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Diagnostic Accuracy and Usefulness of Intraoperative Margin Assessment by Frozen Section in Gastric Cancer

Koki Nakanishi, MD[1], Shinji Morita, MD[1], Hirokazu Taniguchi, MD[2], Sho Otsuki, MD[1], Takeo Fukagawa, MD[1], and Hitoshi Katai, MD[1]

[1]Department of Gastric Surgery, National Cancer Center Hospital, Tokyo, Japan; [2]Pathology and Clinical Laboratory Division, National Cancer Center Hospital, Tokyo, Japan

ABSTRACT

Background. Intraoperative frozen examination is clinically important for negative margin confirmation in cancer surgery. We investigated the diagnostic accuracy of frozen-section assessment and risk factors for positive resection margins by studying gastric cancer specimens from 1115 patients treated at our hospital.

Methods. The results of gastric cancer patients who had undergone intraoperative margin assessment, employing frozen examination, with curative intent in our unit between 2000 and 2017 were retrospectively analyzed. Frozen section assessments were compared with the corresponding permanent section assessments to evaluate the accuracy, sensitivity, and specificity of the former. The causes of discordances between two assessments were examined. In addition, risk factors associated with positive margins were identified.

Results. In total, 1241 specimens were obtained from the 1115 patients. The accuracy, sensitivity, and specificity of frozen-section assessments were 99.4%, 99.5%, and 97.8%, respectively. There were eight discordant cases. Two false-negative cases required another gastrectomy after final pathological diagnosis because of missed neoplastic cells. Six false-positive cases underwent unnecessary additional resection due to false positive results. In our frozen series, 89 cases had a positive margin on permanent section. Multivariate regression analysis of patients with positive surgical margins revealed large diameter ($\geq$ 50 mm) and T4 tumor to be independent risk factors.

Conclusions. Intraoperative frozen examination is a highly accurate method that is useful for achieving negative margins. This procedure is especially recommended for patients with a tumor larger than 50 mm in maximum diameter or serosal invasion to confirm a negative margin.

Gastric cancer is the fifth most common malignancy worldwide.[1] Surgical resection is still the most promising treatment approach for resectable gastric cancers. A complete surgical resection (R0) is necessary not only to achieve a cure but also to improve the outcomes of patients with curatively resectable gastric cancer,[2,3] To achieve R0 resection, it is important to ascertain the resection margin status, because it has a major influence on the surgical therapeutic strategy. According to the Japanese Gastric Cancer Association treatment guideline, Version 4, an adequate margin should be obtained macroscopically, depending on tumor depth and infiltration patterns.[4] If a clear margin cannot be secured, it is advisable to examine the margin of the resected specimen by the frozen-section (FS) method.

The major merit of subjecting the margin of the resected specimen to intraoperative frozen examination is that additional resection can be performed immediately in cases with a positive margin. On the other hand, this procedure is time-consuming and costly, and the FS diagnosis is not consistently accurate. When the FS result is negative and the permanent section (PS) result is positive (false negative), additional treatments, for example, another surgery after the initial operation, should be scheduled. When the FS is positive, and the PS is negative (false positive), excessive treatment might be administered. To the best of our knowledge, there is little information about the

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S. Morita, MD
e-mail: smorita@ncc.go.jp

correlation between FS and PS results in gastric cancer surgery.[5–7] Furthermore, the ratio of false positivity to false negativity has not been fully clarified. We investigated the diagnostic accuracy and usefulness of the FS method. Moreover, risk factors for positive resection margins by intraoperative frozen examination also were assessed.

