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# Primary Malignant Lymphomas of the Stomach

## - Pathological and Clinical Analyses of 38 Resected Cases -

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***The stomach is the most frequent site of extranodal lymphoma and primary gastric lymphoma might be distinguished from the nodal lymphoma by its different pathogenesis and prognosis. Based on the Isaacson's classification, clinico-pathologic reviews of 38 resected primary gastric lymphomas were done. Immunohistochemical stainings for PCNA, B and T cell markers, bcl-2 and p53 were performed. Eighteen were of low grade and 20 were of high grade. There were significant differences between low and high graders in the aspect of the size, depth of lesion, gross type, immunophenotype, staining intensity for PCNA, expressions of bcl-2 and p53. The overall 2-year survival rate was 85.3%. Factors with prognostic significance on survival by univariate analyses included immunophenotype, histologic grading and PCNA staining pattern. After multivariate analyses, immunophenotype proved to be a significant factor. We think that the histologic grading by Isaacson's classification and the immunohistochemical stainings performed were useful in pathologic and/or clinical aspects. The excellent survival rate in this study was partly due to the selection of resectable cases. However, earlier diagnosis and appropriate treatment might have contributed to the improved prognosis of gastric lymphoma in recent years.***

**Key Words** : *Primary gastric lymphoma, Isaacson's classification, Immunohistochemical stainings, Univariate survival analyses, Multivariate survival analyses*

## INTRODUCTION

Gastric lymphoma is an uncommon neoplasm accounting for 1 to 7% of primary gastric malignancies (Freeman et al.,1972 ; Dragosics et al.,1985 ; Cogliatti et al.,1991). Stomach is the most frequent site of primary extranodal malignant lymphomas, and the survival data have shown that the prognosis is much better compared to nodal lymphomas as well as gastric carcinomas (Lewin et al., 1978 ; Dworkin et al., 1982). Although many previous studies have aimed at finding out the nature and prognostic factors in primary gastric lymphoma, most of them have been reported conflicting results, because various histologic classifications were used and many of the reported prognostic factors were interrelated.

Recently, with the advance of immunohistochemical techniques, the cell of origin of primary gastric lymphoma can be more effectively addressed (Grody et al., 1985 ; Wolf et al., 1990). Studies about bcl-2 oncogene and p53 tumor suppressor gene and estimation of

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proliferative activity using bromodeoxyuridine labeling index or proliferating cell nuclear antigen (PCNA) were essential elements in recent approaches to tumor biology including malignant lymphoma (Bauer et al.,1986 ; Kamel et al., 1991 ; Villuendas et al., 1992 ; Doussis et al., 1993 ; Pezzella et al., 1993 ; Sebo et al., 1993). However, few studies were done with gastric lymphoma (LeBrun et al., 1992). This study was performed in order to clarify the nature, prognosis and prognostic factors in gastric lymphoma. Thirty-eight resected gastrectomy specimens of malignant lymphoma at stage IE and IIE were analyzed. Cases of only gastrofiberscopic biopsies and of stage III and IV at presentation were excluded. Isaacson's classification (Isaacson and Norton, 1994) was used as a framework for the histologic classification since it was based on the concept of mucosa associated lymphoid tissue lymphoma (MALToma). Updated Kiel classification (Lennert and Feller, 1992) was partly used for the lymphomas having no MALToma feature.

Immunohistochemical stainings for PCNA, bcl-2 and p53 were performed as well as B (L26) and T (UCHL-1) cell markers in order to provide more objective parameters in the evaluation of the histologic grading and biologic behavior of the gastric lymphoma. For the statistical analysis both univariate and multivariate analysis were used.

