

## Lymph Node Metastasis in Cancer of the Middle-Third Stomach: Criteria for Treatment with a Pylorus-Preserving Gastrectomy

YASUHIRO KODERA, YOSHITAKA YAMAMURA, YUKIHIDE KANEMITSU, YASUHIRO SHIMIZU, TAKASHI HIRAI, KENZO YASUI, TAKESHI MORIMOTO, and TOMOYUKI KATO

Department of Gastroenterological Surgery, Aichi Cancer Center, 1-1 Kanokoden, Chikusa-ku, Nagoya, Aichi 464-8681, Japan

**Abstract** A retrospective study was conducted to establish the criteria for performing a pylorus-preserving gastrectomy. This study was performed on 491 patients who had cancer of the middle-third stomach and had been curatively treated with a distal gastrectomy. The incidence of node metastasis for each lymph node station (the group of regional lymph nodes which have been anatomically defined and classified by the Japanese Classification of Gastric Carcinoma) was evaluated with reference to the depth of invasion, tumor size, and circumferential location, to show any significant correlations with an increase in tumor diameter or in the depth of tumor invasion. The benefits of resecting each station was then evaluated based on the incidence of metastasis to each station and the rate of long-term survivors among those with metastasis to each station. The benefit was substantial for the lymph nodes along the lesser curvature, along the right gastroepiploic artery, and at the base of the left gastric artery, while the advantages were almost negligible for the suprapyloric nodes and right paracardial nodes. In conclusion, carcinoma that fulfills either of the following conditions may thus be indicated to undergo a pylorus-preserving gastrectomy: (i) restricted to a depth of m or sm1, (ii) a depth of sm2 or mp with a diameter of less than 2 cm, (ii) a depth of sm2 or mp and located in the greater curvature.

**Key words** Limited operation · Early gastric carcinoma · Lymph node metastasis

### Introduction

Surgeons in Japan have exerted considerable efforts to improve the survival of patients with gastric carcinoma by performing extended (D2) lymphadenectomies.<sup>1,2</sup> An extended lymphadenectomy and histopathologic scrutiny of the resected specimens along the lines of Japanese Classification for Gastric Carcinoma<sup>3</sup> have resulted in an accumulation of a vast amount of knowledge regarding the anatomical extent of lymph node metastasis observed for various types and stages of gastric carcinoma. As a result, it is now well known that such extended lymphadenectomies are unnecessary at least for certain subsets of early gastric carcinoma with a limited incidence of nodal involvement.<sup>4,5</sup> This knowledge has led surgeons to perform various types of limited surgical procedures that are intended to improve the quality of life while sacrificing the extent of lymph node resection. An ultimate example of such procedures would be an endoscopic mucosal resection<sup>6</sup> which is now performed throughout Japan.

A pylorus-preserving gastrectomy (PPG), originally reported as a treatment option in gastric ulcer surgery,<sup>7</sup> is now also performed for selected cases of gastric carcinoma<sup>8–11</sup> in which a distal gastrectomy (DG) had been the standard treatment of choice. PPG has been reported by several investigators to be beneficial in terms of the postoperative quality of life and is also associated with significantly lower incidences of early dumping syndrome, bile regurgitation in the remnant stomach, and cholelithiasis<sup>8,10–12</sup> as well as a significant decrease in the postoperative body weight loss.<sup>13</sup> However, these benefits have yet to be proven by a prospective randomized trial. The patients treated with this procedure, in the meantime, should be carefully selected and limited to those who are least likely to suffer from its various shortcomings in terms of radicality.<sup>8</sup> This is because the preservation of several branches of the vagal nerve, considered either