PATIENTS AND METHODS

All gastric adenocarcinoma patients who underwent intraoperative margin assessment by FS between January 2000 and June 2017 with curative intent in our unit were retrospectively analyzed. Baseline characteristics, histopathological data, and postoperative variables were obtained from medical records. Pathological staging was determined according to the *TNM Classification of Malignant Tumors, 7th Edition*.[8] All of the patients underwent gastroendoscopy, and the horizontal extent of tumors was determined by obtaining biopsies before surgery. When the tumor margin was unclear in superficial tumors, we routinely placed endoscopic metallic clips to determine the resection line based on the results of the biopsies performed preoperatively. When laparoscopic surgery was scheduled, India ink was injected into the submucosa at the anterior wall near the tumor for subsequent surgical identification. The decision to conduct intraoperative FS was made by the primary surgeon, as soon as the resected specimen results were obtained as follows. The cut was placed to assure an adequate surgical margin, as recommended by the Japanese gastric cancer treatment guidelines.[4] The resected stomach was immediately opened after gastrectomy, and the distance between the proximal and distal resection margins was measured in the operating room. If the recommended margin distance, as specified by the Japanese gastric cancer treatment guidelines, could not be obtained or tumor infiltration was suspected, the cut end was submitted for intraoperative FS.

A single, board-certified pathologist evaluated the specimens on FS after cryo-fixation, slicing, and hematoxylin–eosin (H&E) staining. After confirming the FS diagnosis, the frozen specimen tissue was thawed. Subsequently, two board-certified pathologists evaluated the specimens on PS after formalin fixation, paraffin embedding, and routine H&E staining had been performed. Special stains and immunohistochemistry were conducted, if considered to be warranted by the pathologist.

Margin status on FS assessment was classified as negative (FS0) or positive (FS1) based on the presence or absence of macroscopic tumor involvement at the cut line. Margin status on PS analysis was also classified as PS0 or PS1 in a similar manner. The resected histopathological specimens were measured according to the Japanese classification of gastric cancer.[9]

FS assessments were compared to the corresponding PS assessments to evaluate the accuracy, including sensitivity and specificity, of the FS method. The traditional 2×2 contingency approach was used. Clinicopathological findings in each group were compared employing the Chi square test and the Mann–Whitney U test. Logistic regression analysis was used to determine independent risk factors for positive margin status. All statistical analyses were conducted using SPSS, version 22.0 for Windows (SPSS Inc., Chicago, IL). Values of $P < 0.05$ were taken to indicate statistically significant differences.

RESULTS

From 1115 patients who underwent gastrectomy with curative intent, 1241 specimens were submitted for intraoperative margin assessment by FS to confirm resection margin negativity. Demographics and clinicopathological features of each group are summarized in Table 1. The median age of the patients was 65 (range 24–91) years; 823 were men and 418 were women. Total gastrectomy, including complete gastrectomy, was performed in 463 (37.3%) patients and distal gastrectomy in 478 (38.5%). Function-preserving gastrectomy indicated for early gastric cancers was performed in 295 (23.8%) patients. The resected stump was proximal in 1019 patients and distal in 222. On histopathological examination, advanced gastric cancer (102 in the muscularis propria, 249 in the subserosa, 253 in the serosa, and 17 with invasion of adjacent structures) was confirmed. Others had early gastric cancer or no residual disease after showing a pathological complete response to preoperative chemotherapy. A total of 181 had pathological node stage pN1, 131 had pN2, and 191 had pN3 disease.

There were eight discordant (0.64%) cases, of which two (0.16%) were false negative (FS0-PS1) and six (0.48%) false positive (FS1-PS0). In 1146 patients (92% of all cases), no tumor involvement was seen in either FS or PS specimens (FS0-PS0). In 87 patients (7.0% of all cases), there was tumor involvement in both FS and PS specimens (FS1-PS1). The correlation between the FS and PS results is shown in Table 2. The overall accuracy, sensitivity, and specificity of the FS method for margin assessment were 99.4%, 97.8%, and 99.5%, respectively. The negative and positive predictive values were 99.8% and 93.5%.

The false negative (FS0-PS1) rate was 0.16% (2/1241). Clinicopathological features are summarized in Table 3. All cases were examined employing proximal margin assessments, which revealed superficial depressed type

TABLE 1 Clinicopathological features of all patients with FS analysis (n = 1241)—stratified by FS0-PS0, FS0-PS1, FS1-PS0, and FS1-PS1 cohorts

