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ORIGINAL ARTICLE

Clinicopathological Variation of Lauren Classification in Gastric Cancer

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Abstract The investigation of prognostic factor for gastric cancer is still desirable because of dismal prognosis in gastric cancer. Lauren's classification is currently a useful histological classification. There are few large series evaluating the prognostic significance of Lauren's classification in gastric cancer. From January 1987 to December 2013, a total of 3071 patients received gastrectomy for gastric cancer. According Lauren's classification, 1423(46.3 %) patients were intestinal type, 1000 patients (32.6 %) were diffuse type, and 648 patients (21.1 %) were mixed type. The clinicopathological characteristics and prognosis in Lauren's classification were analyzed in these patients. Our results showed that patients with intestinal type gastric cancer (57.7 %) had a better 5-year overall survival than diffuse type (45.6 %) and mixed type (43.4 %, $P<0.001$). The clinicopathological characteristics showed that gastric cancer patients with intestinal type were older ($P<0.001$), male predominant ($P<0.001$), smaller tumor size ($P<0.001$), distal stomach predominant ($P<0.001$), relative well differentiated ($P<0.001$), less advanced Borrmann type ($P<0.001$), less scirrhous type stromal reaction($P<0.001$), less infiltrating type of Ming's histology type($P<0.001$), less tumor invasion depth and less lymphovascular invasion ($P<0.001$). Multivariate analysis with overall survival as an endpoint showed that age ($P=0.005$), Borrmann classification ($P<0.001$), pathological T category ($P=0.023$), pathological N category ($P<0.001$) and Lauren's classification ($P=0.003$) were significant correlated in gastric cancer. Lauren's classification is an independent prognostic factor in gastric cancer patient undergoing gastrectomy. Lauren's classification can serve as a prognostic marker for gastric cancer patient receiving gastrectomy. The clinicopathological appearance and prognosis of mixed type gastric cancer is similar to diffuse type gastric cancer.

Keywords Gastric cancer · Gastrecotomy · Lauren's classification

Synopsis for table and contents Lauren's classification is an independent prognostic factor in gastric cancer after gastrectomy. The clinicopathological appearance and prognosis of mixed type gastric cancer is similar to diffuse type gastric cancer.

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Introduction

Gastric cancer is one of the most common malignancies in the gastrointestinal tract. It leads the third cancer related death worldwide. In Taiwan, gastric cancer is still the seventh most common malignancy and the sixth major cause of cancer mortality [1]. Surgical resection with a curative intent is still the major therapeutic strategy for gastric cancer. Extended lymph node dissection is a standard procedure for gastric cancer surgery [2, 3]. However, the prognosis of gastric cancer remains poor because of aggressive cancer behavior and higher recurrent rate.

Numerous pathological classifications were proposed for evaluation of the tumor behavior in gastric cancer. Lauren's classification is the most useful and widely applicable classification systems in gastric cancer. This classification system was proposed by Lauren since 1965 [4]. Generally, Lauren's classification is classified into intestinal type and diffuse type. The histology of the two type gastric cancer used to have distinct epidemiology and prognosis in gastric cancer [5, 6]. Besides, a group of gastric cancer patients have both intestinal and diffuse type in the gastric cancer specimen, which is separated into mixed type. There are few studies that evaluated the behavior and prognosis of mixed type gastric cancer. We also enrolled this type gastric cancer and evaluated the clinicopathological behavior and prognosis in gastric cancer patients.

Currently, genetic alteration in Lauren's classification has been investigated because of distinct epidemiology, pathology and prognosis. Since the biological behavior is quite difference in intestinal type and diffuse type gastric cancer, many researchers investigated the epigenetic regulation and biological tumor behavior between intestinal and diffuse type gastric cancer. The significance of Lauren's classification is emerging comparing to other histological classification. This study aims to investigate the clinical relevance and variation of gastric cancer with Lauren's classification in the clinicopathological characteristics and prognosis in gastric cancer patients.

