Acta Med. Nagasaki 49: 93－97

Factors Influencing Proper Clinical Evaluation of Depth of Tumor Invasion in Gastric Cancer

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The purpose of this study was to elucidate the factors that influence the clinical evaluation of the depth of tumor invasion in patients with T1 (tumor invasion of mucosa or submucosa) gastric cancer. The depth of tumor invasion was determined in 593 patients with gastric cancer. Patients were divided into two groups based on the agreement between clinical and pathological evaluation of depth of tumor invasion. Of 320 patients with clinical T1 gastric cancer, consistent diagnoses were made in 308 (96.2%) patients (consistent diagnosis group) while inconsistent diagnoses were made in 12 (3.8%) patients (inconsistent diagnosis group). In the clinical T1 gastric cancer, multivariate logistic regression analysis revealed that the disagreement between the clinical and pathological evaluation of the depth of tumor invasion was independently related to two variables; tumor location (upper stomach) and maximum tumor diameter ($\geq$30 mm). For clinical T1 gastric cancer with $\geq$30 mm in maximum tumor diameter located in the upper stomach, caution should be exercised when selecting therapy.

ACTA MEDICA NAGASAKIENSIA 49: 93－97, 2004

Keywords: Depth of tumor invasion; Clinical findings; Gastric cancer

Introduction

The prognostic significance of several clinicopathological factors in patients with gastric cancer has been evaluated previously. The only factor found consistently to influence prognosis is the extent of the disease: the extent of tumor invasion of the gastric wall (T stage), the presence or absence of lymph node involvement (N stage), and peritoneal and distant metastases (M stage).[1] The choice of therapy is also based on the stage of the disease defined by the aforementioned three factors. Above all, the depth of tumor invasion was reported to be the best predictor of prognosis.[2,3] In this regard, endoscopic ultrasonography (EUS) was reported to be useful in preoperative determination of the T stage.[4-7] In patients with gastric cancer invading the mucosa or submucosa (T1), the prognosis was satisfactory and surgery with reduced lymph nodes dissection might be chosen.[8] In the evaluation of the T1 depth of tumor invasion, the EUS was found to be accurate and most reliable with accuracy rate ranging from 80 to 93.5%.[9-11] However, some reports indicated that in 38.7% of patients with cancers that invaded the muscularis propria, the T stage was underestimated at T1 gastric cancer by EUS.[12] In our department, the accuracy of T1 diagnosis by EUS was 89.2% (unpublished results). Conversely, inaccuracy was 10.8% and was due to poor findings on EUS. The inaccurately diagnosed cases could be separated into two groups. One group was that the poor finding of EUS was recognized by other examinations, while the other group was that the poor finding of EUS was unrecognized. In the former group, the clinical findings were corrected to be consistent with the pathological findings on the basis of the findings of endoscopy or other diagnostic imaging. However, in the latter group, the clinical findings were different from the pathological findings. With regard to the choice of therapy, it is essential to distinguish clinical T1 gastric cancer with inconsistent clinical and pathological diagnoses.

The purpose of this study was to clarify the factors that influence the accurate diagnosis of depth of tumor invasion in clinical T1 gastric cancer.

Patients and Methods

Patients

A total of 593 patients with gastric cancer representing all patients

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Received April 9, 2004; Accepted August 11, 2004

who underwent gastric resection at Nagasaki University Hospital between January 1993 and December 2003 were included in this retrospective study. Patients who had a synchronous or metachronous cancer of the stomach were excluded. None of the patients had received preoperative chemo- or radiotherapy. Written informed consent was obtained from each patient.

In addition to the pathological diagnosis of gastric cancer by endoscopic biopsy, each patient underwent upper gastrointestinal series (UGIS), abdominopelvic ultrasonography, computed tomography (CT), endoscopy and EUS prior to surgery. The EUS was performed using radical sector-scan transducers (EU-M20; Olympus, Tokyo, Japan) with frequency of 20 MHz microscanner (UM3R; Olympus) mainly by an experienced gastric surgeon. Prior to the examination, 20 mg of scopolamine butylbromide was administered subcutaneously. After visual evaluation of the lesion with the endoscope, the stomach was filled with de-aerated water to enable observation of the lesion through the water and evaluation of the depth of tumor invasion by microscanner via the endoscope. Pathological diagnosis and classification of the resected gastric cancer tissues were made according to the Japanese Classification of Gastric Carcinoma.[13]

In this study, we classified patients into two groups based on the difference between clinical findings and final findings on the depth of tumor invasion. The first group included patients in whom the pathological T stage was not different from the clinical T stage (consistent diagnosis group, n=544, 91.7%). The second group included patients in whom the pathological T stage exceeded the clinical T stage (inconsistent diagnosis group, n=49, 8.3%). Among 320 patients with clinical T1 gastric cancer, 308 (96.2%) were of the consistent diagnosis group and 12 (3.8%) were of the inconsistent diagnosis group. The study included 383 cases classified as pathological Type 0 gastric cancer. Of these, 344 (89.8%) patients were diagnosed pathologically as T1 depth invasion, while 39 (10.2%) as $\geq$T2 depth invasion.

