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ORIGINAL ARTICLE

Key nodal stations for predicting splenic hilar nodal metastasis in upper advanced gastric cancer without invasion of the greater curvature

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Abstract

Background: Standard surgery for upper advanced gastric cancer without invasion of the greater curvature (UGC-GC) is spleen-preserving D2 total gastrectomy without dissection of the splenic-hilar nodes (#10). However, some patients with nodal metastasis to #10 survive more than 5 years due to nodal dissection of #10. If nodal metastasis to #10 is predictable based on the positivity of other nodes dissected by the current standard surgery without #10 nodal dissection, physicians may be able to consider #10 dissection.

Methods: This study retrospectively reviewed data from the National Cancer Center Hospital in Japan between 2000 and 2012. We selected cases that met the following criteria: (1) D2 or more total gastrectomy with splenectomy, (2) UGC-GC, and (3) histological type is gastric adenocarcinoma. We performed univariate and multivariate analyses concerning lymph node stations associated with #10 metastasis.

Results: A total of 366 patients were examined. A multivariate analysis revealed that #10 metastasis was associated with positivity of the nodes along the short gastric arteries (#4sa) and distal nodes along the splenic artery (#11d) (#4sa: $p = 0.003$, #11d: $p = 0.016$). When either key node was positive, the metastatic rate of #10 was 24.4%, and the therapeutic value index was 13.3.

Conclusions: #4sa and #11d were key lymph nodes predicting #10 nodal metastasis in UGC-GC. When these key nodes are positive on computed tomography before surgery or according to a rapid pathological examination during surgery, dissection of #10 should be considered even if upper advanced tumors are not invading the greater curvature.

KEYWORDS
rapid pathological examination, splenic hilar nodal dissection, total gastrectomy with splenectomy, upper advanced gastric cancer without invasion of the greater curvature

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1 | INTRODUCTION

Gastric cancer remains one of the most common cancers worldwide.[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] The standard surgical treatment for upper advanced gastric cancer when the tumor does not invade the greater curvature (UGC-GC) is spleen-preserving D2 total gastrectomy without dissection of splenic-hilar nodes, which was established by the JCOG0110 phase III trial from our country.[4] The splenic-hilar nodes are defined as the #10 lymph node (LN) station (#10) according to the Japanese Gastric Cancer Classification (15th edition).[5]

Although JCOG0110 demonstrated non-inferiority of spleen-preserving surgery for the overall survival and an extremely low incidence of metastasis to #10 (2.4%),[4] there are some patients who have nodal metastasis to #10 and survive for more than 5 years with nodal dissection of #10 by splenectomy. Therefore, if nodal metastasis to #10 is predictable based on the positivity of other nodes dissected by the current standard surgery without #10 nodal dissection by splenectomy, physicians may be better able to consider #10 dissection.

In our previous study, we revealed that a posterior location and undifferentiated-type histology were independent risk factors for #10 metastasis in cases of upper advanced gastric cancer without invasion of the greater curvature.[6] However, even in the previous group with an extremely high risk of metastasis to #10 (tumors located in the posterior wall and an undifferentiated histology), the incidence of #10 metastasis was only 14.9%, which is not sufficiently high to select #10 nodal dissection by splenectomy, as splenectomy carries a high risk of surgical morbidity and mortality. A more efficient mode of selection for predicting #10 metastasis is necessary.

Another approach may be to identify key LNs related to #10 metastasis. The present study therefore explored the key nodal stations related to #10 metastasis and assessed the efficacy of #10 nodal dissection by splenectomy for select cases in UGC-GC.

2 | METHODS

2.1 | Patients

We retrospectively reviewed the clinical records of patients who were diagnosed with primary gastric cancer and underwent total gastrectomy with splenectomy between January 2000 and December 2012 at the National Cancer Center Hospital in Japan. This study excluded patients who had been diagnosed with pathological T0 or T1, those for whom the main lesion was in the middle-lower or whole body, patients who received R1 or R2 resection, those with invasion of the greater curvature line, and those who were not diagnosed with adenocarcinoma.

Resected specimens were evaluated in line with the Japanese Classification of Gastric Carcinoma (15th edition).[5]

2.2 | Surgical methods

Open total gastrectomy with D2 (#1-12a) LN dissection, including #10 lymphadenectomy by splenectomy, was performed following the Japanese gastric cancer treatment guidelines of each era.[7–10] The indication of total gastrectomy for upper advanced gastric cancer has not been changed since 2000. The surgery was performed by experienced surgeons in all cases.

