

# Incidence of lymph node metastasis in intramucosal gastric cancer measuring 30 mm or less, with ulceration; mixed, predominantly differentiated-type histology; and no lymphovascular invasion: a multicenter retrospective study

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## Abstract

**Background** Intramucosal gastric cancer,  $\leq 3$  cm ( $\leq 30$  mm) with ulceration, and mixed histology (predominantly differentiated), was previously considered curative after endoscopic resection, and additional surgery was thought to be unnecessary. However, as the evidence base for these criteria remains insufficient, the Japanese Gastric Cancer Treatment Guidelines, ver. 3 (2010) specify that this pathology should be considered noncurative and recommend additional surgery. We report the frequency of lymph node metastasis in patients with these conditions based on a multicenter study.

This article is a modified version of that published in the Japanese journal *Stomach and Intestine* in October 2013 (Vol. 48, No. 11) in the Japanese language, entitled “Clinicopathologic characteristics of intramucosal gastric cancer with differentiated-type dominant mixed type—Multicenter study on surgical resection of early gastric cancer.” More cases were included in the analysis, which is reflected in this updated version of the manuscript.

**Methods** Of patients with early gastric cancer who underwent gastrectomy with lymph node dissection, those with a mixed, predominantly differentiated tumor type, ulceration, a tumor diameter  $\leq 3$  cm, and no lymphovascular invasion were entered into this study.

**Results** Four hundred and seven patients met the criteria, 21 of whom were excluded owing to a lack of available information. Thus, a total of 386 patients were included in the analysis, from 37 of the 42 member institutions. The mean study duration was 125 months. The most common combination of mixed histology was tub2 + por (67 %). None of the 386 patients had lymph node metastasis (95 % confidence interval, 0–0.8 %).

**Conclusion** The results of this retrospective study indicate that the risk of lymph node metastasis was less than 1 % among patients with the criteria defined here, considered to be criteria for noncurative resection as per the current guidelines, and suggest that observation alone without additional surgery may result in a good outcome.

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**Keywords** Early gastric cancer · Undifferentiated adenocarcinoma · Mixed histology · Endoscopic submucosal dissection · Additional indication

## Introduction

As endoscopic submucosal dissection (ESD) [1] is well established and widely used in Japan, clinical studies to evaluate the expanded indications have been conducted [2–4]. ESD enables the complete removal of large lesions, in contrast to endoscopic mucosal resection (EMR), and hence allows detailed histopathological evaluation [5]. However, the optimal treatment strategy for a tumor with mixed histology remains in question [6, 7]. In contrast to the WHO Classification of Tumours of the Digestive System [8], the Japanese Classification of Gastric Carcinoma [9] has long adopted the policy that histological type is determined by its predominant component. Thus, the study by Gotoda et al., which gave the evidence of the current gold standard for the indications of endoscopic treatment [10], evaluated tumors on the basis of their predominant histology, but did not address mixed histology.

The Japanese gastric cancer treatment guidelines 2010 (ver. 3), revised in October 2010 [11], specify that “a tumor  $\leq 3$  cm, differentiated-type histology, pT1a (M), ulceration or scar, and associated with some areas of undifferentiated-type histology” should be regarded as criteria for noncurative resection, and thus additional surgical treatment is required, because evidence of the possibility of curative resection is insufficient. Previously, these tumors were treated as differentiated-type tumors if this was the predominant histology, and tumors  $\leq 3$  cm, pT1a (M) disease, and presence of ulceration were judged for curative resection as are lesions that do not contain any undifferentiated component. Unfortunately, little is known about the frequency of lymph node metastasis in early gastric cancer with mixed but predominantly differentiated-type histology, pT1a (M), ulceration, and a diameter  $\leq 3$  cm. Further study is urgently needed, but endoscopic resection is commonly used to treat patients with these tumors, and surgical resection is rarely performed, making it difficult to prospectively evaluate lymph node metastasis. We report here the frequency of lymph node metastasis on the basis of an analysis of previous surgical resection cases from multiple institutions.

## Methods

Surgically treated patients in the member hospitals between 1971 and 2013 with the following criteria were enrolled in this study. The member institutions were affiliated with the Japan Gastrointestinal Endoscopy Study Group (Representative: Prof. Manabu Muto, M.D., Ph.D., Therapeutic

Oncology, Graduate School of Medicine and Faculty of Medicine, Kyoto University), or the Stomach Cancer Study Group (Representative: Prof. Mitsuru Sasako M.D., Ph.D., Upper GI Surgery Division, Department of Surgery, Hyogo College of Medicine) of the Clinical Oncology Group (JCOG, <http://www.jcog.jp/index.htm>). The Institutional Review Board approved the study protocol.

