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ORIGINAL ARTICLE – PERITONEAL SURFACE MALIGNANCY

The Suggestion of Revised Criteria for Endoscopic Resection of Differentiated-Type Submucosal Gastric Cancer

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ABSTRACT

Background. Early gastric cancer that meets the expanded criteria for endoscopic resection (ER) is expected to be associated with a negligible risk for lymph node metastasis (LNM); however, recent studies have reported LNM in submucosal gastric cancer patients who met the existing criteria. In this study, we develop the revised criteria for ER of submucosal gastric cancer with the aim of minimizing LNM.

Methods. We analyzed the clinicopathological data of 2461 patients diagnosed with differentiated, submucosal gastric cancer who underwent surgery at three tertiary hospitals between March 2001 and December 2012, and re-analyzed the pathological slides of all patients. The depth of submucosal invasion was measured histopathologically in two different ways (the classic and alternative methods) to obtain accurate data.

Results. Of the enrolled subjects, 306 (17.0%) had LNM. The width of submucosal invasion correlated well with the LNM. We defined the depth and width of submucosal infiltration associated with the lowest incidence of LNM. None of the 254 subjects developed LNM when the following criteria were met: tumor diameter $\leq$ 3 cm, submucosal invasion depth $<$ 1000 μm (as measured using the alternative method), submucosal invasion width $<$ 4 mm, no lymphovascular invasion, and no perineural invasion; however, LNM was observed in 2.7% of subjects (6/218) who met the existing criteria.

Conclusions. We revised the criteria for ER by adopting the alternative method to measure the depth of submucosal invasion and adding the width of such invasion. Our criteria better predicted LNM than the current criteria used to select ER to treat submucosal gastric cancer.

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Endoscopic resection (ER) has been one of the curative treatments in patients with early gastric cancer (EGC) who meet the absolute criteria for ER. ER is not recommended for treating submucosal (SM) gastric cancer because of the high risk for lymph node metastasis (LNM).[1–5] Gotoda et al. developed expanded criteria for ER,[3] and, as a result, the Japanese Gastric Cancer Association and European Society of Gastrointestinal Endoscopy declared the expanded indications for curative resection of SM gastric cancer to include en bloc resection, a negative resection margin, no lymphovascular invasion (LVI), tumor diameter $\leq$ 3 cm, a histologically differentiated tumor type, and a tumor depth from the muscularis mucosa $<$ 500 μm.[6] Although ER has been commonly performed in Asian countries using these expanded criteria, the rate of LNM remains around 4%;[7–9] therefore, the expanded criteria should be revised.

Furthermore, there have been many efforts to identify additional factors predicting LNM after ER of EGC. These additional factors include gross tumor appearance, the method by which SM invasion is measured, and the significance of any poorly differentiated tumor component.[10–14] Grossly elevated morphology in differentiated and SM gastric cancers is associated with a high rate of LNM.[10,11] The depth of SM invasion may vary with the shape of the muscularis mucosa.[12] Some authors have proposed an alternative method of measuring depth as the distance from the lowest point of an imaginary line drawn in the plane of the muscularis mucosa to the point of deepest tumor penetration.[12] Eom et al. suggested a range reduction in the depth of SM invasion to obtain a high negative predictive value.[13] Another study found that the presence of a poorly differentiated carcinoma component in the SM layer of a differentiated EGC was an independent risk factor for LNM development.[14] Choi et al. proposed that the width of the SM invasion and the superficial tumor size ratio ($\leq$ 0.04) might independently predict LNM in patients with SM gastric cancer who meet the expanded criteria.[15]

However, the cited studies all sought to identify a single factor predictive of LNM; thus, most studies enrolled only small numbers of subjects. We thought it useful to perform a large-scale analysis integrating various relevant factors. This study aimed to identify new criteria for ER of EGC associated with SM invasion that minimize the incidence of LNM.

