**ORIGINAL ARTICLE**

# Oncological safety of proximal gastrectomy for T2/T3 proximal gastric cancer

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## Abstract

**Background** It remains unclear whether total gastrectomy is necessary for patients with proximal T2/T3 gastric cancer. To explore the oncological safety of proximal gastrectomy for proximal T2/T3 gastric cancer, in this study, we evaluated the metastatic rates in and the therapeutic effect of dissection of key distal lymph node stations that are usually excluded in proximal gastrectomy.

**Methods** In this study, we examined 202 patients seen between January 2000 and December 2012, who underwent total gastrectomy with lymph node dissection (D1/D1+/D2; 2/17/183) and was pathologically diagnosed as T2/T3 gastric cancer exclusively located in the upper third of the stomach. The theoretical therapeutic necessity of dissecting lymph nodes at each lymph node station was evaluated based on the therapeutic index calculated by multiplying the frequency of metastasis at each station and the 5-year survival rate of patients with metastasis to that station.

**Results** The 5-year overall survival rate (95% confidence interval) was 72.9% (65.5–80.3). The metastatic rates at #4d and #12a were very low (0.99% and 0.006%, respectively), and those at #5 and #6 were zero, and therapeutic indices for #4d, #5, #6 and #12a were zero. On the other hand, the most frequent metastatic station was #3, followed by #1, #2 and #7 (overall metastatic rate > 12%), which was consistent with the order of the therapeutic indices.

**Conclusions** Considering the nodal stations that need to be dissected, proximal gastrectomy would be the choice and oncologically safe for patients with T2/T3 proximal gastric cancer.

**Keywords** Proximal gastrectomy · Proximal gastric cancer · Therapeutic effect

## Introduction

A recent global estimate has revealed that gastric cancer is the fifth most common cancer worldwide, with 951,600 new cases reported in 2012 [1]. Recently, in both Western and Asian countries, while the incidence of classical gastric cancer located in the antrum has been decreasing, the frequency of cancer in the upper third of the stomach has been increasing [2, 3]. When selecting surgery for proximal cancers, the survival benefit and quality of life must be considered. Total gastrectomy and proximal gastrectomy would be the surgical procedures of choice for proximal tumors. A recent multicenter study demonstrated that proximal gastric

cancer patients who received proximal gastrectomy had a better quality of life than those who underwent total gastrectomy [4]. Therefore, proximal gastrectomy would be recommended, provided its oncological safety is preserved.

Several studies have reported equivalent overall survival between proximal gastrectomy and total gastrectomy for early proximal gastric cancer [5, 6]. However, the oncological safety of proximal gastrectomy for advanced disease remains unclear. According to the Japanese Gastric Cancer Guideline [7], the recommended surgery for proximal gastric cancer is total gastrectomy with D2 nodal dissection for advanced disease and proximal gastrectomy with D1 + dissection for early tumors. In selecting proximal or total gastrectomy, one of the key considerations for securing oncological safety is the frequency of nodal metastasis at and efficacy of dissection of #4d, #5, and #6, which are usually excluded in proximal gastrectomy. Most previous reports examined the nodal status and efficacy of dissection

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in all cases of advanced disease taken together and supported the necessity of total gastrectomy [8]. However, since the frequency of nodal metastasis differs entirely depending on the tumor depth (approximately 20% in T1, 40–50% in T2, 60% in T3, and 70% in T4 disease) [8], it remains unclear whether total gastrectomy is necessary for T2 or T3 tumors.

To explore the oncological safety of proximal gastrectomy for proximal T2/T3 gastric cancer, we evaluated the metastatic rates and therapeutic necessity of dissection of key distal lymph node stations in patients with proximal T2/T3 gastric cancer localized upper third of the stomach who had undergone total gastrectomy with lymph node dissection.

## Patients

We retrospectively reviewed the clinical records of 202 patients who had been diagnosed as pT2/pT3 gastric cancer only located at the upper third of the stomach and had undergone R0 total gastrectomy with lymph node dissection between January 2000 and December 2012 at the National Cancer Center Hospital of Japan. The patients were followed up until death or for 5 years, whichever came earlier. Patients with remnant gastric cancer, with postoperative confirmation of stage IV disease (#16 LN metastasis, positive cytology), with large type3 (> 80 mm) and type4, or who had received neoadjuvant chemotherapy or had multiple gastric cancer (more than 2 lesions) were excluded. Resected specimens were examined and evaluated according to the Japanese classification of gastric carcinoma (15th edition) [9].

