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ORIGINAL ARTICLE

TNM staging system may be superior to Lugano and Ann Arbor systems in predicting the overall survival of patients with primary gastrointestinal lymphoma

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Summary

Purpose: *To assess the survival predicting value of TNM, Lugano, and Ann Arbor staging systems in patients with primary gastrointestinal lymphoma (PGL).*

Methods: *101 patients with PGL were reviewed. All of them were staged according to TNM, Lugano, or Ann Arbor staging system. Five-year survival overall survival/OS rate was used as major clinical outcome. The prognostic value of different variables like depth of tumor infiltration (T), lymph node status (N), metastasis (M), sex, age, LDH, ECOG performance status (PS), subtypes, and tumor sites were assessed in relation to clinical outcome.*

Results: *The median follow-up time was 46.6 months (range 1.3-158.6). The estimated 5-year OS rate was 74.22%. In gastric lymphoma ,the 5-year OS rate was well correlated with stage in the TNM system (stage I 100.00%, stage II 87.18%, stage III 75.17%, and stage IV 16.67%. p<0.0001), but there were inverse 5-year OS or overlapped survival in the Lugano (81.48% in stage II, 85.71% in stage IIE) and Ann Arbor systems (69.47% in stage IIE , 66.67% in stage IIIE). In aggressive lymphomas, the 5-year OS of TNM stage I, stage II, stage III , and stage IV was 100.00%, 81.34%, 63.52%, and 16.00%, respectively (p=0.0002), but there were overlapped survival curves in Lugano and Ann Arbor systems. The 5-year OS of patients with T1 or T2 was significantly superior compared to patients with T3 or T4 (96.15 vs 67.92%, p=0.0087), and multivariate Cox analysis showed that T (p=0.0181) and M (p=0.0031) were the covariates prognostically significant for OS.*

Conclusion: *TNM staging system may be superior to Lugano and Ann Arbor system in predicting OS of patients with PGL.*

Key words: *Ann Arbor, Lugano, primary gastrointestinal lymphoma, TNM, 5-year survival*

Introduction

The gastrointestinal tract is the predominant site of extranodal lymphomas, and the PGLs represent about 3-4% of all malignant diseases arising in the gastrointestinal tract [1]. The most frequent location of PGL is the stomach, accounting for approximately 75% of all primary sites. The second most frequent location is the small bowel (8.6%), and the third the ileocecal region (about 7.0%) [2]. As far as pathologic subtypes are concerned, the vast majority of lymphomas seen in the gastrointestinal tract are non-Hodgkin's lymphomas of mature B-cell origin, while T-cell non-Hodgkin's lymphomas are extremely rare in the stomach and other parts of gastrointestinal tract [3]. In the East, diffuse large B-cell lymphoma (DLBCL) is the most common subtype, and extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) is the second most common subtype [4,5].

Generally speaking, a good staging system is very helpful for treatment choice and evaluation of prognosis. However, in some studies the authors

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applied different staging systems to describe the extent of PGL, and this made comparisons difficult. Although Ann Arbor staging system seemed not to be fit to PGL, some researchers still use it in their studies [6,7]. Lugano staging system was constructed by Rohatiner and colleagues in 1994. In Lugano staging system, Ann Arbor stage III had been removed and supradiaphragmatic nodal disease was included in stage IV [8]. Besides, the international tumor-node-metastasis (TNM) staging system was a third system for PGL staging. In this system the depth of lymphoma infiltration (T), the number of involved lymph nodes (N) and involvement of extranodal sites (M) played crucial roles in the stage evaluation of PGL.

To date, there is no consensus regarding the optimal staging system for patients with PGL. This study was undertaken to assess the value of three different staging systems (TNM, Lugano, and Ann Arbor) in predicting the clinical outcome of patients with PGL.