mandatory or at least beneficial to the preservation of the pyloric functions, can only be accomplished at the expense of certain lymphadenectomy procedures. In order that the pyloric ring functions adequately following PPG, the preservation of the pyloric branch which originates from the hepatic branch of the vagal nerve is considered mandatory.<sup>14</sup> This calls for a preservation of the anterior vagal trunk to the point where the hepatic branch originates. To ensure that these branches are preserved, a lymphadenectomy of lymph node station no. 5 (suprapyloric nodes) should be abandoned, and a resection of lymph node station no. 1 (lymph nodes along the right cardia) may also become technically difficult. Furthermore, a preservation of the celiac branch of the posterior vagal trunk has also been done in combination with a PPG by several Japanese surgeons.<sup>8-10</sup> This calls for the preservation of the posterior vagal trunk to the point where the celiac branch originates, for which the lymphadenectomy procedures for station nos. 7 (along the left gastric artery) and 9 (along the celiac axis) as well as no. 1 need to be compromised. At the same time, a pyloric cuff measuring 1.5 cm in size is generally retained, thus indicating that the PPG is not desirable for lesions located in the distal antrum. With PPG, on the other hand, lymph node station nos. 3, 4d, and 6 can be dissected adequately.

The current study was performed to establish the eligibility criteria for performing PPG through retrospective analyses of recent clinicopathologic data concerning the anatomical extent of nodal metastasis and the survival in the carcinoma of the middle third of the stomach. All patients underwent an extended lymphadenectomy. Based on these data, a prospective study to elucidate the feasibility and benefits of this interesting but experimental approach will be launched.

## Materials and Methods

During the decade between 1988 and 1997, 491 patients with gastric carcinoma that fulfill all of the following criteria were operated on at the Aichi Cancer Center: (i) a histologically proven solitary gastric carcinoma, (ii) treated by a potentially curative resection, (iii) treated by a distal gastrectomy with an extended (D2 or D3) lymphadenectomy, and (iv) located in the middle third of the stomach with an anal tumor clearance of 5 cm or more. Location of the tumor according to the Japanese Classification of Gastric Carcinoma<sup>15</sup> was M in 429, MU in 23, and ML in 39 patients. These patients underwent a long-term follow-up of  $1870 \pm 932$  days (median  $\pm$  standard deviation) or until death.

The depth of invasion evaluated by one representative slice of the resected specimen was classified

into the following categories according to the Japanese Classification of Gastric Carcinoma:<sup>3</sup> m, mucosal; sm, submucosal; mp, as far as muscularis propria; ss, subserosal; se, with serosal invasion; si, with invasion to the adjacent structure. Submucosal cancer was further classified into two categories in which sm1 is characterized by a slight invasion of the submucosa to a depth of less than 0.5 mm from the muscularis mucosae, and sm2 denotes a more extensive involvement of the submucosa.<sup>15</sup> The maximum diameter measured with the resected specimens was classified into the following categories: less than 10 mm, 11–20 mm, 21–30 mm, 31–40 mm, 41–60 mm, and over 61 mm. The incidence of nodal metastasis was evaluated for each of the clinicopathologic variables described in this section.

The incidence of lymph node metastasis was also evaluated independently for each of the lymph node stations defined by the Japanese Classification<sup>3</sup> regardless of the presence or absence of metastasis to the other stations. Likewise, the survival of the patients with metastasis to a particular lymph node station was evaluated regardless of any other clinicopathologic factors. From these data, the index of the therapeutic benefit for resecting a particular lymph node station was calculated by multiplying the incidence of metastasis to the station and the 5-year survival rate of patients with metastasis to the same station, as described by Sasako et al.<sup>16</sup> The incidence of metastasis to each station was also evaluated based on the tumor diameter and tumor location. Through these analyses, the clinical relevance of resecting station nos. 1, 3, 4d, 5, 7, and 9 was evaluated independently, and a subset with small or no risk of metastases to station nos. 1 and 5 was thus indicated for PPG.

## Statistical Analysis

The cumulative survival rates of the patients in this study were evaluated by the Kaplan-Meier method. The chi-squared test was performed to assess whether the incidence of node metastasis increased as the depth of invasion or the tumor size increased. Student's *t*-test was employed for comparisons of the tumor diameter between each category of the depth of invasion.