Variable	FS0-PS0 (N = 1146)	FS0-PS1 (N = 2)	FS1-PS0 (N = 6)	FS1-PS1 (N = 87)	p value
Gender					0.848
Male/female	759/387	1/1	5/1	58/29	
Age (yr)					0.008
Median (range)	65 (24–91)	66 (65–67)	75 (56–82)	63 (33–88)	
Operation type					0.013
Total gastrectomy and complete gastrectomy	411	0	3	49	
Distal gastrectomy	449	2	2	25	
Function-preserving gastrectomy	281	0	1	13	
Others	5	0	0	0	
Approach					0.049
Laparotomy/laparoscopy	1013/133	1/1	6/0	83/4	
Margin type					0.522
Proximal/distal	945/201	2/0	5/1	67/20	
Specimen type					< 0.001
Esophagus	435	0	3	45	
Stomach	618	2	3	27	
Duodenum	93	0	0	15	
Tumor size, mm					< 0.001
Mean ± SD	58 ± 41	78 ± 3	72 ± 19	93 ± 59	
Macroscopic type					0.004
Superficial (type 0)	644	2	2	36	
Expansive growth (type 1, 2)	160	0	1	8	
Infiltrative growth (Type 3, 4)	292	0	3	41	
Unclassifiable (type 5)	50	0	0	2	
Location					< 0.001
Esophagogastric junction	134	0	0	23	
Upper	279	0	3	24	
Middle	528	2	2	23	
Lower	195	0	0	14	
Entire stomach	10	0	1	3	
Cross-section site					0.004
Anterior	134	0	1	5	
Posterior	188	0	0	20	
Lesser curvature	558	0	4	34	
Greater curvature	118	2	1	4	
circumferential	148	0	0	24	
Lauren type					0.542
Intestinal type	472	0	4	33	
Diffuse/mixed type	666	2	2	54	
Others	8	0	0	0	
T stage					< 0.001
T0[a]	5	0	0	0	
T1	520	0	1	22	
T2	102	0	2	4	
T3	249	0	1	18	
T4	270	2	2	43	

TABLE 1 continued

Variable	FS0-PS0 (N = 1146)	FS0-PS1 (N = 2)	FS1-PS0 (N = 6)	FS1-PS1 (N = 87)	p value
Lymphatic vessel invasion					< 0.001
Present/absence	619/527	2/0	6/0	66/21	
Lymph node metastasis					< 0.001
N0	643	1	2	30	
N1	181	0	1	10	
N2	131	0	3	15	
N3	191	1	0	32	
Stage (UICC)					< 0.001
0[a]	5	0	0	0	
I	548	0	2	23	
II	260	1	1	14	
III	299	1	3	39	
IV	34	0	0	11	
Any recurrence	213	0	2	38	< 0.001
Local recurrence	6	0	0	2	0.149
Distant recurrence	211	0	2	37	< 0.001

FS0 frozen section negative; *FS1* frozen section positive; *PS0* permanent section negative; *PS1* permanent section positive; *UICC* Union for International Cancer Control

[a]Five cases with complete response to neoadjuvant chemotherapy

TABLE 2 Accuracy of FS assessment for evaluation of margin status

All margin assessment			Permanent section		
			Positive	Negative	Total
	Frozen section	Positive	87	6	93
		Negative	2	1146	1148
		Total	89	1152	1241
Sensitivity	97.8%				
Specificity	99.5%				
Positive predictive value	93.5%				
Negative predictive value	99.8%				
Accuracy	99.4%				

tumors by preoperative diagnosis but infiltrative growth type by pathological diagnosis. Isolated and scattered poorly differentiated adenocarcinoma was detected in the submucosa by PS assessment, but this tumor type was not detectable by FS assessment. Both false-negative cases underwent another curative surgical resection a few months after the initial operation. Neither local recurrence nor distant metastasis was observed in either of the patients with false-negative results.

The false-positive (FS1-PS0) rate was 0.48% (6/1241). Clinicopathological features are summarized in Table 4. Of these six cases, three were diagnosed as having an adenocarcinoma intraoperatively, whereas the other three were found to have atypical cells indicating a high possibility of tumor infiltration. Thus, five patients underwent additional resection, just one of whom required conversion from distal gastrectomy to total gastrectomy, because a superficial tumor larger than 10 cm was located in the lesser curvature. However, the final diagnosis changed based on pathological examination. None of these six patients experienced local recurrence but two developed distant metastasis: one had infiltrative growth and the other an advanced stage tumor. Given the importance of quality of life after gastrectomy, additional resection should be kept at a minimum to preserve gastric function.