METHODS

Study Design

This multicenter, retrospective study involved three tertiary hospitals in South Korea (Severance Hospital, the National Cancer Center, and Pusan National University Hospital). We collected the medical records and pathological slides of 2461 patients who underwent curative gastrectomy and who were diagnosed with differentiated, SM gastric cancer between March 2001 and December 2012. All underwent D1 + α/β or D2 lymph node dissection.[6] Patients with multiple gastric cancer were excluded from this study. Furthermore, we did not enroll patients undergoing additional gastrectomy following non-curative ER. Of the 2461 included patients, 601 were excluded because the pathological slides were of poor quality, and 62 were excluded because they did not meet the enrolment criteria after careful pathological analysis. We ultimately enrolled 1798 patients whose clinical data and pathological slides we re-analyzed. Researchers at each institution met several times to ensure uniformity in terms of data analysis. The study was approved by the Institutional Review Boards of Severance Hospital (number 4-2015-0688), the National Cancer Center (number NCC2016-0072), and Pusan National University Hospital (number PNUH2013-3).

Patients and Pathological Evaluation

We evaluated the clinicopathological characteristics of patients based on medical records, and re-analyzed the pathological slides. All surgical specimens were fixed in 5% (v/v) formaldehyde and the tumors and surrounding normal tissues embedded in paraffin. Tissue blocks were cut into 4-mm-thick sections and stained with hematoxylin and eosin prior to light microscopy. Experienced gastrointestinal pathologists at each institution (HK, MCK, DYP, and SA) re-examined all pathological slides in the same manner. Various risk factors were evaluated via a dedicated pathological review.

Gross tumor appearance was classified using the criteria of the Japanese Gastric Cancer Association.[16] Histological tumor type was classified using World Health Organization and Japanese criteria.[16] The maximal horizontal diameter of the SM layer invasion (as measured microscopically) was defined as the SM invasion width (electronic supplementary Fig. S1). We measured the depth of SM invasion using two methods, one of which (the classic method used in the current expanded criteria) was the calculation of the distance from the lowest point of the muscularis mucosa to the point of deepest tumor penetration. Alternatively, we measured the distance from the lowest point of an imaginary line drawn in the plane of the adjacent intact

muscularis mucosa to the point of deepest tumor penetration (alternative method). The muscularis mucosa can be hypertrophied or disrupted by tumor, therefore an alternative method is to measure invasion depth, using the lowest point of an imaginary line drawn in the plane of the muscularis mucosa. Thus, the most important difference between these methods is the calculation of distance by drawing an imaginary line of the normal muscularis mucosa layer (electronic supplementary Fig. S2).[12]

We defined ulcer formation as a deformity of the muscularis mucosa or fibrosis evident in the SM layer. The tumor infiltrative pattern was scored as expanding or infiltrative.[16] We also measured the proportions of poorly differentiated carcinoma components within all tumors and the presence or absence thereof in the SM layer. Such a component was considered present in the SM layer when that component constituted $> 5\%$ of the layer.[14] When evaluating LNM, we examined at least 15 dissected lymph nodes. Cases with < 15 dissected lymph nodes were excluded from the study.

Statistical Analysis

The Chi square and Fisher's exact tests were used to compare categorical variables, and Student's *t* test and the Mann–Whitney *U* test were used to compare continuous variables. A p value < 0.05 was considered to reflect statistical significance. Multivariate logistic regression analyses were used to identify risk factors for LNM. We used SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) for statistical analysis.

RESULTS

Potential Risk Factors for Lymph Node Metastasis

The incidence of LNM in all patients was 17.0%. We performed univariate analyses to identify clinicopathological factors associated with LNM (electronic supplementary Table S1). Elevated gross appearance, tumor size > 3 cm, pathological classification (moderate differentiation, papillary), and an infiltrative pattern were all significantly associated with LNM. The existence of poorly differentiated carcinoma components within the tumor and the SM layer significantly influenced LNM status. The depth of SM invasion was significantly greater in the LNM group regardless of the measurement method used. In addition, the SM invasion width was significantly greater in the LNM group. We determined appropriate cut-offs of continuous variables for multivariate analyses. The cut-offs for tumor size and depth of SM invasion were those of the expanded ER criteria, and the cut-off for SM invasion width was set to 4 mm. Thus, tumor size > 3 cm, SM invasion depth ≥ 500 μm (as measured using the classic method), SM invasion width ≥ 4 mm, a pathological classification of non-well-differentiated adenocarcinoma, LVI, and perineural invasion all correlated significantly with LNM in multivariate logistic regression analyses (electronic supplementary Table S2).

