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# The role of tumor size in surgical decision making after endoscopic resection for early gastric cancer

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**Abstract**
*Background* Endoscopic resection (ER) is curative treatment option for early gastric cancer (EGC). Additional surgery is required when the tumor pathology is beyond ER indication. It is unclear whether tumor size can be correlated with indications for surgery after ER. Therefore, we aimed to access the role of tumor size for surgical decision making after ER.
*Methods* We reviewed clinicopathological data from 3246 patients underwent gastrectomy for EGC. The patients were classified into three groups as follows: the ulcer-negative intramucosal cancer with undifferentiated histology, ulcerative intramucosal cancer with differentiated histology, and minute submucosal (SM1) cancer with differentiated histology. The probability of additional surgery after ER was defined as at least one positive result for lymph node metastasis, lymphovascular invasion or perineural invasion. The probability was compared between individual tumor size and ER size criteria in each group using area under receiver operating characteristic curves.
*Results* The probabilities of ulcer-negative intramucosal cancer with undifferentiated histology, SM1 cancer with differentiated histology and ulcerative intramucosal cancer with differentiated histology were 4.2, 22.1 and 2.5 %. In the ulcerative intramucosal cancer with differentiated histology group, these probabilities increased when the difference in tumor size was >1 mm compared with ER size criteria. The probability was not increased when there was a >10-mm tumor size difference compared with ER size criteria in the other two groups.
*Conclusions* Tumor size was correlated with ER criteria in patients with ulcerative intramucosal cancer with differentiated histology after ER but was not strictly correlated with ER criteria in the other two patient groups. However, further study may be necessary to validate our results in the future.

**Keywords** Tumor size · Additive treatment · Endoscopic resection · Early gastric cancer

Endoscopic resection (ER), which includes endoscopic mucosal resection and endoscopic submucosal dissection, is a curative treatment option for early gastric cancer (EGC). ER ensures improved quality of life for patients compared with surgery and has been adopted increasingly to treat EGC with minimal risk of lymph node metastasis (LNM) [1]. Favorable outcomes of ER for EGC have been associated with two factors: complete resection of the primary tumor and the possibility of LNM after ER. The generally accepted indications of ER for EGC are (i) intramucosal differentiated adenocarcinoma without ulceration, regardless of size, (ii) ulcerative intramucosal differentiated adenocarcinoma of ≤30 mm, and (iii) differentiated adenocarcinoma of ≤30 mm with minute

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submucosal invasion (SM1, ≤500 μm) [2]. Risk factors for the possibility of LNM after ER include the presence of lymphovascular invasion (LVI), depth of invasion >500 μm into the submucosa, undifferentiated-type histology, large tumor size, and the presence of perineural invasion (PNI) [3, 4]. It is recommended that patients with these risk factors receive additional surgery after ER to treat EGC when the resected tumor pathology is beyond ER size criteria. However, when the resected tumor size after ER is several millimeters larger than the upper size limit of ER curative size criteria, it has not been determined whether additional surgery is necessary if other risk factors related to LNM are met. Thus, the aim of this study was to investigate the role of tumor size in making decisions regarding optimal treatment strategies for EGC after ER.

## Patients and methods

### Study designs

We retrospectively reviewed clinicopathologic findings of 3246 patients surgically treated for EGC from January 2005 to December 2012 at Severance and Gangnam Severance Hospital. These data included tumor size, ulceration, and histologic grade such as differentiated and undifferentiated types using the Japanese classification. There were 1119 patients categorized into three groups based on ER criteria [3], with the exception of tumor size, as follows: Group 1 included patients with ulcer-negative intramucosal cancer with undifferentiated-type histology, Group 2 included ulcerative intramucosal cancer with differentiated-type histology, and Group 3 included minute submucosal (SM1) cancer with differentiated-type histology.

### Assessment of probability of additional surgery after ER

We evaluated a series of pathologic features in surgical specimens obtained from each patient group. Since the presence of LVI or PNI has been associated with LNM after ER for EGC, the probability of additional surgery for lymph node dissection after ER was defined as the presence of LVI, PNI or LNM in surgical specimens. We further compared size differences between individual tumor size and ER size criteria in each group.

### Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD). We calculated receiver operating characteristic (ROC) curves by evaluating the probability of requiring additional treatment between individual tumor size and ER size criteria at 1-mm intervals. Area under ROC curves (AUROCs) were used to assess diagnostic accuracy. AUROCs are the most commonly used method for summarizing the overall accuracy, in which an area of 1 represents a perfect test and an area of 0.5 represents a noninformative test. All analyses were undertaken using SPSS ver. 20.0 for Windows (SPSS, Chicago, IL, USA) and a two tailed $P$ value <0.05 indicated statistical significance.

## Results

### Characteristics of the three groups based on ER criteria for EGC

Table 1 shows the characteristics of the three groups based on ER criteria for EGC. The number of enrolled patients was 625 (19.2 %) in Group 1, 246 (7.5 %) in Group 2, and 249 (7.7 %) in Group 3. Among these groups, the probability of additional surgery was 4.2 % ($n = 26$) in Group 1, 2.5 % ($n = 6$) in Group 2 and 22.1 % ($n = 55$) in Group 3.

### Probability of additional surgery based on the size difference between an individual tumor and ER criteria

Figure 1 shows the ROC curves illustrating the probability for requiring additional surgery between individual tumor size and ER size criteria in Group 1, patients with ulcer-negative intramucosal cancer with undifferentiated-type histology. The AUROC values are shown in Table 2. In this group, a tumor size of 21 mm showed a significantly higher probability for requiring additional surgery compared with the ER size criterion of 20 mm. However, the probability was not significantly increased when the size difference was >10 mm.

Figure 2 shows the ROC curves illustrating the probability for requiring additional surgery in Group 2, patients with ulcerative intramucosal cancer with differentiated-type histology following ER. The AUROCs of the probability according to tumor sizes of 30, 31, 32, 33, 34, and 35 mm were 0.6370, 0.6726, 0.6726, 0.6789, 0.6851, and 0.6851, respectively (Table 3). The probability of undergoing additional surgery after ER was significantly increased when a tumor size difference of 1 mm was compared with the ER size criterion of 30 mm in this group.

Figure 3 demonstrates that the probability for additional surgery was not increased in Group 3, patients with SM1 cancer of differentiated-type histology with a >10-mm size difference compared with an ER size criterion of 30 mm. The AUROCs of the probability between tumor size and ER size criteria are shown in Table 4 and were not statistically significant.

**Table 1** Characteristics of three groups according to the criteria of endoscopic resection for EGC

| | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| Number (%) | 625 (19.2) | 245 (7.5) | 249 (7.7) |
| Size (mm, mean ± SD) | 22.8 ± 16.8 | 20.9 ± 13.7 | 26.7 ± 16.9 |
| Probability of additional surgery (*n*, %)[a] | 26 (4.2) | 6 (2.5) | 55 (22.1) |

[a] Defined as at least one positive result of LNM, LVI, or PNI

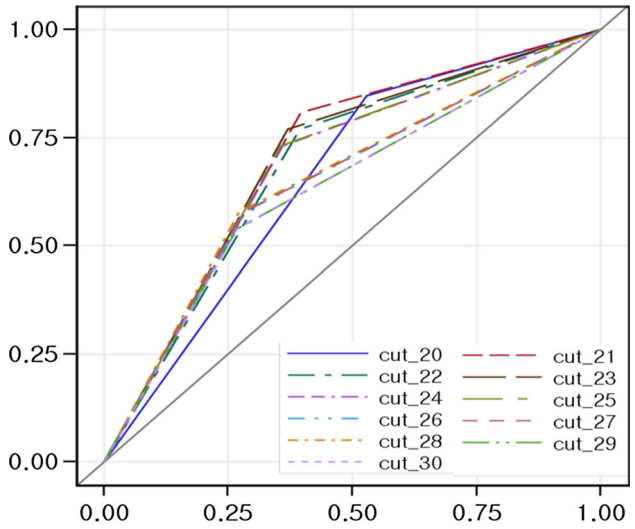


**Fig. 1** Receiver operating characteristic (ROC) curves demonstrating the probability between individual tumor size and size criteria following endoscopic resection in Group 1