A flow chart based on FS and PS assessments is presented in Fig. 1. Of the 1148 negative frozen specimens, 1146 had a negative margin on PS. However, two cases were positive on PS and underwent additional resection at a later date. Meanwhile, of the 93 positive frozen specimens,

TABLE 3 Breakdown of false-negative FS assessments

No.	Age/ gender	Margin type	Specimen type	Planned operation	Macroscopic type	Histologic type	Tumor size (mm)	T staging	pStage (UICC)	Intraoperative assessment	Affects on surgical management	Permanent assessment	Final status	Local recurrence	Distant metastasis	RFS (Month)
1	65/F	Proximal	Stomach	Laparoscopic assisted distal gastrectomy	0-IIc	Signet ring cell	80	4a	IIB	Negative	Additional resection at a later date	Missed neoplastic cells	R0	–	–	34
2	67/M	Proximal	Stomach	Distal gastrectomy	0-IIc	Poorly	54	4a	IIIC	Negative	Additional resection at a later date	Missed neoplastic cells	R0	–	–	5

tub1 well-differentiated adenocarcinoma; *tub2* moderately differentiated adenocarcinoma; *poorly* poorly differentiated adenocarcinoma; *UICC* Union for International Cancer Control; *RFS* relapse-free survival

87 were from cases with negative margins on PS who underwent immediate repeat resection. Six cases positive on FS did not undergo further additional surgery. Of these, four cases had other noncurative factors (2 with positive lavage cytology, 1 with peritoneal dissemination, and 1 with locally advanced malignancy involving the hepatoduodenal ligament), and the remaining two had widespread serosa-invasive tumors with extensive lymph node metastasis. All six cases remained free of local recurrence but died due to distant metastases.

Univariate and multivariate logistic regression analyses of factors associated with positive margin status are summarized in Table 5. On univariate analysis, the positive margin status correlated with larger tumor size ($\geq$ 50 mm; $P < 0.001$), T stage (pT4 cancer; $P < 0.001$), infiltrative growth type (type 3 or 4; $P = 0.004$), presence of lymph node metastasis ($P = 0.013$), and esophageal or duodenal stump cancer types ($P < 0.001$). There was no correlation with Lauren type histology. On multivariate analysis, larger tumor size ($\geq$ 50 mm; $P < 0.001$) and T stage (pT4 cancer; $P < 0.001$) remained significantly associated with positive margin status.

DISCUSSION

In the present study, we sought to clarify the accuracy of FS assessment. There were only six false-positive cases by FS assessment, and these inaccurate results did lead to excessive treatment, whereas 81 received immediate additional resection, which achieved a complete surgical cure.

With a given probability, there are cases with discordance of results between the FS and PS assessments. Previous studies showed the accuracy, sensitivity, and specificity of the FS assessment to be 95.8–98.8%, 70.7–91.7%, and 100%, respectively, based on investigations of 66-520 patients.[5–7] In our single-institution study, the corresponding figures were 99.4%, 97.8%, and 99.5%. There are several potential explanations for our better outcomes compared with those of previous studies. The first possible reason might be high diagnostic accuracy for discriminating between poorly cohesive carcinoma and normal cells. The presence of histiocytes and lymphocytes can make distinguishing between these cells and poorly cohesive carcinoma confusing.[5,10] Spicer et al.[5] reported six false-negative cases, four of whom were attributable to a failure to detect the foci of poorly cohesive carcinoma. The ratio of missing foci to all poorly cohesive carcinoma was 3.4% (4/119) in their study, whereas our corresponding ratio was 0.6% (4/687). When we encounter cells that cannot be discriminated from poorly cohesive carcinoma on FS, we generally obtain another deeper section. This

