



Review Article

Oncological relevance of proximal gastrectomy in advanced gastric cancer of upper third of the stomach

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ABSTRACT

Background: The oncological relevance of proximal gastrectomy in advanced gastric cancer remains unclear. We aimed to examine the frequency of lymph node metastasis in advanced gastric cancer to determine the oncological validity of proximal gastrectomy selection.

Materials and methods: This study included consecutive 71 patients with locally advanced gastric cancer in the upper third of the stomach who underwent total gastrectomy at our institution between 2001 and 2017. Lymph node metastasis and its therapeutic value index were examined to identify candidates for proximal gastrectomy. Metastatic and 3-year overall survival rates of numbers 3a and 3b lymph nodes were examined from 2010 to 2019.

Results: The metastatic rate and therapeutic value index of numbers 4d, 5, 6, and 12a lymph nodes were zero or low. The number 3 lymph node had a metastatic rate and therapeutic value index of 36.6 % and 31.1, respectively. The metastatic and 3-year overall survival rates of the number 3a lymph node were 32.7 % and 89 %, respectively, whereas those of the number 3b lymph node were 3.8 % and 100 %, respectively. All patients with positive metastasis to the number 3b lymph node received adjuvant chemotherapy. Histopathological findings of positive metastasis to the number 3b lymph node were located in the lesser curvature, and the tumor diameter exceeded 40 mm.

Conclusion: For advanced gastric cancer of the upper third of the stomach, the indications of localization to the lesser curvature and a tumor diameter of >40 mm should be considered cautiously.

Introduction

Gastric cancer is the third leading cause of cancer-related deaths and the sixth most common cancer globally [1]. Recently, the incidence of gastric cancer in the upper third of the stomach has increased in Western and Asian countries [2–4]. Surgical procedures for early gastric cancer of the upper third of the stomach include proximal gastrectomy (PG) and total gastrectomy (TG). According to the Postgastrectomy Syndrome Assessment Scale study, PG is better than TG in terms of body weight loss, necessity for additional meals, diarrhea, and dumping syndrome [5]. Oncologically, in early gastric cancer, PG does not differ from TG in terms of recurrence or the long-term survival rate [6–10]. The Japanese Gastric Cancer Guidelines recommend PG for early gastric cancer in the upper third of the stomach [11], however, its use in advanced gastric cancer is unknown. For esophagogastric junction cancers of cT2–T4, the frequency lymph node (LN) metastasis was reported in a multicenter

prospective study [12]. Conversely, the frequency of LN metastasis in advanced gastric cancer of the upper third of the stomach has not yet been established, as there are only a few reports [13–17] and the oncological appropriateness of selecting PG is unclear. In particular, the frequency of number (No.) 3b LN metastasis is important for surgical selection when PG is selected because No. 3b LN dissection is insufficient with preservation of the distal lesser curvature, although there are few reports examining the No. 3b LN¹⁸.

The oncological relevance of proximal gastrectomy in advanced gastric cancer remains unclear. Therefore, this study aimed to examine the frequency of LN metastasis in advanced gastric cancer of the upper third of the stomach to determine the oncological validity of PG selection.

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Materials and methods

Ethics statements

The study protocol was approved by the Ethics Committee of Osaka Medical and Pharmaceutical University Hospital (approval No.: 2020–005), which waived the need for informed consent owing to the retrospective nature of the study.

Study design and population

This retrospective cohort study screened 340 patients with gastric cancer who underwent TG at Osaka Medical and Pharmaceutical University Hospital, Japan between January 2001 and December 2017. We excluded patients who had microscopic or macroscopic residual disease following surgery (R1 or R2 resection), macroscopic type 4 or large type 3 (>80 mm) gastric cancer, received neoadjuvant chemotherapy, had tumors located in the middle or lower third of the stomach, or were diagnosed with pT1 gastric cancer.

Clinical and pathological characteristics

The patients' preoperative characteristics included age, sex, the presence or absence of splenectomy, extent of LN dissection, tumor location, maximum tumor diameter, macroscopic type, histological type, pathological T factor, pathological N factor, pathological stage, and presence or absence of adjuvant chemotherapy. The pathological factors were defined according to the Japanese Classification of Gastric Carcinoma [19]. LN dissection was performed in accordance with the Japanese Gastric Cancer Treatment guidelines [11].

Pathological LN metastasis and therapeutic value of LN dissection

To examine the dissection effect on each LN, we used the therapeutic value index for LN dissection devised by Sasako et al. [15] The therapeutic value index for LN dissection was obtained by multiplying the rate of nodal metastasis with the 5-year overall survival (OS) for each nodal station. The 5-year OS was obtained from patients' hospital records.

