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Has the Accuracy of Preoperative Diagnosis Improved in Cases of Early-stage Gastric Cancer?

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Abstract

Background Adequate preoperative evaluation for gastric cancer staging is essential to develop an individualized treatment strategy involving surgery with reduced lymphadenectomy and laparoscopic gastrectomy.

Methods A total of 509 gastric cancer patients with clinical Stage IA or IB disease were divided into two groups: 304 patients were admitted in 2000 or earlier (Group A), and 205 patients were admitted in 2001, when multidetector computed tomography (MD-CT) was available, or later (Group B). We evaluated the accuracy of the preoperative diagnoses of tumor depth, lymph node involvement, and tumor stage.

Results With respect to tumor depth, 94.5 and 52.8% of patients were staged correctly in cT1 and cT2 patients, respectively. Among both cT1 and cT2 patients, the underestimated rates were lower in Group B than in Group A. For nodal metastasis, 83.2 and 30.0% of patients were staged correctly in cN0 and cN1 patients, respectively. Among the cN0 patients, 82.1 and 84.7% of Group A and Group B patients, respectively, were staged correctly. Among the cN1 patients, none of the patients in Group B was underestimated, while 9.7% of Group A patients were underestimated. There was a significant increase in the percentage of correctly staged patients and a decrease in the percentage of underestimated patients in Group B in comparison to Group A in both cStage IA and cStage IB patients.

Conclusions Remarkable advances have been observed in the accuracy of preoperative staging in the early stage of gastric cancer. However, it is necessary to continue to develop accurate preoperative and intraoperative diagnostic systems.

Introduction

Total or subtotal radical gastrectomy with D2 lymphadenectomy has been widely utilized for cases of both early and advanced gastric cancer in order to improve mortality rates in Japan. Although curative resection for malignancies is essential for improving the survival rate, such surgical procedures can cause persistent functional disorders and reduce a patient's quality of life. In addition, the pathological analyses of resected specimens have revealed that lymph node involvement, especially metastasis to the second-tier lymph nodes, is rare in patients with early gastric cancer [1, 2]. Therefore, it is necessary to establish individualized treatment strategies for surgery and lymphadenectomy based on accurate preoperative or clinical staging [3].

Recently, customized surgery with reduced lymphadenectomy depending on the stage of disease has been recommended in the guidelines for treating gastric cancer by the Japanese Gastric Cancer Association [4], which maintained that the range of lymph node dissection should be determined based on clinical and surgical findings. In addition, these guidelines for gastric cancer treatment recommended that laparoscopic gastrectomy should be performed only in patients with Stage IA or IB disease as a clinical trial. Adequate preoperative evaluation for accurate gastric cancer staging is essential in order to perform such surgical procedures safely.

In the present study we evaluated the advances in the accuracy of preoperative evaluation of tumor depth, lymph

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node metastasis, and disease stage in patients with early gastric cancer.

Materials and methods

Patients

Five hundred nine patients with clinical Stage IA or IB disease underwent curative gastrectomy for primary gastric cancer at the National Defense Medical College Hospital from 1994 to 2007. To determine the evolution of the accuracy of preoperative diagnosis over time, we split the period of evaluation into two eras: Group A comprised 304 patients who were admitted in 2000 or earlier, and Group B comprised 205 patients who were admitted 2001 or later. Multidetector computed tomography (MD-CT) has been available in our institution since 2001. No patient underwent laparoscopic gastrectomy in these periods.

The clinical, pathological, and final findings of the patients were described according to the second English edition of the Japanese Classification of Gastric Carcinoma (JCGC), which was edited by the Japanese Gastric Cancer Association [5]. Clinical (c) findings were defined as any findings during diagnostic evaluation, including findings from preoperative computed tomography (CT) scans, gastrointestinal endoscopic examinations, abdominal ultrasonography (AUS), and upper gastrointestinal series that were evaluated by surgeons and/or radiologists. No patient underwent preoperative endoscopic ultrasound (EUS) in this study. The tumor depth was evaluated in all patients prior to surgery using findings from gastrointestinal endoscopic examinations and upper gastrointestinal series. Lymph node metastasis was evaluated by AUS and CT scan. Four MD-CT had been available since 2001 and 64 MD-CT has been available since 2004 at our institution; single-detector-row CT was used prior to 2001. Lymph nodes were considered metastatic if they were larger than 8 mm in short-axis diameter in our computer database [6, 7]. The lymph node station number was classified according to the JCGC [5]. Perigastric lymph nodes were generally classified as first-tier lymph nodes (N1), and station 7, 8a, 9, 11p, 11d, 12a, 14v lymph nodes (along the left gastric artery, common hepatic artery, celiac axis, proximal half of the splenic artery, distal half of the splenic artery, proper hepatic artery, and superior mesenteric vein at the lower border of the pancreas, respectively) were classified as second-tier lymph nodes (N2) depending on the tumor location. Station 10 lymph nodes, located at the hilum of the spleen, were also classified as N2 in the cases of gastric cancer in the upper third of the stomach. The final (f) findings were described based on the clinical, surgical, and pathological findings.