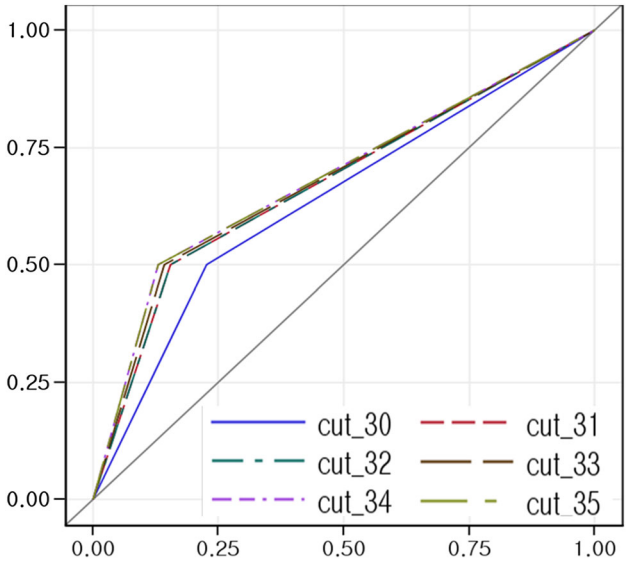


**Fig. 2** Receiver operating characteristic (ROC) curves demonstrating the probability between individual tumor size and size criteria following endoscopic resection in Group 2

**Table 2** The value of AUROCs according to tumor size in Group 1

| Cut off values (mm) | AUROCs | *P* value |
|---|---|---|
| 20 | 0.6585 | |
| 21 | 0.7060 | 0.020 |
| 22 | 0.6876 | 0.290 |
| 23 | 0.6993 | 0.140 |
| 24 | 0.6859 | 0.404 |
| 25 | 0.6876 | 0.376 |
| 26 | 0.6474 | 0.807 |
| 27 | 0.6482 | 0.821 |
| 28 | 0.6524 | 0.893 |
| 29 | 0.6357 | 0.628 |
| 30 | 0.6357 | 0.628 |

*AUROCs* area under the ROC curves

**Table 3** The value of AUROCs according to tumor size in Group 2

| Cut off values (mm) | AUROCs | *P* value |
|---|---|---|
| 30 | 0.6370 | |
| 31 | 0.6726 | <0.001 |
| 32 | 0.6726 | <0.001 |
| 33 | 0.6789 | <0.001 |
| 34 | 0.6851 | <0.001 |
| 35 | 0.6851 | <0.001 |

*AUROCs* area under the ROC curves

## Discussion

ER has been established as a standard curative treatment option for EGC with negligible risk of LNM [5]. In Korea, the rate of accurate EGC diagnosis has increased, and there has been increased focus on improving quality of life and minimizing invasive procedures. Initially, the Japanese Gastric Cancer Association criteria for ER were strictly limited to the absolute indication [6]. However, the rate of en bloc resection and curative resection for EGC increased, leading to expanded criteria for EGC that result in curative resection. The rate of curative resection in a recently published Korean data was reported to be 96.4 % with the absolute criteria, 78.7 % with the expanded criteria and 41.2 % beyond the expanded criteria, with 5-year disease-free survival rates of 98.2, 98.5 and 84.6 %, respectively [7].

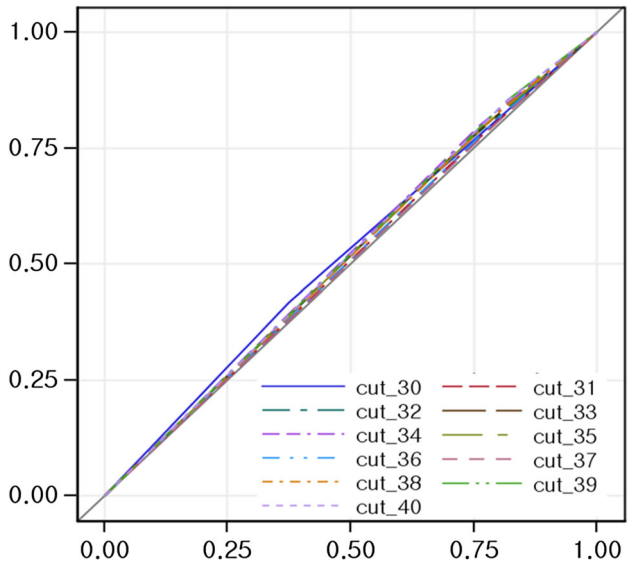


**Fig. 3** Receiver operating characteristic (ROC) curves demonstrating the probability between individual tumor size and size criteria following endoscopic resection in Group 3

