Effect of World Health Organization (WHO) Histological Classification on Predicting Lymph Node Metastasis and Recurrence in Early Gastric Cancer

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Background: The World Health Organization (WHO) histological classification for gastric cancer is widely accepted and used. However, its impact on predicting lymph node metastasis and recurrence in early gastric cancer (EGC) is not well studied.

Material/Methods: From 1987 to 2005, 2873 EGC patients with known WHO histological type who had undergone curative resection were enrolled in this study. In all, 637 well-differentiated adenocarcinomas (WD), 802 moderately-differentiated adenocarcinomas (MD), 689 poorly-differentiated adenocarcinomas (PD), and 745 signet-ring cell adenocarcinomas (SRC) were identified.

Results: The distribution of demographic and clinical features in early gastric cancer among WD, MD, PD, and SRC were significantly different. Lymph node metastasis was observed in 317 patients (11.0%), with the lymph node metastasis rate being 5.3%, 14.8%, 17.0%, and 6.3% in WD, MD, PD, and SRC, respectively. Univariate and multivariate analyses indicated that gender, tumor size, gross appearance, depth of invasion, and WHO classification were significantly associated with lymph node metastasis. Recurrence was observed in 83 patients (2.9%), with the recurrence rate being 2.2%, 4.5%, 3.0%, and 1.6% in WD, MD, PD, and SRC, respectively. Multivariate analysis confirmed that MD, elevated gross type, and lymph node metastasis were independent risk factors for recurrence in EGC. MD patients showed worse disease-free survival than non-MD patients (P=0.001).

Conclusions: WHO classification is useful and necessary to evaluate during the perioperative management of EGC. Treatment strategies for EGC should be made prudently according to WHO classification, especially for MD patients.

MeSH Keywords: Gastric Emptying • Giant Lymph Node Hyperplasia • Histological Techniques • Recurrence • World Health Organization

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Background

Early gastric cancer (EGC) has been defined as a carcinoma confined to the mucosa or submucosa, regardless of the presence of lymph node metastasis (LNM). Patients with EGC generally have an excellent prognosis after curative resection; the 5-year survival rate is reported to be around 90% [1–3]. It is well known that LNM in EGC is associated with prognosis [4–7], and predicting LNM preoperatively is very important for minimal treatment. However, it is still very difficult to precisely diagnose N-stage in EGC, even when endoscopic ultrasonography (EUS) and computed tomography (CT) are used.

Recurrence in EGC is very rare but does occur. Previous studies have reported recurrence rates in EGC to be 1.4–6.0% [6,8–11]. Recurrence in EGC causes treatment failure and leads to 13.7–23% of all related deaths [12,13]. However, independent predictors for recurrence in EGC have not been well studied because of the low recurrence rate [6,8,10,11].

The World Health Organization (WHO) histological classification is widely accepted and used for diagnosis in gastric cancer, but its impact on perioperative management has not been studied. Using this classification, gastric adenocarcinoma is divided into 4 main categories: papillary, tubular, mucinous, and signet-ring cell carcinoma (SRC). Tubular adenocarcinoma is further graded as 3 subcategories: well-differentiated adenocarcinoma (WD), moderately-differentiated adenocarcinoma (MD), and poorly-differentiated adenocarcinoma (PD) [14]. The WHO classification is commonly divided into 2 major categories in clinical study: differentiated and undifferentiated type (Nakamura's classification) [15]. The former includes WD, MD, and papillary adenocarcinoma, and the latter includes PD, SRC, and mucinous adenocarcinoma. Undifferentiated histological type is usually considered to have a higher probability of LNM than differentiated type in EGC. However, some studies

showed no difference between these 2 types [16]. Furthermore, some investigators reported that SRC had a similar or decreased probability of LNM and better prognosis than non-SRC in EGC [17,18]. It seems that Nakamura's classification may have some limitations when applied to EGC, so we conducted this study to evaluate the impact of WHO classification on predicting lymph node metastasis and recurrence in EGC.

Material and Methods

Between January 1987 and April 2005, a consecutive series of 2925 patients with EGC underwent curative resection in the Department of Surgery at Yonsei University, Seoul, Korea. Histological diagnosis was made according to the WHO classification [14]. Due to very limited case numbers, 11 papillary adenocarcinomas (0.4%), 17 mucinous adenocarcinomas (0.6%), and 24 unclassified adenocarcinomas (0.8%) were excluded. Therefore, the remaining 2873 patients with 637 WD cases (22.2%), 802 MD cases (27.9%), 689 PD cases (24.0%), and 745 SRC cases (25.9%) were enrolled in this study. For patients with mixed histological type, we recorded the dominant part in Nakamura's classification. Age, sex, tumor size, lesion number, gross appearance, depth of invasion, status of lymph node metastasis, WHO classification, and presence of recurrence were analyzed.