D2 lymph node dissection was defined as the complete removal of all second-tier lymph nodes. D1 lymph node dissection was defined as the removal of perigastric and station 7 or additional station 8a and/or station 9 lymph nodes according to the depth, size, and location of the tumor. D1 dissection is recommended as the standard treatment for early gastric cancer without obvious lymph node metastasis [4]. Incomplete D1 lymphadenectomy (D0) using sentinel lymph node navigation surgery was employed in patients with early gastric cancer who underwent a potentially curative resection [3, 8].

Statistical analysis

Data are expressed as the mean ± SD. Statistical analyses were performed using either the Mann-Whitney *U* test or the χ^2 test. Survival rates were obtained by the Kaplan-Meier method and the statistical significance was determined by the log-rank test. A $p < 0.05$ was considered statistically significant. All analyses were performed using the StatView version 5.0 software program (SAS Institute Inc., Cary, NC, USA).

Results

Demographic data of gastric patients with clinical Stage IA or IB disease (Table 1).

The mean age of Group B patients was older than that of Group A patients, but there was no significant difference in gender between the two groups. Patients in Group B had a greater mean tumor size (particularly the cT1 patients) and had a higher frequency of tumors located in the upper third of the stomach than patients in Group A. Furthermore, Group B patients underwent limited gastrectomy more often than Group A patients. Group B patients underwent D1 lymphadenectomy more frequently and D2 lymphadenectomy less frequently than Group A patients. There were no significant differences between the two groups in regard to the final findings of tumor depth, nodal involvement, gross tumor type, histology according to Lauren's classification, and degree of lymphatic and venous invasion. There was a significant difference in the distribution of clinical diagnoses in terms of tumor depth and nodal metastasis. Group A patients were diagnosed more frequently as cT1N1, while Group B patients were diagnosed more frequently as cT2N0 (Fig. 1). Although a difference in the distribution of the final stage of disease was observed, there was no significant difference in the 5-year estimated survival rate between the two groups.

Table 1 Demographic data of gastric patients with clinical Stage IA or IB disease

	Group A ($n = 304$)	Group B ($n = 205$)	p Value
Age (years)	60.6 ± 10.9	63.4 ± 10.5	<0.01
Male/Female	215/59	146/59	0.90
Tumor size (mm)			
cT1	27.2 ± 19.2	32.2 ± 22.7	<0.05
cT2	37.2 ± 20.5	37.5 ± 15.9	0.94
Total	29.2 ± 19.8	33.9 ± 20.8	<0.05
Tumor location			
Upper third	36 (11.9%)	49 (23.9%)	<0.01
Middle third	168 (55.3%)	85 (41.5%)	
Lower third	100 (32.9%)	71 (34.6%)	
Operative procedure			
Distal gastrectomy[a]	227 (74.7%)	118 (57.6%)	<0.01
Total gastrectomy	53 (17.4%)	34 (16.6%)	
Proximal gastrectomy	20 (6.6%)	23 (11.2%)	
Limited gastrectomy	4 (1.3%)	30 (14.6%)	
Extent of lymphadenectomy			
D0	13 (4.3%)	10 (4.9%)	<0.01
D1	107 (35.2%)	119 (58.0%)	
D2	184 (60.5%)	76 (37.1%)	
Tumor depth			
fT1	250 (82.2%)	163 (79.5%)	0.68
fT2	49 (16.1%)	37 (18.0%)	
fT3	5 (1.6%)	5 (2.4%)	
Nodal involvement			
fN0	248 (81.6%)	167 (81.5%)	0.53
fN1	49 (16.1%)	36 (17.6%)	
fN2	7 (2.3%)	2 (1.0%)	
Gross type			
Elevated	78 (25.7%)	71 (34.6%)	0.13
Depressed	194 (63.8%)	110 (53.9%)	
Flat	25 (8.2%)	18 (8.8%)	
Mixed	7 (2.3%)	6 (2.9%)	
Histology (Lauren's classification)			
Intestinal type	178 (58.6%)	121 (59.0%)	0.92
Diffuse type	126 (41.4%)	84 (41.0%)	
Lymphatic invasion			
ly0	163 (53.6%)	107 (52.2%)	0.63
ly1	99 (32.6%)	76 (37.1%)	
ly2	35 (11.5%)	18 (8.8%)	
ly3	7 (2.3%)	4 (2.0%)	
Venous invasion			
v0	237 (78.0%)	141 (68.8%)	0.07
v1	54 (17.8%)	47 (22.9%)	
v2	13 (4.3%)	16 (7.8%)	
v3	0 (0%)	1 (0.5%)	