Patients and Methods

From January 1987 to December 2013, a total of 3071 patients diagnosed with gastric cancer received surgical resection for gastric cancer at the Department of Surgery, Taipei Veterans General Hospital. Prior to surgery, chest films, upper gastrointestinal endoscopy, and computed tomography scans were performed. Patients with evidences of distant visceral organ metastasis or carcinomatosis would not undergo surgical intervention and would instead refer to oncologists for chemotherapy evaluation. After laparotomy, peritoneal lavage cytology was collected for each patient. Subtotal gastrectomy was performed for distal or middle third lesions, while total gastrectomy was performed for proximal third lesions. Standard D2 lymph node dissection was performed in patients with curative intent. Patients who could not receive gastric resection, including bypass surgery or only exploratory laparotomy, were excluded in this study. All the surgical specimens were examined by experienced pathologists. Gross features of the specimens were based on tumor size, tumor location and the Borrmann's classification. The Borrmann's classification was defined as superficial type, Borrmann type I (polypoid tumor), Borrmann type II (ulcerated tumor with sharp demarcated margin), Borrmann type III (ulcerated tumor without demarcated margin and infiltrating to surrounding gastric wall), and Borrmann type IV (diffuse infiltrating tumor). Borrmann type I &II are well-defined tumor (localized type) while Borrmann type III & IV are ill-defined tumor appearance (infiltrating type). The microscopic features of histology, pathology and cell differentiation were analyzed according to cell grade of tumor differentiation, stromal reaction type (Medullary, intermediate and scirrhous type), Lauren's histological classification (intestinal or diffuse type), Ming's histological classification [7] (expanding or infiltrating type), and lymphovascular invasion patterns. Patients with positive cytology report after operation would be classified as M1 disease. The staging systems were based on 7th edition of American Joint Committee (AJCC) TNM classification for gastric cancer [8].

After surgery, patients were followed up at our outpatient department every 3 months. Recurrence was defined as first evidence in image finding of tumor relapsing, cytological analysis of ascites form abdominal tapering, endoscopic findings of tumor recurrence, and/or metastases from bone scan.

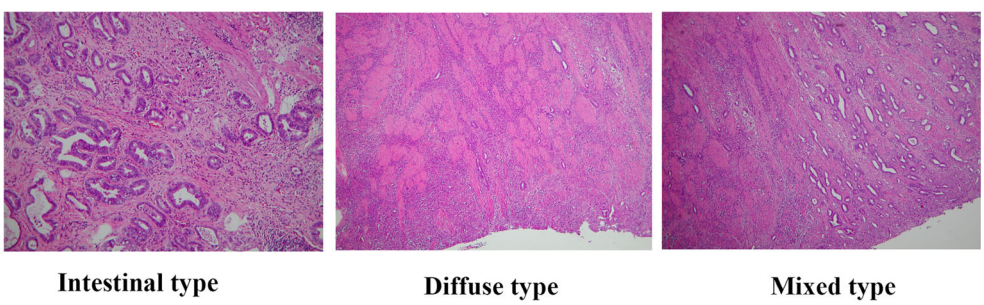

Fig. 1 Histology pattern of Lauren's classification: intestinal type, diffuse type and mixed type gastric cancer

Table 1 Clinicopathological characteristics of 3071 gastric cancer patients with Lauren's classification

Variable	Intestinal type (n=1423)	Diffuse type (n=1000)	Mixed type (n=648)	P value
Age				
<65 yrs	369	569	230	<0.001
≧65 yrs	1054	431	418	
Sex				
Male	1192	617	480	<0.001
Female	231	383	168	
Tumor size				
<4 cm	669	307	194	<0.001
4-8 cm	593	432	327	
>8 cm	161	261	127	
Tumor location				
Upper stomach	255	146	108	<0.001
Middle stomach	418	413	247	
Lower stomach	728	376	272	
Whole stomach	22	65	21	
Cell grade				
Poorly differentiated	195	965	514	<0.001
Moderately differentiated				
Well differentiated	1164	28	132	
	64	7	2	
Gross appearance				
Superficial type	560	278	159	<0.001
Borrmann type 1&2	329	139	130	
Borrmann type 3&4	534	583	359	
Stromal reaction type				
Medullary type	425	240	74	<0.001
Intermediate type	866	281	381	
Scirrhous type	132	479	193	
Ming's				
Expanding	696	107	68	<0.001
Infiltrating	727	893	580	
Nodal Involvement				
Negative	754	337	171	<0.001
Positive	669	663	477	
Lymphovascular invasion				
no	644	360	148	<0.001
yes	779	640	500	
Depth of cancer invasion				
mucosa	752	307	207	<0.001
submucosa	302	300	232	
proper muscle	325	340	189	
serosa	44	53	20	
Overall Survival rate (5 year)	57.7 %	45.6 %	43.4 %	<0.001
Disease-Free Survival rate (5 year)	55.8 %	41.5 %	42.0 %	<0.001
AJCC TNM stage				
I	656	245	139	<0.001
II	262	198	134	
III	417	446	293	
IV	88	111	82	