All the patients with pT1a (M) tumors of differentiated type whose size was 3 cm or less with ulcerative change were listed, and those having undifferentiated component without lymphovascular invasion were enrolled in this study. To assess the histological type, all specimens were reviewed to determine the percentages of differentiated components (well- and moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma) and undifferentiated components (poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma). Histological type was determined according to the proportions of intramucosal differentiated and undifferentiated components at histopathology. Mixed, predominantly differentiated-type histology was defined as the major component of differentiated type more than 50 % with undifferentiated-type component less than 50 %. If it was difficult to decide the histological type at the original institutions, central pathology review was performed.

Information on patient background (age and gender), tumor location (U, upper third; M, middle third; L, lower third), major histological type (differentiated type), mixed histology (with undifferentiated type), and the presence or absence of lymph node metastasis was collected.

## Results

Forty-two medical institutions participated in this study (Table 1). From these institutions, a total of 407 subjects from 37 institutions met the eligibility criteria. Of these patients, 386 were included in this analysis, excluding 21 patients with missing data, none of who had lymph node metastasis. The mean study duration was 125 months (median, 86.5 months; range, 12–408 months). Patient characteristics are detailed in Table 2.

Median patient age was 61 years (range, 24–87 years), and 69 % of the subjects were men. The most common tumor location was M (56 % of the subjects), and 86 % of cases were superficial depression type (IIc, IIb, IIc + IIb). Median tumor diameter was 2 cm (range, 0.2–3 cm).

The most common tumor histology (differentiated type) was tub2 (88 % of cases), followed by tub1 (11 %). Predominant histology of the mixed undifferentiated component was classified as por in 77 % of cases, sig in 22 % of cases, and muc in 2 % of cases (Table 3). The most

**Table 1** The 42 participating medical institutions, number of subjects, and study duration

Name of medical institution	No. of subjects	Study duration	Months
The Cancer Institute Hospital of JFCR	65	1980–2012/12	384
National Cancer Center Hospital	35	1997/5–2012/12	182
National Hospital Organization Shikoku Cancer Center	25	1989/12–2013/3	279
National Cancer Center Hospital East	21	2002/2–2010/6	100
Osaka Medical College	21	1993/6–2009/10	196
Niigata Cancer Center Hospital	20	1971–2005/12	408
Toranomon Hospital	18	2006/4–2012/9	77
Yamagata Prefectural Central Hospital	18	1983/4–2013/3	360
Kitasato University	16	1986/6–2010/6	289
Yokohama City University Medical Center	15	2000/5–2013/2	153
Hiroshima City Hospital	14	2009/1–2012/12	48
Keiyukai Sapporo Hospital	13	1985–2010/12	300
Tochigi Cancer Center	12	2001/11–2010/7	104
Ishikawa Prefectural Central Hospital	11	1995/1–2012/12	216
Shizuoka Cancer Center	10	2002/9–2013/3	126
Niigata University Medical & Dental Hospital	10	1995–2006	132
Kanagawa Cancer Center	9	2006/1–2012/3	74
Hyogo Cancer Center	6	2005/4–2009/12	56
Shizuoka General Hospital	5	2005/1–2012/12	96
Osaka Medical Center for Cancer and Cardiovascular Diseases	5	2005/3–2010/9	66
Osaka City General Hospital	5	1999–2013	168
Oita University Hospital	4	1998/1–2010/1	145
Iwate Medical University	4	2007/1–2013/3	74
Kyoto University Hospital	4	2009/1–2013/3	51
Chiba Cancer Center	4	2008/1–2012/7	55
Toyama Prefectural Center Hospital	3	1998/1–2001/12	48
Tsubame Rosai Hospital	3	2000/1–2009/12	120
Tokyo Metropolitan Bokutoh Hospital	2	2005/4–2010/3	60
Kobe University	2	2000/1–2005/12	72
Kochi Health Sciences Center	1	2005/3–2009/2	48
NTT Medical Center Tokyo	1	2012/1–2012/12	12
Itami City Hospital	1	2008/4–2013/3	60
Miyagi Cancer Center	1	2008/1–2010/12	36
Hyogo College of Medicine	1	2008/1–2012/12	60
Sendai Medical Center	1	2005/1–2012/12	96
Aichi Cancer Center Hospital	0	2007/4–2010/3	36
Hiroshima City Asa Hospital	0	Unknown	
Ibaraki Prefectural Central Hospital and Cancer Center	0	Unknown	
Saku Central Hospital	0	Unknown (the past 2 years)	24
Showa University	0	2009/4–2010/8	17

common combination was tub2 + por, which accounted for 67 % of cases, followed by tub2 + sig (20 %) and tub1 + por (10.1 %).

The frequency of lymph node metastasis is shown in Table 4. None of the 386 subjects in this study had lymph node metastasis (95 % confidence interval, 0–0.8 %).