Methods

We performed a retrospective review of 101 patients with PGL treated/followed from February 2001 to September 2012 at the affiliated hospital to Jiangnan University (Wuxi No. 4 Hospital). In all of the patients the diagnosis was established histologically from gastrointestinal system specimens obtained surgically and/or endoscopically. The histological type of lymphoma was determined based on the morphological cell appearance and immunophenotype characteristics using the WHO classification criteria. The patients included in the study were analyzed for the following characteristics: sex, age, clinical disease stage according to Ann Arbor, Lugano, and TNM (7th Edn) staging systems, LDH, ECOG PS score, subtypes of lymphoma, type of therapy, and disease outcome.

Statistics

To compare the value of survival prediction of three staging systems (TNM, Lugano, and Ann Arbor) in patients with PGL, 5-year OS rate was used as major clinical outcome. Survival curves were plotted by the Kaplan–Meier method and compared by the log rank test. All probability values were two-sided. Statistical significance was set at $p<0.05$. OS was computed from diagnosis to the date of death, whatever the cause, or last follow-up. The prognostic value of different variables for clinical outcome (depth of tumor infiltration, lymph node status, metastasis, sex, age, LDH, ECOG PS scores, subtypes, tumor sites, etc.) was assessed by multivariate analysis using the Cox multiple regression model. The distribution of patients staged by different staging systems was tested by Wilcoxon two-sample test.

Results

Clinical and pathological characteristics

Patients with PGL were retrospectively analyzed. From February 2001 to September 2012, 101 patients with PGL were accrued in this study, and all were treated in surgical, medical, and/or radiotherapeutic departments. Their median age on presentation was 61 years (range 25-86); 57 were male and 44 female. The disease pathological characteristics are shown in Table 1.

Treatment and follow-up

Chemotherapy was the predominant treatment in these patients, and the majority received chemotherapy with curative intent (N=83; 82.18%). The most common chemotherapy regimen was cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) in aggressive lymphoma and cyclophosphamide, vincristine,

Table 1. Localization and histology of 101 primary gastrointestinal lymphoma patients

Localization/histology	*N (%)*	*Total, N (%)*
Gastric		
DLBCL	39 (38.61)	
MALT	15 (14.85)	
T-NHL	5 (4.95)	
HD	1 (0.99)	
Plasmoblast	1 (0.99)	
B-NHL	6 (5.94)	67 (66.34)
Intestinal		
MALT	5 (4.95)	
DLBCL	4 (3.96)	
T-NHL	2 (1.98)	
B-NHL	1 (0.99)	12 (11.88)
Ileocecal		
DLBCL	7 (6.93)	
MALT	2 (1.98)	
Folicular	2 (1.98)	
T-NHL	2 (1.98)	
B-NHL	1 (0.99)	14 (13.86)
Colorectal		
DLBCL	3 (2.97)	
MALT	3 (2.97)	
HD	1 (1.98)	7 (6.93)
Mesenterium		
DLBCL	1 (1.98)	1 (0.99)