## Results

### Patient Characteristics

There were 290 men and 201 women. The age of the patients ranged from 25 to 85 years, the mean  $\pm$  SD being  $57.9 \pm 11.2$ . The depth of invasion according to the Japanese Classification<sup>3</sup> was m in 222, sm in 127 (sm1 in 41 and sm2 in 86), mp in 54, ss in 59, and se or

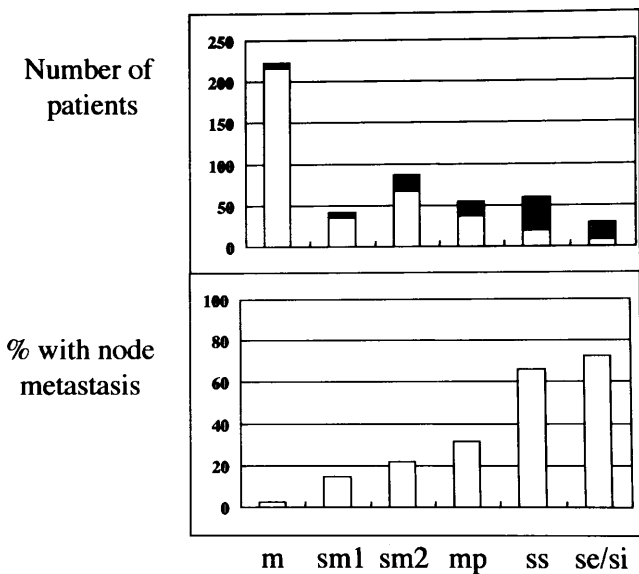
si in 29. A maximum diameter of the tumor was  $36 \pm 21$  mm (mean  $\pm$  SD, range: 5–150 mm),  $30 \pm 18$  mm for m,  $28 \pm 15$  mm for sm1,  $35 \pm 17$  mm for sm2,  $40 \pm 24$  mm for mp,  $52 \pm 22$  mm for ss, and  $55 \pm 25$  mm for se and beyond. The difference in the diameters was statistically significant between sm1 and sm2 ( $P = 0.047$ ) and between mp and ss ( $P = 0.004$ ), while no difference was observed between m and sm1, sm2 and mp, and ss and se.

The 5-year survival rate of all the patients was 87%, and those of depths m, sm1, and sm2 exceeded 90% with no significant differences between the three groups. Three treatment-related deaths were recorded and the mortality rate was 0.6%.

The extent of the lymphadenectomy performed was D2 in 451 patients and was more extended in 34 patients. This means that all of the patients underwent a complete removal of lymph node station nos. 1, 3, 4d, 5, 6, 7, 8a, 9, and 11. The number of lymph nodes retrieved was  $35 \pm 14$  (mean  $\pm$  SD, range: 8–95). Lymph node metastasis was histologically confirmed in 107 patients (21.8%).

*Incidence of Lymph Node Metastasis*

The incidence of node metastasis increased significantly ( $P < 0.0001$  by the chi-squared test) as the cancer invaded deeper into the gastric wall (Fig. 1). The



**Fig. 1.** Incidence of node metastasis and depth of cancer invasion. **Top** Number of patients belonging to each category of depth of invasion are shown. The *dark bar* shows the number of patients with metastasis. **Bottom** Incidence of lymph node metastasis for the tumors with various depths of invasion as defined in the Japanese Classification of Gastric Carcinoma

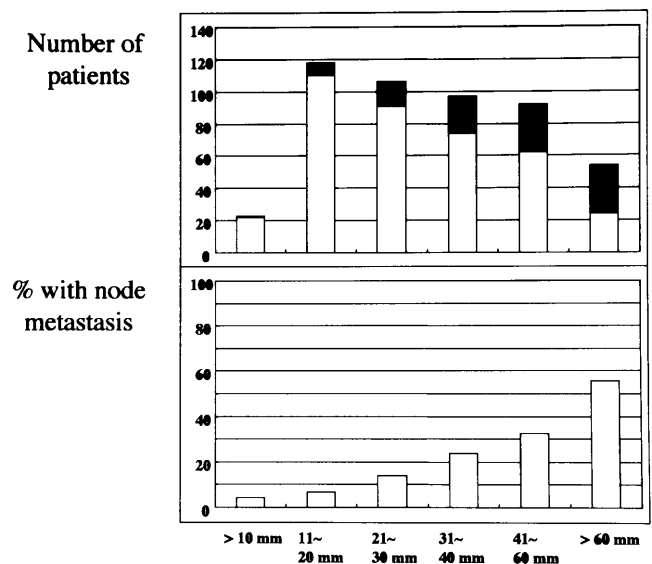
incidence of node metastasis in the patients with lesions belonging to each category of the cancer depth was as follows: 2.3% (5 of 222) for m, 19.7% (25 of 127) for sm (14.6% for sm1 and 22.1% for sm2), 31.5% (17 of 54) for mp, 66.1% (39 of 59) for ss, and 72.4% (21 of 29) for se and beyond. The increase in the incidence of node metastasis was also statistically significant ( $P < 0.0001$ ) as the diameter of the tumor increased (Fig. 2).