Metastasis of nos. 3a and 3b LNs

The No. 3 LN was divided into 3a and 3b LNs according to the revision of the 14th edition of the Japanese Classification of Gastric Carcinoma in 2010 [19]. Since D2 LN dissection of PG did not include the station No. 3b LN in the Japanese Gastric Cancer Treatment Guidelines in 2021 [11], the metastatic rate was examined in patients who underwent TG confined to the upper third of the stomach from

January 2010 to December 2019.

Since 2010, when the observation period was short and the number of cases was small, LN metastasis and 3-year OS rates were examined from 2010 to 2019. The analyses from 2001 and 2017 and from 2010 to 2019 shared similar exclusion criteria.

Statistical analysis

Continuous variables are presented as means \pm standard deviation. Kaplan–Meier survival curves were constructed. All statistical analyses were performed using JMP Pro 15 (version 15, SAS Institute, Cary, NC, USA).

Results

Clinical and pathological characteristics

The patient selection flowchart is shown in Fig. 1; 71 patients who underwent TG were enrolled in this study. The clinical and pathological characteristics of the patients are presented in Table 1. Overall, 90.1 % of patients underwent D2 or more LN dissection, and 30 % underwent splenectomy. Regarding histological type, 54.9 % of patients had the differentiated type and 45 % had the undifferentiated type. LN metastasis was observed in 59.1 % of cases, and 35.2 % of patients received neoadjuvant chemotherapy.

Table 1

Patients' clinical and pathological characteristics.

	All patients, n = 71
Age, y, mean \pm standard deviation	68.3 \pm 9.25
Sex, male/female	53/18
Splenectomy, n (%)	30
Lymph node dissection	
D1+/D2/D2+	7/54/10
Tumor location	
Ant/Gre/Post/Less/Circ	11/5/12/39/4
Tumor diameter, mean \pm standard deviation (mm)	43 \pm 9.25
Macroscopic type	
0/I/II/III	24/6/18/23
Histological type	
Differentiated/undifferentiated/others	39/29/3
Pathological T factor	
T2/T3/T4	23/37/11
Pathological N factor	
N0/N1/N2/N3	29/20/18/4
Pathological stage	
I/II/III	11/41/19
Adjuvant chemotherapy, n (%)	35.2

Data are presented as number unless otherwise stated.

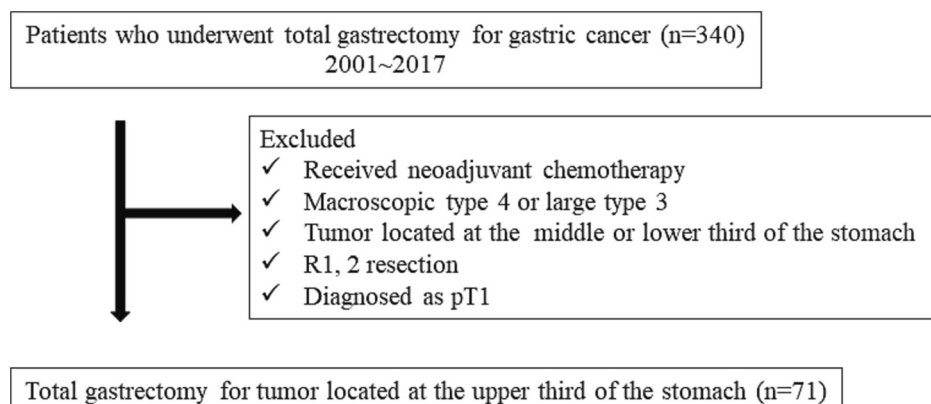


Fig. 1. Flowchart of the patients assessed in this study.

Rate of LN metastasis and therapeutic value index of LN dissection for each nodal station

The LN metastatic rate, 5-year OS rate, and therapeutic value index of LN dissection at each nodal station are shown in Table 2. Both the metastatic rates and therapeutic value indexes of Nos. 5 and 12a LNs were zero. The metastatic rate of the No. 6 LN was extremely low at 1.4 %, and the therapeutic value index was zero. Both the metastatic rate and therapeutic value index of the No. 4d LN were extremely low at 2.8 % and 2.1, respectively. However, the highest metastatic rate and therapeutic value index were 36.6 % and 31.1 for the No. 3 LN, followed by 22.5 % and 18.2 for the No. 1 LN and 15.4 % and 9.7 for the No. 2 LN, respectively.