### Surgical methods

Total gastrectomy with D1 (#1-#7), D1+ (D1 plus #8a, #9 and #11p), or D2 (D1 + plus #11d and #12a) lymph node dissection had been performed depending on the clinical stage according to the Japanese gastric cancer treatment guideline [7]. The surgery had been performed by experienced surgeons in all cases.

### Postoperative therapy and follow-up

Based on the results of the ACTS-GC trial in Japan [10], S-1 has been the standard postoperative chemotherapy regimen since 2007. Therefore, after 2007, postoperative adjuvant chemotherapy with S-1 was principally administered when the final tumor stage was consistent with the ACTS-GC criteria. Before 2007, S-1 was administered only for patients who participated in the ASCTS-GC and were allocated to the S-1 group. Outpatient follow-up involved physical examination and blood tests, including tumor marker evaluation, every 3 months for the first 2 years postoperatively. Chest and abdominal computed tomography were performed every 6 months for the first 3 years, and then annually until 5 years postoperatively.

## Clinical and pathological factors

The 8th edition of the Union for International Cancer Control tumor–node–metastasis classification of gastric carcinoma was used for the tumor staging [11]. We reviewed the following clinical and pathological factors: age, sex, splenectomy (yes/no), extent of lymph node dissection, tumor location, maximum tumor diameter, macroscopic type according to the Borrmann classification, histological type, pathological T factor, pathological N factor, pathological stage, and adjuvant chemotherapy (yes/no). The cross-sectional, circumferential location of each tumor was defined according to the Japanese Gastric Cancer Association (JGCA) classification [9], in which the stomach wall is divided into four equal parts. The JGCA classification of gastric cancer was used to evaluate the degree of tumor progression and the histological grade. The histopathological diagnosis was determined by experienced pathologists. The LN stations were numbered according to the JGCA classification of gastric carcinoma [9]. Table 1 shows the definition of each lymph node station.

## Therapeutic value of lymph node dissection

To evaluate the therapeutic value of dissection at each LN station, we used the therapeutic value index presented by Sasako et al. [8]. The therapeutic value index of nodal dissection (as a percentage) was obtained by multiplying the LN metastasis rate by the 5-year survival rate. The rate of LN metastasis was calculated by multiplying the number of patients with LN metastasis at each station by the number of those in whom that station was retrieved. The 5-year overall survival (OS) rate in patients with LN metastasis was calculated for each nodal station, regardless of LN metastasis at other stations. OS was defined as the period from the date of surgery to the date of death due to any cause. Data for patients who did not experience an event were censored on the date of final observation. Survival data were obtained from hospital records. The study was conducted with the approval of the Institutional Review Board of the National Cancer Center (No. 2017-077).

## Statistical analysis

All statistical analyses were performed using the SPSS statistical software (ver. 24; SPSS Inc., Chicago, IL, USA). The chi-squared test and Student's $t$-test were used for statistical analysis. Kaplan–Meier survival curves were constructed.

**Table 1** Lymph node station

| | |
|---|---|
| No. 1 | Right paracardial nodes |
| No. 2 | Left paracardial nodes |
| No. 3 | Lesser curvature nodes |
| No. 4sa | Left greater curvature nodes along the short gastric arteries |
| No. 4sb | Left greater curvature nodes along the left gastroepiploic artery |
| No. 4d | Right greater curvature nodes along the right gastroepiploic artery |
| No. 5 | Suprapyloric nodes |
| No. 6 | Infrapyloric nodes |
| No. 7 | Nodes at the root of the left gastric artery |
| No. 8a | Nodes along the common hepatic artery |
| No. 9 | Nodes at the celiac artery |
| No. 10 | Nodes around the splenic hilum |
| No. 11p | Nodes along the proximal splenic artery |
| No. 11d | Nodes along the distal splenic artery |
| No. 12a | Nodes along the proper hepatic artery |