2.3 | Postoperative therapy and follow-up

Based on the results of the ACTS-GC trial in Japan,[11] S-1 has been the standard postoperative chemotherapy regimen since 2007. 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 a physical examination and blood tests, including a tumor marker evaluation, every 3 months for the first 2 years after operation. Chest and abdominal computed tomography (CT) were performed every 6 months for the first 3 years and then annually until 5 years after the operation.

2.4 | Clinical and pathological factors

The 8th edition of the Union for International Cancer Control tumor–node–metastasis classification of gastric carcinoma was used for tumor staging.[12] We reviewed the following clinical and pathological factors: age, sex, extent of LN dissection, tumor location, maximum tumor diameter, macroscopic type, histological type, pathological T factor, pathological N factor, pathological stage. The cross-sectional, circumferential location of each tumor was defined according to the Japanese Gastric Cancer Association (JGCA) classification.[5] We defined the deepest part of the tumor as the dominant area of invasion. The JGCA classification of gastric cancer was used to evaluate the tumor progression and histology. The histopathological diagnosis was determined by experienced pathologists. The LN stations were numbered according to the JGCA classification of gastric carcinoma.[5]

2.5 | Therapeutic value of each LN

To evaluate the therapeutic value at each LN station, we used the therapeutic index presented by Sasako et al.[13] The therapeutic index of nodal dissection (as a percentage) was obtained by multiplying the LN metastasis rate by the 5-year survival rate. The overall survival

(OS) was defined as the period from the date of surgery to the date of death from any cause or the date of the last follow-up examination. Data for patients who did not experience an event were censored on the date of final observation. Survival data were obtained from the hospital records.

The study was conducted with the approval of the Institutional Review Board of the National Cancer Center (No. 2017–077).

2.6 | Statistical analyses

All statistical analyses were performed using the SPSS software program (ver. 28; SPSS Inc.). The chi-squared test was used for the statistical analyses. The risk factors for #10 metastasis were examined by a logistic regression analysis. *p* values of <0.05 were considered statistically significant.

3 | RESULTS

3.1 | Background characteristics and histopathological findings of the patients

The patient flow diagram registered for this study is shown in Figure 1. Among the 876 patients who underwent total gastrectomy and splenectomy, 366 met the inclusion criteria and were enrolled in this study. Metastasis to #10 was observed in 16 patients (4.4%). Table 1 shows the background characteristics of the patients.

Table 2 describes the incidence of #10 metastasis by each nodal station in a univariate logistic regression analysis. Nodal stations #1, #2, #4sa, #4sb, #4d, #7, #11p, and #11d were significantly related to #10 positivity.

3.2 | Incidence of #10 metastasis by LN station

Among the variables shown in Table 2 and 3, those with a *p* value of <0.1 (i.e. #1, #2, #3, #4sa, #4sb, #4d, #7, #11p, and #11d) were entered into a multivariate logistic regression analysis. #4sa and #11d remained significant stations independently predicting #10 nodal positivity in UGC-GC.

3.3 | Incidence, 5-year OS rate, and therapeutic value index of #10 stratified by key nodal stations

Based on the key nodal stations identified, the risk of #10 metastasis was separated into four groups (Table 4). When these LNs were negative, the metastatic rate and index of #10 were both very low. When either #4sa or #11d was positive, the metastatic rate of #10 was 17.6%–19%, and the therapeutic index was 9.52–11.8. When both nodes were positive, the metastatic rate and index were both very high. When either or both #4sa or #11d were positive, the metastatic rate of #10 was 24.4%, and the therapeutic value index was 13.3.

