Metastatic patterns and surgical methods for lymph nodes No. 5 and No. 6 in proximal gastric cancer

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Abstract

Objective: The current surgical treatment guidelines for early proximal gastric cancer (PGC) still lack agreement. Lymphadenectomy of lymph nodes No. 5 and No. 6 is the major difference between total and proximal gastrectomy. We elucidated the appropriate surgical procedure for PGC by investigating the pathological characteristics and prognostic significance of lymph nodes No. 5 and No. 6.

Methods: In total, 333 PGC patients who underwent total gastrectomy were enrolled in this study. We investigated their clinicopathological characteristics and the metastatic patterns of the lymph nodes. Patients with metastasis in lymph nodes No. 5 and No. 6 were combined into one group and we compared the difference in survival between those with and without metastasis in lymph nodes No. 5, 6 (lymph nodes No. 5 and No. 6 in any group of metastasis) for different subgroups.

Results: The metastatic rates for lymph nodes No. 5 and No. 6 in PGC were 9.91% and 16.11%, respectively. The metastatic rate for both lymph nodes No. 5, 6 was 20.42%. Multivariate analysis showed that positive metastasis in lymph node No. 4, depth of invasion, and tumor size were independently correlated with the presence of metastasis in lymph nodes No. 5, 6.

Conclusions: When lymph node No. 4 is positive (intraoperative pathology) or tumor size ≥5 cm or T4 stage, lymphadenectomy should be performed for lymph nodes No. 5 and No. 6, and total gastrectomy is recommended.

Keywords: Gastrectomy; lymph nodes No. 5 and No. 6; metastasis; prognosis; proximal gastric cancer

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Introduction

Gastric cancer is a common digestive system malignant tumor throughout the world, and it had the fifth highest incidence and the third mortality rate after lung cancer (1,2). Proximal gastric cancer (PGC) occurs in the upper third of the stomach and it accounts for about 23% of cases of gastric cancer, which is the second highest after distal gastric cancer. PGC is characterized by a large tumor size, strong invasive ability, high incidence of lymph node metastasis, and a poor prognosis (3). The incidence of PGC has increased significantly in China in recent years (4).

Radical surgery is still the most effective cure for PGC and the Japanese Gastric Carcinoma Association (JGCA) guidelines (14th edition) suggest that patients with PGC should accept D2 lymphadenectomy radical surgery, but the lymphadenectomy ranges are not the same because the surgical approach differs, and the choice of total gastrectomy or proximal gastrectomy is still controversial (5). D2 total gastrectomy includes lymph nodes No. 1−7, 8a, 9, 10, 11p and 12a, and thoracic surgeons advocate D1 + proximal gastrectomy, including lymph nodes No. 1, 2, 3a,
4sa, 4sb, 7, 8a, 9 and 11p. Lymph nodes No. 5 and No. 6 are defined as the third metastatic region, which indicates a low overall survival (OS) rate and poor prognosis (6). However, few studies have focused on the clinicopathological features and metastatic patterns of lymph nodes No. 5 and No. 6. Metastasis is frequently detected in lymph nodes No. 5 and No. 6 in advanced cancer patients, and some clinicopathological factors related to metastasis in lymph nodes No. 5 and No. 6 could be used as predictive factors.

Total gastrectomy with D2 lymphadenectomy is indicated in patients with advanced PGC as the standard treatment in the JGCA guidelines (14th edition). Some reports suggest that proximal gastrectomy can be performed radically and safely for early PGC, with survival rates equivalent to those of total gastrectomy while also preserving the physiological functions of the gastric remnant (7,8). Lymphadenectomy of lymph nodes No. 5 and No. 6 plays a key role in the decision regarding surgical treatment.

According to these considerations, we analyzed the pathological characteristics and prognostic significance of metastasis in lymph nodes No. 5 and No. 6 for PGC patients.

**Materials and methods**

**Patients**

In total, we enrolled 649 patients with PGC who underwent D2 total gastrectomy between January 1980 and December 2012 (follow-up to November 2015) at the Department of Surgical Oncology, the First Affiliated Hospital of China Medical University. The enrolled patients comprised 258 males and 75 females who were aged from 26 to 83 years, with a median age of 57 years. Lymph nodes were divided into groups for pathological examination, and the site and number of metastatic lymph nodes was recorded after operation in the pathology report.