TABLE 4 Breakdown of false-positive frozen section assessments

No.	Age/gender	Margin type	Specimen type	Planned operation	Macroscopic type	Histologic type	Tumor size (mm)	T staging	pStage (UICC)	Intraoperative assessment	Affects on surgical management	Permanent assessment	Final status	Local recurrence	Distant metastasis	RFS (Month)
1	79/M	Proximal	Stomach	Distal gastrectomy	2	tub2	74	2	IIA	Atypical cells indicating a high possibility of adenocarcinoma	Additional resection of the proximal stomach	Atypical cells suspected to be regenerating epithelium	R0	–	–	66
2	56/M	Proximal	Esophagus	Total gastrectomy	3	Poorly	55	4a	IIIB	Poorly differentiated adenocarcinoma	Additional resection of the esophagus	Histiocytes	R0	–	+	6
3	77/M	Distal	Stomach	Proximal gastrectomy	0-IIc	tub2	58	2	IB	Atypical cells indicating a high possibility of adenocarcinoma	Additional resection of the distal stomach	Histiocytes	R0	–	–	3
4	72/M	Proximal	Esophagus	Total gastrectomy	4	tub1	90	3	IIIA	Atypical cells indicating a high possibility of adenocarcinoma	Additional resection of the esophagus	Histiocytes	R0	–	–	114
5	82/F	Proximal	Stomach	Distal gastrectomy	0-IIc	tub1	100	1b	IA	Low grade well differentiated adenocarcinoma	Convert to Total gastrectomy	Histiocytes	R0	–	–	96
6	65/M	Proximal	Esophagus	Total gastrectomy	3	Poorly	55	4a	IIIB	Poorly differentiated adenocarcinoma	Additional resection of the esophagus	Histiocytes	R0	–	+	6

tub1 well-differentiated adenocarcinoma; *tub2* moderately differentiated adenocarcinoma; *poorly* poorly differentiated adenocarcinoma; *UICC* Union for International Cancer Control; *RFS* relapse-free survival

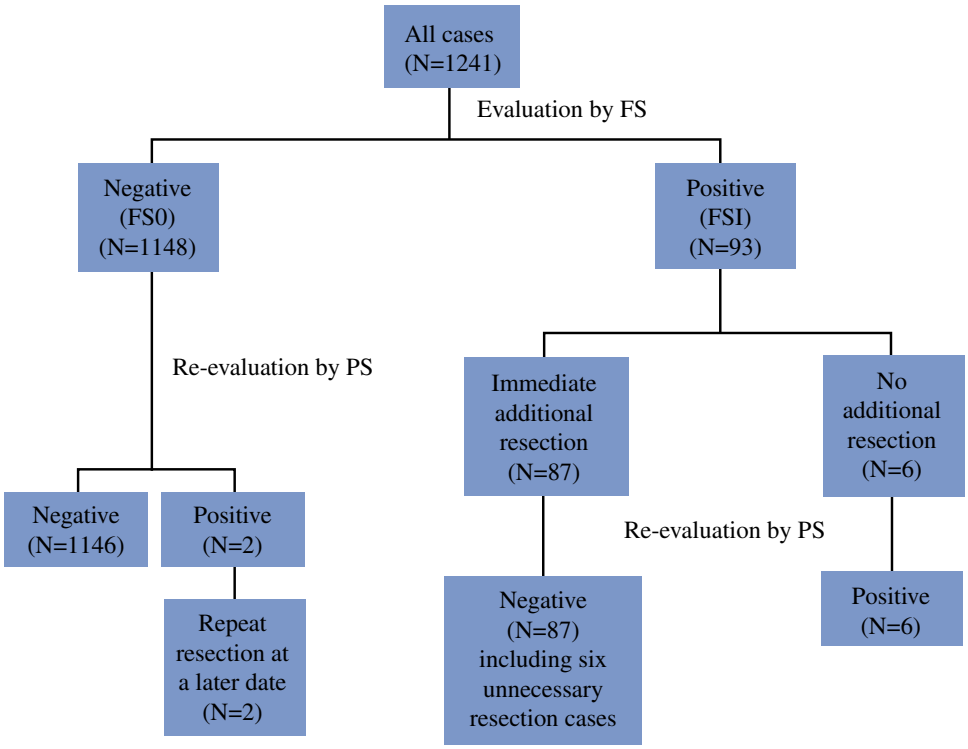

FIG. 1 Therapeutic algorithm for margin status based on FS and PS assessments. *FS* frozen section; *PS* permanent section; *FS0* frozen section negative; *FS1* frozen section positive; *PS0* permanent section negative; *PS1* permanent section positive

