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ORIGINAL ARTICLE

Is It Reasonable to Treat Early Gastric Cancer with Mucosal Infiltration and Well Differentiation by Endoscopic Submucosal Resection?

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Abstract
Background While limited endoscopic submucosal dissection (ESD) is increasingly applied in the treatment of early gastric cancer, preoperative prediction of lymph node metastasis is very critical for determining treatment strategies preoperatively. Thus, the aim of this study was to accurately assess the prevalence and pattern of lymph node metastasis in early gastric cancer patients and to identify the best candidates for ESD.
Methods From September 2008 to December 2013, a total of 539 patients with early gastric cancer were retrospectively analyzed in the present study. Of them, 503 patients underwent radical gastrectomy and 36 patients underwent ESD. The clinicopathological features were collected and correlations with lymph node metastasis were analyzed. The survival rates of patients were also analyzed.
Results Lymph node metastasis was observed in 80 of 503 patients (15.9 %). Among these, the rate for mucosal cancer was 8.3 %, and 20.1 % for submucosal cancer. By univariate analysis, risk factors for lymph node metastasis were growth pattern, tumor size, pathological type, depth of invasion, lymphatic-vascular invasion, and neural invasion. By multivariate analysis, risk factors for lymph node metastasis were tumor size, pathological type, depth of invasion, and lymphatic-vascular invasion. The incidence of lymph node metastasis was 0 % in the well-differentiated mucosal cancers, irrespective of tumor size. For the well-differentiated mucosal cancers, the overall survival rates were comparable between patients underwent gastrectomy with lymph node dissection and patients underwent ESD (100 vs 100 %).
Conclusions The most important factors for predicting lymph node metastasis in early gastric cancer are tumor size, pathological type, depth of invasion, and lymphatic-vascular invasion. Well-differentiated mucosal gastric cancers could be candidates for ESD.

Keywords Early gastric cancer · Endoscopic submucosal dissection · Radical gastrectomy · Lymph node metastasis

Introduction

Early gastric cancer (EGC) is defined as the tumor invasion confined to the mucosa or submucosa, irrespective of the presence or absence of regional lymph node metastasis (LNM).[1,2] The incidence of EGC has been increasing worldwide with appearance of screening programs and advanced diagnostic techniques.[3] EGCs have a low presence of LNM and favorable survival after radical surgery.[4,5] LNM are present in only 3–5 % of mucosal cancer versus 10–25 % of submucosal cancer.[6–10] LNM is an important risk factor affecting the prognosis. The 5-year survival rate of EGC after surgery with LNM is 84–89 %, while that without LNM is up to 90 %.[11,12]

The standard treatment for EGC is radical gastrectomy with lymph node clearance.[13] It could provide an excellent prognosis in patients with EGC.[14] On the other hand, ESD is an alternative treatment as it is minimally invasive, conserves the whole stomach, provides good postoperative quality of life, and obtains equal survival results compared with surgical procedures.[15,16] However, the ESD is only meaningful if LNM could be excluded. Thus, identifying patients with high

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risk of LNM is critically important for ESD application. Although clinical and pathological factors, such as tumor size, depth of invasion, differentiation status, and ulcerated lesions, could be used to predict the risk of LNM,[17] the extent of LN dissection is still debated and the indications for ESD is still in exploration.[18]

Given this situation, we retrospectively analyzed the clinical and pathological data of 539 patients with EGC who had undergone radical surgical resection or ESD without lymphadenectomy. The aim of the present study was to accurately assess the prevalence and pattern of LNM in EGC patients, analyze the risk factors of LNM preoperatively, and to identify the best candidate patients for ESD.

Materials and Methods

Patients

This study was performed in the Xijing Hospital of Digestive Diseases affiliated to the Fourth Military Medical University. From September 2008 to December 2013, a total of 4457 patients with gastric cancer were given surgical resection in our department. Excluding patients with neoadjuvant chemotherapy, 539 patients with pathological confirmation of EGC (503 patients underwent D2 gastrectomy and 36 patients underwent ESD) were enrolled in the present study. This study was approved by the Ethics Committee of Xijing Hospital, and written informed consent was obtained from all patients before surgery.