For abbreviations see text

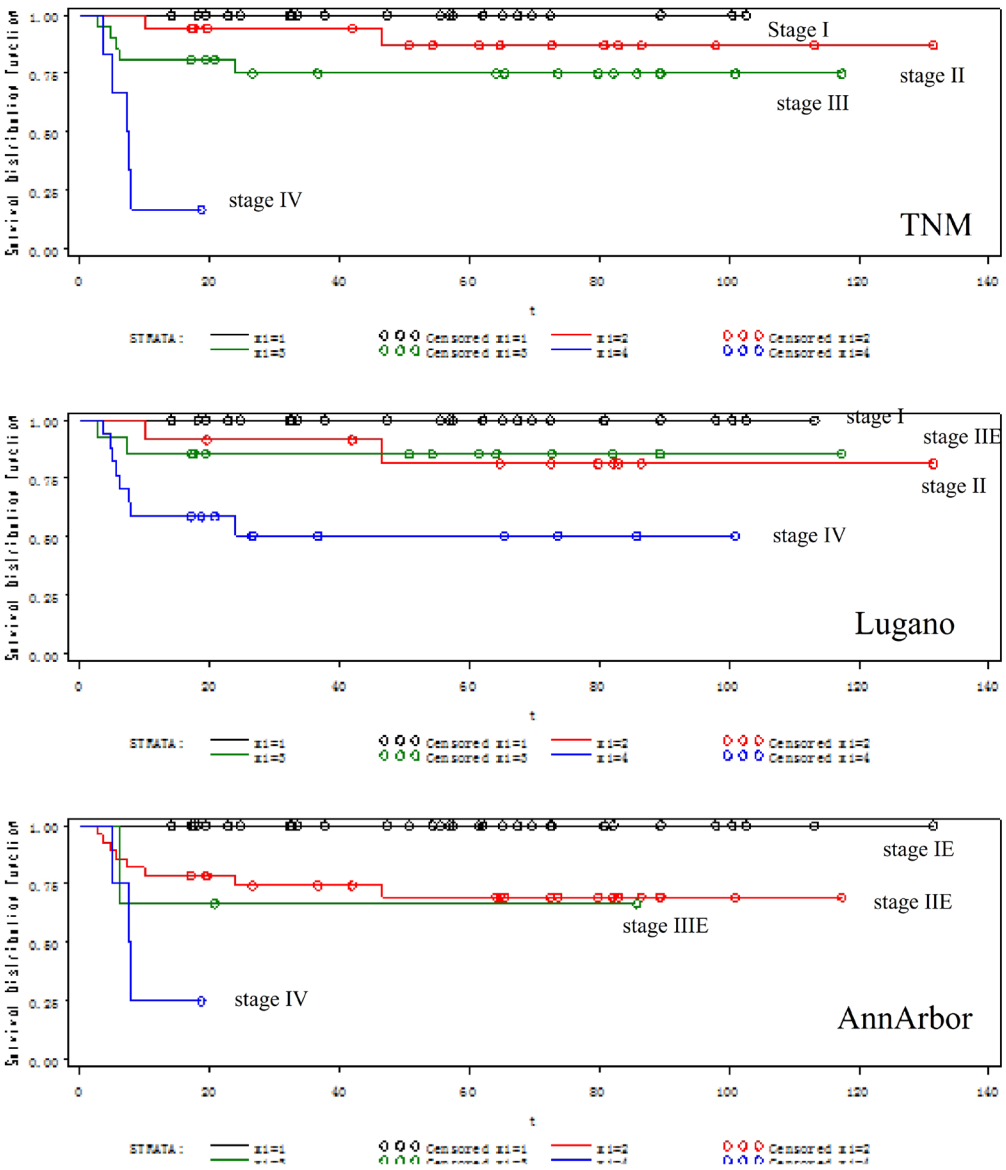

Figure 1. Overall survival in patients with primary gastric lymphoma stratified by stage according to TNM, Lugano, and Ann Arbor systems (p<0.0001) in TNM and Ann Arbor systems and p=0.005 in Lugano system.

and prednisolone (COP) in indolent lymphoma. Surgical resection was performed in 73 patients (72.3%) for therapeutic or diagnostic purposes. The most common types of surgical treatment were total tumor resection and lymph node dissection. Patients who received radiotherapy were treated with extended-field irradiation with 30–45Gy. Only 11 patients (10.89%), including 10 patients with DLBCL and 1 with B-cell lymphoma, received rituximab-based treatment. The median follow-up for surviving patients was 46.6 months (range 1.3-158.6). At the time of the current analysis, 25 patients (24.8%) had died. The estimated 5-year overall survival rate was 74.22%, and the median overall survival was not reached.