The standard surgical treatment was a total or subtotal gastrectomy with D2 lymph node dissection in accordance with the guidelines of the Japanese Research Society for Gastric Cancer (JRSGC) [19]. Curative resection (R0) was defined as no tumor remaining macroscopically and microscopically. The gross appearance was classified according to the JRSGC standard: cancer lesion I, II a as elevated type; IIb as flat type; IIc, and III as depressed type. Gross type of the largest area in mixed types was recoded, such as recode IIa in IIa + IIc. Routine follow-up

Table 1. Demographic and clinical features of early gastric cancer. (2873 cases).

Features	WD	MD	PD	SRC	P value
Case number	637 (22.2%)	802 (27.9%)	689 (24.0%)	745 (25.9%)	
Age (Mean ±SD, years)	59.5±9.4	58.0±10.4	54.0±11.8	49.1±12.0	<0.001*
Gender (male/female)	73.2%/26.8%	74.7%/25.3%	60.7%/39.3%	52.5%/47.5%	<0.001**
Location (U/M/L)	10.2%/42.4%/47.4%	9.9%/46.3%/43.9%	16.1%/45.9%/37.9%	13.3%/55.0%/31.7%	<0.001**
Gross type (elevated/flat/depressed)	24.0%/33.4%/42.5%	20.2%/29.87%/50.0%	10.9%/33.1%/55.9%	5.4%/40.8%/53.7%	<0.001**
Size (≤2.0 cm/>2.0 cm/unknown)	61.5%/37.8%/0.6%	55.4%/44.0%/0.6%	50.4%/48.9%/0.7%	53.3%/46.3%/0.4%	0.005**
Depth of invasion (mucosa/submucosa)	62.3%/37.7%	38.3%/61.7%	39.2%/60.8%	67.8%/32.2%	<0.001**

U,M,L – indicates upper, middle and lower third of the stomach. * One way anova test; **, χ^2 test.
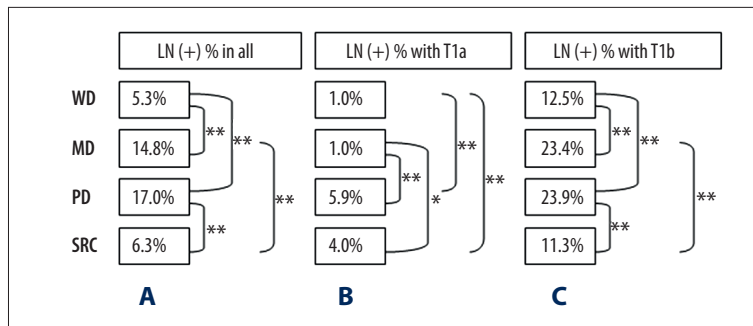
Figure 1. (**A–C**) Lymph node metastasis rate according to WHO classification adjusted by depth of invasion. Only significant differences are marked. ** $P<0.001$, * $P<0.05$, $P>0.05$ is not marked. WD – well-differentiated; MD – moderately-differentiated; PD – poorly-differentiated; SRC – signet ring cell; LN – lymph node; T1a – invaded to mucosa; T1b – invaded to submucosa.

Table 2. Multivariate analysis of risk factors for lymph node metastasis in EGC.

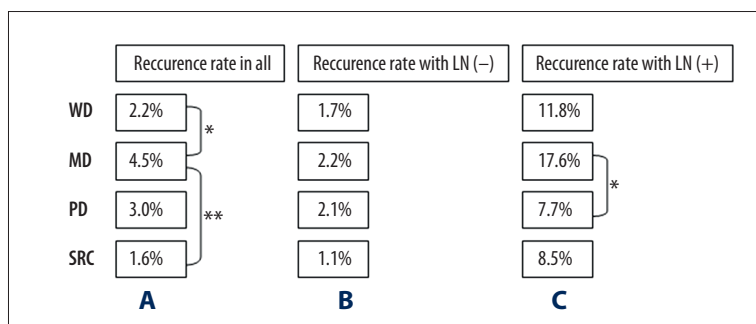|	Hazard ratio	95% C.I.	P value
Age	1.002	0.991–1.014	NS
Gender			0.008
Male	1		
Female	1.416	1.096–1.829	
Tumor size			<0.001
≤2.0 cm	1		
>2.0 cm	1.778	1.375–2.299	
Tumor location			NS
Upper	1		
Middle	1.371	0.922–2.041	
Lower	1.078	0.713–1.630	
Gross appearance			0.022
Non-elevated	1		
Elevated	1.428	1.052–2.940	
Depth of invasion			<0.001
Mucosa	1		
Submucosa	6.388	4.551–8.967	
Histology*			<0.001
WD	1		
MD	1.920	1.404–2.631	<0.001
PD	2.308	1.683–3.165	<0.001
SRC	1.371	0.782–2.703	NS
Histology**			NS
Differentiated	1		
Undifferentiated	1.343	0.829–2.177	