*Benefit of Resecting Each Lymph Node Station Based on the Incidence of Metastasis to Each Station and the Survival of the Patients with the Metastasis to Each Station*

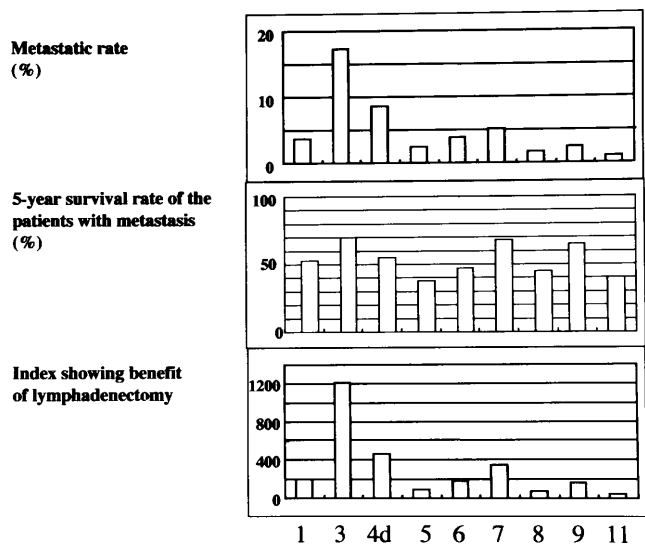
The incidence of node metastasis to each lymph node station is summarized in Fig. 3, together with the 5-year survival of the patients with metastasis to the station and the index showing clinical benefit of resecting the particular nodes. The index was dramatically high for node station no. 3, followed by station nos. 4d and 7. The index for station no. 5, despite its being classified as group 1, was relatively low for the patients evaluated in the current study.

*Criteria for Performing PPG Based on the Risk of Metastasis to Various Lymph Node Stations with Reference to the Diameter, Depth, and Location of the Tumor*

The node-positive tumor with the smallest diameter for each category of the tumor depth (classified as



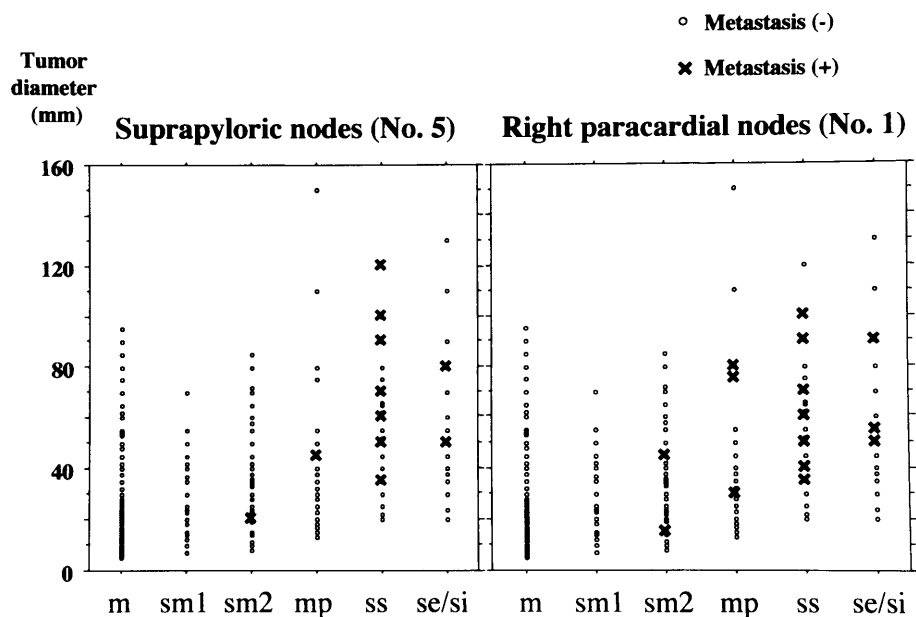
**Fig. 2.** Incidence of node metastasis and tumor diameter. **Top** The various diameters of the patients are shown. The *dark bar* shows the number of patients with metastasis. **Bottom** Incidence of lymph node metastasis for the tumors with various tumor diameters