All patients were diagnosed as gastric cancer by endoscopic biopsy followed by pathologic confirmation. Preoperative staging was determined by endoscopic ultrasonography (EUS) and enhanced abdominal-thoracic computed tomography (CT).

Surgical Procedure

All patients were treated with proximal, distal, or total gastrectomy with a combined D2 lymphadenectomy depending on the location and macroscopic type of tumor. All the surgical procedure and the extent of lymph node clearance were based on the recommendations of the Japanese Guidelines Gastric Cancer Treatment.[19]

ESD

The Patient's cardiorespiratory functions were monitored throughout the procedure. After sedation, ESD was performed using a conventional single-channel endoscope. The marking dots were made 5 mm outside the margin of the lesion. Normal saline solution containing 0.001 % epinephrine and 0.002 % indigo carmine was injected into the submucosal layer. An initial incision was made with a needle knife outside the line of the marking dots. Then, a circumferential incision was made around the lesion with an insulation-tipped knife. Then, the submucosal layer was dissected directly using an insulation-tipped knife.

Pathology

Poorly differentiated adenocarcinoma, signet ring cell carcinoma and mucinous adenocarcinoma were classified as undifferentiated (UD) tumors. All of the dissected lymph nodes were separated and classified by the surgeon into subgroups according to the AJCC lymph node mapping system for gastric cancer. The pathological classifications of primary tumor, degree of lymph node involvement, and presence of organ metastases were defined according to the TNM classification by pathologists in the department of pathology.

Data Collection

We collected preoperative data including gender, age, tumor location, macroscopic appearance, ulcer, growth pattern, and tumor size. The differentiation status, depth of invasion, LNM, lymphatic-vascular invasion (LVI) and neural invasion were also collected according to the pathological examination.

Follow-up

The patients were followed up till October 2014 by enhanced chest and abdominal CT and gastroscopy every 3 months after discharge. Death within 30 days or before discharge from hospital was considered as operative death.

Statistical Analysis

Data were processed using SPSS 16.0 for Windows. Discrete variables were analyzed using chi-squared test or Fisher's exact test. Significant predictors identified by univariate analysis were assessed by multivariate analysis using the logistic regression analysis. Survival was analyzed by the Kaplan-Meier method. The P values were considered to be statistically significant at the 5 % level.

Results

The relationship between clinicopathological characteristics and LNM are shown in Table 1. Overall, EGCs accounted for 12.1 % (539/4457) of all resected gastric cancer. Of 503 EGC patients who had D2 gastrectomy, 180 cases were intramucosal tumors with 8.3 % of these had LNM, while 323 cases penetrated with submucosa and 20.1 % of these

Table 1 Univariate analysis of the risk factors of LNM for the entire study group

Characteristics	Lymph node metastasis		
	Presence (n=80)	Absence (n=423)	P value
Gender			
Male	61 (76.3 %)	336 (79.4 %)	0.5503
Female	19 (23.7 %)	87 (20.6 %)	
Age (years)			
<45	19 (23.8 %)	63 (14.9 %)	0.1251
45–65	46 (57.5 %)	259 (61.2 %)	
>65	15 (18.7 %)	101 (23.9 %)	
Tumor location			
Upper third	8 (10.0 %)	79 (18.7 %)	0.1406
Middle third	15 (18.8 %)	83 (19.6 %)	
Lower third	57 (71.2 %)	261 (61.7 %)	
Macroscopic appearance			
Flat	4 (5.0 %)	40 (9.5 %)	0.6334
Elevated	24 (30.0 %)	117 (27.7 %)	
Depressed	50 (62.5 %)	255 (60.2 %)	
Mixed	2 (2.5 %)	11 (2.6 %)	
Ulcer			
Presence	23 (28.8 %)	148 (35.0 %)	0.3053
Absence	57 (71.2 %)	275 (65.0 %)	
Growth pattern			
Infiltrative	64 (80.0 %)	285 (67.4 %)	0.0248
Expanding	16 (20.0 %)	138 (32.6 %)	
Tumor size (cm)			
≤2	33 (41.3 %)	280 (66.2 %)	<0.0001
>2	47 (58.7 %)	143 (33.8 %)	
Pathological type			
Well differentiated	5 (6.3 %)	167 (39.5 %)	<0.0001
Moderately differentiated	20 (25.0 %)	118 (27.9 %)	
Poorly differentiated	46 (57.5 %)	114 (26.9 %)	
Signet ring cell or mucinous	9 (11.2 %)	24 (5.7 %)	
Tumor depth			
T1a	15 (18.8 %)	165 (39.0 %)	0.0005
T1b	65 (81.2 %)	258 (61.0 %)	
Lymphatic-vascular invasion			
Yes	45 (56.3 %)	62 (14.7 %)	<0.0001
No	35 (43.7 %)	361 (85.3 %)	
Neural invasion			
Yes	36 (45.0 %)	92 (21.7 %)	<0.0001
No	44 (55.0 %)	331 (78.3 %)	