## MATERIALS AND METHODS

Forty-six resected cases of gastric malignant lymphomas were listed from 1985 to 1992 in the files of the Department of Pathology, Seoul National University College of Medicine. Three of them were excluded initially because of their systemic leukemic presentation. Another two were deleted from this study because their pathologic materials were unfortunately lost. According to the Lewin's (1978) study, the definition of primary gastric lymphoma includes those patients who presented with gastrointestinal symptoms. However, more recent study by Shiu et al. (1982) used more strict criteria for the primarity of gastric lymphoma, that is, no lymphoma disease was revealed outside of the stomach and its vicinity at the time of initial therapy as determined by all diagnostic tests. We used Shiu's criteria and three more cases were excluded because extragastric lymphomas associated were proved at the time of initial diagnosis (one submandibular gland, one breast and one Waldeyer's ring). Finally, 38 cases remained. All specimens were fixed in 10% buffered neutral formalin, embedded in paraffin and subjected to hematoxylin and eosin. Histologic special stainings such as periodic acid-Schiff or reticulin were done on some of the cases. Immunohistochemical stainings were performed for PCNA, UCHL-1, L26, bcl-2, and p53 (all antibody profiles used were from Dako, Denmark) on one to three representative sections by ABC method. Histologic grading was done according to the Isaacson's classification (Isaacson and Norton, 1994). The stage of disease at the time of diagnosis was assessed according to the Ann Arbor system (Carbone et al., 1971). For the follow up study, clinical information were obtained by evaluation of individual clinical records of all patients. The median follow up period was 24 months. All clinico-pathologic variables were assessed histologically by low and high graders and analyzed statistically using the chi-square test. Survival data were then analyzed by using PC-SAS system version 6.04. The survival curves were obtained using Kaplan-Meier method. Statistical evaluation was performed by Wilcoxon and log-rank techniques for the univariate analyses and Weibull model for the multivariate analyses.

## RESULTS

### Histologic findings

The histologic subtypes of the 38 gastric lymphomas graded according to the Isaacson's classification are listed in Table 1. Eighteen cases (47%) were low grade and 20 cases (53%) were high grade. Low grade MALToma including 4 lymphoplasmacytic/plasmacytoid immunocytoma was the most common type (Fig. 1). Four of them were previously diagnosed as diffuse CB/CC and another two were as pseudolymphoma. Foci of follicular colonization were observed in one of the MALToma, however, no MALToma revealed area of follicular lymphoma architecture. Two centroblastic and

**Table 1.** Histologic grading of 38 primary gastric lymphomas by Isaacson

| | |
|---|---|
| Low grade | 18 (47%) |
| MALT type | 15 |
| centroblastic/centrocytic | *3 |
| High grade | 20 (53%) |
| MALT type | 3 |
| centroblastic | 12 (*1) |
| immunoblastic | 2 |
| T cell, pleomorphic medium sized and large cell | 3 |

* cases with areas of follicular architecture

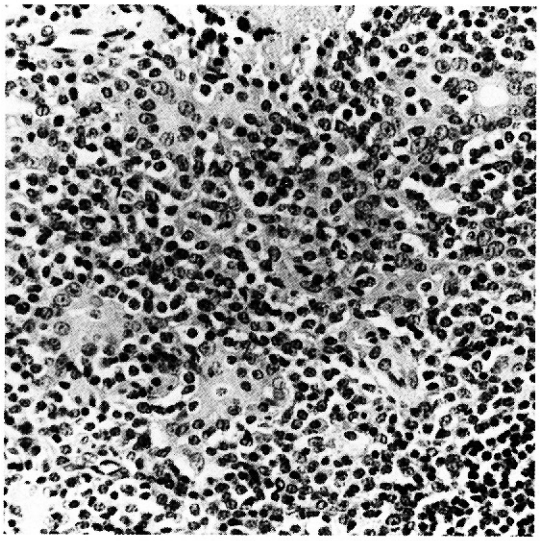

Fig. 1. A low grade MALToma containing lymphoepithelial lesions with infiltration of gastric gland epithlium by centrocyte-like cells (H & E, ×200).

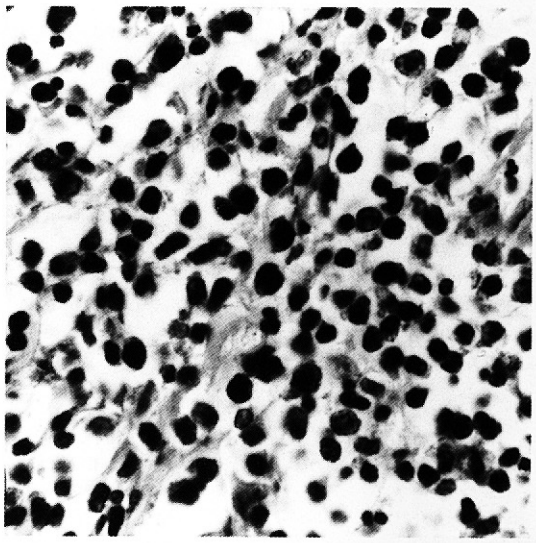

Fig. 2. Polymorphic cellular infiltration of T cell lymphoma showing nuclear irregularity, lobulation and condensation (H & E, ×400).