# Results

## Background characteristics and histopathological findings of the patients

The flow diagram of the patients registered for this study is shown in Fig. 1. The number of patients who underwent gastrectomy with nodal dissection during the study period was 5957, of which 850 patients underwent total gastrectomy for tumor located on upper third area (esophagogastric junction cancer defined by Nishi's classification were not included); of the latter, 356 patients were diagnosed histopathologically as having T2 (MP) or T3 (SS) disease. Patients who were diagnosed as having large type 3 ($\geq 80$ mm) or type 4 tumors, had tumors invading the middle third of the stomach, had received neoadjuvant chemotherapy, had more than 2 lesions, fulfilled the criteria for Stage IV, or had undergone R1 or R2 resection were excluded; finally, a total of 202 patients fulfilled the eligibility criteria and were enrolled in this study.
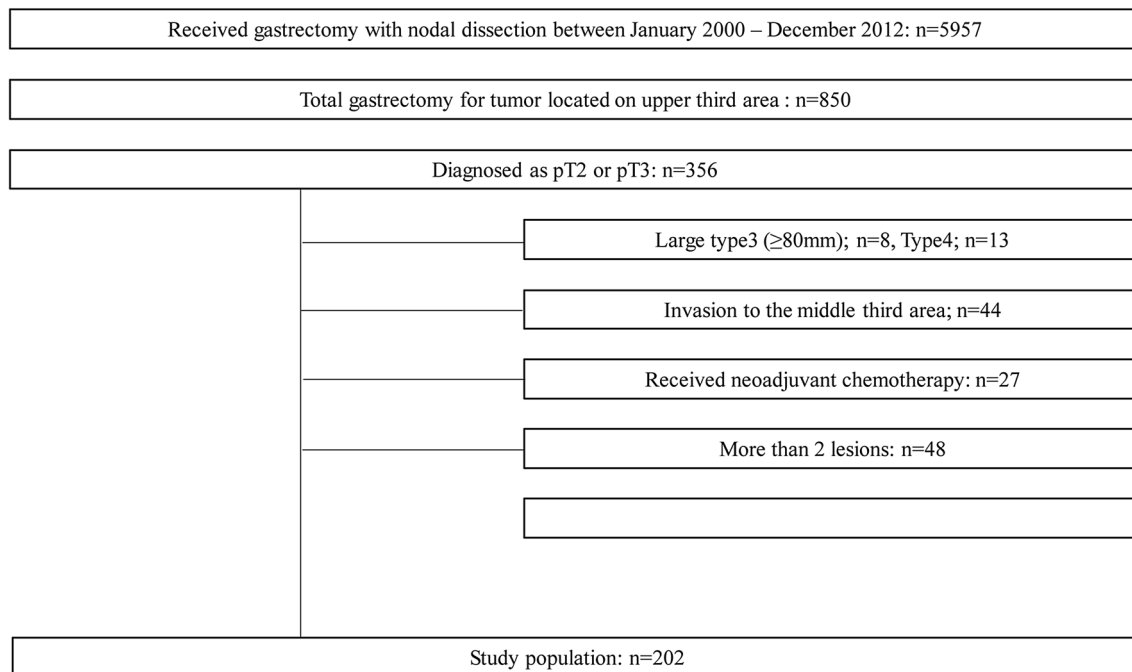


**Fig. 1** Study flow diagram of the 5957 patients who had undergone gastrectomy for gastric cancer between January 2000 and December 2012

Table 2 describes the background characteristics and histopathological findings of the patients. 90.6% of patients had received D2 dissection, and 36.6% had undergone splenectomy. Histologically, 58.4% had differentiated-type cancer and 38.6% had undifferentiated-type cancer. Four patients had endocrine carcinoma (ECC) and two patients had tumors with other histologies (squamous cell carcinoma in one, and carcinoma with lymphoid stroma in the other). Lymph node metastasis was observed in 56.4% of cases. The median follow-up period of the survivors exceeded 5 years (79.5 months), and the 5-year overall survival rate (95% confidence interval) was 72.9% (65.4–80.3).