Revision of the Current Criteria for Endoscopic Resection (ER)

To identify additional risk factors for inclusion in the expanded criteria, we explored the relationships between the results of multivariate analyses and LNM incidence. SM invasion width exhibited a linear relationship with LNM incidence (Fig. 1). Therefore, we graded the SM invasion depth and width stepwise to identify the values associated with the lowest incidence of LNM. We measured LNM incidence as the change in the depth and width of SM infiltration by 100 μm and 1 mm, respectively. Cases of LVI or perineural invasion were excluded, and patients with tumor sizes ≤ 3 cm were included (in line with the current criteria). Table 1 shows the incidence of LNM by invasion width and depth measured using the classic method. When the SM invasion width was < 1 mm, the incidence of LNM was zero; however, when the invasion width was > 1 mm, the incidence of LNM increased. Table 2 shows the incidence of LNM by invasion width and depth measured using the alternative method. The incidence of LNM was zero when the SM invasion width was < 1 mm; however, when the invasion width was < 4 mm, LNM was not observed when the SM invasion depth was < 1000 μm. Further inclusion of tumor size, pathological classification, or the presence/absence of a poorly differentiated carcinoma component did not decrease the incidence of LNM (electronic supplementary Tables S3 and S4).

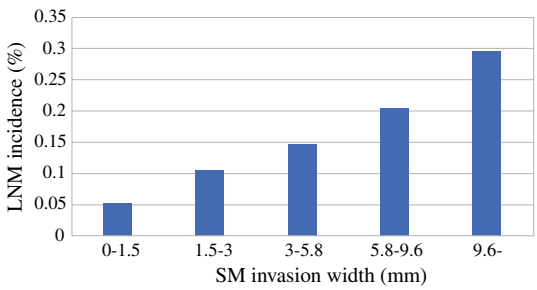

FIG. 1 Correlation between the width of SM invasion and the incidence of LNM. *SM* submucosal, *LNM* lymph node metastasis

TABLE 1 Incidence of lymph node metastasis according to depth of invasion measured using the classic method and submucosal invasion width in < 3-cm-sized differentiated submucosal cancers without lymphovascular invasion and perineural invasion

Depth, μm	Width					
	<1 mm (%)	<2 mm (%)	<3 mm (%)	<4 mm (%)	<5 mm (%)	<6 mm (%)
<300	0/67 (0)	1/100 (1.0)	1/109 (0.9)	2/116 (1.7)	2/117 (1.7)	3/121 (2.5)
<400	0/89 (0)	1/136 (0.7)	2/153 (1.3)	3/169 (1.8)	3/175 (1.7)	4/181 (2.2)
<500	0/101 (0)	1/153 (0.7)	2/177 (1.1)	3/198 (1.5)	3/210 (1.4)	5/217 (2.3)
<600	0/110 (0)	1/171 (0.6)	2/209 (1.0)	3/233 (1.3)	4/251 (1.6)	6/259 (2.3)
<700	0/114 (0)	1/185 (0.5)	2/230 (0.9)	3/255 (1.2)	4/277 (1.4)	6/285 (2.1)
<800	0/116 (0)	1/191 (0.5)	2/244 (0.8)	3/274 (1.1)	4/300 (1.3)	6/312 (1.9)
<900	0/118 (0)	1/197 (0.5)	2/260 (0.8)	3/294 (1.0)	4/322 (1.2)	6/335 (1.8)
<1000	0/120 (0)	1/200 (0.5)	2/265 (0.8)	3/300 (1.0)	4/330 (1.2)	6/345 (1.7)
<1100	0/122 (0)	1/208 (0.5)	2/280 (0.7)	3/322 (0.9)	5/357 (1.4)	7/372 (1.9)
<1200	0/122 (0)	1/208 (0.5)	2/282 (0.7)	3/326 (0.9)	5/361 (1.4)	7/376 (1.9)
<1300	0/122 (0)	1/209 (0.5)	2/285 (0.7)	3/335 (0.9)	5/374 (1.3)	8/392 (2.0)
<1400	0/123 (0)	1/211 (0.5)	2/289 (0.7)	3/341 (0.9)	5/382 (1.3)	8/401 (2.0)
<1500	0/123 (0)	1/211 (0.5)	2/290 (0.7)	3/343 (0.9)	6/386 (1.6)	9/406 (2.2)
<1600	0/123 (0)	1/213 (0.5)	2/296 (0.7)	3/352 (0.9)	6/397 (1.5)	10/424 (2.4)
<1700	0/123 (0)	1/213 (0.5)	2/296 (0.7)	3/352 (0.9)	6/398 (1.5)	10/426 (2.3)
<1800	0/123 (0)	1/213 (0.5)	2/296 (0.7)	3/354 (0.8)	6/400 (1.5)	10/428 (2.3)
<1900	0/124 (0)	1/214 (0.5)	2/298 (0.7)	4/361 (1.1)	7/408 (1.7)	11/438 (2.5)
<2000	0/124 (0)	1/214 (0.5)	2/301 (0.7)	4/364 (1.1)	7/411 (1.7)	11/442 (2.5)