* Indicates WHO histological classification; ** Indicates Nakamura's classification.

for EGC patients was every 3 months during the first 2 years, every 4 months during the third year, every 6 months during the next 2 years, and every year thereafter. Mean follow-up time was 78.0 months. Recurrence was confirmed by clinical and radiological examination.

All statistical analyses were conducted using the statistical program SPSS 13.0 (SPSS, Chicago, IL, USA). Clinicopathological characteristics were analyzed by the 2-tailed t test, one-way ANOVA test, or χ^2 test. Logistic regression was used to estimate risk factors for lymph node metastasis. The log-rank test

Table 3. Recurrence site according to WHO histological classification.

	WD	MD	PD	SRC
Loco-regional				
Remnant & anastomosis	2	3	4	4
Regional LN	3	4	1	0
Local surgical area	2	4	2	0
Peritoneal	0	7	5	0
Haematogenous				
Liver	3	12	2	4
Lung	0	2	1	1
Bone	1	0	2	2
Brain	0	0	2	0
Extra-abdominal LN	0	0	1	1
Multiple patterns	3	4	1	0
Total	14 (16.7%))	36 (43.4%)	21 (25.3%)	12 (14.5%)
Recurrence incidence	2.2%	4.5%	3.0%	1.6%

	Reccurence rate in all	Reccurence rate with LN (−)	Reccurence rate with LN (+)
WD	2.2%	1.7%	11.8%
MD	4.5%	2.2%	17.6%
PD	3.0%	2.1%	7.7%
SRC	1.6%	1.1%	8.5%
	A	**B**	**C**

Figure 2. (**A–C**) Recurrence rate according to WHO classification adjusted by lymph node status. Only significant differences are marked. ** $P<0.001$, * $P<0.05$, P>0.05 is not marked. WD – well-differentiated; MD – moderately-differentiated; PD – poorly-differentiated; SRC – signet ring cell; LN – lymph node.

was used for survival analysis. In all statistical analyses, a *P* value of <0.05 was considered to be significant.

Results

Clinical characteristics

The demographic and clinical features of WHO classifications are presented in Table 1. Distribution of age, sex, tumor location, tumor size, gross appearance, and depth of invasion among WD, MD, PD, and SRC were significantly different. It is noteworthy that SRC correlated with younger age and female sex, and that MD and PD showed a significantly higher proportion of submucosal involvement.

Lymph node metastasis

The LNM rate according to WHO classification was compared. Regardless of depth of invasion, LNM rate was 5.3%, 14.8%, 17.0% and 6.3% in WD, MD, PD, and SRC, respectively. LNM rate was significantly higher in MD and PD than in WD and SRC ($P<0.001$) (Figure 1A). In mucosa cancer, LNM incidence was 1.0%, 1.0%, 5.9%, and 4.0% in WD, MD, PD, and SRC, respectively. It was significantly higher in PD and SRC than in WD and MD, with no statistical difference between WD and MD, or PD and SRC (Figure 1B). In submucosa cancer, LNM incidence was 12.5%, 23.4%, 24.0%, and 11.3% in WD, MD, PD, and SRC, respectively (Figure 1C), with comparison results similar to those in Figure 1A.

Univariate analysis of LNM in EGC showed that sex, gross appearance, tumor size, depth of invasion, and WHO classification were associated with LNM, while age, tumor location, and Nakamura's classification were not. In multivariate

Table 4. Multivariate analysis of risk factors for recurrence in EGC.