All the patients underwent a standard follow-up procedure by means of outpatient clinic consultation, and/or communication with patients through telephone or letter, once every 3 months for the first 3 years and then every 6 months thereafter. Follow-up of the entire study population was conducted until death or the cut-off date (November 30, 2015). Of these, four died in the postoperative period, 25 with non-R0 resection were excluded, and none received neoadjuvant therapy. At the time of the last follow-up, six were lost. These patients were also excluded in this study.

**Surgical approach**

D2 total gastrectomy includes lymphadenectomy of lymph nodes No. 1−7, 8a, 9, 10, 11p, and 12a, with Roux-en-Y reconstruction according to the gastric cancer protocol revised by the JGCA in 2013 (14th edition). Clinicopathological data were classified according to the 8th edition of the American Joint Committee on Cancer TNM staging system (2015).

The study was approved by the Research Ethics Committee of China Medical University (Shenyang, China). Written informed consent was obtained from all patients.

**Evaluation of clinical parameters**

We analyzed the risk factors for metastasis in lymph nodes No. 5 and No. 6 in PGC using univariate and multivariate analyses. OS was compared in the patients with and without metastasis in lymph nodes No. 5 and No. 6. Tumor size and T stage subgroups were analyzed separately.

The specificity, sensitivity, accuracy, positive predictive rate and negative predictive rate for metastasis in lymph node No. 4 when predicting metastasis in lymph nodes No. 5, 6 were analyzed by χ² analysis.

**Statistical analysis**

OS was determined by Kaplan-Meier survival analysis. Statistical differences in the survival curves were estimated using the log-rank test. Relevant factors that affected the prognosis were analyzed with the log-rank test. Two-tailed χ²-tests were used for statistical comparisons in the univariate analysis. Logistic regression analysis was performed to identify independent factors correlated with metastasis in lymph nodes No. 5 and No. 6 by multivariate analysis. P<0.05 was considered statistically significant.

All of the statistical analysis and graphical plots were performed using IBM SPSS Statistics (Version 21.0; IBM Corp., New York, USA).

**Results**

**Patient characteristics**

This study included 333 PGC patients who underwent total gastrectomy, where 33 (9.91%) patients were positive
in No. 5 lymph nodes, 51 (16.11%) patients were positive in No. 6 lymph nodes, with an overlap for 16 patients who had metastasis in both lymph nodes No. 5 and No. 6, and 68 (20.42%) patients were positive in lymph nodes No. 5, 6 (lymph nodes No. 5 and No. 6 in any group of metastasis). Our data showed that the clinicopathological factors comprising tumor size and depth of invasion were risk factors for metastasis in lymph nodes No. 5 and No. 6 according to univariate analysis (Table 1).

**Lymph node metastatic discipline**

The rates of metastasis in the lymph node groups in advanced PGC ranged from high to low in the lymph node

| Variables          | No. 5, 6 (+) (N=68) | No. 5, 6 (−) (N=265) | P     |
|--------------------|---------------------|----------------------|-------|
| Sex                |                     |                      | 0.451 |
| Male               | 55                  | 203                  |       |
| Female             | 13                  | 62                   |       |
| Age (year)         |                     |                      | 0.387 |
| <40                | 4                   | 10                   |       |
| 40–60              | 28                  | 139                  |       |
| >60                | 36                  | 116                  |       |
| Borrmann           |                     |                      | 0.529 |
| 0                  | 4                   | 18                   |       |
| 1–2                | 12                  | 33                   |       |
| 3–4                | 52                  | 214                  |       |
| Tumor size (cm)    |                     |                      | 0.002 |
| <5                 | 12                  | 94                   |       |
| ≥5                 | 56                  | 171                  |       |
| Differentiation    |                     |                      | 0.108 |
| Undifferentiated   | 48                  | 159                  |       |
| Differentiated     | 20                  | 106                  |       |
| Lauren             |                     |                      | 0.891 |
| Intestinal         | 39                  | 152                  |       |
| Diffuse            | 29                  | 113                  |       |
| T                  |                     |                      | <0.001|
| T1                 | 0                   | 22                   |       |
| T2                 | 0                   | 25                   |       |
| T3                 | 18                  | 101                  |       |
| T4a                | 39                  | 102                  |       |
| T4b                | 11                  | 15                   |       |

Table 1 Clinicopathological characteristics of PCG patients who underwent D2 total gastrectomy according to No. 5, 6 lymph nodes status

PCG, proximal gastric cancer.