Rate of LN metastasis and 3-year OS of Nos. 3a and 3b LNs

From January 2010 to December 2019, 275 patients with gastric cancer underwent TG at Osaka Medical and Pharmaceutical University Hospital. Using exclusion criteria similar to those in Fig. 1, 52 patients with advanced gastric cancer of the upper third of the stomach were analyzed. Because of the small number of cases in 2010, the analysis was conducted until 2019, with a 3-year survival rate. The LN metastatic and 3-year OS rates of the Nos. 3a and 3b LNs are shown in Table 3. The metastatic rate of the No. 3a LN was extremely high at 32.7 %, and the 3-year OS rate was 89 %. However, the metastatic rate of the No. 3b LN was 3.8 %, and the 3-year OS was 100 %. Two patients had No. 3b LN metastases; their pathological characteristics are shown in Table 4. One patient was diagnosed with pT2N2 (Nos. 1, 3, 3a, and 3b) pStage disease, and the other patient was diagnosed as having pT2N3a (Nos. 1, 3a, and 3b) pStage disease. Pathologically, the tumors were both differentiated and undifferentiated. Concerning the macroscopic type, one was type 0, and the other was type 3. Both tumors were located in the lesser curvature. The tumor diameters were 40 and 69 mm, respectively, both of which were > 40 mm.

Discussion

In the present study, we examined the frequency of LN metastasis and the therapeutic value of LN dissection for advanced gastric cancer in the upper third of the stomach to determine the oncological validity of PG selection. The therapeutic value indexes of Nos. 4d, 5, 6, and 12a LNs were zero or extremely low. This result is comparable to those of previous studies [13,14,16,17]. Yura et al. reported that the metastatic rates of Nos. 4d and 12a LNs for advanced gastric cancer in the upper third of the stomach were extremely low, those of Nos. 5 and 6 LNs were zero,

Table 2
Metastatic rate and therapeutic index value after dissection of LNs at each LN station.

LN station	No. of metastatic/retrieved LNs	Metastatic rate (%)	5-y overall survival rate (%)	Therapeutic index value
1	16/71	22.5	81	18.2
2	11/71	15.4	63	9.7
3	26/71	36.6	85	31.1
4sa	3/70	4.3	100	4.3
4sb	3/71	4.2	100	4.2
4d	2/70	2.8	75	2.1
5	0/71	0	0	0
6	1/71	1.4	0	0
7	7/71	9.8	75	7.3
8	3/71	4.2	0	0
9	4/70	5.7	100	5.7
10	1/37	2.7	0	0
11p	5/66	7.5	100	7.5
11d	3/59	5.0	66	3.3
12a	0/37	0	0	0

LN, lymph node; No., number.

Table 3
Metastatic and 3-year overall survival rates after dissection of Nos. 3a and 3b LNs.

LN station	No. of metastatic/retrieved LNs	Metastatic rate (%)	3-y overall survival rate (%)
3a	19/55	32.7	89
3b	2/55	3.8	100

LN, lymph node; No., number.

Table 4
Pathological characteristics of patients with No. 3b LN metastasis.

	n = 2
Tumor diameter, median (mm)	54.5 (40, 69)
Differentiated/undifferentiated/others	2/0/0
Ant/Gr/Post/Less/Circ	0/0/0/2/0
Type 0/I/II/III	1/0/0/1
pT2/pT3/pT4	2/0/0
pN1/pN2/pN3	0/1/1
pStage I/II/III	0/1/1

LN, lymph node.

Data are presented as number unless otherwise stated.

and the therapeutic value indexes of Nos. 4d, 5, 6, and 12a LNs were zero [17]. However, that study included only T2/T3 cases and did not include T4 cases. Additionally, many of the patients were enrolled before 2007, when the ACTS-GC trial in Japan reported its results [20] and few patients received S-1 as adjuvant chemotherapy. This means that the 5-year OS and therapeutic value index may be higher; however, we acknowledge the report of a very low metastatic rate. Ri et al. reported that the therapeutic value indexes of Nos. 4d, 5, 6, and 12a LNs for gastric cancer in the upper third of the stomach were zero or extremely low [16]. This study was interesting in that it examined the clinical T factor, which is in line with clinical practice. However, it is possible that the metastatic rates of each LN station were underestimated because nearly 10 % of the cases were pathological T1. Furthermore, none of the studies examined the No. 3b LN. Therefore, it is not possible to determine the oncological relevance of PG for volvulus.