Table 1 continued

	Group A ($n = 304$)	Group B ($n = 205$)	p Value
Clinical diagnosis			
cT1N0	213 (70.1%)	129 (62.9%)	<0.001
cT1N1	31 (10.2%)	9 (4.4%)	
cT2N0	60 (19.7%)	67 (32.7%)	
Final stage			
IA	225 (74.0%)	140 (68.6%)	0.04
IB	43 (14.1%)	48 (23.4%)	
II	29 (9.5%)	12 (5.9%)	
IIIA	7 (2.3%)	5 (2.5%)	
5-year survival rate	89.9%	88.7%	0.68

Data are expressed as the mean ± SD

[a] Includes a pylorus-preserving gastrectomy

Accuracy of clinical findings compared to the final findings

In regard to the depth of the tumor, 361 (94.5%) of 382 patients were staged correctly in cT1 patients, whereas 67 (52.8%) of 127 patients were staged correctly in cT2 patients (Table 2). Among the cT1 patients, 96.4% of Group B patients were staged correctly, while 93.4% of Group A patients were staged correctly. There was a statistically significant difference between the two groups in regard to the cT1 diagnostic accuracy. Among the cT2 patients, only 55.0 and 50.7% of patients in Group A and Group B, respectively, were staged correctly. However, in both the cT1 and cT2 patients, the underestimated rates were lower in Group B than in Group A.

In regard to the nodal metastasis, 390 (83.2%) of 469 patients were staged correctly in cN0 patients, whereas only 12 (30.0%) of 40 patients were staged correctly in cN1 patients (Table 3). Among the cN0 patients, 82.1 and 84.7% of Group A and Group B patients, respectively, were staged correctly. In contrast, 88.9% of Group B cN1 patients were staged correctly, whereas only 12.9% of Group A cN1 patients were staged correctly. Among the cN1 patients, none were underestimated in Group B, while 9.7% of Group A patients were underestimated. There was no difference in the underestimated rates in cN0 patients.

We evaluated the accuracy of the clinical stage in comparison to the final stage (Table 4). There was a significant increase in the percentage of correctly staged patients and a decrease in the percentage of underestimated patients in Group B in comparison to Group A patients in both cStage IA and cStage IB cases.

Thereafter, we evaluated the accuracy of preoperative clinical findings in comparison to the final findings