an immunoblastic lymphoma with residual foci of low grade MALToma were classified as high grade MALToma. Three lymphomas which show histologic characteristics of peripheral T cell type (Fig. 2) all belonged to the high grade (pleomorphic, medium-sized and large cell). Most cases showed a diffuse architectural pattern throughout the sections and only four lymphomas showed areas of follicular architecture. Three of them were centroblastic/centrocytic (CC/CB) and one was centroblastic (CB) type. None of the lymphomas reveal evidence of mantle cell origin.

## Gross findings

26 cases (68%) were grossly single lesion and 12 (32%) were multiple. Five cases (13%) revealed more than three lesions. Among the low grade lymphomas 8 (44%) were multiple whereas 4 (20%) of the high graders were multiple. The previous data for gastric adenocarcinoma in Seoul National University Hospital (Park et al., 1991) showed only 38 multiple lesions (2%) out of 2320 cases. The multiplicity of lesions was significantly different between lymphoma and adenocarcinoma of the stomach ($p<0.05$). Topographic location of lymphomas within the resected stomach were body 44%, pyloric antrum 43% and fundus 13%, which showed a meaningful difference ($p<0.05$) compared to that of the adenocarcinomas (body 29%, pyloric antrum 64% and fundus 6%) from the same previous study (Park et al., 1991). The mean diameter of lymphomas was 6.9 cm, ranging from 1 to 15 cm ascertained by mesuring the maximal tumor dimension. Seventeen (45%) were less than 6 cm and 21 (55%) were over 6 cm. Among the low graders 11 (59%) were less than 6 cm whereas in high graders 14 (70%) were over 6 cm, which revealed a significant difference ($p<0.05$). The depth of direct tumor invasion into the gastric wall was assessed. Infiltration to the mucosa and submucosa occurred in 12 (32%), to the proper muscle in 6 (16%), and to the subserosa in 20 (52%). Ten (56%) of the low graders revealed mucosal and submucosal limited lesions compared with 14 cases (70%) of subserosal invasion in the high graders ($p<0.05$). Table 2 summarized the above gross findings.

We classified the gross types of the gastric lymphomas into five (type I : discrete polypoid, type II : superficial depressed, type III : ulceropolypoid, type IV : giant rugae, and type V : mixed) according to the previous study done by coworkers of the pathology and radiology departments (Choi et al., 1984). Eleven (29%) of the 38 studied cases were type I, 7 (18%) were type II, 15 (39%) were type III, one (3%) was type IV and 4 (11%) were type V. 50% of the low graders were type I and 70% of the high graders were type III, which had statistically significant difference ($p<0.05$). Table 3 was

**Table 2.** Gross findings of 38 gastric lymphomas

| | Lymphoma | High grade | Low grade | *Adenocarcinoma |
|---|---|---|---|---|
| No. of lesions | | | | |
| single | † 68% | 80% | 56% | † 98% |
| multiple | † 32% | 20% | 44% | † 2% |
| Location | | | | |
| body | † 44% | 45% | 41% | † 29% |
| pyloric antrum | † 43% | 35% | 48% | † 64% |
| fundus | † 13% | 20% | 11% | † 6% |
| Size | | | | |
| < 6cm | 45% | † 30% | † 59% | |
| > 6cm | 55% | † 70% | † 41% | |
| Depth | | | | |
| mucosa, submucosa | 32% | † 10% | † 56% | |
| proper muscle | 16% | † 20% | † 11% | |
| subserosa | 52% | † 70% | † 34% | |

p value : † < 0.05
* The data were adopted from Park et al (1991)

**Table 3.** Gross types of 38 gastric lymphomas

| | Lymphoma | High grade | Low grade |
|---|---|---|---|
| I : Ddiscrete polypoid | 29% | † 10% | † 50% |
| II : Superficial depressed | 18% | 10% | 28% |
| III: Ulceropolypoid | 39% | † 70% | † 6% |
| IV: Giant rugae | 3% | 0% | 6% |
| V : Mixed type | 11% | 11% | 11% |

p value : † < 0.05
These gross types of the gastric lymphoma were according to Choi et al. (1984)