had LNM. In addition, 107 of 503 patients (21.3 %) had LVI and 128 patients (25.4 %) had neural invasion.

Univariate analysis of the risk factors for LNM showed that growth pattern, tumor size, pathological type, depth of invasion, LVI, and neural invasion were associated with LNM. Tumor size, pathological type, depth of invasion, and LVI remained significant in multivariate analysis (Table 2). In patients with mucosal tumors, univariate analysis showed that female gender, age, tumor size, pathological type, and LVI were associated with LNM (Table 3), but only pathological type showed significant difference in multivariate analysis (Table 4). In patients with submucosal tumors, univariate analysis showed that growth pattern, tumor size, pathological type, LVI, and neural invasion were associated with LNM (Table 5),

Table 2 Multivariate analysis of the risk factors of LNM for the entire study group

Variables	*P* value	Hazard ratio	Confidence interval
Growth pattern	0.5172	1.252	0.634–2.474
Tumor size	0.0182	1.967	1.122–3.447
Pathological type	0.0002	1.925	1.357–2.729
Tumor depth	0.0069	2.518	1.288–4.921
Lymphatic-vascular invasion	<0.0001	7.449	3.138–17.683
Neural invasion	0.5712	1.277	0.548–2.977

Table 3 Univariate analysis of the risk factors of LNM for mucosal gastric cancer

Characteristics	Lymph node metastasis		
	Presence (n=15)	Absence (n=165)	*P* value
Gender			
Male	8 (53.3 %)	133 (80.6 %)	0.0221
Female	7 (46.7 %)	32 (19.4 %)	
Age (years)			
<45	8 (53.3 %)	28 (17.0 %)	0.0004
45–65	2 (13.3 %)	103 (62.4 %)	
>65	5 (33.4 %)	34 (20.6 %)	
Tumor location			
Upper third	0 (0.0 %)	27 (16.4 %)	0.2317
Middle third	3 (20.0 %)	25 (15.1 %)	
Lower third	12 (80.0 %)	113 (68.5 %)	
Macroscopic appearance			
Flat	0 (0.0 %)	20 (12.1 %)	0.2838
Elevated	2 (13.3 %)	35 (21.2 %)	
Depressed	13 (86.7 %)	105 (63.7 %)	
Mixed	0 (0.0 %)	5 (3.0 %)	
Ulcer			
Presence	5 (33.3 %)	59 (35.8 %)	1.000
Absence	10 (66.7 %)	106 (64.2 %)	
Growth pattern			
Infiltrative	7 (46.7 %)	89 (53.9 %)	0.6019
expanding	8 (53.3 %)	76 (46.1 %)	
Tumor size (cm)			
≤2	6 (40.0 %)	118 (71.5 %)	0.0182
>2	9 (60.0 %)	47 (28.5 %)	
Pathological type			
Well differentiated	0 (0.0 %)	77 (46.7 %)	0.0011
Moderately differentiated	4 (26.7 %)	42 (25.5 %)	
Poorly differentiated	8 (53.3 %)	35 (21.2 %)	
Signet ring cell or mucinous	3 (20.0 %)	11 (6.6 %)	
Lymphatic-vascular invasion			
Yes	3 (20.0 %)	4 (2.4 %)	0.0135
No	12 (80.0 %)	161 (97.6 %)	
Neural invasion			
Yes	2 (13.3 %)	8 (4.8 %)	0.1975
No	13 (86.7 %)	157 (95.2 %)	

