, hydroxydoxorubicin, vincristine, prednisone), 20 MACOP-B (methotrexate, adriamycin, cyclophosphamide, oncovin, prednisone, bleomycin), six were given m-BACOD (methotrexate, bleomycin, adriamycin, cyclophosphamide, oncovin, dexamethasone) and five ProMaCE-CytaBOM (prednisone, methotrexate, adriamycin, cyclophosphamide, etoposide, cytarabine, bleomycin, oncovin, methotrexate). The other eight DLCL patients received adriamycin-free regimens such as COP (or CVP; cyclophosphamide, oncovin (vincristine), prednisone). In the MZL group, 15 patients were given adriamycin-free regimens and five had CHOP. The median number of chemotherapy courses was six (range 2–12 for DLCL and 2–16 for MZL). Eight patients had involved field radiation therapy (30 Gy), usually as an adjuvant following surgery, chemotherapy or both. One elderly patient with MZL was electively treated with radiation therapy alone.

**Table IV.** First treatment of 121 patients with primary intestinal lymphoma.

| Treatment | DLCL Number of patients (%) ($n = 87$) | MZL Number of patients (%) ($n = 34$) | *P* |
|---|---|---|---|
| Single therapy | 26 (30) | 23 (68) | 0·0001 |
| Chemotherapy | 12 (14) | 9 (27) | |
| Surgery | 14 (16) | 13 (38) | |
| Radiotherapy | 0 (0) | 1 (3) | |
| Combined therapy | 61 (70) | 11 (32) | 0·0001 |
| Surgery + chemotherapy | 56 (64) | 9 (26) | |
| Surgery + chemotherapy + radiotherapy | 2 (2) | 1 (3) | |
| Chemotherapy + radiotherapy | 2 (2) | 1 (3) | |
| Surgery + radiotherapy | 1 (1) | 0 | |

*Response, relapse rate and salvage therapy*

Sixty-five patients (75%, 95% CI, 64–83) with DLCL and 22 with MZL (65%, 95% CI, 46–80) achieved CR. Three and 11 further patients, respectively, attained PR. Fifteen patients with aggressive and one with low-grade lymphoma proved refractory, and four, all with DLCL, died of treatment-related toxicity (Table V). In univariate analysis, age < 60 years was the only factor associated with the likelihood of CR in DLCL, while in MZL no factor was found to be predictive for the achievement of CR. The stepwise regression model failed to identify any independent predictive prognostic factor for attaining CR. In the group of 30 PR and NR/PD patients, one with DLCL and two with MZL were effectively rescued by further chemotherapy (Figs 1 and 2). Among 65 DLCL and 22 MZL patients in CR, 49 (56%, 95% CI, 45–67) and 11 (32%, 95% CI, 17–51) are still alive in first CR, while two with low-grade lymphoma died in CR of heart disease (Figs 1 and 2). Sixteen patients with DLCL and nine with MZL lymphoma eventually relapsed. Nine relapsed in sites of prior disease and 13 in other sites. Three more DLCL patients relapsed in both previous and new sites. Following relapse, two MZL and six DLCL patients obtained a second CR, which has been maintained to date in six, while two have died in remission of other causes. Among the other 17 patients, six are still alive with lymphoma and 11 died of disease (Figs 1 and 2).

**Table V.** First response to different treatments of 121 patients with primary intestinal lymphoma.

| | DLCL ($n=87$) Number of patients (%) | MZL ($n=34$) Number of patients (%) |
|---|---|---|
| Complete response | 65 (75) | 22 (65) |
| Partial response | 3 (3) | 11 (32) |
| No response/progression | 15 (17) | 1 (3) |
| Dead of toxicity | 4 (5) | 0 |

*Overall survival*

There were 29 (33%) deaths in the DLCL group and 10 (28%) in the MZL group. Twenty-three patients with DLCL died of disease, four of treatment-related toxicity, one of heart disease and one of breast cancer (Fig 1). In the MZL group, eight patients died of lymphoma and two of heart disease (Fig 2). Estimated OS at 5 years for DLCL and MZL lymphoma was 68% (95% CI, 55–78) and 65% (95% CI, 43–81) respectively (Figs 3 and 4). OS varied according to MIPI, from, respectively, 86% and 87% for DLCL and MZL patients with 0–1 risk factors to 50% and 32% for patients with >1 risk factors ($P=0{\cdot}01$ and $P=0{\cdot}02$) (Fig 5A and B).