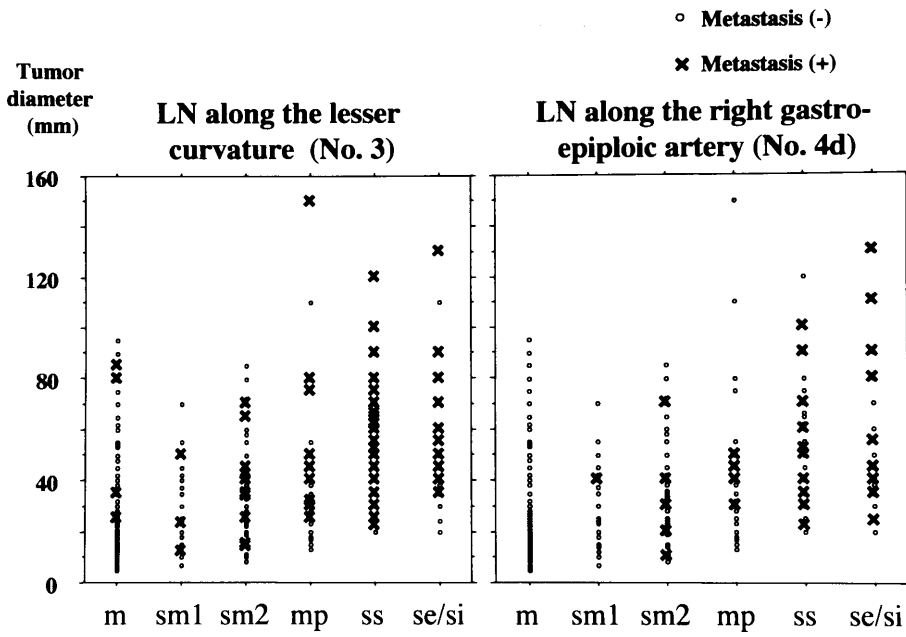
**Fig. 3.** Incidence of node metastasis and the anatomical location of lymph nodes. **Top** Incidence of metastasis to each lymph node station (the group of regional lymph nodes which have been anatomically defined and classified by the Japanese Classification of Gastric Carcinoma). **Middle** Five-year survival rate of the patients with metastasis to each lymph node station. **Bottom** Index showing the benefits of a resection at each lymph node station. The index is calculated by multiplying the incidence of metastasis to a station with the 5-year survival of the patients with metastasis to the same station. For example, the metastatic rate of station no. 1 (3.7%) multiplied by the 5-year survival rate of the patients with metastasis to station no. 1 (53%) equals the index of 196 for station no. 1

described in the Japanese Classification of Gastric Carcinoma) can be identified for each of the node station nos. 1, 3, 4d, 5, 6, 7, 8a, and 9 through observations of the plots shown in Figs. 4–7. As described elsewhere, metastasis to station no. 3 was the most frequent and was relatively common even for the lesions rated as depths m and sm1. Metastasis to station no. 4d was also frequent for lesions of depth sm2 or more. Metastasis to station no. 7, despite its being ranked as group 2, was frequently observed, with one case of depth m and two cases of depth sm1 having the metastasis despite a tumor diameter of around 2 cm. On the other hand, no metastasis to station nos. 1, 5, 6, and 8a was observed for tumors with a depth of sm1 or less. Likewise, no metastasis to these nodes was observed for cancers with a depth of sm2 or mp within 2 cm of diameter, with the exception of one case. This exceptional lesion was located in region M with a diameter of 1.5 cm and a depth of sm2, and had only one metastatic node which was found in lymph node station no. 1.