Table 4 Multivariate analysis of the risk factors of LNM for mucosal gastric cancer

Variables	*P* value	Hazard ratio	Confidence interval
Gender	0.596	0.699	0.187–2.619
Age	0.773	1.143	0.460–2.840
Tumor size	0.270	2.003	0.583–6.877
Pathological type	0.011	2.502	1.234–5.074
Lymphatic-vascular invasion	1.000	–	–

Table 5 Univariate analysis of the risk factors of LNM for submucosal gastric cancer

Characteristics	Lymph node metastasis		
	Presence (*n*=65)	Absence (*n*=258)	*P* value
Gender			
Male	53 (81.5 %)	204 (79.1 %)	0.7330
Female	12 (18.5 %)	54 (20.9 %)	
Age (years)			
<45	11 (16.9 %)	35 (13.6 %)	0.1931
45–65	44 (67.7 %)	156 (60.5 %)	
>65	10 (15.4 %)	67 (25.9 %)	
Tumor location			
Upper third	8 (12.3 %)	52 (20.2 %)	0.1890
Middle third	12 (18.5 %)	58 (22.5 %)	
Lower third	45 (69.2 %)	148 (57.3 %)	
Macroscopic appearance			
Flat	4 (6.2 %)	20 (7.8 %)	0.9446
Elevated	22 (33.8 %)	82 (31.8 %)	
Depressed	37 (56.9 %)	150 (58.1 %)	
Mixed	2 (3.1 %)	6 (2.3 %)	
Ulcer			
Presence	18 (27.7 %)	89 (34.5 %)	0.3760
Absence	47 (72.3 %)	169 (65.5 %)	
Growth pattern			
Infiltrative	57 (87.7 %)	196 (76.0 %)	0.0435
Expanding	8 (12.3 %)	62 (24.0 %)	
Tumor size (cm)			
≤2	27 (41.5 %)	162 (62.8 %)	0.0029
>2	38 (58.5 %)	96 (37.2 %)	
Pathological type			
Well differentiated	5 (7.7 %)	90 (34.9 %)	<0.0001
Moderately differentiated	16 (24.6 %)	76 (29.5 %)	
Poorly differentiated	38 (58.5 %)	79 (30.6 %)	
Signet ring cell or mucinous	6 (9.2 %)	13 (5.0 %)	
Lymphatic-vascular invasion			
Yes	42 (64.6 %)	58 (22.5 %)	<0.0001
No	23 (35.4 %)	200 (77.5 %)	
Neural invasion			
Yes	34 (52.3 %)	84 (32.6 %)	0.0039
No	31 (47.7 %)	174 (67.4 %)	

Table 6 Multivariate analysis of the risk factors of LNM for submucosal gastric cancer

Variables	*P* value	Hazard ratio	Confidence interval
Growth pattern	0.120	2.080	0.826–5.235
Tumor size	0.043	1.947	1.021–3.711
Pathological type	0.005	1.815	1.199–2.746
Lymphatic-vascular invasion	0.000	6.283	2.897–13.630
Neural invasion	0.767	0.889	0.408–1.937

and only tumor size, pathological type, and LVI showed significant difference in multivariate analysis (Table 6).

Based on the results of univariate and multivariate analyses, correlation of predictive factors and LNM were analyzed. In patients with mucosal cancers, 77 patients (42.7 %) with well-differentiated type had no LNM, irrespective of tumor size. By contrast, both moderately differentiated and undifferentiated type mucosal tumors had LNM, irrespective of tumor size (Fig. 1). In patients with submucosal cancers, nearly all subgroups had LNM, irrespective of tumor size, pathological type, and LVI (Fig. 2).