**Table 4.** Clinical findings of 38 gastric lymphomas

| | Lymphoma | High grade | Low grade |
|---|---|---|---|
| Mean age | 52.2 (21-84) | 55.2 | 49 |
| Sex (M:F) | 1.53 :1 | 1.86 :1 | 1.25 :1 |
| Stage | | | |
| I | 55% | 50% | 61% |
| II | 45% | 50% | 39% |
| Treatment modality | | | |
| surgery | 49% | 40% | 59% |
| surgery+radiation | 8% | 5% | 12% |
| surgery+chemotherapy | 38% | 45% | 29% |
| all three modalities | 5% | 10% | 0% |

the gross types of the gastric low and high grade lymphomas.

## Clinical findings

Among the 38 patients 23 were males and 15 were females with a male to female ratio of 1.53 :1. The age of the patients ranged from 21 to 84 years, with a mean of 52.2. There was no significant difference in age and sex distribution between low and high graders. The pathologic stages were stage I (confined to the stomach) in 21 (55%) and stage II (infiltration beyond the stomach and/or involvement of regional lymph nodes) in 17 (45%). The stages of low and high graders did not reveal significant difference ($p>0.05$).

The treatment modalities were surgery alone in 49%, radiotherapy after the surgery in 8%, chemotherapy before or after surgery in 38% and all three modalities in 5%. The treatment modalities between the low and high graders revealed no significant difference ($p>0.05$). The clinical findings are summarized in Table 4.

## Immunohistochemical studies

Table 5 listed the overall results of the immunohistochemical stainings. The staining patterns of PCNA were evaluated as diffuse or focal by the estimation of the areas of positive staining (more or less than 50% of total examined areas) and as high, intermediate or low by numbering of positive cells within the positively stained areas (more than 2/3, 1/3 to 2/3, less than 1/3). There were diffuse high pattern in 22 (59%), diffuse low in 6 (16%), diffuse intermediate in 3 (8%), focal high in 5 (14%) and focal intermediate in 1 (3%). Most of the high graders revealed diffuse high pattern (90%) whereas many of the low graders showed diffuse low or focal patterns (70%) ($p<0.05$).

Ninety percents of the gastric lymphomas showed the B cell immunophenotype. Among the three cases which histologically showed the features of peripheral T cell lymphoma, two expressed UCHL1 while one did not. All of the low graders revealed B cell immuno-

Table 5. Immunohistochemical profiles of 38 gastric lymphomas

| | Lymphoma | † High grade | † Low grade |
|---|---|---|---|
| PCNA | | | |
| diffuse high | 59% | 90% | 24% |
| diffuse low | 16% | 0% | 35% |
| diffuse intermediate | 8% | 10% | 6% |
| focal high | 14% | 0% | 29% |
| focal intermediate | 3% | 0% | 6% |
| Immunophenotype | | | |
| B cell | 90% | 80% | 100% |
| T cell | 5% | 10% | 0% |
| other* | 5% | 10% | 0% |
| bcl-2 | | | |
| (+) | 27% | 5% | 53% |
| (-) | 73% | 95% | 47% |
| p53 | | | |
| (+) | 32% | 50% | 11% |
| (-) | 68% | 50% | 89% |

p values : † < 0.05
* UCHL(-) / L26(-) lymphomas

phenotype while two T cell type and two UCLHL(-)/L26(-) type all belonged to the high graders ($p<0.05$).

Ten cases (27%), all of them were B cell lymphomas, expressed the bcl-2. Nine (53%) of the low graders (7 MALToma and 2 CB/CC) and only one (5%) of the high graders expressed bcl-2 ($p<0.05$). As for the p53, 12 cases (32%) revealed positive staining, including ten (50%) of the high graders and 2 (11%) of the low graders ($p<0.05$).

### Statistical analyses of survival

The overall 2-year survival rate was 85.3%. The significant prognostic factors by univariate analyses were histologic grading by Isaacson's classification ($p=0.02$), tumor cell immunophenotype (B cell versus non-B cell, $p=0.001$) and PCNA staining pattern ($p=0.05$). The invasion depth of the primary lesion had an equivocal significance ($p=0.06$) (Fig. 3-6).

Multivariate analyses using Weibull model revealed only tumor cell immunophenotype with a significant value ($p=0.006$) when testing on 11 parameters including age, sex, size, number of lesion, gross type, histologic grading, invasion depth, stage, PCNA pattern, immunophenotype and treatment modality.

