World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i45.12851

World J Gastroenterol 2015 December 7; 21(45): 12851-12856
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Retrospective Study

Clinicopathological characteristics of clinical early gastric cancer in the upper-third stomach

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Author contributions: Ichikawa D designed this research; Ichikawa D, Komatsu S, Kosuga T, Konishi H, Okamoto K, Shiozaki A, Fujiwara H and Otsuji E performed this research; Ichikawa D wrote the manuscript.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors have no conflicts of interest to disclose.

Data sharing statement: No additional data are available.

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Received: March 18, 2015
Peer-review started: March 19, 2015
First decision: April 23, 2015
Revised: May 16, 2015
Accepted: August 31, 2015
Article in press: August 31, 2015
Published online: December 7, 2015

Abstract

AIM: To elucidate the clinicopathological characteristics of clinically early gastric cancer in the upper-third stomach and to clarify treatment precautions.

METHODS: A total of 683 patients with clinical early gastric cancer were enrolled in this retrospective study, 128 of whom had gastric cancer in the upper-third stomach (U group). All patients underwent a double contrast barium examination, endoscopy, and computed tomography (CT), and were diagnosed preoperatively based on the findings obtained. The clinicopathological features of these patients were compared with those of patients with gastric cancer in the middle- and lower-third stomach (ML group). We also compared clinicopathological factors between accurate-diagnosis and under-diagnosis groups in order to identify factors affecting the accuracy of a preoperative diagnosis of tumor depth.

RESULTS: Patients in the U group were older (P = 0.029), had a higher ratio of males to females (P = 0.015), and had more histologically differentiated tumors (P = 0.007) than patients in the ML group. A clinical under-diagnosis occurred in 57 out of 683 patients (8.3%), and was more frequent in the U group than in the ML group (16.4% *vs* 6.3%, P < 0.0001). Therefore, the rates of lymph node metastasis and lymphatic invasion were slightly higher in the U group than in the ML group (P = 0.071 and 0.082, respectively). An under-diagnosis was more frequent in histologically undifferentiated tumors (P = 0.094) and in those larger than 4 cm (P = 0.024). The median

follow-up period after surgery was 56 mo (range, 1-186 mo). Overall, survival and disease-specific survival rates were significantly lower in the U group than in the ML group (P = 0.016 and 0.020, respectively). However, limited operation-related cancer recurrence was not detected in the U group in the present study.

CONCLUSION: Clinical early gastric cancer in the upper-third stomach has distinguishable characteristics that increase the risk of a clinical under-diagnosis, especially in patients with larger or undifferentiated tumors.

Key words: Upper-third stomach; Diagnosis; Gastric cancer

Core tip: The clinicopathological features of patients with gastric cancer in the upper-third stomach (U group) were compared with those of patients with gastric cancer in the middle- and lower-third stomach (ML group). The rate of clinical under-diagnoses was significantly higher in the U group than in the ML group and more frequent in histologically undifferentiated tumors and in those larger than 4 cm.

Ichikawa D, Komatsu S, Kosuga T, Konishi H, Okamoto K, Shiozaki A, Fujiwara H, Otsuji E. Clinicopathological characteristics of clinical early gastric cancer in the upper-third stomach. *World J Gastroenterol* 2015; 21(45): 12851-12856 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i45/12851.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i45.12851

INTRODUCTION

Although the incidence of gastric cancer (GC) has recently plateaued, the frequency of GC in the upper-third stomach has increased[1-4]. In Asian countries, the detection of early GC in the upper-third stomach has also been increasing[2,3]. Less invasive treatment options, such as endoscopic submucosal dissection (ESD) and laparoscopic proximal gastrectomy, have recently been performed on patients with early GC in the upper-third stomach in an attempt to preserve postoperative functions and improve the quality of life of these patients[5-9].

These recent findings prompted us to investigate the clinicopathological characteristics of early GC in the upper-third of the stomach. Treatment strategies are generally selected based on the preoperative findings of several examinations; therefore, we herein focused on patients with clinical early GC (T1) diagnosed preoperatively. In the present study, we retrospectively examined the clinicopathological characteristics of clinical early GC in the upper-third stomach and compared them with those in other regions. We also determined treatment precautions for patients with clinical early GC in the upper-third stomach.