An algorithm of the treatment for EGCs had been made (Fig. 3). Patients with well-differentiated mucosal cancer have a chance to be treated with ESD, irrespective of tumor size. For the rest of patients, surgical treatment such as laparoscopic or open gastrectomy with lymph node dissection should be performed. Finally, in order to investigate the feasibility of ESD for patients with well-differentiated mucosal cancer. The survivals of 36 patients with well-differentiated mucosal cancer and treated with ESD were analyzed in comparison to that of 77 patients with well-differentiated mucosal cancer and treated with D2 gastrectomy. The results showed that there was no significant difference in the overall survival rates between the two groups (100 vs 100 %, $P>0.05$).

Discussion

Despite the increasing application of ESD in patients with EGC, the risk factors associated with LNM have not been fully evaluated. Thus, accurate delineation of risk factors for LNM has become increasingly important. The current study showed that the independent predictive factors for LNM in EGC patients were tumor size, pathological type, tumor depth, and LVI.

The incidence of LNM in EGC ranges from 2.6 to 9.0 % in mucosal tumors and 16.5 to 23.6 % in submucosal tumors.[20,21] In this study, the rates of LNM in mucosal and submucosal tumors were 8.33 and 20.12 %, respectively, which was similar to the previous reports. Although the LNM rate in EGC is relatively low, it has been shown that the presence of LNM predicts a poor prognosis. Thus, series of studies have attempted to explore the risk factors of LNM.

By analyzing clinicopathological characteristics and LNM, we confirmed that tumor size, pathological type, depth of invasion, and LVI were independent predictive factors for LNM in EGC patients. These results were in line with previous reports.[22] However, although ulceration was considered as one of the independent risk factors of LNM in several studies,[23] it was not significant in the present study. In general, the presence of an ulcer is determined by endoscopic and pathological findings in the previous studies. In the present study, presence of an ulcer was determined by endoscopy. Determination of an ulcer could be various depending on different observers or researchers and the time of gastroscopy. In addition, it could also be affected by the previous biopsy.

When EGC was analyzed by grouping into mucosal and submucosal cancers, the independent risk factors for LNM were quite different in the two groups. Shen et al. reported that tumor size was the unique risk factor for LNM in mucosal tumor, while histological classification and tumor size were independent risk factors for LNM in submucosal tumor.[24] Li et al. demonstrated that tumor size and LVI were independent risk factors for LNM in mucosal undifferentiated tumor.[22] An et al. reported that tumor size and LVI were independent risk factors for LNM in submucosal tumor.[25] In our present study, when the tumors were confined to mucosal layer, female