*Disease-free survival*

Twenty-five of 87 CR patients (29%) eventually relapsed and 11 died of lymphoma. The 5-year estimate of DFS was 68% (95 CI, 52–79) for DLCL and 50% for MZL lymphoma (95% CI, 23–72) (Figs 3 and 4).

*Event-free survival*

Thirty-eight patients (44%) with DLCL and 24 with MZL (69%) suffered from an adverse event. In the DLCL group, four patients died, 18 were NR/PD and 16 relapsed. Among 35 patients with MZL, three died, 12 were NR/PD and nine relapsed. The 5-year EFS rate for DLCL patients was 50% (95% CI, 37–61), while for those with MZL was 26% (95% CI, 11–43). EFS varied according to MIPI from, respectively, 55% and 44% for DLCL and MZL patients with 0–1 risk factors to 40% and 0% for patients with >1 risk factors ($P=0{\cdot}05$ and $P=0{\cdot}03$) (Figs 6A and B).

*Prognostic factors*

Preliminary analysis of MIPI risk categories showed that only 16 patients (12 DLCL and 4 MZL) belonged to the high-risk group (≥ 3 risk factors), while all 49 patients (38 DLCL and 11 MZL) with >1 risk factors had a poor clinical outcome (5-year OS and EFS ≤ 50%) (data not shown). Therefore, we decided to include in further analysis only two of the three original MIPI risk categories: low, with 0–1 risk factors and high, with >1 risk factor. In the univariate