## DISCUSSION

Primary gastric lymphoma is an uncommon neoplasm and accounts for about 1.1% of primary gastric

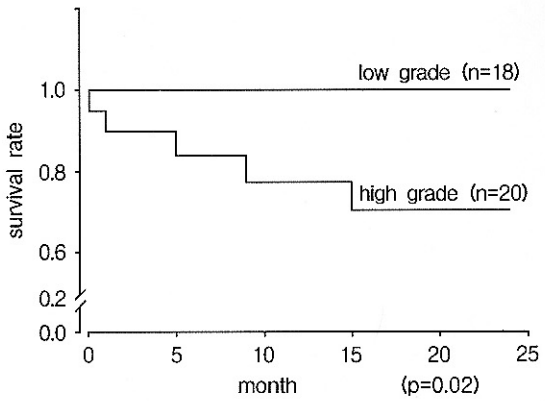


Fig. 3. Univariate analysis of survival by histologic grading by Isaacson's classification

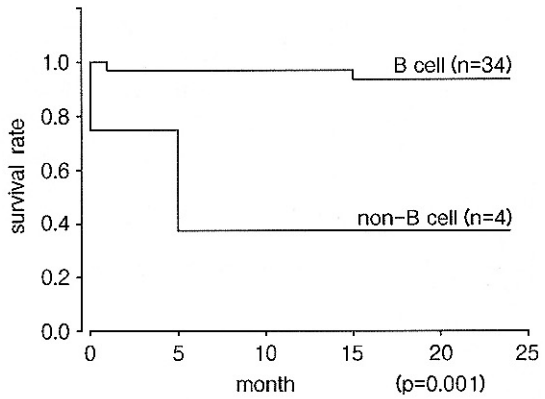


Fig. 4. Univariate analysis of survival by tumor cell immunophenotype

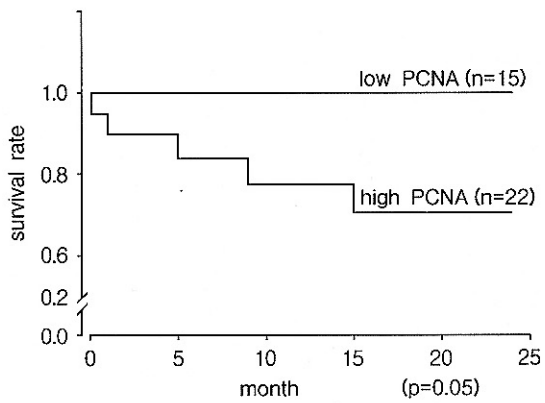


Fig. 5. Univariate analysis of survival by PCNA staining pattern

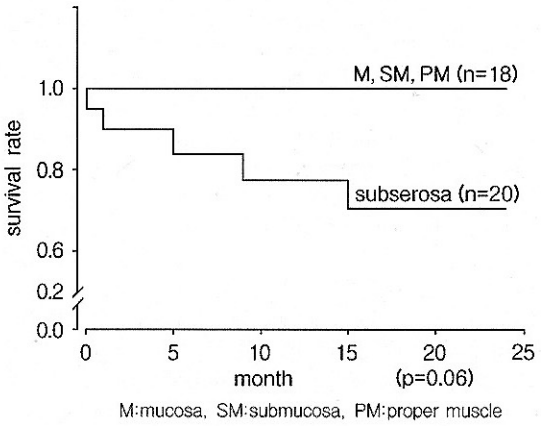


**Fig. 6.** Univariate analysis of survival by depth of primary lesion

neoplasms in Korea (Park et al., 1991). The authors investigated the clinico-pathologic aspects of 38 resected primary gastric non-Hodgkin's lymphomas. They were histologically graded by the Isaacson's classification and all clinical and pathologic findings were compared between the low and high graders. Lymphomas which lack MALToma feature were classified according to the updated Kiel classification. The reason for using the Isaacson's classification was that most low grade lymphomas in the stomach are currently interpreted as MALToma and in a significant proportion of high grade B cell lymphomas have residual foci of low grade MALToma (Issacson et al., 1986 ; Myhre and Isaacson, 1987 ; Chan et al., 1990 ; Cogliatti et al., 1991 ; Isaacson and Norton, 1994). In our study, four lymphomas with the features of lymphoplasmacytic/plasmacytoid immuncytoma, three with previous diagnosis of diffuse CB/CC type and 2 pseudolymphomas were all reclassified as low grade MALToma. Three of the high graders with focal MALToma area were classified as high grade MALToma, which gave an evidence of blastic transformation of the low graders to high graders. Follicular lymphomas of the gut are known to be very rare, constituting 1 to 3% in large series (Weingrad et al.,1982 ; Dragosics et al.,1985 ; LeBrun et al.,1992). Brooks and Enterline (1983) once reported that 20% of all gastric lymphomas had at least some nodular component. In our series, four (10%) revealed foci of follicular structure in superficial or deep area of the tumor. Recent immunohistochemistry proved that over 80% of gastric lymphoma were B cell immunophenotype (Grody et al., 1985 ; Berger et al., 1987 ; Wolf et al., 1990) with cytoplasmic monoclonal immunoglobulin. In our study, 90% had B cell immunophenotype. Variable numbers of true histiocytic lymphomas were reported in the previous studies (Seo et al., 1982 ; Grody et al, 1985). In our study, no one revealed such histologic features and although no immunohistochemical staining for the histiocytic lymphoma was performed, it must be rare because only two cases were unclassifiable by either T or B lymphocyte markers.