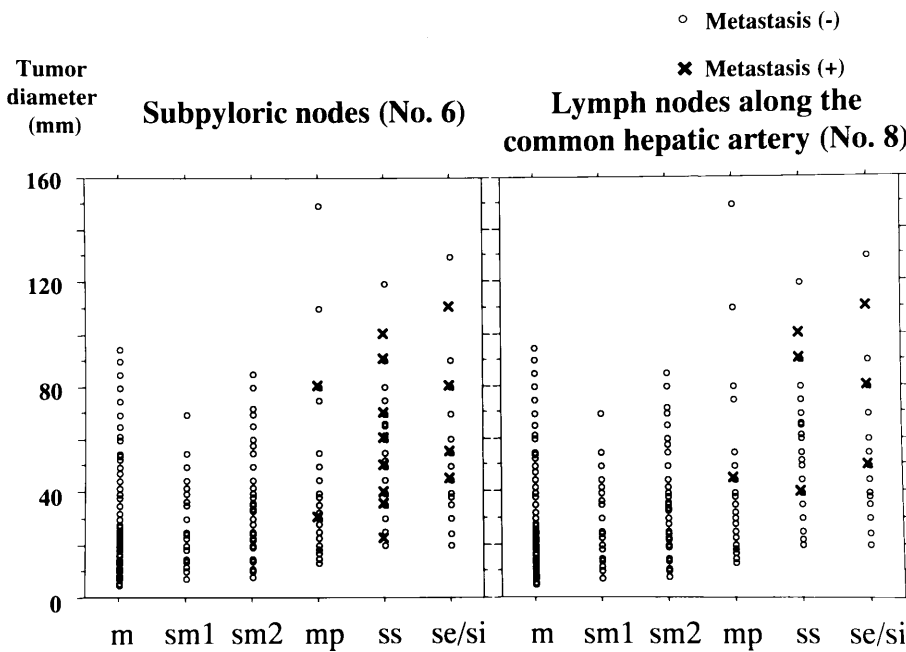
Node metastasis was rarely observed for the lesions located in the greater curvature when the tumor invaded no deeper than the muscularis propria. This finding was better than for lesions located in the lesser curvature (Fig. 8). The only metastasis observed for early cancer of the greater curvature was found along the greater curvature (no. 4d). For the tumors located in the greater curvature, the dissemination of the cancer cells through the intramural lymphatic network into lymph nodes of the lesser curvature (no. 3) and further into the station nos. 1, 5, and 7 seems to occur as a late event.



**Fig. 4.** Tumors with the without metastasis to the lymph node stations that cannot be resected when a pylorus-preserving gastrectomy is performed; suprapyloric nodes (no. 5) and right paracardial nodes (no. 1). Each tumor was plotted according to the tumor diameter and the depth of invasion. No metastasis was observed for the tumors demonstrating depths m and sm1



**Fig. 5.** Tumors with and without metastasis to the lymph node stations that can be resected adequately even with a pylorus-preserving gastrectomy; the lymph nodes (LN) along the lesser curvature (no. 3) and along the right gastroepiploic artery (no. 4d). Each tumor was plotted according to the tumor diameter and the depth of invasion. Metastasis to station no. 3 was frequent for the tumors of all depths including m and sm1