	Hazard ratio	95% C.I.	P value
Age	1.013	0.992–1.035	NS
Gender			NS
Male	1		
Female	0.721	0.437–1.188	
Tumor size			NS
≤2.0 cm	1		
>2.0 cm	0.875	0.540–1.417	
Tumor location			NS
Upper	1		
Middle	0.891	0.430–1.846	
Lower	1.047	0.501–2.189	
Gross appearance			0.002
Non-elevated	1		
Elevated	2.159	1.312–3.552	
Depth of invasion			NS
Mucosa	1		
Submucosa	1.273	0.738–2.195	
Histology*			0.050
Non-MD	1		
MD	1.592	1.000–2.536	
Histology**			NS
Differentiated	1		
Undifferentiated	1.077	0.544–2.132	
Lymph node status			<0.001
Negative	1		
Positive	6.745	4.254–10.694	

* WHO histological classification was divided into MD and non-MD (including WD, PD and SRC) because of highest recurrence rate in univariate analysis; ** Indicates Nakamura's classification.

analysis (Table 2), all univariate risk factors proved to be independent risk factors for LNM. It was noteworthy that MD and PD had more likelihood of lymph node metastasis, while SRC did not.

Recurrence

At routine follow-up, 2.9% of patients (83 out of the 2873) had recurrence. The recurrence pattern according to WHO classification is presented in Table 3. Recurrence rates were 2.2%, 4.5%, 3.0%, and 1.6% in WD, MD, PD, and SRC, respectively. The proportion of MD recurrence cases was the largest (43.4%), followed by PD (25.3%), WD (16.7%), and SRC (14.5%). It was noteworthy that 33.3% (12 out of 36) of MD recurrence cases developed liver metastasis.

The recurrence rate according to WHO classification was compared in Figure 2. Regardless of lymph node status, MD showed a higher recurrence rate than WD ($P<0.05$) and SRC ($P<0.001$), while no statistical difference was observed between other types (Figure 2A). In node-negative patients, recurrence rates were 1.7%, 2.2%, 2.1%, and 1.1% in WD, MD, PD, and SRC, respectively, with no significant difference (Figure 2B). In node-positive patients, recurrence rates were 11.8%, 17.6%, 7.7%, and 8.5% in WD, MD, PD, and SRC, respectively. MD showed a significantly higher recurrence rate than PD ($P<0.05$). No significant difference was observed between other types (Figure 2C).

Univariate analysis of recurrence in EGC indicated that age, gross appearance, depth of invasion, lymph node metastasis, and WHO classification were associated with recurrence in
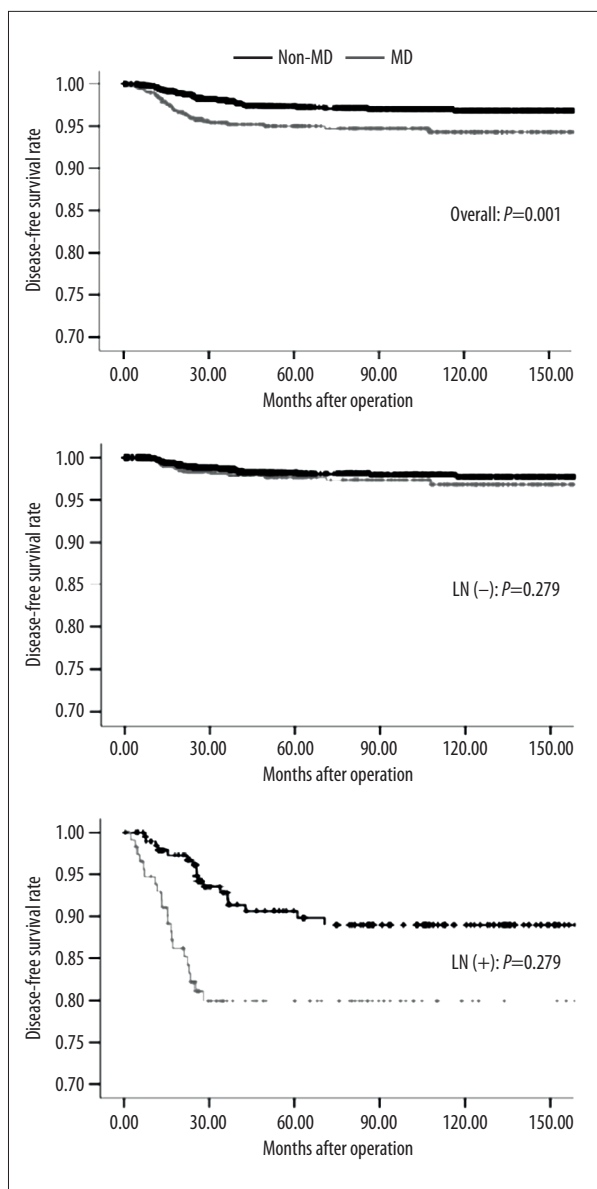
Figure 3. Disease-free survival curve in MD and non-MD patients according to lymph node status.