P<0.05, statistical significance

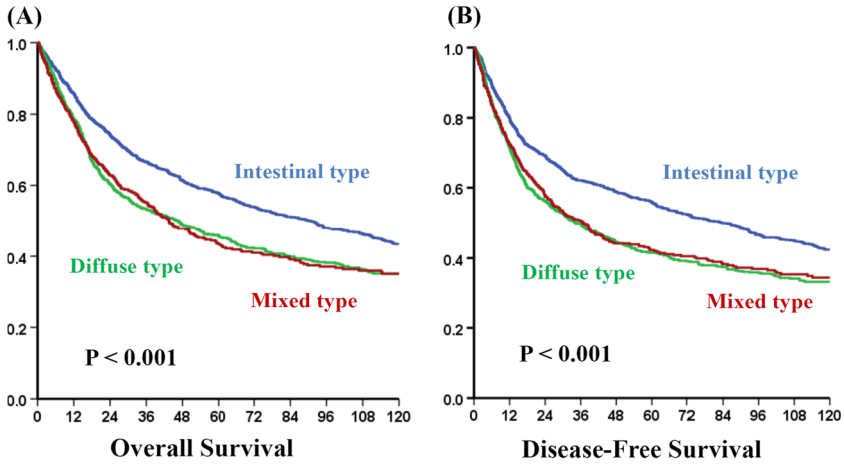

Fig. 2 **a**. Overall survival months of gastric cancer patients in Lauren's classification, $P<0.001$ (log rank test). **b**. Disease free survival months of gastric cancer patients in Lauren's classification, $P<0.001$(log rank test)

The relapse pattern of tumor recurrence was recorded in detail. The follow-up data were prospectively collected and regularly updated. The overall survival (OS) is defined from the date of operation to the date of death or the latest follow-up. The disease-free survival (DFS) is defined as the length of period after the operation for gastric cancer during which the patient survives without recurrence.

The intestinal type gastric cancer preserves the glandular appearance, which is related to environmental factor. The diffuse type used to have diffusely infiltrating cells without glandular architecture which is used to be related to genetic factor. The mixed type describes that there are both intestinal type and diffuse type in the tumor specimen (Fig. 1).

All statistical analyses were carried out using the SPSS software version 18.0 (SPSS Inc., Chicago, IL USA). Clinicopathological differences were compared with chi-square tests. Survival was evaluated by a Kaplan-Meier curve analysis and log-rank test. Prognostic factors were evaluated with a Cox regression model. A P value<0.05 was considered statistically significant.

Results

Among these gastric cancer patients, there are 1423 intestinal type (46.3 %), 1000 diffuse type (32.6 %) and 648 mixed type (21.1 %) gastric cancer. The intestinal type to diffuse type ratio is 1.42. The clinicopathological characteristics indicates that gastric cancer patients with intestinal type were older ($P<0.001$), male predominant ($P<0.001$), smaller tumor size ($P<0.001$), distal stomach predominant ($P<0.001$), relative well differentiated ($P<0.001$), less advanced Borrmann type ($P<0.001$), less scirrhous type stromal reaction($P<0.001$), less infiltrating type of Ming's histology type($P<0.001$), less tumor invasion depth and less lymphovascular invasion ($P<0.001$) (Table 1).

The overall survival of gastric cancer patients with intestinal type, diffuse type and mixed type are 57.7 %, 45.6 % and 43.4 % respectively ($P<0.001$). The disease free survival of gastric cancer patients with intestinal type, diffuse type and mixed type are 55.8 %, 41.5 % and 42.0 % respectively ($P<0.001$). There were significant differences in overall

Table 2 Multivariate analysis with overall survival as an endpoint in 3071 gastric cancer patients

Variables	Multivariate analysis		
	P value	Hazard ratio	95 % confidence interval
Age	**0.005***	1.172	1.048–1.311
Tumor size	0.074	1.084	0.992–1.185
Borrmann classification	**<0.001***	1.172	1.074–1.278
Cell grade	0.928	1.005	0.896–1.128
Stromal reaction	0.121	1.074	0.981–1.176
Lymphovascular invasion	0.796	1.020	0.879–1.183
TNM pathologic T category[#]	**0.023***	1.086	1.012–1.165
TNM pathologic N category[#]	**<0.001***	1.301	1.233–1.372
Lauren's histology	**0.003***	1.132	1.044–1.227

