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Original article

Lymph node metastasis and preoperative diagnosis of depth of invasion in early gastric cancer

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Abstract

Background. **No reports have, to date, focused on the relationship between preoperative determination of the depth of invasion and lymph node metastasis. The present study, under the leadership of the Japanese Gastric Cancer Association, was designed to form a basis for decision making in limited treatment for early gastric cancer (EGC).**

Methods. **From eight major hospitals in Japan, 2672 gastric cancers whose preoperative depth of invasion was mucosal(M-cancer), and 6209 EGCs, consisting of 3584 mucosal(m-) and 2625 submucosal(sm-) cancers, were collected by questionnaire. All registered patients underwent gastrectomy with D1 or more extensive lymphadenectomy between 1985 and 1998.**

Results. **The accuracy of preoperative diagnosis of depth of invasion of M-cancers was 80.2% (2144/2672). However, of the total of 2432 M-cancers in which no nodal involvement was observed intraoperatively (N0), histological examination of the resected specimens confirmed that lymph node metastasis was absent in 2353 (96.8%). The frequencies of lymph node metastasis in early gastric, m-, and sm-cancers were 8.9%, 2.5%, and 17.6%, respectively. Node involvement was associated with a higher frequency of undifferentiated than differentiated histology, as well as with greater tumor size. The incidences of lymph node metastasis in m-cancers with a diameter of less than 4 cm, and in sm-cancers with a diameter below 1 cm were 1.3% (37/2837) and 4.9% (4/82), respectively. These metastases rarely extended beyond the first tier.**

Conclusion. **N0 and M-cancers, m-cancers less than 4 cm in diameter, and sm-cancers no larger than 1 cm in diameter may be appropriate indications for limited surgery.**

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Key words Early gastric cancer · Lymph node metastasis · Preoperative diagnosis

Introduction

Early gastric cancer (EGC), defined as a tumor with invasion confined to the mucosa or submucosa, is now recognized as a curable malignancy [1–30]. The reported frequency of lymph node metastasis in EGC varies from 5.7% to 29% [1–26,31–38]. Most studies have reported that the presence of lymph node metastasis decreases the survival rate of EGC patients [7–30]. The different frequencies oßf nodal involvement in mucosal versus submucosal cancer are well known. The reported frequency of lymph node metastasis in submucosal cancer varies from 9.7% to 24.3% [4–18,28–37,39–41], whereas that in mucosal cancer is low (0%–6.4%) [4–18,31–37,42]. Recently, different treatment methods have been employed for mucosal and submucosal cancers. For the mucosal cancers, limited treatments, e.g., endoscopic mucosal resection [32–35,42] or local resection, with [43] or without [16,17,35,36,44] lymphadenectomy, are indicated. Therefore, preoperative diagnosis of depth of invasion is very important for selecting the most appropriate treatment procedures. However, few studies have focused on the relationship between the preoperative diagnosis of depth of invasion and lymph node metastasis.

This study, carried out under the auspices of the Japanese Gastric Cancer Association, was designed to determine the accuracy of preoperative diagnosis of the depth of invasion and the frequency of lymph node metastasis in EGC. The present results will form a basis

for decision making in regard to limited treatment for EGC.

Patients and methods

Data on patients with single EGC were collected by questionnaire from eight major hospitals in Japan. Items on the questionnaire were as follows: preoperative diagnosis of depth of invasion of the tumor, intra-operative findings of nodal involvement, and histological examinations of the resected specimens. All patients underwent gastrectomy with D1 or more extensive lymphadenectomy between 1985 and 1998. The methods of determining depth of invasion preoperatively varied among institutes. Endoscopy, endoscopic ultrasonography, and barium gastrography were used routinely. Tumor size in this study was determined histologically, using the resected specimen, and the histology was classified as differentiated and undifferentiated types. Extent of lymph node metastasis (*n* number) and classification of macroscopic shape were based on the *General rules for the gastric cancer study* (12th edition). No attempt was made herein to assess whether ulceration was present in tumorous lesions. Lymph node metastasis was diagnosed as positive intraoperatively, by the presence of hard and swollen nodes, and/or by frozen section analysis.

In the present study, tumors with invasion histologically confined to the mucosa or the submucosa were defined as m-cancer and sm-cancer, respectively. Tumors in which invasion was preoperatively considered to be confined to the mucosa were diagnosed as M-cancers. Statistical analyses were performed using the χ^2 test. The accepted level of significance was $P < 0.05$.