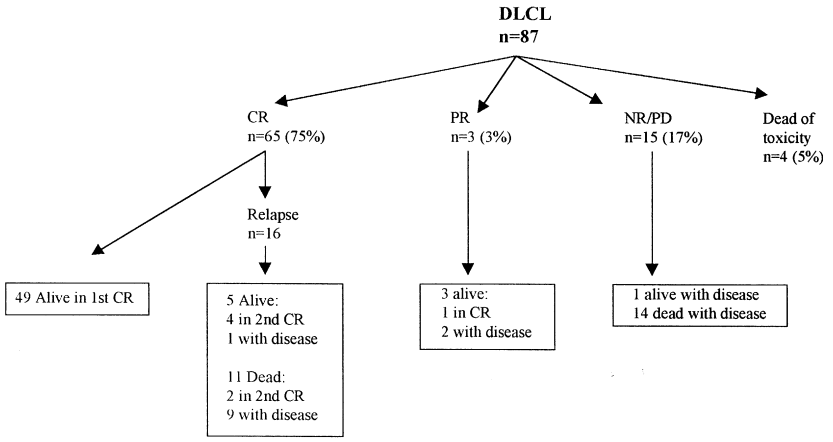


**Fig 1.** Flow diagram of clinical outcome of 87 patients with DLCL intestinal lymphoma.

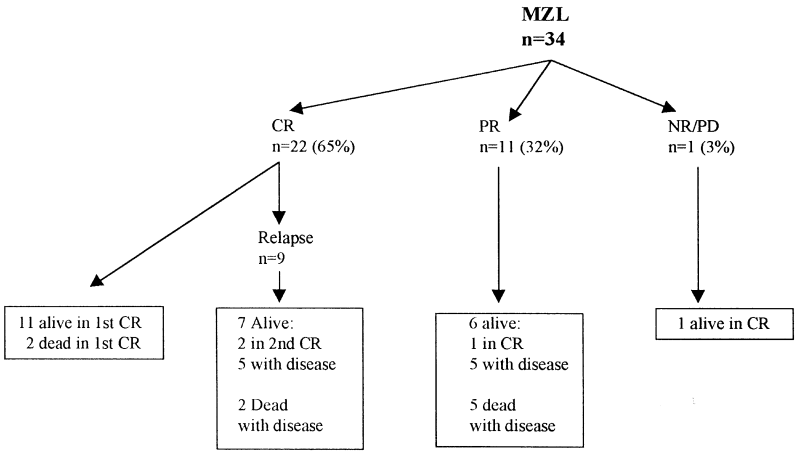


**Fig 2.** Flow diagram of clinical outcome of 34 patients with MZL intestinal lymphoma.

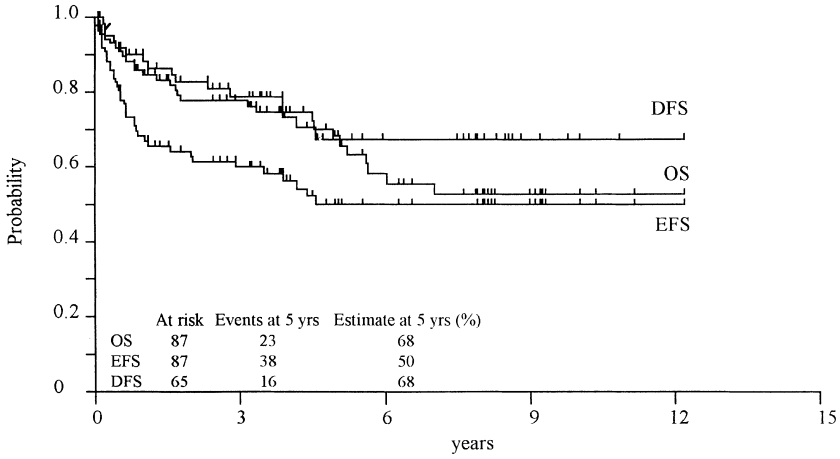


**Fig 3.** Overall survival (OS), event-free survival (EFS) and disease-free survival (DFS) of 87 patients with DLCL intestinal lymphoma.

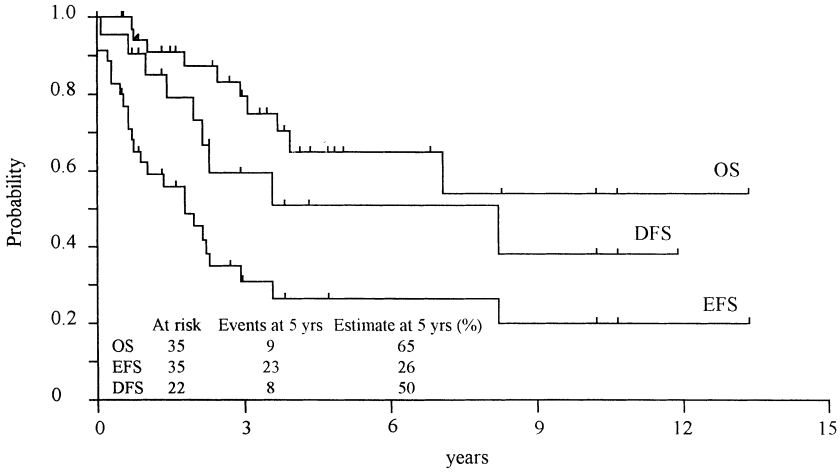


**Fig 4.** Overall survival (OS), event-free survival (EFS) and disease-free survival (DFS) of 35 patients with MZL intestinal lymphoma.

analysis the presence of two or more risk factors according to MIPI was the only adverse factor for OS and EFS (data not shown). In DLCL patients, the MIPI score maintained its independent value for EFS after multivariate analysis (RR = 2·1, 95% CI, 1·0–4·5; $P = 0·04$), while it was not significant for OS (RR = 2·1, 95% CI, 0·9–5·2; $P = 0·08$). Similarly, MIPI was not significant for EFS in patients with MZL (RR = 3·1, 95% CI, 0·8–11·2; $P = 0·08$) and failed to be predictive for OS (RR = 4·8, 95% CI, 0·5–44·4; $P = 0·16$). A multivariate analysis of the single risk factors included in stage-modified IPI showed that elevated LDH predicted OS (RR = 2·5, 95% CI, 1·0–6·2; $P = 0·05$) and age > 60 years