Distribution of patients staged by different staging system

When staged by the TNM system, 53 patients (52.5%) belonged to stage I or stage II and 48 patients (47.5%) belonged to stage III or stage IV. When staged by the Lugano system, 44 patients (43.6%) belonged to stage I or stage II and 57 patients (56.5%) belonged to stage IIE or stage IV. However, when staged by the Ann Arbor system, as many as 89 patients (88.1%) belonged to stage I or stage II, and only 12 patients (11.9%) belonged to stage III or stage IV. Wilcoxon two-sample test showed that there was not significant difference between TNM and the Lugano systems (p=0.2458), but there was significant difference when compar-

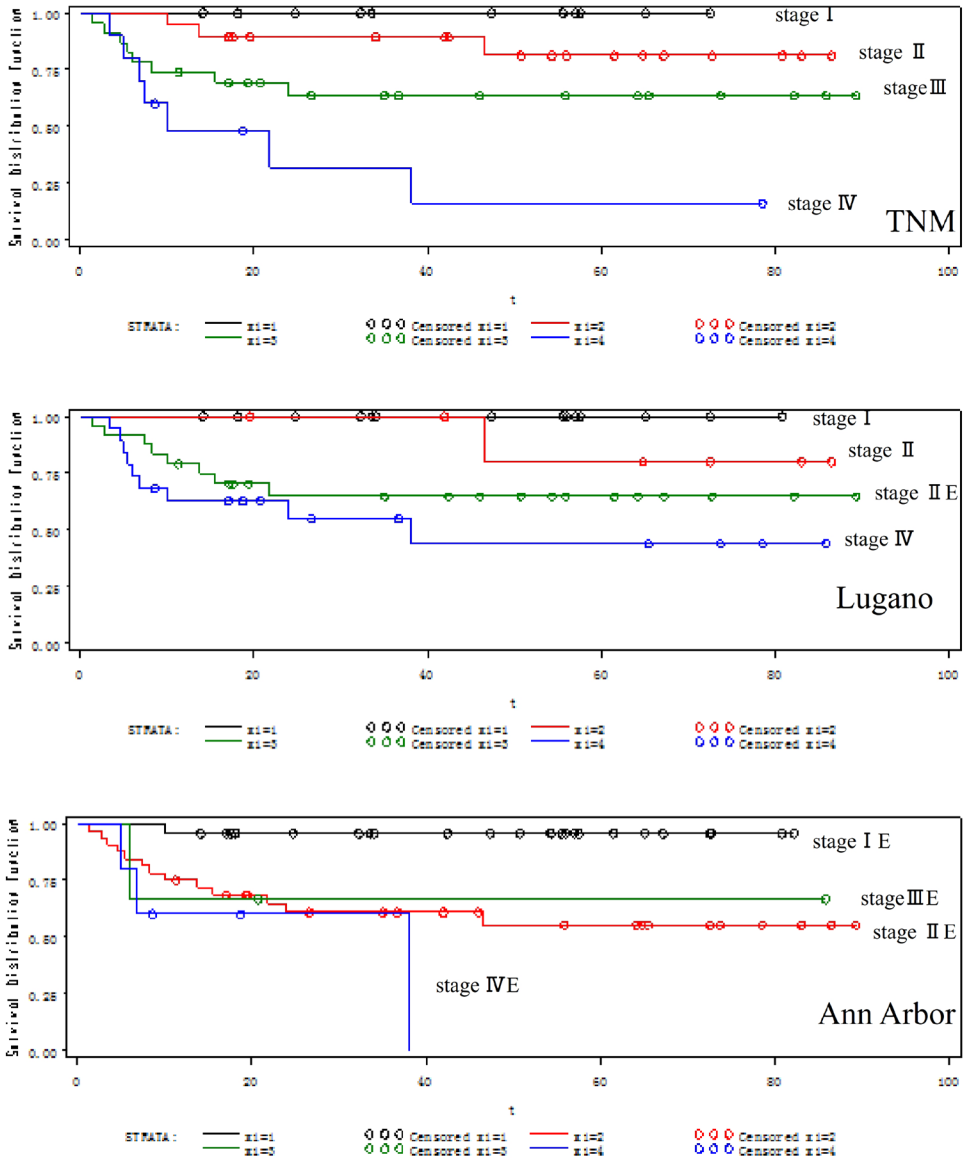

Figure 2. Overall survival in patients with aggressive gastrointestinal lymphoma stratified by stage according to TNM, Lugano, and Ann Arbor systems (p=0.0002, 0.0124, and 0.0043 in TNM, Lugano, and Ann Arbor systems, respectively).