The No. 3 LN is an important LN in gastrectomy with lymph node dissection in advanced gastric cancer of the upper third of the stomach because its metastatic rate and therapeutic value index were as high. This result was similar to those of previous studies [13,14,16,17]. However, PG with dissection of the No. 3 LN, including the No. 3b LN, results in a very small remnant stomach and cannot provide the benefits of PG compared with TG. Therefore, in the 2021 Japanese Gastric Cancer Treatment Guidelines, the No. 3b LN is not included in D2 LN dissection during PG. [11]

Haruta et al. were the first to examine the frequency of metastasis and the therapeutic value index of Nos. 3a and 3b LNs for advanced gastric cancer in the upper third of the stomach [18]. The reported metastatic rate and therapeutic value index of the No. 3a LN were high at 54.9 % and 24.8, respectively, whereas those of the No. 3b LN were extremely low at 2.2 % and 1.1, respectively. However, esophagogastric junction cancers were also included, and the proportion of advanced gastric cancers in the upper third of the stomach remains unknown. In addition, it is unknown whether patients will receive adjuvant chemotherapy after TG. The clinicopathological features of the No. 3b LN-positive cases were also described. The tumor was >40 mm in diameter and localized to the lesser curvature.

Herein, the metastatic and 3-year OS rates of the No. 3b LN were 3.8 % and 100 %, respectively. The metastatic rate of the No. 3b LN was similarly low; however, patients with positive metastases survived. This may be because both patients received S-1 as adjuvant chemotherapy for 1 year after TG. Although the number of cases was small, the clinicopathological features were similar to those reported by Haruta et al. Both patients had tumors measuring >40 mm in diameter that were

localized to the lesser curvature.

The present study had several limitations. First, this was a single-center, retrospective study. As this is a university hospital, it includes more elderly patients and those with severe comorbidities than non-university hospitals. Survival rates may have been lower because some patients may have died of other causes of death due to illnesses that may have contributed to TG. Second, the sample size was small. Additionally, the No. 3 LN was divided into 3a and 3b only since 2010 when the Japanese Classification of Gastric Carcinoma was revised to the 14th edition [19], so the study period was not long. Further, it is difficult for a single center to produce a therapeutic value index; therefore, a multi-center study is desirable. Adjuvant chemotherapy is also an important factor in the prognosis of gastric cancer. Although this study had a small sample size, the data obtained from patients who received adjuvant chemotherapy for No. 3b LN metastases were valuable. Finally, preserving distal stomach function, including reservoir capacity and gastric acid secretion, facilitates the absorption of non-heme iron and calcium in the intestines, promotes the production of Castle's intrinsic factor, supports the secretion of hormones such as ghrelin, and sustains optimal motor activity [21–23]. Although oncological considerations may permit the option of PG, it is crucial to acknowledge potential challenges associated with a residual stomach that may be insufficient to maintain optimal functionality. Issues such as reflux esophagitis and other complications could reduce the overall quality of life of the patient. According to the Postgastrectomy Syndrome Assessment Scale study, PG is superior to TG in terms of body weight loss, the need for additional meals, diarrhea, and dumping syndrome [5]. However, it should be noted that the Postgastrectomy Syndrome Assessment Scale study exclusively involved patients with pathological Stage IA/IB, where the preservation rate of the celiac and pyloric branch of the vagal nerve is relatively high, and the remaining stomach is considered adequately large. Therefore, in cases of advanced gastric cancer, where nerve-sparing rates are anticipated to be substantially low, and the residual stomach may be small owing to PG, it is imperative to perform a comprehensive assessment of the quality of life.

Conclusions

For locally advanced gastric cancer in the upper third of the stomach, PG with D2 lymph node dissection may be considered acceptable. However, the indications of localization of the lesser curvature and tumors >40 mm in diameter for PG with D2 lymph node dissection should be considered cautiously.

CRedit authorship contribution statement

Yoshiro Imai: Data curation, Investigation, Project administration, Visualization, Writing – original draft, Writing – review & editing, Methodology, Validation. **Ryo Tanaka:** Writing – review & editing. **Kentaro Matsuo:** Writing – review & editing. **Mitsuhiro Asakuma:** Writing – review & editing. **Sang-Woong Lee:** Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval statement

The study protocol was approved by the Ethics Committee of Osaka Medical and Pharmaceutical University Hospital (approval number: 2020-005).

Informed consent statement

The Ethics Committee of Osaka Medical College and Pharmaceutical University Hospital waived the need for informed consent because of the retrospective nature of the study.

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