Comparison of the New and Existing Expanded Criteria for ER

Table 3 shows that patients with differentiated SM cancers were free of LNM (0/254, 0%) when the tumor size was ≤ 3 cm, the SM invasion depth was < 1000 μm using the alternative method, and the SM invasion width was < 4 mm using our revised criteria. If the SM invasion width was > 4 mm (and the other parameters did not change), the incidence of LNM increased (3/42, 7.1%). When the existing criteria were applied to our cohort data, the incidence of LNM was 2.7% (6/218, 95% confidence interval 1.3–5.9%); however, when we applied our revised criteria to the same study population, more patients were eligible for ER, none of whom had LNM (0/254, 95% confidence interval 0–1.5%) (Table 4).

DISCUSSION

SM gastric cancer is associated with a higher rate of LNM than mucosal gastric cancer; great caution is required when deciding to use ER.[17,18] Our multicenter study enrolled a large number of subjects and integrated and analyzed risk factors significant in the context of LNM. Therefore, we were able to develop the revised criteria for ER of SM gastric cancer as a better predictor of LNM than the current criteria.

SM invasion depth has generally been defined as the distance from the lower border of the muscularis mucosa to the deepest extent of tumor penetration;[19] however, it has been suggested that this is inappropriate. Kim et al. showed that the muscularis mucosa varies in nature, being divided into tissue of normal, discontinuous, and hypertrophic types.[12] These researchers suggested using an alternative method to measure invasion depth, using the lowest point of an imaginary line drawn in the plane of the muscularis mucosa. This method tends to yield greater depths than the classic method but deals well with variations in SM invasion depth associated with deformation of the muscularis mucosa. It is well known that the greater the invasion depth, the higher the LNM rate.[10,18] Our criterion for SM invasion depth was > 500 μm. This was beyond the expanded criterion, but the measurement method used was not the classic method. It was associated with a lower incidence of LNM when combined with SM invasion width. Although there may be a matter of concern regarding LNM related to our SM invasion depth criterion deeper than the current criterion, the SM invasion depth of the classic and alternative methods are different in the same patient. For example, the SM invasion depth of the alternative method was deeper than that of the classic method when the same study population was measured (electronic supplementary Table S1).

A previous study found the extent of SM invasion was a risk factor for LNM.[20] LNM risk should be predicted by a combined evaluation of the extent of lymphatic invasion

TABLE 2 Incidence of lymph node metastasis according to depth of invasion measured using the alternative method and submucosal invasion width in < 3-cm-sized differentiated submucosal cancers without lymphovascular invasion and perineural invasion