## Discussion

It is now well established that gastric carcinoma sometimes exhibits mixed histology, and these tumors are commonly classified on the basis of the dominant histological type alone. According to the WHO classification of tumors of

**Table 2** Patient and disease characteristics

All subjects	386	%
Age (years)		
Median	61	
Range	24–87	
Gender		
Male	265	68.7
Female	121	31.3
Tumor location		
U (Upper third)	44	11.4
M (Middle third)	215	55.7
L (Lower third)	127	32.9
Macroscopic type		
Superficial elevated (IIa, I + IIa)	7	1.8
Superficial depression (IIc, IIb, IIc + IIb)	331	85.8
Depression (IIc + III, III + IIc, III)	35	9.1
Combined (IIa + IIc, IIc + IIa)	12	3.1
Unclassified (IIa + IIc + III)	1	0.2
Longest diameter (mm)		
Median	20	
Range	2–30	
Major tumor type (differentiated-type)		
tub1	47	12.2
tub2	339	87.8
pap	0	0
Mixed histology (undifferentiated-type)		
por	297	76.9
sig	83	21.5
muc	6	1.6

**Table 3** Frequency of the combination of major tumor type and mixed histology classification

	Mixed histology		
	por	sig	muc
Major tumor type			
tub1	39 (10.1 %)	7 (1.8 %)	1 (0.3 %)
tub2	258 (66.8 %)	76 (19.7 %)	5 (1.3 %)

**Table 4** Frequency of lymph node metastasis in early gastric cancer patients with mixed, predominantly differentiated-type tumors; pT1a (M); ulceration; and tumor diameters  $\leq 3$  cm

No. of patients	386
No. of patients with lymph node metastasis	0
Incidence of lymph node metastasis	0 %
95 % confidence interval	0–0.8

digestive organs, histological type of gastric adenocarcinoma is decided by predominance, but grading should be evaluated by differentiation. On the other hand, the Japanese Classification of Gastric Carcinoma has long adopted the policy that histological type is determined by its predominant component, and minor components are added. Grading is not evaluated in the Japanese classification; i.e., small foci of signet ring cell is not regarded as a high-grade tumor.

ESD, which is a newly developed and widely applied technique at present, allows a larger lesion to be completely resected with one entire specimen and hence enables more detailed histopathological evaluation. Our previous study evaluated clinicopathological differences between a pure differentiated type (differentiated adenocarcinoma alone) and a mixed, predominantly differentiated type (combination of differentiated adenocarcinoma and undifferentiated adenocarcinoma), and concluded that the frequency of lymph node metastasis was significantly greater for the mixed, predominantly differentiated type than for the well-differentiated type [7]. On the basis of these findings, a distinction should be made between the pure differentiated type and the mixed, predominantly differentiated type.

According to the description of an expanded indication for curative resection in the Japanese gastric cancer treatment guidelines (ver. 3), when the result of the pathological examination after ESD shows that the tumor has differentiated-type histology, T1a (M) staging, ulceration, a diameter  $\leq 3$  cm, and no vascular invasion, patients with such tumors could be followed up without additional surgery. However, if the tumor has a mixed, predominantly differentiated-type histology with an undifferentiated component, the guidelines recommend additional resection because there are insufficient data to support observation alone. Therefore, we evaluated early gastric cancer patients with mixed, predominantly differentiated-type tumors, T1a (M), ulceration, a tumor diameter  $\leq 3$  cm, and no lymphovascular invasion, who underwent surgical resection, to study the frequency of lymph node metastasis. The results indicate that there was no lymph node metastasis among these patients.

The most common histology patterns of mixed, predominantly differentiated-type tumors in our previous single-center study [7] were tub2 + por (57 %; 30 of 53 cases) and tub2 + sig (34 %; 18 of 53 cases), and the results of the multicenter study reported here were very similar, as the most common pattern was tub2 + por (67 %), followed by tub2 + sig (20 %). This result supports the hypothesis that tumor extension and dedifferentiation both occur in differentiated-type tumors, particularly in tub2 tumors.

This study had some limitations. First, we did not confirm each patient's data because this was a multicenter,

retrospective study. Furthermore, the pathological diagnostic criteria might vary from institution to institution. Actually, there were two cases with lymph node metastases at the first evaluation. After central pathological review, the diagnosis of those two cases was changed from predominantly differentiated type into predominantly undifferentiated type. Moreover, sometimes it is very difficult to measure the size of undifferentiated components and decide which component is predominant.

However, endoscopic resection is currently the most common treatment for this type of carcinoma, and collection of patients who undergo surgical resection for such tumors is hardly possible. The new guidelines (ver. 4) [12] have been just revised on the basis of the results of this study, and follow-up without additional surgery is recommended as part of the treatment strategy to avoid unnecessary surgery, allowing more patients to preserve the entire stomach, which will be significant in terms of both medical economics and the patient's quality of life.

In conclusion, although "a tumor  $\leq 3$  cm, with predominantly differentiated histology, pT1a (M), ulceration, and association with some areas of undifferentiated-type histology" was considered to preclude curative resection according to the previous guidelines (ver. 3), the results of this retrospective multicenter study suggest that there is almost no risk of lymph node metastasis and that no further treatment may be necessary in such cases, with observation alone being sufficient.

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#### Compliance with ethical standards

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with Helsinki Declaration of 1964 and later versions.

**Conflict of interest** The authors declare that they have no conflict of interest.

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