No. 3, No. 1, No. 2, No. 7, No. 4, No. 8a, No. 10, No. 11, No. 6, and No. 5 groups. Univariate analysis and further multivariate analysis showed that No. 4, No. 8a and No. 11 was an independent predict factor for No. 5, 6 lymph nodes as shown in Table 2. Logistic regression analysis showed that lymph node No. 4, tumor size and T stage were independent risk factors for metastasis in lymph nodes No. 5, 6 (Table 3).

**Survival analysis**

PGC patients who underwent total gastrectomy had a long-term survival rate of 42% and a median survival time of 42 months.

Patients with metastasis in lymph node No. 4 as well as metastasis in lymph nodes No. 5, 6 had an the 5-year OS of 31.7%, which was lower than that in the patients without metastasis in lymph nodes No. 5, 6 (36.7%). Though the difference between the two groups was not statistically significant (P=0.192). When lymph node No. 4 was negative, there was no significant difference between the patients with and without metastasis in lymph nodes No. 5, 6. The survival curves are shown in Figure 1.

Subgroup analysis of tumor size identified a significant difference in survival between patients with and without metastasis in lymph nodes No. 5, 6 when the tumor size was ≥5 cm (43.7% vs. 57.6%, P=0.041), but not in those with a tumor size <5 cm (58.3% vs. 59.8%, P=0.867) (Figure 2).

In the T1–T3 stage, there was no significant difference between the 5-year survival rate of patients with and without metastasis in lymph nodes No. 5, 6 (48.7% vs. 49.3%, P=0.755). In the T4 stage, the OS of patients without positive results for lymph nodes No. 5, 6 was 35.7%, which was significantly higher than that for those with negative results for lymph nodes No. 5, 6 (20.4%, P=0.036) (Figure 3).

Metastasis in lymph node No. 4 was a better significant predictor based on intraoperative pathological examination, with a sensitivity of 81.25% and specificity of 85.44%, compared with that of tumor size and T stage (Table 4).

**Discussion**

PGC is characterized by a large tumor size, deep invasion, high malignancy, and low differentiation. The prognosis is worse than that for other forms of gastric cancer. The current guidelines for PGC comprise lymphadenectomy of the gastric cancer located in the upper third of the stomach,
but the recommendations for the distal second station lymph nodes No. 5 and No. 6 are not clearly stated. Thus, there is some controversy regarding the surgical procedures for proximal gastrectomy or total gastrectomy for PGC (9-11). We combined metastasis in lymph nodes No. 5 and No. 6 in the analysis performed in this study.

Previous studies determined the metastatic rate for distal lymph nodes in advanced PGC as 18.7% (12). In the present study, we found that the metastatic rates in lymph

| Variables | Univariate | Multivariate |
|-----------|------------|--------------|
| No. 1     |            |              |
| +         | 35         | 112          |
| –         | 33         | 153          |
| No. 2     |            |              |
| +         | 27         | 87           |
| –         | 41         | 178          |
| No. 3     |            |              |
| +         | 34         | 99           |
| –         | 34         | 166          |
| No. 4     |            |              |
| +         | 41         | 56           |
| –         | 27         | 209          |
| No. 7     |            |              |
| +         | 46         | 148          |
| –         | 22         | 117          |
| No. 8a    |            |              |
| +         | 37         | 59           |
| –         | 31         | 206          |
| No. 9     |            |              |
| +         | 22         | 68           |
| –         | 46         | 197          |
| No. 10    |            |              |
| +         | 20         | 58           |
| –         | 48         | 207          |
| No. 11    |            |              |
| +         | 28         | 68           |
| –         | 40         | 197          |
| No. 12a   |            |              |
| +         | 20         | 71           |
| –         | 48         | 194          |

OR, odds ratio; 95% CI, 95% confidence interval.

Table 3 Multivariate analysis of factors predicting No. 5, 6 lymph node metastasis

| Variables | OR       | 95% CI     | P     |
|-----------|----------|------------|-------|
| No. 4     | 7.447    | 3.871–14.328 | <0.001 |
| No. 8a    | 2.227    | 1.008–4.921  | 0.048 |
| No. 11    | 1.333    | 1.025–1.734  | 0.032 |
| Tumor size| 11.368   | 6.051–20.552 | <0.001 |
| T stage   | 12.335   | 9.114–28.054 | <0.001 |

OR, odds ratio; 95% CI, 95% confidence interval.
nodes No. 5 and No. 6 for PGC patients who underwent total gastrectomy were 9.91% and 16.11%, respectively. The number of patients who were positive for lymph nodes No. 5 and No. 6 was 68, with a metastasis rate of 20.42%. This result is similar to those reported in previous studies, where the metastasis rate in lymph node No. 5 was 9.14%.