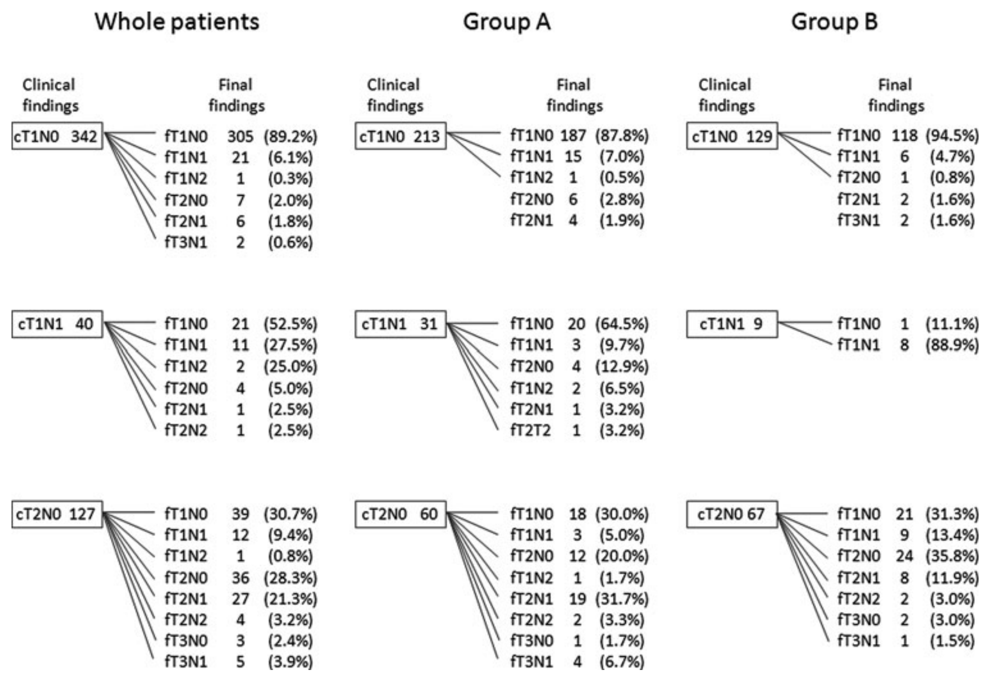

Fig. 1 Comparison of tumor depth and nodal involvement according to clinical and final findings

Table 2 Accuracy of diagnosis of tumor depth in the clinical findings compared to the final findings among Group A and Group B

	Group	fT1	fT2	fT3	fT4	Correctly diagnosed (%)	Underestimated (%)	Overestimated (%)	*p* Value*
cT1	A	228	16	0	0	93.4	6.6	N/A	0.03
	B	133	3	2	0	96.4	3.6	N/A	
	Total	361	19	2	0	94.5	5.5	N/A	
cT2	A	22	33	5	0	55.0	8.3	36.7	0.51
	B	30	34	3	0	50.7	4.5	44.8	
	Total	52	67	8	0	52.8	6.3	40.9	

N/A = not applicable

* Group A versus Group B

Table 3 Accuracy of diagnosis of lymph node metastasis in the clinical findings compared to that of the final findings among Group A and Group B

	Group	fN0	fN1	fN2	fN3	Correctly diagnosed (%)	Underestimated (%)	Overestimated (%)	*p* Value*
cN0	A	224	45	4	0	82.1	17.4	N/A	0.81
	B	166	28	2	0	84.7	15.3	N/A	
	Total	390	73	6	0	83.2	16.8	N/A	
cN1	A	24	4	3	0	12.9	9.7	77.4	<0.01
	B	1	8	0	0	88.9	0	11.1	
	Total	25	12	3	0	30.0	7.5	62.5	

N/A = not applicable

* Group A versus Group B

according to Lauren's histological classification (Table 5). We observed an improvement in the accuracy of diagnosis in both intestinal-type and diffuse-type tumors; however, there was a greater increase in the percentage of correctly diagnosed patients and a greater decrease in the percentage of underestimated patients with the intestinal type than with the diffuse type, especially in Group A.

Table 4 Accuracy of diagnosis of tumor stage in the clinical findings compared to that of the final findings among Group A and Group B

	Final stage								
	Group	IA	IB	II	IIIA	Correctly diagnosed (%)	Underestimated (%)	Overestimated (%)	*p* Value*
cStage IA	A	187	21	5	0	87.8	12.2	N/A	<0.01
	B	118	7	2	2	91.5	8.5	N/A	
	Total	305	28	7	2	89.2	10.8	N/A	
cStage IB	A	38	22	24	7	24.2	34.1	41.8	<0.01
	B	22	41	10	3	53.9	17.1	28.9	
	Total	60	63	34	10	37.7	26.3	35.9	

N/A = not applicable

* Group A versus Group B

Table 5 Accuracy of diagnoses in the clinical findings compared to that of the final findings according to the Lauren's histological classification