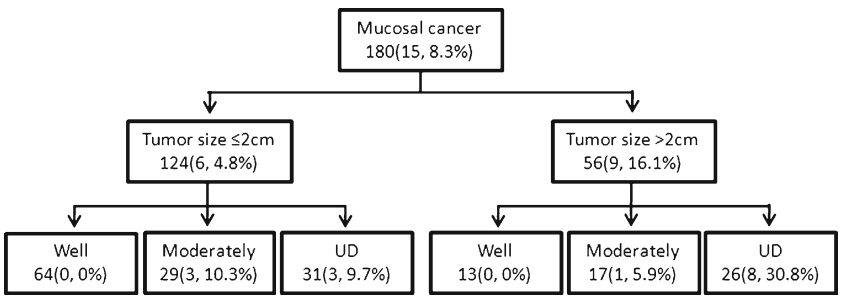

Fig. 1 Correlation of predictive factors and LNM for mucosal cancer

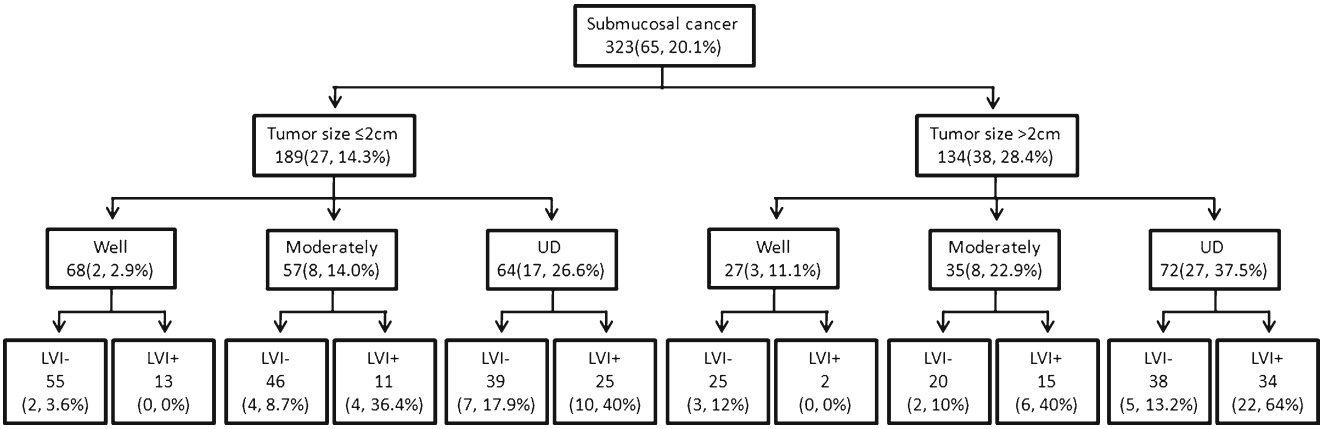

Fig. 2 Correlation of predictive factors and LNM for submucosal cancer

gender, age, tumor size, pathological type, and LVI showed significant correlation with LNM, but only pathological type showed significant difference in multivariate analysis. When the tumor penetrated into submucosal layer, growth pattern, tumor size, pathological type, LVI, and neural invasion were significantly associated with LNM, and only tumor size, pathological type, and LVI showed significant difference in multivariate analysis. The differences of independent risk factors observed in these studies may result from different race, sample size, pathological examination, etc.

ESD for EGC not only preserves gastric function but also maintains the patient's quality of life. However, if LNM exists at the time of ESD, recurrence is very likely. Thus, clinicopathological characteristics are investigated in the current study as predictive factors for LNM.[26] According to the treatment guidelines for gastric cancer in Japan, the indications for ESD are non-ulcerated, differentiated, intramucosal tumor less than 2 cm but without LVI. In addition to the Japanese Guideline, many researchers have also attempted to extend the criteria for ESD treatment. In this regard, although ESD for EGC is widely adapted in Japan and Korea using various criteria,[27,28] it remains uncertain whether these guidelines for ESD are suitable to patients in China. Therefore, we retrospectively analyzed the pattern of LNM in EGC patients who were admitted to our center. For patients with mucosal tumor, correlation of pathological type and LNM were analyzed based on multivariate analysis. For patients with submucosal tumor, rates of LNM were analyzed according to tumor size, pathological type, and LVI based on multivariate analysis. We found that no LNM was detected in well-differentiated mucosal cancer, and in contrast, nearly all patients had LNM in other type of EGC, irrespective of tumor size, pathological type, and LVI.

Many researchers want to find the factors that predicting LNM in EGC prior to treatment. In previous studies, it has been suggested that depth of invasion and LVI were two important risk factors for predicting LNM and for determining treatment strategies. However, accurate diagnosis of EGC and