## Calculated therapeutic value index for each nodal station

The metastatic rates, 5-year survival rates, and therapeutic indices are shown in Table 3. The metastatic rates at #4d (right greater curvature nodes along the right gastroepiploic artery) and #12a (nodes along the proper hepatic artery) were very low (0.99% and 0.006%, respectively), and the rate was zero at #5 (suprapyloric nodes) and #6 (infrapyloric nodes); thus, the therapeutic index was zero for #4d, #5, #6 and #12a. Two patients had #4d LN metastasis: one

**Table 2** Background characteristics and histopathological findings of the patients

|  | All patients $N = 202$ |
| --- | --- |
| Age (years, mean ± SD) | 65.3 ± 11.0 |
| Gender |  |
| Male/female | 161/41 |
| Splenectomy yes/no | 74/128 |
| Extent of lymph node dissection D1/D1+/D2 | 2/17/183 |
| Tumor location |  |
| Ant/gre/post/less/circ | 25/14/40/112/11 |
| Tumor diameter (mm) | 50.0 (14–150) |
| Macroscopic type |  |
| 0/I/II/III/V | 61/20/86/30/5 |
| Histological type |  |
| Differentiated/undifferentiated/ECC/others | 118/78/4/2 |
| UICC 8th/JGGC 15th |  |
| Pathological T factor |  |
| T2/T3 | 73/129 |
| Pathological N factor |  |
| N0/N1/N2/N3a/N3b | 88/46/44/20/4 |
| Pathological stage |  |
| IB/IIA/IIB/IIIA/IIIB/IIIC | 44/62/36/39/17/4 |
| Adjuvant chemotherapy yes/no | 45/157 |

*UICC* union for international cancer control, *JCGC* Japanese classification of gastric carcinoma

was diagnosed as having pT3N3a (#1, #4sb, #4d, #9, #11p) pStage IIIB disease, and the other as having pT3N2(#4sb, #4d, #10) pStage IIIA disease. The patients who had metastasis at #12a were diagnosed as having pT3N3a (#2, #4sa, #7, #10, #12a) pStage IIIB. These three patients had died within 5 years after surgery, therefore, the calculated therapeutic index was zero for #4d and #12a. On the other hand, the most frequently involved metastatic station was #3 (lesser curvature nodes), followed by #1 (right paracardial nodes), #2 (left paracardial nodes), and #7 (nodes at the root of the left gastric artery); the metastatic rates at all of these stations were > 12%. The node station with the highest therapeutic index was #3, followed by #1, #2, and #7 (therapeutic index > 6).

## Discussion

In the present study, we examined the therapeutic effect of dissection of key distal lymph node stations, that is, #4d, #5, #6, and #12a, in patients with T2/T3 proximal gastric cancer. The metastatic rate was zero in the key distal lymph node stations of #4d, #5, #6 and #12a (0/73) in patients with T2 disease, and very low (#4d, 1.55% (2/129); #12a, 0.88% (1/114)) or zero (#5, #6: 0/129) in patients with T3 disease. Patients who had lymph node metastasis at #4d or #12a died within 5 years after surgery, therefore, the calculated therapeutic index for #4d, #5, #6 and #12a in patients with T2/T3 proximal gastric cancer was zero. The therapeutic efficacy of dissection of these key distal lymph nodes was zero, suggesting that oncological safety would be ensured by proximal gastrectomy, without need for total gastrectomy. On the other hand, node stations with the high therapeutic indices were located close to the primary tumor and were those that are included in proximal gastrectomy.

These results are consistent with those reported from several previous studies [8, 12, 13]. Sasako et al. [8] reported that the therapeutic indices for #5 and #6 were very low in patients with tumors mainly located in the upper third of the stomach (#5, 0.0; #6, 0.4; $n = 287$) as compared to those with tumors in the middle third (#5, 0.8; #6, 3.9; $n = 385$) or lower third (#5, 3.9; #6, 21.3: $n = 457$) of the stomach. However, the indices were calculated for T2–T4 cancers, so that the validity of the results for T2/T3 tumors alone was still unclear. Ooki et al. [12] reported the incidences of metastases at individual lymph node stations. Patients with T2 proximal gastric cancer ($n = 27$) had no nodal metastasis at #4d, #5 or #6, and they concluded that patients with tumors not more advanced than T2 qualified for proximal gastrectomy. Patients with T3 proximal gastric cancer ($n = 82$) disease had low rates of metastasis at #4d (3.7%), #5 (2.4%) and #6 (0%), and the 5-year disease-specific survival (DSS) rate in patients with LN metastasis at these stations (#4d, #5