		Lauren' classification	Correctly diagnosed (%)	Underestimated (%)	Overestimated (%)	*p* Value*
cT1	Group A	Intestinal	96.0	4.0	N/A	<0.05
		Diffuse	89.4	10.6	N/A	
	Group B	Intestinal	97.7	2.3	N/A	0.18
		Diffuse	94.1	5.9	N/A	
cT2	Group A	Intestinal	60.7	3.6	35.7	0.42
		Diffuse	50.0	12.5	37.5	
	Group B	Intestinal	50.0	0	50.0	0.17
		Diffuse	51.5	9.1	39.4	
cN0	Group A	Intestinal	86.8	13.2	N/A	0.05
		Diffuse	75.4	24.6	N/A	
	Group B	Intestinal	88.8	11.2	N/A	0.16
		Diffuse	78.8	21.3	N/A	
cN1	Group A	Intestinal	5.3	0	94.7	0.01
		Diffuse	25.0	25.0	50.0	
	Group B	Intestinal	80.0	0	20.0	>0.99
		Diffuse	100.0	0	0	

N/A = not applicable

* Group A versus Group B

Discussion

We observed remarkable advances in the accuracy of clinical diagnosis of early gastric cancer, which should be especially due to the accurate diagnosis of patients with cN1 tumors. We also observed a significant decrease in the frequency of underestimation of tumor depth, lymph node metastasis, and tumor stage during the more recent time period.

The accuracy of preoperative diagnosis of early gastric cancer is reported to be 92.4–95.4% [9, 10]. These findings suggest that the remaining 4.6–7.6% of patients who were clinically diagnosed as early gastric cancer cases are actually advanced gastric cancer cases. These cases should undergo a standard gastrectomy with D2 lymph node dissection as a curative treatment according to the Japanese guidelines for gastric cancer [4].

CT, AUS, and EUS are widely used to evaluate the preoperative tumor depth and degree of nodal metastasis [6, 7, 10]. Yang et al. [7] evaluated the preoperative tumor depth in gastric cancer patients using 64 MD-CT and reported that the diagnostic accuracy was 88%. Although Yang et al. [7] demonstrated that the tumor was detected in 90% of early gastric cancer cases and 100% of advanced gastric cancer cases with multiplanar reformation (MPR), we did not observe the efficacy of preoperative CT in evaluating tumor depth in this study because early gastric cancer tumors were frequently missed by CT scan, especially single-detector-row CT.

Habermann et al. [6] compared the accuracy of preoperative staging of gastric cancer using helical single-detector-row CT and EUS. They concluded that EUS was superior to CT with respect to the evaluation of tumor depth and lymph node metastasis; however, their study did not include cases of early gastric cancer. Although EUS has been reported to be the one of the most useful modalities for obtaining an accurate preoperative diagnosis of tumor depth and nodal involvement [11–13], the EUS procedure is relatively complex and is not available in all hospitals in Japan. In fact, very few patients underwent EUS in our institution during the investigation periods, and thus we excluded those patients who underwent preoperative EUS from this study. Nevertheless, among the cT1 patients, Group B patients were staged more accurately than Group A patients; furthermore, the underestimated rates were lower in Group B than in Group A in both cT1 and cT2 patients.

One of the most important factors affecting the prognosis of patients with gastric cancer is lymph node involvement [14, 15]. Many previous studies employed CT and EUS to assess the degree of lymph node metastasis in gastric cancer cases [6, 7, 11, 16–19]. The size, location, and attenuation values of the lymph nodes are important factors for detecting their status [20]. However, there is a lack of reliable CT and EUS criteria for differentiating between benign and metastatic lymph nodes. To achieve higher sensitivity, many researchers, including the present authors, designated a short-axis diameter of 8 mm as the size criterion for metastatic lymph nodes. This designation provides higher sensitivity and lower specificity than 10 mm [16]. Yang et al. [7] reported that 64 MD-CT could predict lymph node metastasis in 80% of gastric cancer patients, which was superior to that obtained by single-detector-row CT and 4 MD-CT; moreover, the accuracies of predicting lymph node metastasis ranged from 58.6 to 75% with the older techniques [6, 16, 18]. Breathing artifacts, such as some vessels and nerves, may be regarded as positive lymph node metastasis in the older techniques (Fig. 2a, b). These findings support our current data demonstrating the recent advances in the sensitivity of diagnosis of lymph node metastasis because 64 MD-CT has been available only in recent years. However, we could not find any difference in detection rate and sensitivity of diagnosis of lymph node metastasis between 4 MD-CT and 64 MD-CT (data not shown).