**Table 4** The value of AUROCs according to tumor size in Group 3

| Cut off values (mm) | AUROCs | *P* value |
|---|---|---|
| 30 | 0.5209 | |
| 31 | 0.5067 | 0.830 |
| 32 | 0.5133 | 0.906 |
| 33 | 0.5146 | 0.921 |
| 34 | 0.5186 | 0.969 |
| 35 | 0.5134 | 0.903 |
| 36 | 0.5045 | 0.817 |
| 37 | 0.5070 | 0.784 |
| 38 | 0.5135 | 0.900 |
| 39 | 0.5175 | 0.952 |
| 40 | 0.5175 | 0.952 |

*AUROCs* area under the ROC curves

In contrast, even though ER indications were strictly applied, the incidences of residual tumor and LNM among surgical cases due to non-curative resection were 39.5 and 9.3 %, respectively [8]. Li et al. [9] reported that the rate of LNM was 28 % in submucosal cancer patients and 50 % in patients with a tumor size >20 mm and LVI, suggesting that additional surgery should be considered if ER pathology reveals EGC lesions with a tumor size >20 mm, submucosal invasion and the presence of LVI. To avoid the risk of local recurrence and undetectable LNM, additional surgical treatment is recommended in cases with the possibility of non-curative resection by ER. Evaluating non-curative resection can be determined by reviewing resected tumor specimens to consider the possibility of LNM.

Clinical outcomes can be improved by predicting the risk factors for LNM after ER and determining definite indications for additional surgery. Many studies have reported that venous invasion is closely related to LNM [10, 11] and PNI associated with LNM [4]. Undifferentiated-type histology and lymphatic invasion are also known risk factors for LNM after ER [12]. However, indications for additional surgery after ER for EGC have not been clearly established. As a result, some patients without nodal metastasis may undergo unnecessary surgical operations.

Some studies have reported that a larger tumor size could be a risk factor of LNM after ER for EGC [3, 13]. Recently, Katsube et al. [14] reported that in addition to submucosal invasion≥0.5 mm, a diameter ≥30 mm was a risk factor for LNM. However, few studies have addressed the usefulness of additional surgery after ER for EGC beyond the ER size criteria. Our study aimed to define the effect of tumor size after ER on the probability of requiring additional surgery after ER when other risk factors related to LNM meet ER criteria. Based on our results, the probability of requiring additional surgery after ER increased when the tumor size difference was >1-mm compared with ER size criteria in ulcerative intramucosal cancer with differentiated-type histology (Group 2). However, in the other two groups, the probability of undergoing additional surgery after ER was not increased with a >10-mm tumor size difference compared with ER size criteria. This indicates that additional surgery after ER may not be strictly indicated based on ER size criteria if other risk factors related to LNM meet ER criteria, with the exception of ulcerative intramucosal cancer with differentiated-type histology (Group 2).

Our study has some limitations. First, the probability of additional surgery after ER was evaluated retrospectively in patients who underwent gastrectomy. A prospective study of patients undergoing ER is necessary to confirm the role of tumor size after ER. Second, the data represent a relatively small number of patients enrolled from a single center, and a relatively small number of patients were evaluated to assess the probability of additional surgery after ER, particularly in Group 2. In addition, the risk assessment of nodal metastasis was performed at a 1-mm interval between tumor size and ER size criteria. Further studies using a larger number of patients may be necessary to determine the interval between tumor size and ER size criteria precisely.

In conclusion, tumor size was correlated with ER criteria in patients with ulcerative intramucosal cancer with differentiated histology after ER but was not strictly

correlated in the other two patient groups. Further studies will be necessary to validate these results.

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**Compliance with ethical standards**

**Disclosures** Drs. Hae Won Kim, Yoo Jin Lee, Jie-Hyun Kim, Jae Jun Park, Young Hoon Youn, Hyojin Park, Jong Won Kim, Seung Ho Choi, Sung Hoon Noh have no conflict of interest or financial relationships relevant to this publication.

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