*, $P<0.05$, statistical significance

[#], American Joint Committee on Cancer (AJCC), Cancer Staging Manual, seventh edition, T category: T1, T2, T3, T4; N category: N0, N1, N2, N3

Table 3 Recurrence rate in gastric cancer with Lauren's classification

Variables	Recurrence		
	Positive	Negative	Total
Laruen's classification			
Intestinal type	642	781	1423
Diffuse type	304	596	1000
Mixed type	406	342	648
Total	1352	1719	3071

Intestinal type recurrence rate: 54.9 %, Diffuse type recurrence rate: 59.6 %, P=0.013

survival and disease free survival between intestinal type and diffuse type cancer. Interestingly, the survival between diffuse type and mixed type were similar (Fig. 2).

Multivariate analysis with overall survival as an endpoint showed that age (P=0.005), Borrmann classification (P<0.001), pathological T category (P=0.023), pathological N category (P<0.001) and Lauren's classification (P=0.003) were significantly correlated in gastric cancer. Lauren classification is an independent predictor for overall survival between intestinal type and diffuse type in gastric cancer (Hazard ratio: 1.132, 95 % confidence interval: 1.044–1.227). (Table 2)

Compared to the recurrence rate between intestinal and diffuse type gastric cancer, patient with intestinal type gastric cancer is 54.9 % while patients with diffuse type gastric cancer is 59.6 % (P=0.013). The recurrence rate of diffuse type gastric cancer is higher than intestinal type gastric cancer (Table 3).

Furthermore, we evaluated the prognosis of intestinal type and diffuse type gastric cancer in the subgroup of different stage. The results showed that gastric cancer patients with intestinal type pathological appearance had significantly better survival than those with diffuse type in stage I disease (P<0.001). However, the survival difference between intestinal type and diffuse type is not obvious in stage III gastric cancer (P=0.279). We found that there was stage variation in Lauren's classification in survival analysis. The survival benefit of intestinal type gastric cancer is better than diffuse type, especially in stage I gastric cancer (Fig. 3).

Discussion

Our results showed that intestinal type gastric cancer has better clinicopathological characteristics comparing to diffuse type gastric cancer. The prognosis of gastric cancer patients is better in intestinal type comparing to diffuse type gastric cancer, especially in early stage. Diffuse type gastric cancer exhibits a higher recurrent rate than intestinal type. The clinical appearance and survival of mixed type gastric cancer were similar to diffuse type gastric cancer. In our studies, Lauren classification could be an independent prognostic factor for gastric cancer.

Generally, a predominance of intestinal type to diffuse type is an indicator that environmental influence on the cancer development in the population group. The pathological development of environment-related gastric cancer usually derives from chronic gastritis, resulting mucosal atrophy or atrophic gastritis. It will lead to intestinal metaplasia or dysplasia, which is a pre-malignant lesion. In our series, the intestinal type to diffuse type ratio is 1.42. It means that the environmental factor is still the major cause of gastric cancer development in Taiwan Chinese. Besides, we found that a marked predominance of old age (2.85 fold vs 0.72 fold) and male gender (5.16 fold vs 1.61 fold) in intestinal type gastric cancer comparing to diffuse type gastric cancer. It seems that young female patient exhibits more diffuse type gastric cancer, resulting in more aggressive tumor behavior in gastric cancer.

Few studies evaluate the prognostic significance in mixed type gastric cancer. In our studies, the proportion of mixed type gastric cancer is 21.1 %. Mixed type gastric cancer can be found approximately 1 out of 5 gastric cancer patients in