**Table 3** Details of metastatic rate, overall survival (OS), and therapeutic value index with regional lymph nodes

| Station no. | Metastatic rate (%) | | | 5-year OS (%) with nodal metastasis patients | | | Therapeutic index | | |
|---|---|---|---|---|---|---|---|---|---|
| | T2 | T3 | Total | T2 | T3 | Total | T2 | T3 | Total |
| 1 | 12.3 (9/73) | 31.7 (41/129) | 24.8 (50/202) | 88.9 | 55.1 | 61.1 | 10.9 | 17.5 | 15.2 |
| 2 | 5.48 (4/73) | 17.8 (23/129) | 13.4 (27/202) | 100 | 60.3 | 65.8 | 5.48 | 10.7 | 8.82 |
| 3 | 19.2 (14/73) | 37.9 (49/129) | 31.2 (63/202) | 85.7 | 54.3 | 61.2 | 16.5 | 20.6 | 19.1 |
| 4sa | 5.48 (4/73) | 2.33 (3/129) | 3.47 (7/202) | 66.7 | 66.7 | 62.5 | 3.66 | 1.55 | 2.17 |
| 4sb | 1.37 (1/73) | 1.55 (2/129) | 1.49 (3/202) | NA | 0.00 | 33.3 | NA | 0.00 | 0.50 |
| 4d | 0.00 (0/73) | 1.55 (2/129) | 0.99 (2/202) | – | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 5 | 0.00 (0/72) | 0.00 (0/129) | 0.00 (0/201) | – | – | – | 0.00 | 0.00 | 0.00 |
| 6 | 0.00 (0/73) | 0.00 (0/129) | 0.00 (0/202) | – | – | – | 0.00 | 0.00 | 0.00 |
| 7 | 8.22 (6/73) | 14.7 (19/129) | 12.4 (25/202) | 80.0 | 40.2 | 49.5 | 6.58 | 5.91 | 6.14 |
| 8a | 0.00 (0/71) | 3.15 (4/127) | 2.02 (4/198) | – | 50.0 | 50.0 | 0.00 | 1.58 | 1.01 |
| 9 | 0.00 (0/72) | 9.52 (12/126) | 6.06 (12/198) | 0.00 | 46.9 | 46.9 | 0.00 | 4.46 | 2.84 |
| 10 | 2.44 (1/41) | 4.04 (4/99) | 3.57 (5/140) | NA | 25.0 | 40.0 | NA | 1.01 | 1.40 |
| 11p | 5.71 (4/70) | 8.80 (11/125) | 7.58 (15/195) | 100 | 40.9 | 57.8 | 5.71 | 3.60 | 4.38 |
| 11d | 1.59 (1/63) | 7.01 (8/114) | 4.92 (9/177) | NA | 45.0 | 51.9 | NA | 3.15 | 2.55 |
| 12a | 0.00 (0/48) | 0.88 (1/114) | 0.006 (1/162) | – | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |

and/or #6) was zero. However, the total number of patients diagnosed as having pT2 and pT3 disease was less than half of that in our study, which would make the results less reliable. Haruta et al. [13] surveyed 182 patients with proximal advanced (T2–T4) gastric cancer and reported that the metastatic rates at and therapeutic indices for these stations were very low: 3.3% and 0.6 for #4d, 0.5% and 0.6 for #5, 1.6% and 0.0 for #6, and 0.0% and 0.0 for #12a, respectively. In particular, the metastatic rates of #4d, #5, #6, and #12a were zero in patients with pT2 and pT3 disease. However, the authors did not provide a detailed breakdown of the cases which limited the reliability of the results.