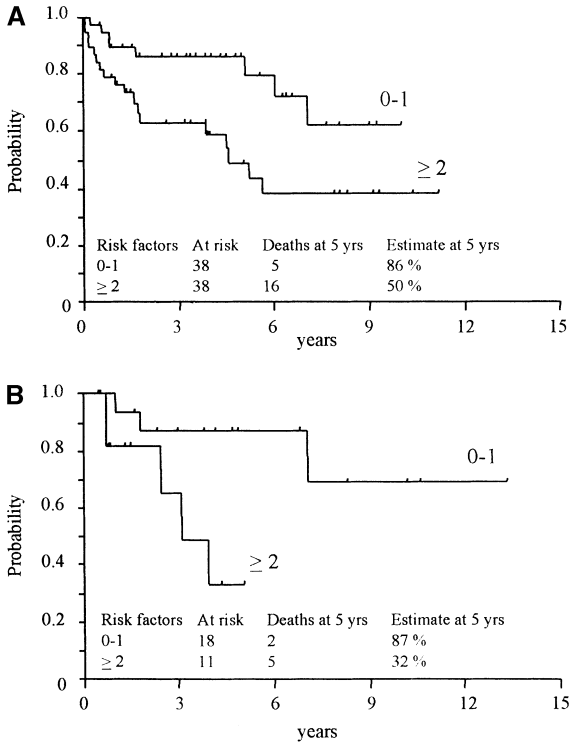


**Fig 5.** (A) Overall survival of 76 patients with DLCL intestinal lymphoma according to the number of MIPI risk factors: 0–1 *vs* ≥ 2 risk factors ($P = 0{\cdot}01$). (B) Overall survival of 29 patients with MZL intestinal lymphoma according to the number of MIPI risk factors: 0–1 *vs* ≥ 2 risk factors ($P = 0{\cdot}02$).

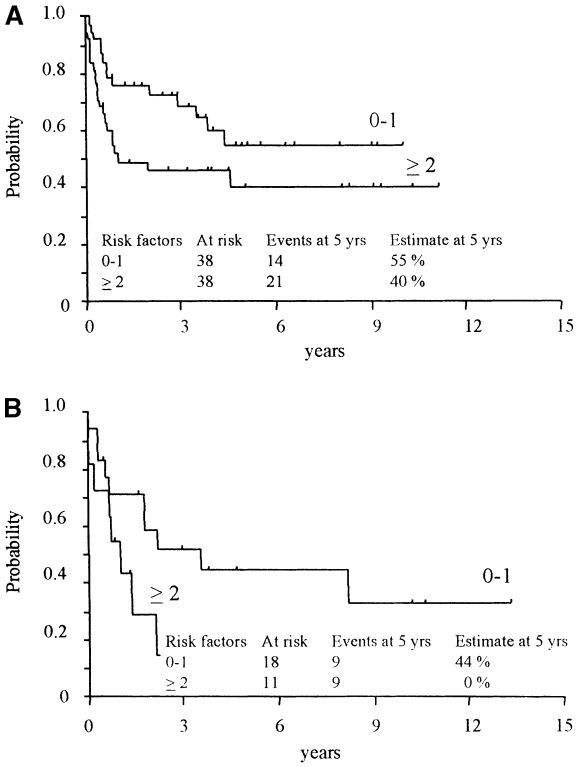


**Fig 6.** (A) Event-free survival of 76 patients with DLCL intestinal lymphoma according to the number of MIPI risk factors: 0–1 *vs* ≥ 2 risk factors ($P = 0{\cdot}05$). (B) Event-free survival of 29 patients with MZL intestinal lymphoma according to the number of MIPI risk factors: 0–1 *vs* ≥ 2 risk factors ($P = 0{\cdot}03$).

predicted EFS (RR = 2·7, 95% CI, 1·2–5·8; $P = 0{\cdot}01$) in patients with DLCL. In patients with MZL, only stage ≥ II was predictive for OS (RR = 12·0, 95% CI, 1·2–114; $P = 0{\cdot}03$).

*Treatment-related issues*

The analysis of OS and EFS, according to different treatments delivered to 76 DLCL patients from both MIPI risk groups, showed that OS and EFS rates of eight patients with 0–1 risk factor who received single therapy were comparable to those of 30 patients receiving combined treatment (5-year OS 71% *vs* 79%; $P = 0{\cdot}69$ and 5-year EFS 45% *vs* 58%, $P = 0{\cdot}39$). In contrast, the outcome of 14 patients with > 1 risk factor who were treated with single therapy was significantly inferior to that obtained in 24 cases treated with surgery followed by chemotherapy (5-year OS 31% *vs* 74%, $P = 0{\cdot}02$; 5-year EFS 17% *vs* 53%, $P = 0{\cdot}05$). Patients with MZL histology and low-risk MIPI category who were treated with single therapy showed a comparable OS to those receiving combined treatment, but lower EFS. However, the difference was not statistically significant due to the small number of cases (5-year EFS 30% *vs* 61%, $P = 0{\cdot}19$). The outcome of 10 patients with low-grade histology and > 1 risk factor was generally poor (5-year OS = 31% and 5-year EFS = 0%).