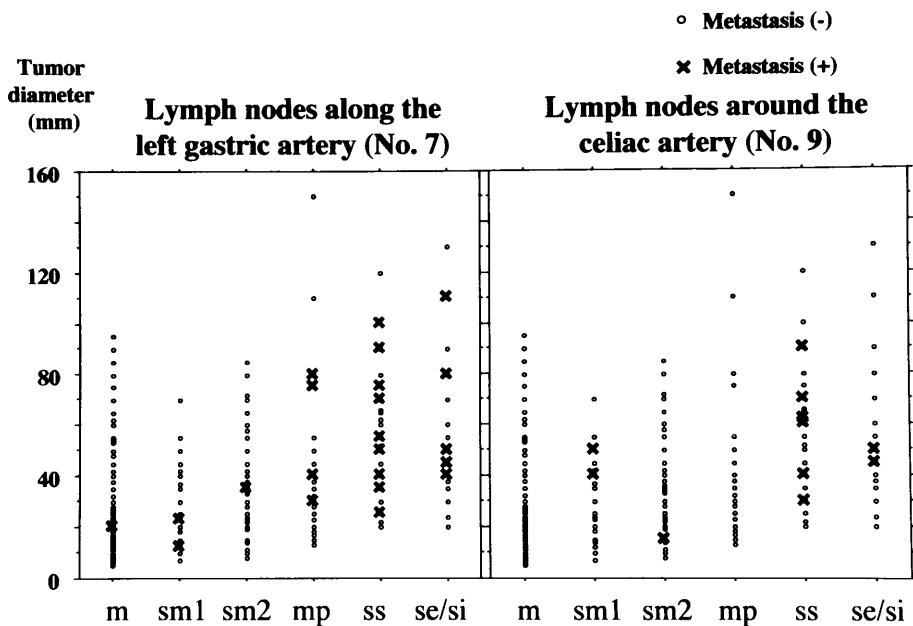


**Fig. 6.** Tumors with and without metastasis to the lymph node stations that can be resected adequately even with a pylorus-preserving gastrectomy; subpyloric lymph nodes (no. 6) and the lymph nodes along the common hepatic artery (no. 8a). Each tumor was plotted according to the tumor diameter and the depth of invasion. Metastasis to station no. 8a was infrequent

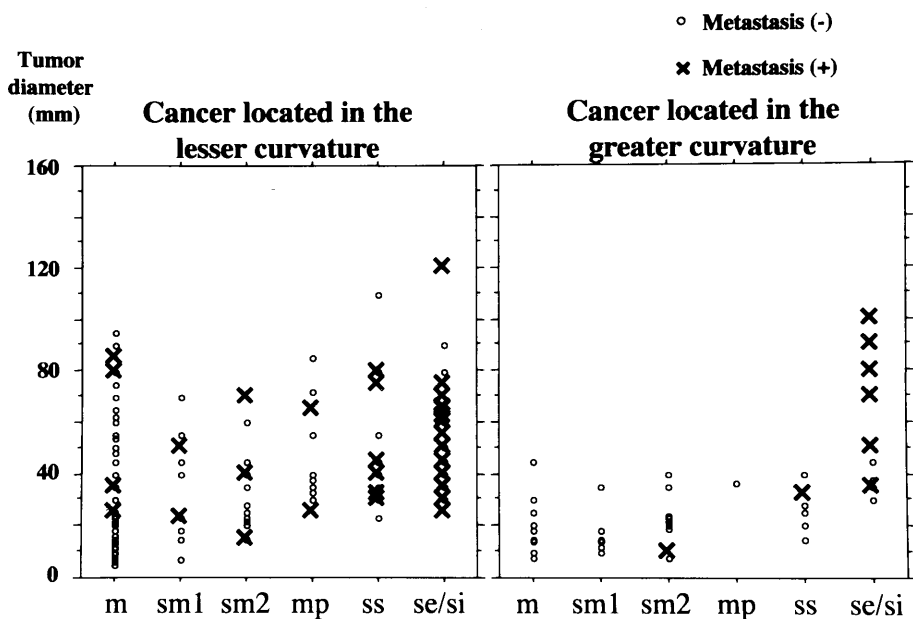
To sum up our findings, tumors that fulfill either of the following conditions in terms of size and depth appear to be indicated for PPG: (i) restricted to a depth of m or sm1, (ii) restricted to a depth of sm2 or mp with a diameter of less than 2cm, and (iii) restricted to a depth of sm2 or mp and located in the greater curvature. These criteria thus identified 121 patients among the 491 analyzed in this study, and indicate that PPG would not be a rare procedure.

**Discussion**

The profile of the anatomical extent of node metastasis for the group of patients analyzed in this study was similar to that of cancer of the middle-third stomach reported from the National Cancer Center, Tokyo in their survey of 1281 patients treated by a potentially curative resection.<sup>16</sup> In both studies, the index showing the benefit of a resection to be low for station no. 5,



**Fig. 7.** Tumors with and without metastasis to the lymph node stations that cannot be resected adequately when celiac branch of the posterior vagal trunk is preserved; lymph nodes along the left gastric artery (*no. 7*) and around the celiac artery (*no. 9*). Each tumor was plotted according to the tumor diameter and the depth of invasion. Metastasis to these stations was not infrequent despite the fact that they belonged to the group 2 lymph nodes