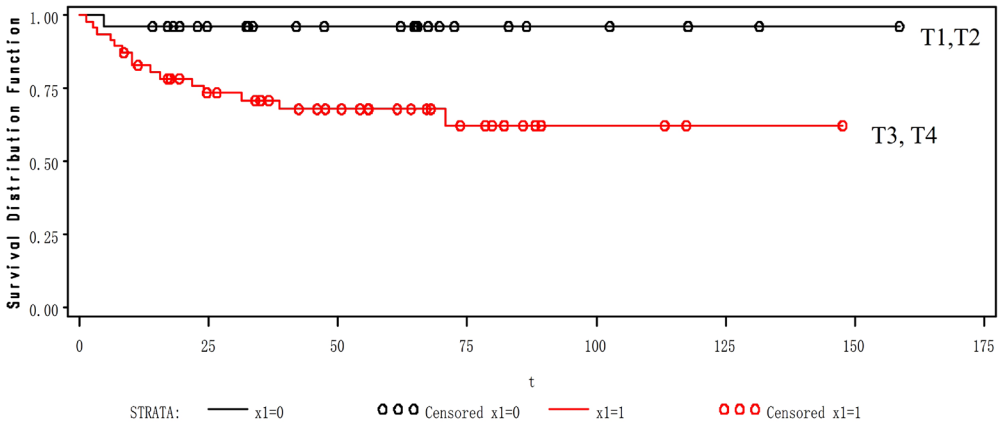

Figure 3. Overall survival in 73 patients with clear pathological T stage after surgery, stratified by depth of tumor infiltration (T)) (x2=6.8932, p=0.087).

Table 2. Distribution of patients staged by different staging systems

Stage	*N (%)*
TNM	
I	26 (25.7)
II	27 (26.7)
III	36 (35.6)
IV	12 (11.9)
Lugano	
I	30 (29.7)
II	14 (13.9)
IIE	33 (32.7)
IV	24 (23.8)
Ann Arbor	
IE	44 (43.6)
IIE	45 (44.6)
IIIE	4 (3.9)
IVE	8 (7.9)

ing Ann Arbor system with the TNM or the Lugano systems, respectively (p<0.0001; Table 2).

Comparison of the three systems in primary gastric and non-gastric lymphomas

Table 3 shows the results of the comparison of the three staging systems in patients with gastric lymphoma (N=67;66.3%) and non gastric lymphoma (N=34;33.7%). In primary gastric lymphoma, the TNM system had the strongest predicting power for survival among all three systems. The 5-year survival rate was well correlated to the stages in the TNM system, but there were inverse 5-year survival rates in the Lugano system (81.48% in stage II, 85.71% in stage IIE) and overlapped survival rates in the Ann Arbor system (69.47% in stage IIE , 66.67% in stage IIIE) (Table 3, Figure 1). In non-gastric lymphoma, the 5-year OS rate still was well-correlated to the stages of the TNM system, but there were equal 5-year OS rates in Lugano (100% in stage I and II) and Ann Arbor system (100% in stage III E and IV E ; Table 3).

Comparison of the three systems in aggressive and indolent primary gastrointestinal lymphoma

The clinically aggressive subtypes (including DLBCL, T-cell, and plasmablastic lymphomas; N=64;63.4%) represented the majority in this group of patients. We compared the three systems in aggressive and indolent (including MALT, HD, and FL; N=29;28.7%) lymphomas. In aggressive lymphoma, the TNM system was better predictor of survival than the Lugano and Ann Arbor systems (Table 4), while the survival curves of the Lugano and Ann Arbor systems were overlaped (Table 4 and Figure 2). In indolent lymphoma, the TNM system still was the best predictor of survival among all three systems. An inverse 5-year survival rate was noticed in the Lugano (83.33%