Preoperative clinical classification of depth of tumor invasion of gastric wall

In this study, clinical staging of the depth of tumor invasion was made based on all available pre-operative examinations by at least three gastric surgeons with $\geq$10-year experience. The clinical classification of depth of tumor invasion was made according to the criteria of the Japanese Classification of Gastric Carcinoma.[13]

Postoperative pathological classification of depth of tumor invasion of gastric wall

The resected specimen was pinned under tension onto a wooden board, and then fixed in 10% formalin. After fixation in formalin for 7 days, the whole tumor was sliced into longitudinal sections of approximately 5 mm thickness. All specimens were embedded in paraffin and then stained with hematoxylin and eosin. The depth of tumor invasion was defined using the sliced specimens according to the Japanese Classification of Gastric Carcinoma.[13]

Maximum tumor diameter

The maximum tumor diameter was measured on the resected specimen under tension before fixation in 10% formalin according to the Japanese Classification of Gastric Carcinoma.[13]

Statistical analysis

Comparison of categorical data between two groups was performed by Fisher's exact probability test for the data of two categories and by chi-square test for those of three or more categories. Comparison of continuous data between two groups was performed using the Mann-Whitney's U-test. We used the multiple linear logistic regression model[14,15] to identify the factors that influenced the accurate diagnosis in relation to the consistent and inconsistent diagnosis groups. The model included factors showing a difference between the consistent diagnosis and inconsistent diagnosis groups at the significance level $p<0.25$.[14] We used Stat View J5.0 (SAS Institute Inc.) for the calculations.

Results

Comparison of clinicopathological features according to depth of invasion

Of 593 patients, 383 patients were diagnosed with pathological Type 0 gastric cancer. They were separated into two groups; the first included patients with pathological T1 depth of tumor invasion gastric cancer (T1 depth invasion group), and the second included patients with pathological $\geq$T2 depth of tumor invasion gastric cancer ($\geq$T2 depth invasion group). As seen in Table 1, there was a statistically significant difference between the two groups with regard to tumor location (long axis of the stomach, $p=0.002$), the existence of depressed component on macroscopic examination ($p=0.015$) and histopathological differentiation ($p<0.001$). We see from Table 1 that the two groups still showed a significant difference in the distribution of tumor location (long axis) when middle and lower stomachs were combined ($p=0.004$). The mean maximum tumor diameter in the $\geq$T2 depth invasion group was significantly larger than that in the T1 depth invasion group ($p<0.001$). However, there were no differences in the other variables measured between the T1 and $\geq$T2 depth invasion groups (Table 1).

Comparison of clinicopathological features of consistent and inconsistent diagnosis groups

There was a statistically significant difference between the inconsistent diagnosis group and consistent diagnosis group with regard to tumor location (long axis of the stomach, $p=0.003$). The mean maximum tumor diameter in the inconsistent diagnosis group patients was significantly larger than in the consistent diagnosis group ($p<0.001$). Furthermore, there was a significant difference in the maximum diameter between the $\geq$30 mm diameter group and

Table 1. Clinicopathological features of 383 Type 0 gastric cancer by T stage

Factor	T1 depth of invasion group (n=344)	≥T2 depth of invasion group (n=39)	*p*-value
Gender			0.572
Female	97 (28.2)[a]	13 (33.3)	
Male	247 (71.8)	26 (66.7)	
Age (years)	(60, 67, 72)[b] 32-88[c]	(55, 63, 70) 41-77	0.051
Tumor location (long axis)			0.002
Upper stomach	48 (14.0)	13 (33.3)	
Middle stomach	153 (44.5)	18 (46.2)	
Lower stomach	143 (41.5)	8 (20.5)	
Tumor location (short axis)			0.081
Anterior wall	72 (21.0)	6 (15.4)	
Posterior wall	81 (23.5)	11 (28.2)	
Lesser curvature	133 (38.7)	19 (48.7)	
Greater curvature	52 (15.1)	1 (2.6)	
Circumferential	6 (1.7)	2 (5.1)	
Maximum tumor diameter (mm)	(14, 20, 37) 3-125	(30, 35, 60) 10-130	<0.001
Depressed component			0.015
Absent	61 (17.7)	1 (2.6)	
Present	283 (82.3)	38 (97.4)	
Histopathology			<0.001
Differentiated	259 (75.3)	17 (43.6)	
Undifferentiated	85 (24.7)	22 (56.4)	

[a]Number of patients (percentage).
[b]Each triplet gives the 25th, 50th and 75th sample percentiles.
[c]Minimum-Maximum.