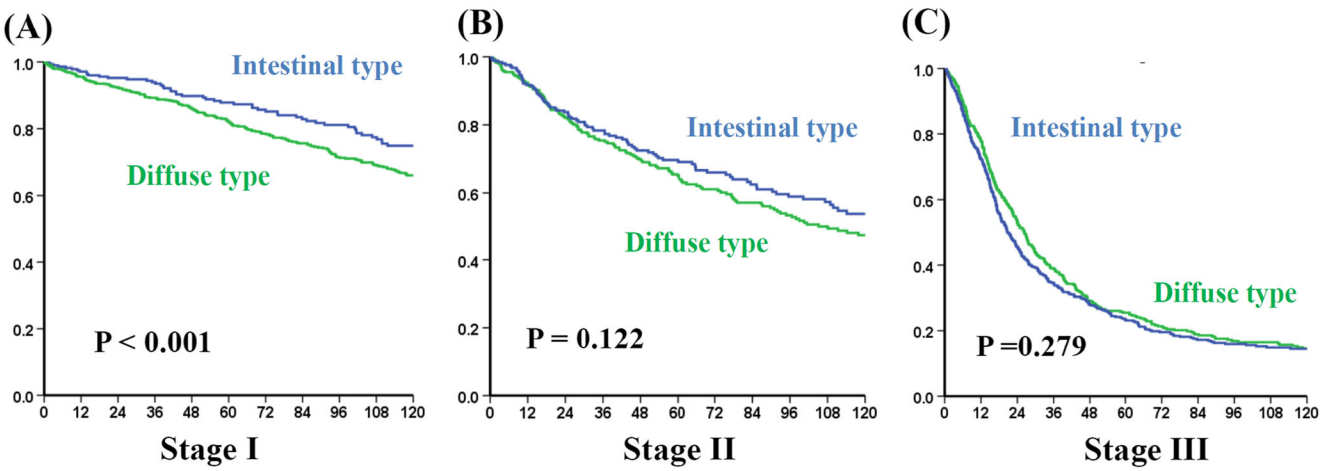

Fig. 3 Survival differences of stage I to stage III gastric cancer between intestinal type and diffuse type

our series. Komatsu et al. [9] reported that mixed type gastric cancer is 25 % in their series and exhibit a worst prognostic factor in stage I gastric cancer. Zheng et al. [10] reported that mixed type present more aggressive features and exhibit different histogenic patterns. In our series, mixed type (43.4 %) gastric cancer patients present worse 5- year overall survival comparing to intestinal type (57.7 %) and diffuse type (45.6 %). However, the prognosis and survival pattern from the survival curve of Fig. 2 seems similar between diffuse type and mixed type. Some researchers suggested combining the mixed type with diffuse type gastric cancer as the same category of diffuse type. Our data seems to support this opinion because of similar survival in mixed type and diffuse type.

There was no previous study evaluating the survival pattern of Lauren classification in each gastric cancer stage. In our series, the intestinal type to diffuse type ratio from stage I to stage III is 2.67, 1.32, 0.93, respectively. The ratio of intestinal type decreased from stage I to stage III. Interestingly, we found that intestinal type gastric cancer presents better survival than diffuse type, especially in stage I gastric cancer, based on the AJCC staging systems (7th edition). The survival difference became vague from stage II to stage III. We are trying to explain this phenomenon of stage variation in Lauren's classification. Perhaps the prognosis of stage III gastric cancer is not just influenced by the histological pattern. Tumor depth or lymph node metastases might play a more important role comparing to Lauren's classification in stage III gastric cancer.

The importance of Lauren's classification is emerging in recent years. Since the distinct biological behavior between intestinal type and diffuse type, researchers were focused on the epigenetic regulation and prognostic biomarkers between these two categories. Currently, Her-2 is reported to be a therapeutic target in gastric cancer. The positive rate of Her-2 is ranging from 9 to 38 % in previous studies [11]. Qiu et al. reported that combination of Lauren classification and Her-2 status is a better prognostic factor in gastric cancer patients. Her-2 negative intestinal type gastric cancer patients presented a better survival comparing to Her-2 positive diffuse type gastric cancer patients [12]. Based on these studies, investigation of biological biomarkers and genetic therapeutic target in intestinal type and diffuse type gastric cancer could be the future work in gastric cancer treatment.

This study reported on a 26-year experience in a single center, and was based on a retrospective investigation. We enrolled all gastric cancer patients, including curative and palliative resections, which can provide complete pathological examinations. Even though we can provide larger patient numbers in our study, selection bias might have existed in this retrospective study. Furthermore, we focused on the clinical outcome in the histological pattern and clinical outcome in gastric cancer. Further studies are necessary for genetic alteration and tumor behavior in intestinal type and diffuse type gastric cancer.

Conclusion

Laruen classification is an independent prognostic factor in gastric cancer after gastrecotmy. The clinicopathological appearance of mixed type gastric cancer and prognosis of mixed type gastric cancer patients is similar to those with diffuse type gastric cancer.

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Compliance with ethical standards

Conflict of interest All authors disclose no financial and personal relationships with other people or organizations that could inappropriately influence their work.

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