Table 3. Comparison of 5-year overall survival rate according to different staging systems in gastric and non gastric primary lymphomas

	Gastric (N=67)				*Non-gastric (N=34)*			
	5-year	*SE*	x^2	*p value*	*5-year*	*SE*	x^2	*p value*
TNM								
I	100.00	0.0000			100.00	0.0000		
II	87.18	0.0858			77.78	0.1386		
III	75.17	0.0971			53.50	0.1457		
IV	16.67	0.1521	36.5258	<0.0001	20.83	0.1844	6.1290	0.1055
Lugano								
I	100.00	0.0000			100.00	0.0000		
II	81.48	0.1194			100.00	0.0000		
IIE	85.71	0.0935			61.75	0.1141		
IV	50.42	0.1285	17.6935	0.0005	17.14	0.1556	8.7219	0.0332
Ann Arbor								
IE	100.00	0.0000			91.67	0.0798		
IIE	69.47	0.0917			49.89	0.1268		
IIIE	66.67	0.2722			0.00	0.0000		
IVE	25.00	0.2165	22.1516	<0.0001	0.00	0.0000	6.8171	0.0780

Table 4. Comparison of 5-year overall survival rate of different staging systems in aggressive and indolent primary gastrointestinal lymphoma

	Aggressive (N=64)				*Indolent (N=29)*			
	5-year	*SE*	x^2	*p value*	*5-year*	*SE*	x^2	*p value*
TNM								
I	100.00	0.0000			100.00	0.0000		
II	81.34	0.1006			85.71	0.1323		
III	63.52	0.1045			65.63	0.1638		
IV	16.00	0.1416	19.2705	0.0002	0.00	0.0000	31.0288	<0.0001
Lugano								
I	100.00	0.0000			100.00	0.0000		
II	80.00	0.1789			83.33	0.1521		
IIE	64.96	0.1013			85.71	0.1323		
IV	43.90	0.1386	10.8771	0.0124	25.00	0.2165	12.4476	0.0060
Ann Arbor								
IE	95.83	0.0408			100.00	0.0000		
IIE	55.34	0.0968			70.00	0.14		
IIIE	66.67	0.2722			0.00	0.00		
IVE	0.00	0.0000	13.1511	0.0043	50.00	0.35	13.6365	0.0034

in stage II, but 85.71% in stage IIE) and the Ann Arbor systems (0 in stage IIIE, but 50 in stage IVE) (Table 4).

The effect of depth of tumor infiltration on survival

The main difference between TNM staging system and the Lugano or Ann Arbor systems was the depth of tumor infiltration (T), with T commonly neglected in the Lugano or Ann Arbor systems. We compared the effect of T on overall survival in 73 patients with clearly pathological T stages after surgery. The results showed that the 5-year survival of patients with T1 or T2 disease was significantly superior in patients with T3 or T4 (96.15 vs 67.92%, x^2=6.8932, p=0.0087; Figure 3). To evaluate independent prognostic covariates for overall survival, a Cox proportional hazard regression covariate analysis was performed. The variables, including sex (male vs female), age (<60 vs ≥60 years), T (T1-2 vs T3-4), N (N0 vs N1-3) , M (M0 vs M1), LDH (normal vs elevated), ECOG PS score (0-1 vs ≥2), subtype (aggressive vs indolent), and tumor primary site (stomach vs non stomach) were entered into the model in one single step if the variable was p<0.05 and removed if p>0.1. Interestingly, only T (p=0.0181) and M (p=0.0031) were independent prognosticators for overall survival, while sex, age, lymph nodes, LDH, PS, subtype and primary tumor site were not independently significant prognostic covariates.