**Fig. 8.** Tumors with the without metastasis to the regional lymph nodes. Each tumor was plotted according to the tumor diameter and the depth of invasion. When the tumor was located in the greater curvature, metastasis to the regional lymph nodes was a rare event. The only metastasis observed for early gastric carcinoma in this region was found in a node that belongs on station no. 4d, which is adjacent to the greater curvature

despite its belonging to the group 1 lymph nodes. On the other hand, metastases were commonly observed to the lymph nodes of station nos. 3 and 4d, and also of station no. 7 which belongs to group 2. The patients curatively treated with a D2 lymphadenectomy were shown in the current study to have a relatively good long-term survival despite metastases to these stations. However, a strict D2 lymphadenectomy would still be regarded as oversurgery for some cases of early gastric carcinoma, given the high morbidity and mortality associated with this procedure.<sup>17,18</sup> Limited surgery

should be applied with care, however, because node metastasis is not uncommon even in early gastric carcinoma (2.3% for m and 19.7% for sm in this study).

The hepatic and pyloric branches of the anterior vagal trunk need to be preserved for PPG, one of the limited procedures that has become increasingly popular in Japan.<sup>14</sup> A refined technique to skeletonize and preserve the autonomic nerves while performing lymphadenectomies has been recently reported in rectal surgery<sup>19</sup> and a similar technique has now also become

popular among gastric surgeons in Japan. However, an en bloc removal of surrounding connective tissues together with the chain of lymph nodes is considered fundamental for the process of lymphadenectomy, and such a procedure becomes increasingly tedious when there is a need to preserve something within the anatomical range to be resected. This is true especially when the nerves are to be preserved, because they can easily become denatured as a result of excessive manipulation or the use of electric cautery. To facilitate the surgical procedure and ensure the preservation of the vagal branches that are considered essential for the preservation of the pyloric functions, a dissection of lymph node station nos. 1 and 5 should preferably be abandoned. Although stations nos. 1 and 5 are rated as group 1 nodes for the carcinoma of the middle-third stomach,<sup>3</sup> the findings of this study demonstrated that surgery without dissecting these nodes is feasible for a group of patients that can be selected adequately according to the depth and diameter of the tumor.

Some surgeons are also keen on preserving the celiac branch of the posterior vagal trunk.<sup>10,20</sup> For this procedure, an en bloc resection of station nos. 7 (lymph nodes along the left gastric artery) and 9 (lymph nodes around the celiac artery) must be abandoned. The current analyses, however, show that metastasis to the no. 7 nodes is surprisingly frequent even for early stage cancer, while a high percentage of long-term survivors among those with metastasis have also been achieved by a D2 operation. The authors therefore recommend an orthodox lymphadenectomy technique for dissecting the left gastric artery at the base to perform an en bloc resection of station nos. 7 and 9. The idea of preserving the celiac branch as a routine procedure for PPG should be discarded. It is also clear from the data obtained that a resection of lymph node station nos. 3 (lymph nodes along the lesser curvature) and 4d (lymph nodes along the right gastroepiploic artery) cannot be avoided even for early gastric carcinoma. Given the high incidence of metastasis and the high percentage of long-term survivors among those with metastasis, the number of patients eligible for a wedge resection of tumors with<sup>21</sup> or without<sup>22</sup> a limited lymphadenectomy is thus considered to be small.

To conclude, PPG with a preservation of the hepatic and pyloric branches is considered feasible only for a subset of gastric carcinoma patients based on the tumor diameter and depth of invasion as described above. It should be borne in mind, however, that the preoperative assessment of the depth of invasion does not always turn out to be correct, despite the frequent use of endoscopic ultrasonography in addition to the use of conventional examinations consisting of barium swallow and endoscopy.

The greatest problem in the preoperative assessment of the depth of tumor invasion has been reported to lie in the discrimination between m and sm1.<sup>23</sup> The preoperative diagnosis would be greatly facilitated if minimal invasion to the submucosa could be ignored and cancer with a depth of sm1 could be treated alongside mucosal cancer (m). Likewise, it is difficult to rule out the possibility of invasion to the muscularis propria somewhere in the entire lesion when massive submucosal invasion exists. The criteria for PPG established in this study is practical for clinical use in that the depths m and sm1 and depths sm2 and mp are generally treated in the same category. A prospective study is warranted to confirm the feasibility of our criteria along with the clinical benefits of preserving the pyloric function.

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