*Toxicity*

Surgical morbidity included anastomosis dehiscence, occlusion, wound infection, hepatitis, deep vein thrombosis and sepsis in seven patients with DLCL and in two with MZL lymphoma. Two patients with aggressive lymphoma died of related complications. Toxic side-effects in 92 patients treated with chemotherapy included perforation and acute bleeding (1·8%), diarrhoea, mucositis, infections, worsening of performance status, peripheral neuropathy and diabetes, accounting for a 39% adverse event rate in DLCL patients and 35% in the MZL group. Treatment-related death rate in the DLCL group was 3%. Five patients, three with DLCL and two with MZL, developed another malignancy (two lung carcinoma, one breast carcinoma, two larynx carcinoma) at a median time of 27 months (range 3–75 months) from diagnosis of primary intestinal lymphoma.

## DISCUSSION

Primary intestinal lymphoma is rather uncommon in western countries, so that the optimal treatment remains undefined. Therefore, the identification of factors that might affect outcome could improve the management of these patients. The International Prognostic Index (IPI) was shown to be an effective prognostic model for advanced DLCL (Shipp & Harrington, 1993) and a model of IPI

including stage II within adverse features successfully predicted the clinical outcome of patients with limited-stage aggressive NHL of both nodal and extranodal origin (Miller *et al*, 1998; Shenkier *et al*, 2002). However, the reported use of the MIPI is still quite limited, particularly in the setting of gastro-intestinal lymphomas. Thus, we decided to contribute to this field and in a previous report (Cortelazzo *et al*, 1999) we showed that MIPI effectively predicted outcome of patients with primary gastric lymphoma. In the present retrospective analysis we extended this observation to include a total of 122 patients with diffuse large B-cell and low-grade MZL confined to the intestine or limited to the abdominal cavity. In both studies we adopted the Lugano classification for gastrointestinal lymphomas (GIL) (Rohatiner *et al*, 1994) because it was designed for GIL and has been utilized in large series of GIL patients (Ibrahim *et al*, 1999, 2001). Moreover, in the present analysis we utilized only two of the three MIPI risk categories (Miller *et al*, 1998; Shenkier *et al*, 2002), as patients with more than one risk factor had a similar poor outcome and only a few patients belonged to high risk categories with three or more adverse features.

Patients' clinical and diagnostic characteristics from this series are similar to those reported in other studies (Herrmann *et al*, 1980; Weingrad *et al*, 1982; Dragosics *et al*, 1985; Aozasa *et al*, 1988; Azab *et al*, 1989; Otter *et al*, 1989; Salles *et al*, 1991; Morton *et al*, 1993; Ruskonè-Fourmestraux *et al*, 1993; Amer & El-Akkad, 1994; D'Amore *et al*, 1994; Kocher *et al*, 1997; Zinzani *et al*, 1997; Sanchez-Bueno *et al*, 1998; Gurney *et al*, 1999; Gobbi *et al*, 2000; Ibrahim *et al*, 2001; Koch *et al*, 2001). Most cases complained of abdominal pain associated with nausea and vomiting and weight loss, and NHL diagnosis was mostly obtained by laparotomy. As reported (Dragosics *et al*, 1985; Ibrahim *et al*, 2001; Koch *et al*, 2001), the ileocaecal region and small bowel were more frequently involved than duodenum, colon and rectum. However, in concordance with Ibrahim *et al* (2001) and in contrast with Koch *et al* (2001), neither primary site, nor multiple intestinal involvement were found to affect response or survival rates. The majority of our patients with DLCL had adverse prognostic features such as B symptoms, advanced stage (≥ II), bulky disease and poor performance status, while those with MZL had a high median age (> 60 years). At completion of pathological or clinical staging, 46% of patients with DLCL and 60% of those with MZL proved to have limited-stage intestinal disease (stage I), while the remainder were found to have an extension to adjacent lymph nodes or advanced intra-abdominal disease (stage II). By including stage II with other adverse factors of IPI, according to Miller *et al* (1998), we were able to discriminate between DLCL and MZL patients with very different prognoses. In fact, for DLCL and MZL patients in the low-risk group (0–1 risk factors), 5-year overall survival estimates were 86% and 87%, respectively, compared with 50% and 32% in the intermediate-/high-risk categories (> 1 risk factor).