4 | DISCUSSION

In the present study, we examined the incidence of #10 metastasis by each nodal station to identify the key nodal stations

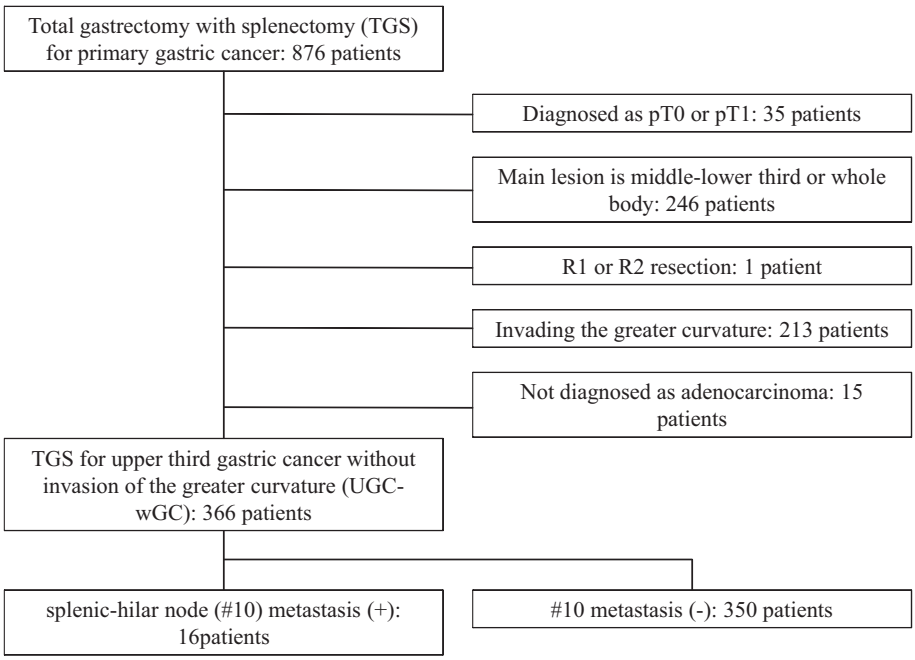

FIGURE 1 Patient flow diagram (from January 2000 to December 2012).

TABLE 1 Background characteristics and histopathological findings of the patients.

Factor	Number of patients ($n = 366$)
Gender	
Male	281 (76.8%)
Female	85 (23.2%)
Age (years-old)	Mean: 63.2, SD: 10.5
Tumor size (mm)	Mean: 69.4, SD: 33.5 (2.5–230)
Macroscopic type	
Type 0	48 (13.1%)
Type 1	38 (10.4%)
Type 2	132 (36.1%)
Type 3	116 (31.7%)
Type 4	32 (8.7%)
Depth of invasion	
pT2	46 (12.6%)
pT3	184 (50.3%)
pT4	136 (37.2%)
Location	
Anterior	44 (12.0%)
Lesser curvature	237 (64.8%)
Posterior	85 (23.2%)
Pathological *N*	
pN0	91 (24.9%)
pN1	86 (23.5%)
pN2	90 (24.6%)
pN3	99 (27.0%)
Histological classification	
Papillary adenocarcinoma (pap)	20 (5.5%)
Tubular adenocarcinoma (tub)	157 (42.9%)
Well-differentiated (tub1)	68 (18.6%)
Moderately differentiated (tub2)	89 (24.3%)
Poorly differentiated (por)	174 (47.5%)
Solid type (por1)	57 (15.6%)
Non-solid type (por2)	117 (32.0%)
Signet-ring cell carcinoma (sig)	6 (1.6%)
Mucinous adenocarcinoma (muc)	9 (2.5%)

predicting #10 metastasis in UGC-GC. Our multivariate analysis revealed that #4sa and #11d were these key nodal stations, and the incidence of #10 metastasis was 24.4% when either #4sa or #11d were positive, providing a more accurate prediction than in the previous study. The therapeutic index of #10 was also clearly high in patients who had metastasis to either #4sa or #11d. We should thus consider total gastrectomy with #10 nodal dissection when these key nodal stations are diagnosed as positive by CT before surgery or by a rapid pathological examination during surgery.

One of the major findings in this study was that #4sa and #11d were the key nodal stations predicting #10 node positivity. Kunisaki et al. previously investigated the staining of regional LNs by injecting activated carbon particles (CH40) into the gastric subserosal layer during surgery to evaluate the lymphatic flow in gastric cancer in 78 patients scheduled for total gastrectomy.[14] Their study demonstrated that the main lymphatic flow from the upper third region drained from #4sa to #10 and then #11d, suggesting that LNs #4sa, #10, and #11d are related to each other. Kinami et al. also investigated the physiological lymphatic flow of gastric cancer by sentinel node biopsy in 416 patients and demonstrated that station #4sa has the potential to metastasize to #10 via left gastroepiploic artery.[15] Based on the above, our results are concordant with the lymphatic flow of gastric cancer.