TABLE 5 Univariate and Multivariate logistic regression analysis of factors associated with positive margin in permanent section

Variables	Univariable [OR: univariate]			Multivariable [OR: multivariate]		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Tumor size ≥ 50 mm	3.810	2.24–6.47	< 0.001	2.450	1.35–4.43	0.003
T stage (pT4 cancer)	3.148	2.03–4.87	< 0.001	1.784	1.02–3.12	0.043
Specimen type (esophagus or duodenum)	2.419	1.53–3.83	< 0.001	1.541	0.94–2.53	0.089
Lymph node metastasis (present)	2.258	1.44–3.54	< 0.001	1.218	0.74–2.01	0.439
Lauren class (diffuse/mixed)	1.209	0.77–1.89	0.404			
Macroscopic type infiltrative growth (type 3, 4)	2.481	1.60–3.84	< 0.001	1.062	0.61–185	0.832

clarifies the cut surface and thereby facilitates the diagnosis, despite the surface being closer to the tumor edge, i.e., only several dozen micrometers from the initial cut surface. This diagnostic technique might contribute to increasing the accuracy of discrimination. Rapid special immunohistochemistry stains have been suggested to increase the accuracy of FS, if necessary.

The second possibility involves the rigorous preoperative examinations conducted. Endoscopic step biopsies were obtained from all of the patients, which allowed the horizontal extent of the tumor or its surroundings to be determined before the operation. If superficial tumors were poorly marginated, endoscopic metal clips were placed at oral and/or anal sites at which cancer negativity had been confirmed. When laparoscopic surgery was scheduled, Indian ink was injected into the submucosa to roughly identify the position of the tumor from the serosal side. These preoperative observations and diagnostic procedures might have contributed to better outcomes.

Another possibility involves the FS assessment ratio. In our unit, 19–172 cases per year were deemed to be suitable candidates for FS, yielding a frequency range of 4.4–38.5%. If numerous apparently negative specimens are submitted, unnecessary validations will raise diagnostic precision. Spicer et al.[5] reported that, of all the resected specimens in their study, 37% underwent FS margin assessment. Compared with their results, our ratio was not particularly high. However, considering our detailed preoperative observations and diagnostic procedures, we submitted numerous apparently negative specimens. One reason our FS margin assessment submission rate was high was that we performed numerous functional preservation surgeries for early-stage cancer. When conducting

functional preservation surgery, we occasionally, although not routinely, obtained both proximal and distal frozen section margins when a sufficient margin could not be obtained macroscopically.

We also sought to clarify the risk factors for positive resection margins by intraoperative frozen examination. The clinicopathological factors correlating with a positive margin were larger tumor size ($\geq$ 50 mm) and pT4 cancer. In our series, 71 cases (10.8%) among the 657 with tumors larger than $\geq$ 50 mm had a positive margin, whereas 45 among 317 pT4 cancer cases (14.2%) had a positive margin. Considering that positive rates are consistent cases with these two factors, it is recommended that FS assessment be performed even if a thorough preoperative examination has been conducted.

One limitation of this study might be selection bias regarding whether or not to conduct FS assessment. These decisions were left to the primary surgeon. Second, our dataset was retrospective, and the study was limited to a single institution. Due to the relatively small number of events, i.e., there were only six false-positive and two false-negative cases, numbers were too small to allow assessment of risk factors for discordant diagnosis. Third, our approach is basically repeat resection a few months after the initial operation when the final margin is positive on PS. Few patients require no further treatment. Therefore, it cannot be concluded that repeat resection offers a good prognosis to patients with large tumors or T4 cancer, which is prone to recurrence. While a positive margin is reportedly associated with poor outcomes in patients with early-stage disease, the association does not persist as an independent poor prognostic factor in later-disease stages.[11–13] Such patients, with far advanced stages of disease, appear to develop distant metastases rather than showing a positive margin.

CONCLUSIONS

Intraoperative margin assessment by FS is a highly accurate examination. Gastric tumors with diameters larger than 50 mm and pT4 cancer are independent risk factors for positive resection margins, and this procedure is especially recommended for such cases.

DISCLOSURE None of the authors has any conflict of interest to declare.

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