Our findings revealed that 8.5 and 17.1% of underestimation occurred in cStage I and cStage II tumors, respectively, during the more recent time period of this study. Despite the significant advances in the diagnosis of N stage recently, we could not find any advance in the diagnosis of cT stage. Kwee and Kwee [21] reviewed the literature regarding the performance of EUS, MD-CT, and MRI. They revealed that the accuracy of MD-CT with respect to tumor depth was 77.1–88.9%, that of EUS was 65–92.1%, and that of MRI was 71.4–82.6%. Thus, the use of these modalities may contribute to better accuracy of diagnosing tumor depth preoperatively, even though these methods were never used in this study.

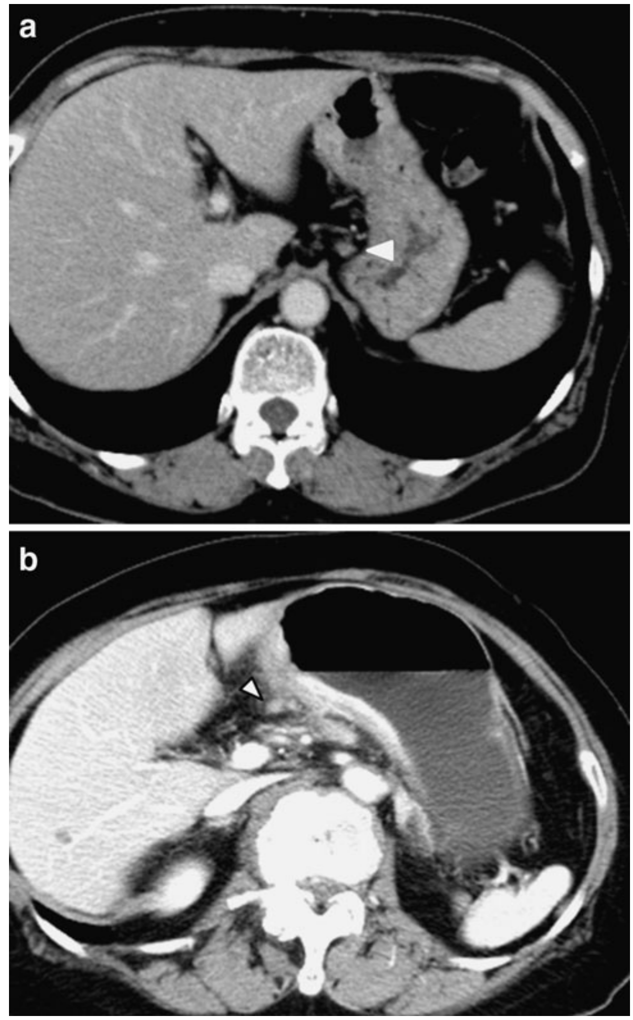

Fig. 2 Representative CT pictures of false-positive lymph node metastasis by single-detector CT and true-positive metastasis by 64 MD-CT. **a** False-negative case; 8-mm lymph node along the lesser curvature (#3) was detected by single-detector CT, but it was not actually a lymph node with metastasis (*arrowhead*). **b** True-positive case; 8-mm infrapyloric lymph node (#6) was detected by 64 MD-CT, and it was pathologically diagnosed as a metastatic lymph node (*arrowhead*)

The frequency of underestimation was markedly increased in cases with diffuse-type histology. Previous reports indicated that accurate preoperative diagnosis of tumor depth is generally more difficult in diffuse-type gastric cancer than in intestinal-type gastric cancer [22]. These diagnostic difficulties in diffuse-type gastric cancer may be partially solved by the advanced technology of MD-CT.

Some studies clearly demonstrated that lymph node size is not a reliable indicator for lymph node metastasis [23, 24]; they showed that approximately half of the metastatic lymph nodes were less than 5 mm in diameter. Although positron emission tomography (PET) has recently been used to evaluate lymph node metastasis in gastric cancer, previous studies have reported that PET is not as sensitive as CT in predicting the regional lymph node status of gastric cancer patients [25–27]. At present, we believe that sentinel lymph node biopsy during surgery may be a promising procedure for decreasing the frequency of preoperative underestimation of lymph node metastasis [8, 28].

In conclusion, we observed remarkable advances in the accuracy of preoperative staging of early gastric cancer in recent years. However, a small percentage of gastric cancer patients clinically diagnosed to be in the early stage of the disease were underestimated. Theoretically, these patients required D2 lymph node dissection as a curative treatment. It is necessary to continue to develop optimal preoperative and intraoperative diagnostic methods in order to determine customized treatment strategies.

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