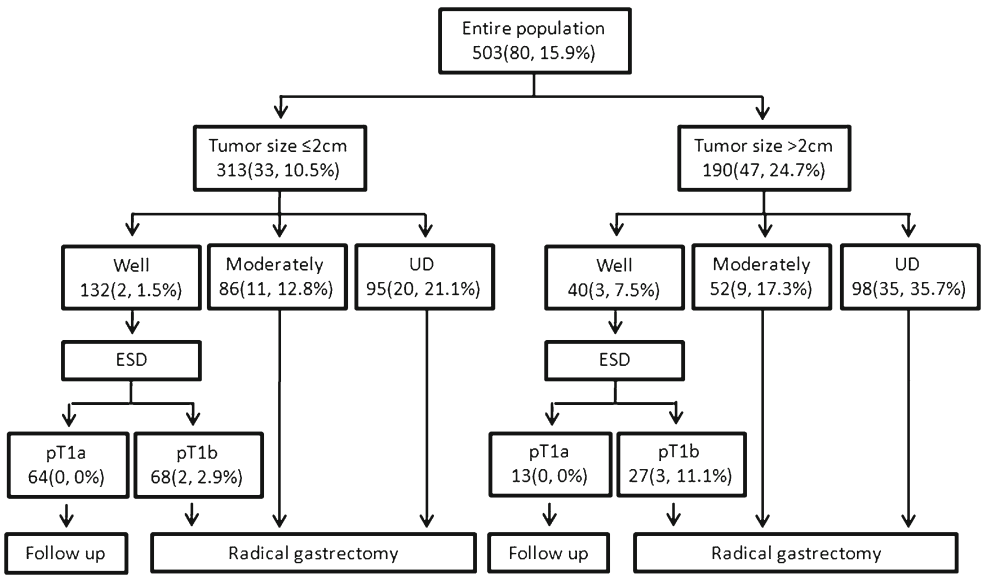

Fig. 3 Treatment strategy for EGC

distinction of mucosal cancer from submucosal cancer preoperatively is very difficult in clinical practice. Although EUS has made it possible to greatly increase the diagnostic accuracy of tumor invasion distance, there still be errors of judgment.[30] In this regard, previous studies have reported that the accuracy of the preoperative workup for EGC was 90.5 %,[29,31,32] the results of the studies suggested that the staging was underestimated in the remaining 9.5 % of patients. In addition, LVI could only be recognized by surgery or endoscopic resection. Therefore, we suggest that LVI and depth of invasion may not be the appropriate parameters to determine ESD or not. Thus, tumor size and pathological type which could be recognized prior to the treatment were used to guide appropriate treatment strategy. Furthermore, the present study indicated that patients with well-differentiated cancer have a chance to be treated with ESD. Then, pathological examination was performed after ESD. If the tumor was confined to mucosal layer, ESD with regular follow-up is sufficient and appropriate in the treatment of such a case. If the tumor penetrated to the submucosal layer, however, a D2 gastrectomy should be further conducted. For moderately differentiated and undifferentiated tumor, D2 gastrectomy should be performed as the first therapeutic strategy.

Next, in order to investigate the feasibility of ESD for patients with well differentiated mucosal cancer, the survivals of patients with well-differentiated mucosal cancer who underwent D2 gastrectomy or ESD were analyzed. The results showed that the overall survivals were comparable between the two groups, indicating that well-differentiated mucosal gastric cancers could be considered as appropriate candidates for ESD.

There are limitations to our study. First, it was a retrospective study based on postoperative examination of resected specimen. To clarify the optimal therapeutic strategy for these tumors, a well-designed randomized clinical trial should be carried out. Second, the sample size of the current study was fairly small, and further study with larger sample size should be carried out to confirm our findings. Third, according to previous studies from Japan, mucosal tumor can be further subdivided into m1, m2, and m3 tumor, and submucosal tumor into sm1, sm2, and sm3 tumor. Unfortunately, subclassifications for mucosal and submucosal tumors were not routinely performed in the current study, which remains to be explored in the future study.

In conclusion, the present study revealed that LNM rate was 15.9 % in EGC patients, with a rate of 8.33 % in mucosal tumors and 20.12 % in submucosal tumors. Independent risk factor of LNM in mucosal tumors was pathological type, and independent risk factors of LNM in submucosal tumors were tumor size, pathological type, and LVI. Well-differentiated mucosal gastric cancers could be considered as appropriate candidates for ESD.

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