EGC. Sex, tumor size, tumor location, and Nakamura's classification were not related to recurrence. In multivariate analysis (Table 4), elevated type (vs. non-elevated, P=0.005), positive lymph node (vs. negative, P<0.001) and MD (vs. non-MD, P=0.049) were independent risk factors for recurrence in EGC, while age and depth of invasion were not.

Disease-free survival was compared between MD and non-MD patients (Figure 3). MD patients had worse disease-free survival than non-MD patients in both overall cases and node-positive cases (P=0.001 and P=0.007, respectively), with no significant difference between MD and non-MD in node-negative cases (P=0.279).

Discussion

The preoperative prediction of LNM is strongly related to the treatment strategy in EGC [20]. However, it is very difficult to make a precise assessment of lymph node status preoperatively. Accuracy for assessment of regional LNM was reported to range from 66% to 87% for endoscopic ultrasonography (EUS) [21–23], and 51% to 70% for spiral computed tomography (CT) [24,25]. Thus, it seemed inadequate to select the treatment strategy based on the auxiliary examination finding only. WHO histological diagnosis is available by endoscopic biopsy preoperatively, and our results showed that WHO histological classification was significantly related to LNM, even when stratified analysis was performed using the major risk factor (depth of invasion, Figure 1). We suggest that WHO histological classification could be a supplemental predictor for LNM in EGC preoperatively, in addition to depth of invasion and tumor size.

In this study, MD patients were associated with higher recurrence rates and worse disease-free survival in EGC after curative resection, even when stratified analysis was performed according to LNM, which is a major risk factor for recurrence (Figure 2). MD appeared to have the most aggressive histological type of recurrence, especially in node-positive patients (recurrence rate: 17.6%; worse disease-free survival than non-MD, P=0.007). Moreover, when recurrence site according to WHO histological classification was analyzed, 14 MD patients had hematogenous recurrence (12 in liver, 2 in lung). It was interesting that MD accounted for nearly half of hematogenous recurrent cases (14 out of 32, 43.8%), which was 3.5 times that of WD patients. Previous studies have indicated that EGC with differentiated histology is related to hematogenous recurrence [26], but we suggest that it is the MD EGC patients who are at high risk of hematogenous recurrence. Thus, using Nakamura's classification for EGC recurrence may overestimate the risk for WD patients. In general, extra attention should be paid to MD patients.

The LNM and recurrence differences among WD, MD, PD, and SRC have never been elucidated before. Some studies have confirmed that SRC has similar or decreased probability of lymph node metastasis and better prognosis than non-SRC in EGC [17,18]. In our results, although the clinicopathologic characteristics were significantly different between SRC and WD, we considered these 2 types to possess similar clinical behavior because both had low LNM incidence and recurrence rates in EGC. However, it was still not clear why significant differences existed among WD, MD, and PD, since the main distinguishing parameter was degree of regular formation. According to the definition of WHO classification, well-differentiated is with well-developed tubular glands that mimic the normal architecture of gastric glands; moderately differentiated is with a glandular component, often with a cribriforming or acinar pattern, but the architecture

is less defined than the well-differentiated tumors; and poorly differentiated is with poor glandular formation, often in small clumps or as isolated cells. Histomorphological complexities may be helpful in interpreting the results, which would include other components besides the major components, such as the intracytoplasmic mucin and extracytoplasmic mucin found in tubular adenocarcinoma. Several studies have documented that admixtures of differentiated and undifferentiated histology are not rare and are related to lymph node metastasis in differentiated submucosa invasive gastric cancer [27,28]. Thus, we infer that MD and PD are more likely than WD to have histomorphological complexities. However, we still do not know why MD has a higher recurrence rate than PD in lymph node-positive cases (Figure 2C). Further studies are needed to elucidate this finding.

In addition, Nakamura's classification failed to produce meaningful results in our study. Thus, we suggest that Nakamura's classification may have some limitations for use in EGC. On the contrary, WHO histological classification played a significant role in predicting LNM and recurrence in EGC. We believe that WHO histological classification should be used to estimate the risk of LNM preoperatively and of recurrence postoperatively in EGC. One possible drawback of this suggestion is that there may be a lack of uniformity in the designation of histological grade because of some degree of subjectivity is involved (such as diagnostic migration among WD, MD, and PD).

Conclusions

WHO histological classification is useful and necessary to evaluate during the perioperative management for EGC. Treatment strategy in EGC should be selected prudently according to WHO histological classification, especially for MD patients because they may have higher risk of recurrence in LNM-positive cases compared with PD patients.

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