Although similar results have been reported from previous studies examining cases of advanced proximal gastric cancer, the following factors (alone or in combination) were not excluded in these studies (large type 3 or type 4 gastric cancers, tumor invading the middle third area, patient administered neoadjuvant chemotherapy, presence of more than two lesions, presence of para-aortic LN metastasis, R1 resection) which could have introduced a bias for interpretation of the prognosis and determination of the metastasis rates at key distal lymph node stations. In the present study, therefore, we set stringent exclusion criteria. At first, we excluded large type 3 or type 4 cancers, because proximal gastrectomy is rarely applicable to such large tumors and it could lead to underestimation of the therapeutic index. Second, patients with remnant gastric cancer were also excluded, because the remnant nodal stations vary depending on the type of primary surgery. Third, we also excluded cases with postoperatively confirmed stage IV disease (LN metastasis in #16, positive cytology) because these subgroups have a poor prognosis and the efficacy of nodal dissection is limited. Fourth, the patients who had received neoadjuvant chemotherapy were also excluded, because

of the influence of chemotherapy nodal metastasis. Lastly, considering surgery to leave the lower half of the stomach, the target lesions were restricted to only those invading the upper third of the stomach. We believe that such stringent criteria are necessary when exploring the applicability of proximal gastrectomy. From this point of view, the results of the present study may be considered as being highly reliable.

Niihara et al. [14] reported sentinel lymph node (SLN) mapping in 385 patients with gastric cancer who fulfilled the inclusion criteria of clinical stage I, including patients with cT2N0 disease. Of the 61 patients who had tumors in the upper third of the stomach, SLNs were found along the left gastric artery (#1, #3 and #7) in many cases, with few or no SLNs found in the distal-half regional node stations (#4d #5, and #6). In cases of proximal gastric cancer, the left gastric artery (LGA; #1, #3, and #7) serves as the predominant route for lymphatic drainage. The right gastric artery (RGA; #5, #8a, and #12a) and right gastroepiploic artery (RGEA; #4d, #6) rarely serve as lymphatic drainage routes. However, the RGA and RGEA may function as key drainage routes in cases where proximal gastric cancer invades the distal part of the stomach, beyond the middle third of the stomach. The RGA and RGEA lymphatic routes possibly represent distant-regional routes for lymphatic drainage from proximal gastric cancer limited to the upper third of the stomach. This may explain why patients with metastasis to these lymph nodes showed a poor prognosis in our study.

There were several limitations to the present study that should be considered when interpreting the results. The first is related to potential selection bias in the cohort, due to the retrospective and single-center nature of the study. Because our hospital is a national high-volume cancer center, patients with severe comorbidities were not entered in this study. This could have resulted in some overestimation of the prognosis and therapeutic index. Moreover, we excluded subgroups with a poor prognosis. Thus, there is only a limited possibility of a decreased reliability of the results of the study. Second, there was some variation in the administration of chemotherapy, as some patients did not receive optimal chemotherapy. Actually, the patients who had lymph node metastasis at #4d or #12a did not receive adjuvant chemotherapy in the present study. Effective chemotherapy would be expected to increase the 5-year survival and therapeutic index. Of 114 patients for whom adjuvant chemotherapy is indicated in the present cohort, 42 patients (36.8%) received S-1 postoperatively but 72 patients (63.2%) did not. 5-yr overall survival rate was 68.7% in the former and was 59.9% in the latter. Although this difference did not reach statistical significance ($p = 0.502$), the patients who received S-1 tended to have better survival. Thus, the results could have been different between cohorts that did/did not receive effective adjuvant chemotherapy. Third, we selected patient for the analyses based on pathologic T categories

because data on clinical T stage were not available for all patients. Since a surgical procedure is selected based on clinical T stage and some discrepancies between the clinical and pathological T stages are unavoidable, future prospective analysis in a cohort of patients with clinical T2/T3 cancer could provide more reliable data to expand the indication for proximal gastrectomy. Fourth, proximal gastrectomy is not uniformly applicable for all tumors located at the upper third of the stomach. Remnant stomach could be very small depending on the tumor size or longitudinal invasion. For such cases, benefit of QOL would be limited. Physicians must select proximal gastrectomy not only by oncological safety but by considering the residual size of the stomach.

In conclusion, the therapeutic index for #4d, #5, #6, and #12a was zero in patients with T2/T3 proximal gastric cancer, which suggested that proximal gastrectomy could be the choice and oncologically safe in patients with T2/T3 proximal gastric cancer.

## Compliance with ethical standards

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