	< 1 mm (%)	< 2 mm (%)	< 3 mm (%)	< 4 mm (%)	< 5 mm (%)	< 6 mm (%)
< 300 μm	0/38 (0)	0/47 (0)	0/47(0)	0/48 (0)	0/48 (0)	0/49 (0)
< 400 μm	0/62 (0)	0/83 (0)	0/85 (0)	0/86 (0)	0/87 (0)	0/91 (0)
< 500 μm	0/80 (0)	0/107 (0)	0/115 (0)	0/121 (0)	0/124 (0)	1/130 (0.8)
< 600 μm	0/98 (0)	0/146 (0)	0/162 (0)	0/172 (0)	1/177 (0.6)	1/183 (0.5)
< 700 μm	0/107 (0)	0/160 (0)	0/180 (0)	0/194 (0)	1/204 (0.5)	1/210 (0.5)
< 800 μm	0/112 (0)	0/175 (0)	0/206 (0)	0/223 (0)	1/236 (0.4)	2/245 (0.8)
< 900 μm	0/117 (0)	0/185 (0)	0/227 (0)	0/248 (0)	1/264 (0.4)	2/273 (0.7)
< 1000 μm	0/119 (0)	0/188 (0)	0/231 (0)	0/254 (0)	1/272 (0.4)	3/282 (1.1)
< 1100 μm	0/120 (0)	1/200 (0.5)	1/260 (0.4)	1/290 (0.3)	3/312 (1.0)	5/323 (1.5)
< 1200 μm	0/120 (0)	1/200 (0.5)	1/264 (0.4)	1/297 (0.3)	3/320 (0.9)	5/332 (1.5)
< 1300 μm	0/121 (0)	1/205 (0.5)	1/275 (0.4)	1/315 (0.3)	3/343 (0.9)	6/357 (1.7)
< 1400 μm	0/122 (0)	1/206 (0.5)	1/277 (0.4)	1/319 (0.3)	3/349 (0.9)	6/364 (1.6)
< 1500 μm	0/122 (0)	1/206 (0.5)	1/278 (0.4)	1/322 (0.3)	3/352 (0.9)	6/368 (1.6)
< 1600 μm	0/122 (0)	1/210 (0.5)	1/288 (0.3)	1/335 (0.3)	3/371 (0.8)	6/390 (1.5)
< 1700 μm	0/122 (0)	1/211 (0.5)	1/289 (0.3)	1/337 (0.3)	3/373 (0.8)	6/393 (1.5)
< 1800 μm	0/122 (0)	1/211 (0.5)	1/289 (0.3)	1/339 (0.3)	3/377 (0.8)	6/400 (1.5)
< 1900 μm	0/123 (0)	1/212 (0.5)	2/293 (0.7)	2/348 (0.6)	4/388 (1.0)	7/413 (1.7)
< 2000 μm	0/123 (0)	1/212 (0.5)	2/294 (0.7)	2/349 (0.6)	5/390 (1.3)	8/416 (1.9)

Lymph node metastasis was not observed in both the submucosal invasion depth < 1000 μm and invasion width < 4 mm groups (shaded area)

and SM involvement. Sanomura et al. suggested that the width of SM invasion should serve as an additional criterion when determining whether ER to treat SM gastric cancer might be curative;[21] however, their cohort included relatively small numbers of patients with undifferentiated-type gastric cancer. Hoteya et al. calculated a virtual SM volume index and suggested this index might correlate with the risk for LVI.[22] Thus, SM invasion width was associated with LNM in several studies, and we usefully quantified that width in our present work.

The greatest concern when using ER to treat EGC is the possibility that LNM may be missed.[2–5] It is essential to define curative resection criteria to allow many patients to undergo ER with a minimal risk of LNM. Compared with the current criteria, our revised criteria increase the depth of SM invasion but lower the LNM incidence by adding the SM invasion width as a new criterion. Therefore, the possibility that the LNM risk may increase is reduced, although the SM invasion depth measured using our alternative method is longer than that of the current criteria. Our revised criteria include the concept of accurately estimating LNM risk by accurately measuring SM invasion burden in SM gastric cancer of current ER criteria. They showed a lower confidence interval than the previous study regarding the current expanded criteria (0–1.5% vs. 0–2.5%).[3] In other words, applying the revised criteria to

TABLE 3 Comparison of the incidence of lymph node metastasis according to the various parameters