Table 2. Clinicopathological features of 320 patients with clinical T1 depth invasion gastric cancer by consistency of clinical and pathological T stages

Factor	Inconsistent diagnosis group (n=12)	Consistent diagnosis group (n=308)	*p*-value
Gender			0.825
Female	3 (25.0)[a]	86 (27.9)	
Male	9 (75.0)	222 (72.1)	
Age (years)	(55, 63, 69)[b] 46-76[c]	(59, 67, 72) 32-88	0.407
Tumor location (long axis)			0.003
Upper stomach	6 (50.0)	42 (13.6)	
Middle stomach	3 (25.0)	137 (44.5)	
Lower stomach	3 (25.0)	129 (41.9)	
Tumor location (short axis)			0.944
Anterior wall	3 (25.0)	67 (21.8)	
Posterior wall	3 (25.0)	74 (24.0)	
Lesser curvature	5 (41.7)	113 (36.7)	
Greater curvature	1 (8.3)	49 (15.9)	
Circumferential	0 (0.0)	5 (1.6)	
Maximal tumor diameter (mm)	(28, 38, 50) 20-130	(13, 20, 33) 3-125	0.001
<30	3 (25.0)	213 (69.2)	0.001
≥30	9 (75.0)	95 (30.8)	
Depressed component			0.335
Absent	1 (8.3)	60 (19.5)	
Present	11 (82.3)	248 (97.4)	
Histopathology			0.938
Differentiated	9 (75.0)	234 (76.0)	
Undifferentiated	3 (25.0)	74 (24.0)	

[a]Number of patients (percentage).
[b]Each triplet gives the 25th, 50th and 75th sample percentiles.
[c]Minimum-Maximum.

the <30 mm diameter group. However, there were no differences in the other factors between the consistent and inconsistent diagnosis groups (Table 2).

Maximum tumor diameter

As stated above, the mean maximum tumor diameter in the ≥T2 depth invasion group was significantly greater than that in the T1 depth invasion group. To elucidate the usefulness of the maximum tumor diameter in discriminating between the T1 depth invasion group and ≥T2 depth invasion group, we defined the sensitivity (specificity) as the probability that the patients in the ≥T2 (T1) depth invasion group are correctly classified as in the same group, and determined the optimal cut-off value for the maximum tumor diameter on the basis of the analysis of receiver operating characteristic (ROC) curves. The cut-off value determined as optimal was 30 mm and the corresponding sensitivity and specificity were 79.5% (=31/39) and 66.3% (=228/344), respectively (Figure 1).

Since the mean maximum tumor diameter in the inconsistent diagnosis group was significantly larger than that in the consistent diagnosis group (Table 2), we examined the property of the maximum tumor diameter cut-off at 30 mm in the discrimination of the consistent and inconsistent diagnosis groups. Among the 12 patients in the inconsistent diagnosis group, the maximum tumor diameter was 30 mm or more in 9 (75.0%), while among 308 patients

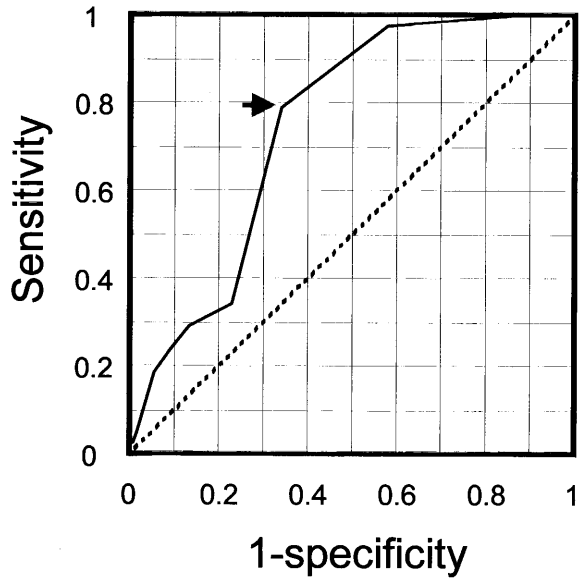

Figure 1. Receiver-operating characteristic (ROC) curve of maximum tumor diameter for distinguishing between T1 depth invasion group and ≥T2 invasion group. The arrow indicates the cut-off point of 30 mm for maximum tumor diameter. We used Stat Mate III (ATMS Co., Ltd) for drawing the curve.