Figure 1 Comparison of survival curves between gastric cancer patients who underwent total gastrectomy with and without No. 5, 6 lymph node metastasis when No. 4 was positive (P=0.192) (A) and negative (P=0.881) (B).

Figure 2 Survival analysis of tumor size identified a significant difference in survival between patients with and without metastasis in lymph nodes No. 5, 6 when tumor size was ≥5 cm (P=0.041) (A) and tumor size <5 cm (P=0.867) (B).

Figure 3 Comparison of survival curves between gastric cancer patients in T1–T3 stage (A) and T4 stage (B) with and without No. 5, 6 lymph node metastasis.
and that in lymph node No. 6 was 10.06% (13).

Some previous studies have suggested that total gastrectomy should be performed in advanced proximal gastric carcinoma (14). We found that positive metastasis in lymph node No. 4, a tumor size $\geq$ 5 cm, and pT4 stage were independent risk factors for metastasis in lymph nodes No. 5 and No. 6. When lymph node No. 4 was positive, the positive rate was as high as 42.3% in lymph nodes No. 5 and No. 6. Therefore, if lymph node No. 4 is found to be enlarged during an operation, we suggest that intraoperative pathological examination should be confirmed and total gastrectomy is recommended with a positive result.

Many methods have been proposed for the preoperative prediction of lymph node metastases (15,16). However, clinicopathological characteristics such as the macroscopic type, size of tumor, or depth of invasion have mostly been used in these systems without considering the lymphatic flow and pattern of lymph node metastasis (17,18). No. 4 located at upstream of lymph node No. 10 and was proved to be an indicator for No. 10 (19). Similarly, we found that the metastatic status of lymph node No. 4 could be used as a predictor of metastasis in lymph nodes No. 5 and No. 6. We showed that the metastatic status of lymph node No. 4 has a significant advantage for making predictions of metastasis in lymph nodes No. 5, 6 with a sensitivity of 81.25% and specificity of 85.44%.

Some studies have shown that tumors with a diameter greater than 3 cm were associated with a lymph node metastatic rate of 19.2% (13,20), thereby suggesting that lymph node metastasis is associated with tumor size. For PGC patients with a tumor size $\geq$ 5 cm, we found that the metastatic rate was as high as 24.7% in lymph nodes No. 5, 6. These results suggest that a tumor diameter greater than 5 cm or deep infiltration of the PGC may indicate metastasis distal to lymph nodes No. 5, 6. When the tumor size was less than 5 cm, the positive rate was only 11.3% in lymph nodes No. 5, 6. For patients with gastric cancers at pT1–T2, no cases were observed with metastasis in lymph nodes No. 5, 6. For patients at pT1–T3, the positive rate for lymph nodes No. 5, 6 was 15.1%, and that at pT4 was 29.9%.

Table 4 Efficacy of No. 4 lymph node compared with tumor size and T stage in predicting No. 5, 6 lymph node metastasis

| Variables | No. 4 (+) | Tumor size | T stage |
|-----------|-----------|------------|---------|
|           | Sensitivity | Specificity | Accuracy | PPV | NPV |
| % | 95% CI | % | 95% CI | % | 95% CI |
| Sensitivity | 81.25 | 75.32–87.33 | 70.00 | 62.36–77.98 | 83.75 | 77.52–89.36 |
| Specificity | 85.44 | 79.66–91.23 | 36.36 | 24.57–48.31 | 21.89 | 6.58–37.14 |
| Accuracy | 89.70 | 83.51–95.47 | 43.07 | 33.15–53.65 | 58.06 | 45.22–71.56 |
| PPV | 75.58 | 68.22–82.21 | 56.81 | 46.57–66.33 | 19.14 | 14.71–34.66 |
| NPV | 94.73 | 89.41–99.38 | 87.69 | 80.46–94.33 | 5.78 | 0.33–16.39 |

PPV, positive predictive value; NPV, negative predictive value; 95% CI, 95% confidence interval.

Conclusions

The results obtained in this study indicated that the incidence of metastasis in lymph nodes No. 5, 6 increased with metastasis in lymph node No. 4, tumor size, and pT stage, and most importantly, patients who were positive for metastasis in lymph node No. 4 had a high risk of distant lymph node metastasis. These associations with lymph node metastasis may help surgeons to determine the most appropriate surgical approach and strategy for patients with PGC in different stages.

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Footnote

Conflicts of Interest: The authors have no conflicts of interests to declare.

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