It is a well accepted finding that gastric lymphomas are more apt to be presented with multiple lesions than gastric adenocarcinoma. Their topographic locations within the stomach were body and antrum and slightly more rostral than adenocarcinoma. The size of the gastric lymphoma is often quite large being on an average about 6 to 10 cm according to the previous reports (Joseph and Lattes, 1966 ; Lewin et al., 1978 ; Shiu et al., 1982 ; Brooks and Enterline, 1983 ; Azab et al., 1989 ; Valicenti et al., 1993). In our study, low graders by Isaacson's classification were significantly smaller (less than 6 cm) than high graders. As with the invasion depth of the primary lesion, low graders were less invasive than high graders. Several gross classifications of the gastric lymphoma had somewhat overlapping features with some clinico-pathologic relevance (Lewin et al., 1978 ; Dragosics et al., 1985 ; Cogliatti et al., 1993). Our classification of type I to V also seemed to be a reliable one being made by radiologico-pathologic correlation. Also, there was a meaningfully different tendency in that low grade lymphomas had polypoid or superficial depressed features and high graders had ulceropolypoid carcinoma-like features.

Clinically, lymphomas of the stomach are known to involve the middle to old aged and have a slight male predominance (Lewin et al., 1978 ; Dworkin et al., 1982 ; Dragosics et al., 1985 ; Cogliatti et al., 1993). Most previous studies used the Ann Arbor staging system and usually had more stage II than stage I (Dragosics et al., 1985 ; Azab et al., 1989 ; Schwarz et al., 1993 ; Valicenti et al., 1993),. compared to more stage I than stage II in our series. There has been no remarkable change in the treatment modality of gastric lymphoma during the past ten years. All patients are treated according to the very same protocol after the pathologic grading and staging. There was no statistically significant difference between low and high graders in the aspect of the stage and treatment modality. Many previous studies reported that stage was one of the most important prognostic factors (Lim et al., 1977 ; Lewin et al., 1978 ; Dragosics et al., 1985 ; Azab et al., 1989 ; Schwarz et al., 1993 ; Secco et

with the histologic grading by Isaacson's classification, tumor cell immunophenotype and PCNA staining pattern. The invasion depth of primary lesion had equivocal significance. Several previous studies employed multivariate analysis to analyze simultaneously the independent effects of multiple variables and the reported significant variables were stage (Lewin et al.,1977 ; Azab et al., 1989 ; Cogliatti et al., 1991), depth of invasion (Lewin et al., 1977 ; Cogliatti et al., 1991), radical resection (Dragosics et al., 1985 ; Azab et al., 1989), multiagent therapy (Cogliatti et al., 1991 ; Valicenti et al., 1993), histologic grade (Azab et al., 1989 ; Cogliatti et al., 1991), tumor size (Valicenti et al., 1993), and initial achievement of complete remission (Azab et al., 1989). In our study, immunohistochemically determined tumor cell type and PCNA staining patterns were added to the analyzed variables and the only significant value was a tumor cell immunophenotype when testing 11 parameters. However, only 4 non-B cell lymphomas were included in this study, the results should be supported by more extensive study and analysis.

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