In gastric cancer invading the greater curvature, #10 metastasis was reported to be relatively high at 13.4%–15.9%. In addition, the therapeutic index in each study was reportedly high at 4.02–7.1.[16–18] Based on these values, #10 nodal dissection is weakly recommended for tumors invading the greater curvature according to the Japanese Gastric Cancer Guideline in 2021.[7] Compared with the values reported for tumors invading the greater curvature, the metastatic rate and index in the present study were considered to very high, even though the patients were limited to those with tumors that had metastasized to either or both #4sa or #11d. Thus, #10 nodal dissection should be considered for select patients with tumors not invading the greater curvature.

Thanks to the spread of minimum invasive gastrectomy, the procedure of nodal dissection of #10 without splenectomy has been reported since 2010s. Huang et al. reported that there were few lymph nodes in the posterior splenic hilum by comparing two groups in a single-center, retrospective study; 336 cases in which the posterior splenic hilum was dissected and 68 cases in which the posterior hilum was not dissected. They also revealed that there was no difference in survival in these two groups.[19] Kinoshita et al. demonstrated the technique of splenic nodal dissection without splenectomy.[20] Their study revealed that splenic nodal dissection without splenectomy might be easy to perform by using the latest 3D computed tomography simulation. Based on the above, a prospective phase-II study (JCOG1809) is currently ongoing to investigate the safety and feasibility of this procedure in the JCOG Gastric Cancer Study Group in our country. Depending on the outcome of this clinical trial, #10 nodal dissection without splenectomy in minimum invasive surgery can be an option.

It is difficult to determine preoperatively whether or not #10 has metastasis. Accurate nodal metastasis of gastric cancer is difficult to diagnose by current sophisticated imaging studies, showing only 62.5% sensitivity and 65.7% specificity on multidetector-row CT.[21] However, these results were based on the following criteria: minor axis of ≥8 mm or major axis of ≥10 mm. High sensitivity can be obtained if the diameter is much bigger, although specificity would be low. Thus, if we can identify large LNs at #4sa and #11d on preoperative CT, the possibility of #10 positivity would

TABLE 2 Incidence of #10 metastasis by lymph nodal station (univariate logistic regression analysis).

Station No.		Metastasis		#10(−)350	#10(+)16	Positivity of#10 (OR)	*p* Value
#1	Right paracardial nodes	+	114	103	11	4.874	<0.001
		−	252	247	5		
#2	Left paracardial nodes	+	51	46	5	2.808	0.041
		−	315	304	11		
#3	Lesser curvature nodes	+	193	181	12	2.693	0.069
		−	173	169	4		
#4sa	Left greater curvature nodes along the short gastric artery	+	28	20	8	12.054	<0.001
		−	338	330			
#4sb	Left greater curvature nodes along the left gastroepiploic artery	+	26	21	5	5.935	<0.001
		−	340	329	11		
#4d	Right greater curvature nodes along the 2nd branch and distal part of the right gastroepiploic artery	+	54	47	7	4.501	<0.001
		−	312	303	9		
#5	Surprapyloric nodes	+	7	6	1	3.419	0.198
		−	359	344	15		
#6	Infrapyrolic nodes	+	21	21	0	Not available	0.315
		−	345	329	16		
#7	Nodes at the root of the left gastric artery	+	83	75	8	3.406	0.008
		−	283	275	8		
#8a	Nodes along the common hepatic artery	+	28	26	2	1.725	0.458
		−	338	324	14		
#9	Nodes at the celiac artery	+	31	29	2	1.543	0.556
		−	335	321	14		
#11p	Nodes along the proximal splenic artery	+	53	46	7	4.587	<0.001
		−	313	304	9		
#11d	Nodes along the distal splenic artery	+	24	17	7	11.091	<0.001
		−	342	333	9		
#12a	Nodes along the proper hepatic artery	+	26	24	2	1.866	0.392
		−	340	326	14		

TABLE 3 Incidence of #10 metastasis by lymph nodal station (multivariate logistic regression analysis).