Moreover, the analysis of treatment-related issues showed that response to different therapies varied according to the incidence of adverse MIPI features. We are aware of the difficulties related to the retrospective nature of this study and to the subgroup analysis of studies not originally designed for this purpose. However, our series included a large number of patients with a rare disease, who received a relatively homogeneous therapy consisting of surgery, followed (in the majority of cases) by a short course of chemotherapy. This enabled the analysis of the response rate of patients with different risk factors and to obtain some indication on the efficacy of treatments given in the two MIPI risk categories.

In the DLCL low-risk group, mostly consisting of younger patients with limited disease, good performance status and a low LDH value, the prevailing treatment was surgery followed by short-term adjuvant adriamycin-based chemotherapy with or without radiotherapy. However, selected cases underwent only surgery because of limited disease or were given chemotherapy due to advanced age or poor performance status. In this setting either combined strategy or single treatment gave similar 5-year OS (79% *vs* 71%, $P = 0{\cdot}7$) and EFS (58% *vs* 45%, $P = 0{\cdot}4$). Our OS rates compared very favourably with other retrospective smaller studies (Lewin *et al*, 1978; Cooper & Read, 1985; D'Amore *et al*, 1994; Ibrahim *et al*, 2001) and with prospective studies, such as the 4-year OS of 62% reported by Salles *et al* (1991) with a more intensive chemotherapy and the 5-year OS of 56% recently reported by Koch *et al* (2001).

In contrast to the above, in the intermediate-/high-risk categories only patients who received combined therapy had a chance of prolonged survival (OS 74% *vs* 31%, $P = 0{\cdot}02$; EFS 53% *vs* 17%, $P = 0{\cdot}05$). The best results were obtained with surgery followed by chemotherapy, but those with chemotherapy alone were the poorest, to underline the critical role of surgery in high-grade intestinal NHL (D'Amore *et al*, 1994; Gobbi *et al*, 2000; Ibrahim *et al*, 2001). Thus, a reasonable first-line therapy of these patients would be surgery, followed by short-term chemotherapy or even radiotherapy as suggested by some retrospective studies (Herrmann *et al*, 1980; Gospodarowicz *et al*, 1983; Geara, 1999). Patients not fit for surgery, but who are able to tolerate anthracyclin chemotherapy, should be given chemotherapy and possibly adjuvant radiotherapy. Our analysis is obviously not informative about this strategy, but a recent trial (Miller *et al*, 1998) showed this combined modality to be superior to chemotherapy alone in early stage nodal and extranodal NHL.

The favourable effect of surgery followed by chemotherapy was also observed in patients with low-grade MZL lymphoma, in whom the EFS rate with combined modality was double that for single treatment. Failures were mainly due to resistance to adriamycin-free regimens or relapse after limited resection. However, adriamycin-containing salvage regimens allowed a prolongation of survival (5-year OS 87–100%), in line with previous reports on gastrointestinal lymphoma of low-grade histology (Aozasa *et al*, 1988; List *et al*, 1988; Azab *et al*, 1989; Liang *et al*, 1991; Radaszkiewicz *et al*, 1992; Chandran *et al*, 1995; Nakamura *et al*, 2000). In contrast, no patient treated with single therapy in the intermediate-/high-risk categories survived

free of disease at 5 years and for this group the 5-year OS was only 31%. Hence, it would appear reasonable, in this group, to adopt surgery, when a radical tumour resection is feasible, followed by short course of adriamycin-containing chemotherapy, as in high-grade disease or, when surgery is not possible, chemotherapy followed by adjuvant radiotherapy. Moreover, similar to gastric MZL, an association has been established between intestinal MZL and *Helicobacter pylori* infection (Isaacson, 1999), with sporadic cases of remission achieved upon antibiotic treatment (Raderer *et al*, 2000). However, the role of this treatment in patients with MZL intestinal lymphoma needs to be further clarified before it is recommended as single-modality or combination treatment in clinical practice.

In conclusion, the MIPI could help the identification of two distinct prognostic classes of patients with primary intestinal lymphoma, a fact that may have therapeutic implications. As most patients with small bowel or colonic lymphoma require surgery for diagnosis or relief of symptoms, and surgery is associated with improved outcome, there is little controversy about the need for resection. The choice of the most appropriate adjuvant treatment should be further investigated in prospective randomized trials.

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