Results

Of a total of 2672 M-cancers, 2144 were m-cancers histologically, i.e., the accuracy of preoperative diagnosis of depth of invasion was 80.2% for M-cancers, and accuracies varied from 67% to 89.9% across the contributing institutes. The frequencies of sm and advanced cancer in the M-cancers were 17.5% and 2.2%, respectively. Of the total of 2432 M-cancers with intraoperative findings indicating the absence of nodal involvement (N0), histological examination of the resected specimens confirmed 2353 (96.8%) to be free of lymph node metastasis. The ratios were similar (95%–98%) across participating hospitals. The n1 and n2 metastases were histologically observed in 2.7% (66/2432) and 0.5% (13/2432), respectively, of N0 and M-cancers. None of the M-cancers had n3 metastasis. The accuracy of macroscopic findings of N0 in M-cancer, according to the histological type of the tumor, is shown in Table 1. Accurate intraoperative evaluations of nodal involvement were significantly fewer in cases with undifferentiated than in those with differentiated tumors.

Table 1. Accuracy of macroscopic findings of N0 lymph node metastasis in M-cancer

	Correct	Incorrect	
Histology	n0	n1	n2
Differentiated ($n = 1606$)	1578 (98.3%)*	24 (1.5%)	4 (0.2%)
Undifferentiated ($n = 825$)	774 (93.8%)	42 (5.1%)	9 (1.1%)

* $P < 0.01$ vs undifferentiated

Table 2. Incidence of lymph node metastasis according to histology

Depth[a]	Differentiated	Undifferentiated
m	25/2273 (1.1%)*	63/1311 (4.8%)
sm	52/1616 (3.2%)*	211/1009 (20.9%)

* $P < 0.01$ vs undifferentiated
[a] See text for definitions of "m" and "sm"

Table 3. Incidence of lymph node metastasis according to tumor size in m-cancer

Tumor size (cm)	Differentiated	Undifferentiated
≦0.9	0/268 (0%)	1/69 (1.4%)
1–1.9	2/699 (0.3%)	5/279 (1.8%)
2.0–3.9	11/950 (1.2%)	18/572 (3.1%)
≧4.0	12/356 (3.4%)	39/391 (10.0%)

In total, 6209 EGCs were collected: 3584 m-cancers and 2625 sm-cancers. The frequency of lymph node metastasis in the present series of EGCs was 8.9% (551/6209). Nodal involvement was observed in 88 (2.5%) of the 3584 m-cancers and in 463 (17.6%) of the 2625 sm-cancers, a significant difference ($P < 0.01$). The incidence of lymph node metastasis according to tumor histology is shown in Table 2. The frequency of nodal involvement was significantly higher in cancers with undifferentiated than with differentiated histology, for both m- and sm-cancers. The incidences of lymph node metastasis, according to tumor size, for m-cancer and sm-cancer, are presented in Tables 3 and 4, respectively. Five m-cancers with diameters less than 4 cm (0.2%; 5/2837) had n2 lymph node metastasis. The features of these tumors are summarized in Table 5. Ten elevated m-cancers had lymph node metastasis (Table 6). All ten cancers were histologically differentiated. Nodal involvement was observed in four sm-cancers with diameters less than 1 cm (4.9%; 4/82) (Table 7).

Discussion

To date, a number of studies have focused on EGC. However, these earlier reports were, with one exception [31], based on the outcomes of fewer than 1500 subjects (80–1475 cases) [1–30,32–42]. Furthermore, there have been no studies on the relationship between preoperative determination of depth of invasion and lymph node metastasis. The present study is the first, to our knowledge, to address this issue in a patient population exceeding 2000.

The reported accuracy of preoperative depth diagnosis of M-cancer varies from 69.2% to 92.2% [45–53], which is consistent with the range in the present results (67%–89.9%). The presence of ulcer fibrosis in the lesion is well known to hamper diagnosis [51–54], but we did not collect data on ulceration in this study. A discrepancy between macroscopic (intraoperative) and histological (postoperative) diagnosis of node involvement has been reported [55–59]. However, in this study, the accuracy of macroscopic findings on node involvement in N0 and M-cancers was quite high (95%–98%), and this was consistent across institutes. Of the 2432 N0 and M-cancers, there were none with n3 metastasis, and n2 metastasis was quite rare (0.5%). Therefore, limited surgery may be appropriate for N0 and M-cancers. The present study demonstrated intraoperative evaluations of nodal involvement to be less reliable in undifferentiated than in differentiated tumors, a finding that is consistent with our previous report [59]. Frozen section analysis of nodes sampled during limited surgery is routinely used at our institute.