	Multivariate		
Variable	Positivity of#10 (OR)	OR (95% CI)	*p* Value
#1	2.252	0.623–8.130	0.216
#2	1.006	0.241–4.202	0.993
#3	0.877	0.206–3.731	0.859
#4sa	8.264	2.016–34.483	0.003
#4sb	1.520	0.121–7.463	0.628
#4d	1.799	0.434–7.463	0.419
#7	1.497	0.422–5.319	0.532
#11p	2.392	0.608–9.434	0.212
#11d	5.025	1.350–18.519	0.016

be deemed high. To explore possibility of preoperative #10 nodal prediction, we examined CT images in 11 patients who had #10 nodal metastasis. Among 11 patients, CT images were available only in seven patients. Of these seven patients, five had clinical nodal metastasis to #4sa and/or #11d which was detected by preoperative CT (71.4%). Although we could not show the data in the remaining patients, these data highlight the possibility of #10 nodal prediction by preoperative CT. Because the present study uses old cohort by which most CT images were lost or were not sophisticated in terms of resolution and slice thickness, future study is necessary to confirm usefulness of preoperative CT using the latest condition. Positron emission tomography (PET) is also useful for such evaluations. Although a previous study revealed that its sensitivity for gastric cancer with diffuse-type histological appearance is low,[22] positive findings for #4sa and #11 on preoperative PET suggest metastasis to #10. Although the method of performing a rapid pathological examination during surgery is not standardized, Matsumoto et al. previously demonstrated the usefulness of rapid immunohistochemical detection of LN micro-metastases during surgery for upper advanced gastric cancer.[23] The significance of our present study will be further enhanced

TABLE 4 Incidence, 5-year survival rate, and therapeutic index of #10 stratified by key nodal stations.

4sa	11d	Number of patients	Incidence of #10 metastasis (%)	5-year survival rate of#10 metastasis (%)	Therapeutic index
No	No	321	1.56 (5/321)	60	0.935
Yes	No	21	19.0 (4/21)	50	9.524
No	Yes	17	17.6 (3/17)	66.7	11.77
Yes	Yes	7	57.1 (4/7)	50	28.57
Yes or yes		45	24.4 (11/45)	54.5	13.32

if methods of performing rapid pathological examinations during surgery are standardized in the future.

Several limitations associated with the present study warrant mention. The first limitation is the period of this cohort. The cohort of this study has older data, which was obtained from 2000 to 2012, because the results of JCOG 0110 was opened within the JCOG Gastric Cancer Study Group in 2014. Second limitation is related to the potential selection bias of the cohort due to the retrospective nature and single-center design of the study. Because our hospital is a national high-volume cancer center, patients with severe comorbidities were not enrolled in this study. This may have resulted in some overestimation of the prognosis and the therapeutic index. Third, we used the pathologic T category, as data on the clinical T stage were not available for all patients. Since the surgical procedure is determined based on the clinical T stage, it would not be generalized to relatively shallow advanced tumors, which could be pathological T1. Fourth, some patients did not receive standard adjuvant chemotherapy. The results may differ in a cohort that received adjuvant chemotherapy. Although there were many changes in the chemotherapeutic strategies, with more effective adjuvant chemotherapy, each index would be further improved theoretically. We therefore believe that our conclusion will not be changed. Fifth, the therapeutic index is a theoretical value that ignores patient characteristics, tumor factors, and the completion of adjuvant treatment and assumes that the OS is proportional to the individual LN metastasis rate. The direct comparison between two groups with different backgrounds has been criticized.

In conclusion, the LN stations of #4sa and #11d were shown to be key for predicting #10 nodal metastasis in UGC-GC. When these key nodes are positive on computed tomography before surgery or according to a rapid pathological examination during surgery, dissection of #10 should be considered even if upper advanced tumors are not invading the greater curvature.

AUTHOR CONTRIBUTIONS

Masashi Nishino and Takaki Yoshikawa conducted the present study. Masashi Nishino wrote the first manuscript, and it was revised by Takaki Yoshikawa. All authors checked the final draft and approved it.

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None.

CONFLICT OF INTEREST STATEMENT

All authors have no financial conflicts of interest to disclose concerning the presentation.

ETHICS STATEMENTS

Approval of the research protocol: All procedures performed in studies involving human participants were in accordance with the approval of the Institutional Review Board of the National Cancer Center (No. 2017–077) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent: Informed consent was not obtained from individual participants included in this study; this study was conducted on an opt-out basis (No. 2017–077).

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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