	Tumor size ≤ 3 cm		Tumor size > 3 cm	
	SM width < 4 mm	SM width ≥ 4 mm	SM width < 4 mm	SM width ≥ 4 mm
SM depth < 1000 μm[a]	0/254 (0)	3/42 (7.1)	6/183 (3.3)	3/36 (8.3)
SM depth ≥ 1000 μm[a]	5/128 (3.9)	31/262 (11.8)	8/70 (11.4)	37/233 (15.9)

SM submucosal

[a]Measured using the alternative method

TABLE 4 Comparison of criteria for endoscopic resection of submucosal invasive early gastric cancer with differentiated histology

Criteria	LNM incidence (%)	95% CI
Tumor ≤ 3 cm, submucosal invasion depth < 500 μm, no lymphovascular invasion, no perineural invasion	6/218 (2.7)[a]	1.3–5.9
Tumor ≤ 3 cm, submucosal invasion depth < 1000 μm measured using the alternative method, no lymphovascular invasion, no perineural invasion, submucosal invasion width < 4 mm	0/254 (0)	0–1.5

LNM lymph node metastasis, *CI* confidence interval

[a]When considering the poorly differentiated component in the submucosa, LNM incidence was 6/204 (2.9%) and 95% CI was 1.4–6.3

the real population could demonstrate fewer LNMs than the expanded criteria. In addition, we categorized SM invasion by reference to SM invasion width and the modified SM invasion depth (Table 3). For example, if the SM invasion depth was 400 μm and the SM invasion width was 5 mm, the incidence of LNM was 7.1%. However, if the SM invasion depth was 900 μm and the SM invasion width 2 mm, the incidence of LNM was zero. The former case would have been regarded as a curative resection had the current criteria for ER been applied; however, surgical treatment of LNM was in fact necessary. The latter resection would have been considered non-curative using the current criteria, and additional surgery would have been scheduled; however, in fact, no LNM was observed and no additional surgery was needed. Therefore, the curability afforded by ER can be determined more accurately when the LNM risk is predicted using our revised criteria.

As the EGC invasion depth is difficult to predict accurately via pretreatment endoscopic examination, precise pathological analysis after ER is essential to determine whether resection is curative.[23] Although the use of the expanded criteria decides the need for additional surgery after ER to treat SM gastric cancer, the incidence of LNM in patients meeting the expanded criteria was not zero but rather 2.7% in our study. Thus, 2.7% of patients might not have undergone lymph node dissection despite the presence of LNM. Many scoring systems have been developed to predict LNM after ER of EGC.[24–28] However, EGC treatment should not only reduce the risk for LNM but also completely treat LNM. Our revised criteria maximize the number of patients who can undergo ER with minimal risk for LNM. We modified SM invasion depth measurement and added SM invasion width to the current expanded criteria.

SM gastric cancer of a mixed-type histology is associated with a higher rate of LNM than the differentiated type.[29] However, we did not use the presence of a poorly differentiated carcinoma component within the tumor when developing our revised criteria because the incidence of LNM was not further reduced when we added it.

Recently, the JCOG0607 study reported that the long-term results of the extended criteria showed the 5-year overall survival (OS) of 97.0% was higher than the threshold 5-year OS (86.1%).[30] However, the number of SM1 cancers meeting the current criteria was small (only 26 cases),[30] and thus this result may be difficult to provide a reliable result for SM1 cancer.

This was a retrospective study and we only reviewed surgically resected specimens to evaluate LNM; this selection criterion may have been a limitation in representing all EGC patients. Another limitation is that we did not perform immunostaining for LVI. Immunostaining could be helpful for identifying LVI involvement in SM gastric cancer, but we could not evaluate this due to the study's retrospective nature.

CONCLUSIONS

We developed the revised criteria for ER of differentiated SM gastric cancer, i.e. tumor size ≤ 3 cm, no LVI, no perineural invasion, an SM invasion depth < 1000 μm (measured using the alternative method), and an SM

invasion width < 4 mm. If these criteria are met, no additional surgery is required. A multinational study should be performed to validate our revised criteria.

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