The frequencies of lymph node metastasis in EGC (8.9%), m-cancer (2.5%), and sm-cancer (17.6%) in the present series confirmed the results of earlier reports. Many previous studies [10–17,29,30,32–34,39–41], although not all [5,18,35,42], showed tumor histology to have no correlation with node involvement. However, in the present study, based on a nationwide investigation, in both m- and sm-cancers, the incidence of lymph node metastasis was significantly higher in undifferentiated than in differentiated tumors. These results are important for determining the optimal treatments for EGCs.

The increase in node involvement with tumor size (irrespective of histology and cancer depth), ascertained in the present study, is consistent with the findings of previous reports [2,5,11–19,32–40,42]. Endoscopic mucosal resection is clearly indicated for differentiated m-cancers less than 1 cm in diameter, given the absence of nodal involvement in these tumors. In m-cancers with a diameter of less than 4 cm, the incidence of node involvement was observed to be low. Therefore, limited surgery can be employed as a curative treatment for such tumors. At our institute, local resection with

Table 4. Incidence of lymph node metastasis according to tumor size in sm-cancer

Tumor size (cm)	Differentiated	Undifferentiated
≦0.9	2/65 (3.1%)	2/17 (11.8%)
1–1.9	36/349 (10.3%)	25/193 (13.0%)
2.0	214/1202 (21.7%)	184/799 (23.0%)

Table 6. Elevated m-cancers with lymph node metastasis

Tumor size (cm)	Tumor location	Macroscopic shape	Extent of metastasis
1–1.9	Lower	IIa + IIc	n2
1–1.9	Lower	IIa + IIc	n2
2–2.9	Lower	I	n1
3–3.9	Lower	I + IIb	n1
3–3.9	Lower	IIa	n1
4–4.9	Lower	IIa + IIc	n1
4–4.9	Lower	IIa + IIc	n1
≧5	Middle	I	n1
≧5	Middle	I + IIa	n1
≧5	Lower	IIa + IIc	n1

Table 7. Four sm-cancers with a diameter less than 1 cm and nodal involvement

Tumor location	Histology	Macroscopic shape	Metastatic site
Upper	Undifferentiated	IIc + III	No. 4sb
Upper	Differentiation	IIc	No. 3
Middle	Undifferentiation	IIc + III	No. 4sb
Lower	Differentiated	I + IIc	No. 6

Table 5. Five m-cancers with a diameter less than 4 cm and n2 metastasis

Tumor size (cm)	Tumor location	Histology	Macroscopic shape[a]	Metastatic site[a]
1–1.9	Lower	Differentiated	IIa + IIc	No. 1
1–1.9	Lower	Differentiated	IIa + IIc	No. 8a
2–2.9	Middle	Undifferentiated	IIc	No. 7
3–3.9	Lower	Differentiated	IIc	No. 7
3–3.9	Middle	Undifferentiated	IIc	Nos. 3, 7

[a] According to the *General rules for the gastric cancer study* (12th edition)

regional lymphadenectomy is indicated for m-cancer less than 4 cm in diameter [43]. Lymph node metastasis to the second tier (n2) was very rare (0.2%) in m-cancers less than 4 cm in diameter. However, careful consideration is needed in deciding whether limited surgery is appropriate for IIa + IIc type m-cancer, because node no. 8a, which was positive in one of our patients (Table 5), is not usually dissected during these procedures. Elevated m-cancers were reported to have very few [32,35,42] or no [7,18,37] lymph node metastases. In the present series, lymph node metastasis was observed with type I and type IIa tumors with diameters exceeding 2 cm and 3 cm, respectively (Table 6). Several studies have shown a high frequency of nodal involvement in macroscopically combined type, e.g., IIa + IIc, as compared with the other tumor types [1,17]. The present results also showed m-cancers with IIa + IIc morphology to be likely to have lymph node metastasis, even when they were less than 2 cm in diameter (Table 6).

A previous study reported that nodal metastasis was absent in sm-cancers less than 1 cm in diameter [34]. Our results indicate the presence of lymph node metastasis in such tumors (Table 7), which is consistent with the findings of other studies [35,40]. However, the extent of lymph node metastasis observed in the present series was consistently within the first tier (n1). Therefore, limited surgery may be appropriate for sm-cancers less than 1 cm in diameter.

Limited surgery, in particular, local resection, should be employed for EGC without lymph node metastasis, whereas additional extended lymphadenectomy is necessary when nodal involvement is observed intraoperatively or on histological examination of the resected specimen. However, most patients who have a diagnosis of M-cancer and N0 can benefit from local resection.

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