Discussion

Today, much effort has been put into the development of specific markers that could predict the treatment results and prognosis of patients with malignant diseases. Tumor stage was one of the most important factors in the choice of therapy and prediction of prognosis. Several different staging systems, including Ann Arbor, Lugano, and TNM systems have been used for PGL. The Ann Arbor staging system was routinely used in nodal non-Hodgkin's lymphoma, but it seemed not to be optimal for PGL [9]. Lugano staging system was a widely used system for PGL, and was a modification of the Ann Arbor system. In the Lugano system Ann Arbor stage III was removed, and stage IV referred to disseminated extranodal involvement or concomitant supradiaphragmatic nodal involvement [8]. TNM staging system is an international language, and was the most important factor which influenced decision-making among oncologists in cancer diagnosis and treatment. For PGL, staging remained a challenge, as there was not a standard staging system for this disease. In this study, to assess the value of the three systems in predicting the clinical outcome of patients with PGL, survival analysis was performed in 101 patients with a histologically proven diagnosis of PGL. When staged by Ann Arbor system, 89 patients (88.1%) had stage I or II, and 12 patients (11.9%) had stage III or IV; however,

only 53 patients (52.5%) had stage I or II (as many as 36 patients changed stage) when staged by the TNM system, and 44 patients (43.6%) had stage I or II (45 patients changed stage) when staged by the Lugano system. When assessing the predictive value of 5-year survival rate of the three systems in a wide and unselected series of patients with PGL TNM and the Lugano systems were better compared to the Ann Arbor system (data not shown). Some authors showed that overall survival of gastric lymphomas was higher when compared with non-gastric lymphomas [7,11]. Our study showed similar results. The 5-year OS of 67 patients with gastric lymphoma was 80.98% vs 61.51% of 34 patients with non-gastric lymphoma (x^2=4.0520, p=0.0441). No matter in the primary gastric or non-gastric lymphoma, the survival-predictive power of TNM system was better compared with Lugano and Ann Arbor systems (Figure 1; Table 3). Furthermore, the clinically aggressive subtypes (N=64; 63.4%) accounted for the majority of this group of 101 patients, so we compared the predictive value of the three systems on survival in aggressive and indolent lymphomas. In aggressive subtypes, the TNM system was also better than the Lugano and Ann Arbor systems (Table 4, Figure 2), and in indolent lymphomas the TNM system still was the best among all three systems (Table 4). The 5-year survival rate in Lugano and Ann Arbor systems was somewhat confusing in patients with indolent gastrointestinal lymphoma (in Ann Arbor system the 5-year survival rate of stage IIIE was 0%, but it was 50% in stage IVE) (Table 4).

In this series of patients, we found that the TNM staging system showed superior survival-predicting ability compared with the Lugano or Ann Arbor system in PGL. In fact, the T part of TNM system plays an important role in the TNM staging system, and it pertains to the anatomical structure of the organs and sufficiently fulfills the requirements for staging the local disease extent [9]. However, it is totally neglected in Ann Arbor system, and tumor invasion from mucosa to serosa all belonged to stage I in the Lugano system. In order to observe the effect of T factor on patients' survival in this study, we tested it in 73 patients who were subjected to surgical treatment and had clearly pathological T stage using Kaplan–Meier and Cox survival analysis. The result showed that T1 and T2 patients had significantly superior survival compared to T3 and T4 patients. Interestingly, the Cox analysis showed that only T (p=0.0181) and M (p=0.0031) were independent predictors for overall survival, while sex, age, lymph node (N), LDH, PS, subtypes (aggressive vs indolent) and tumor primary site were not. In fact, the value of possible prognostic factors (such as age, LDH levels, PS and so on) remains controversial, and no risk factors have been clearly identified in patients with PGL [5,12-15].

To sum up, in this study we compared the capacity of the three staging systems (TNM, Lugano, and Ann Arbor) in predicting the overall survival in patients with PGL, and the results showed that TNM staging system was superior to Lugano and Ann Arbor systems. The depth of tumor infiltration (T) and involvement of extranodal sites (M) were independent prognosticators for overall survival. However, because of the relatively small number of cases, this conclusion needs to be tested in much larger studies.

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