Table 3. Factors leading clinical T staging of gastric cancer to underestimate pathological T stage and their effects[a]

Factor	Odds ratio (95% confidence interval)	*p*-value
Tumor location (long axis)		
Upper stomach	6.9 (2.02-23.26)	0.002
Middle/Lower stomach[b]	1	
Maximum tumor diameter (mm)		
<30[b]	1	
≥30	7.2 (1.85-28.00)	0.004

[a]Based on the multiple linear logistic regression analysis of 320 patients with clinical T1 gastric cancer.
[b]Reference.

in the consistent diagnosis group, the maximum tumor diameter was less than 30 mm in 213 (69.2%).

Factors influencing the discrepancy between clinical and pathological T stage

The factors which differed between inconsistent diagnosis and consistent diagnosis groups at the significance level of $p<0.25$ were the tumor location by long axis and the maximal tumor diameter (Table 2), and we analyzed the effects of these two factors by the multiple linear logistic model. The analysis identified tumor location (long axis) and maximum tumor diameter as significant determinants of the difference between clinical and pathological T stage (Table 3). For example, the odds of the probability that the group of clinical T1 depth invasion gastric cancer includes a patient with pathological ≥T2 depth of tumor invasion gastric cancer are 6.9-fold larger for upper stomach than for middle/lower stomach. Similarly, the odds of the probability that the group of clinical T1 depth invasion gastric cancer includes a patient with pathological ≥T2 depth of tumor invasion gastric cancer are 7.2-fold larger for maximum tumor diameter ≥30 mm than for maximum tumor diameter <30 mm.

Discussion

In this study, we investigated the factors that influenced the preoperative evaluation of depth of invasion in pathological T1 and ≥T2 gastric cancers. According to previous reports, the accuracy of endoscopy or UGIS is <85% due to similar findings in some pathological T1 and ≥T2 gastric cancers.[16,17] Several studies reported the high accuracy of EUS.[4-7] However, some cases diagnosed pathologically as ≥T2 gastric cancer had been diagnosed preoperatively as clinical T1 even when EUS was performed in addition to endoscopy and UGIS. In these cases, the failure of EUS might be unrecognizable. Two reasons may explain this phenomenon. One is related to the size of the tumor; tumor invasion was too small to be detected by EUS.[18] The other might be related to the EUS; application of EUS to the deepest part of the lesion. Tumor location could cause this problem particularly when there is difficulty in receiving the echo.

Our analysis identified four risk factors including tumor location, maximum tumor diameter, presence of a depressed component and histopathology, for pathological ≥T2 invasion in pathological Type 0 gastric cancer (Table 1). There was no significant difference in the histopathology between upper and middle/lower stomach cancers ($p=0.3438$, data not shown). Among these four factors, only tumor location and maximum tumor diameter were found to be independent risk factors for the different diagnosis between clinical and pathological T stages. Accurate estimation of the depth of invasion might be made taking into consideration the presence of a depressed component and histopathology. With regard to tumor location, we found that the upper stomach is a significant contributing factor for the different diagnosis. A previous study reported that the accuracy of EUS was lowest at the greater curvature of the upper stomach and that the accuracy of endoscopy was lowest at the lesser curvature and posterior wall of the upper stomach.[19] Location in the short axis of the upper stomach had no significant impact in our study. Interestingly, Shirakabe and Nishizawa[20] reported that 71% of the gastric cancers that were missed by UGIS were located in the upper stomach. Considered together, these results emphasize the difficulty in the detection and evaluation of gastric cancer in the upper stomach.

The cut-off value of maximum tumor diameter of 30 mm determined by the ROC curve analysis as optimal to discriminate between the inconsistent diagnosis and consistent diagnosis groups also showed a good performance in discriminating T1 depth invasion group from ≥T2 invasion group in pathological Type 0 gastric cancers. Thus, extensive invasion to the deep layers of the stomach wall might explain the different diagnosis.

In our study, of the 28 pathological Type 0 gastric cancers with ≥30 mm maximum tumor diameter in the upper stomach, 11 were pathologically diagnosed as ≥T2 invasion and accurate evaluation of the depth of tumor invasion was lacking in 4. To put it differently, the pathological diagnosis of about 40% of Type 0 gastric cancer with ≥30 mm maximum tumor diameter in the upper stomach was ≥T2 depth of invasion. Furthermore, about 40% of these invasive gastric cancers were incorrectly diagnosed preoperatively.

For such gastric cancers, caution should be exercised particularly when selecting therapy.

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