MATERIALS AND METHODS

Patients

A total of 1856 patients with GC were admitted to Kyoto Prefectural University of Medicine between 1997 and 2013. Of these, 814 patients were diagnosed preoperatively with early GC (clinical T1) and underwent gastrectomy at our University Hospital. Patients with GC in the remnant stomach and with multiple GC detected previously were excluded from this study. A total of 683 patients with clinical T1 GC were enrolled in this retrospective study, 128 of whom had GC in the upper-third stomach. Of these, 59 patients underwent proximal gastrectomy. Lymph node dissection was performed based on the Guidelines of the Japanese Gastric Cancer Association[10].

Evaluations

All patients underwent a double contrast barium examination, endoscopy, and computed tomography (CT) and were diagnosed preoperatively based on the findings obtained. Tumor depth was judged according to previously described criteria[11,12]. Briefly, the endoscopic criteria for mucosal cancer were a smooth surface protrusion, shallow and even depression, erosion with slight marginal elevation, or a flat or superficial spreading lesion. The criteria for submucosal cancer were an irregular or nodular surface with or without abnormal converging folds, such as clubbing and abrupt cutting, an irregular-based ulcer with marginal mucosal elevation, or marked depression with interrupted enlarged folds. The criteria for T2 or higher tumors were irregular based ulceration surrounded by a tumorous bank or marked depression when the tips of converging folds were elevated and merged. In CT examinations, non-visualized lesions and tumors confined to the inner or middle layers of the gastric wall were diagnosed as clinical T1 tumors, and full-thickness wall thickening with/without an irregular surface on the outer layer surrounding the tumors were diagnosed as clinical T2 or higher tumors[13-15]. Endoscopic ultrasonography was also performed in some patients, and the depth of tumor invasion was assessed based on the generally accepted 5-layer sonographic structure of the gastric wall, as recommended by the Union Internationale Contre le Cancer (UICC)/American Joint Cancer Committee (AJCC). The clinicopathological features of these patients were reviewed retrospectively from hospital records and compared with those of patients with GC in the middle- and lower-third stomach. *Helicobacter pylori* infection was not necessarily examined in all cases in this study, therefore, we

Table 1 Clinicopathological characteristics of cT1 gastric cancer in the upper-third stomach

		Upper	Middle or Lower	*P* value
Age (yr)		66.1	62.8	0.029
Sex	Male	94	344	
	Female	34	211	0.015
Macroscopic[1]	Localized	37	148	
	Diffuse	91	405	0.620
	Unknown	0	2	
Histology	Diff.[2]	87	301	
	Undiff.[3]	41	247	0.0072
	Unknown	0	7	
Size (mm)		30.9	28.9	0.340
pT[4]	T1	107	519	
	T2	21	35	< 0.0001
	Unknown	0	1	
pN[5]	Negative	115	523	
	Positive	13	32	0.071
ly[6]	Negative	98	457	
	Positive	27	82	0.082
	Unknown	3	16	
v[7]	Negative	110	497	
	Positive	15	42	0.130
	Unknown	3	16	

[1]Macroscopic: Macroscopic findings; [2]Diff.: Differentiated adenocarcinoma; [3]Undiff.: Undifferentiated adenocarcinoma; [4]pT: Pathological T-category; [5]pN: Pathological lymph node metastasis; [6]ly: Lymphatic invasion; [7]v: Venous invasion.

could not compare infection rates between the two groups. We also compared clinicopathological factors between accurate-diagnosis and under-diagnosis groups in order to identify the factors affecting the accuracy of a preoperative diagnosis of tumor depth. The macroscopic and microscopic classifications of GC were based on the Japanese Classification of Gastric Carcinoma[10].

Statistical analysis

Continuous data were compared using the *t*-test or Mann-Whitney *U* test. The χ^2 test was used to evaluate differences in the proportion of clinicopathological variables. Overall survival (OS) and disease-specific survival (DSS) rates were calculated by the Kaplan-Meier method, with the date of gastrectomy as the starting point. Only deaths from postoperative complications and GC recurrence were considered in the analysis of DSS. Differences in survival were examined by the log-rank test. All statistical analyses were performed using Stat View 5.0 software (SAS Institute, Cary, NC, United States). The significance of differences was accepted at $P < 0.05$.

Table 2 Comparison of clinicopathological factors between accurate- and under-diagnosis groups

		Accurate diagnosis	Under diagnosis	*P* value
Age (yr)	< 65	44	9	
	⩾ 65	63	12	0.088
Sex	Male	77	17	
	Female	30	4	0.390
Macroscopic[1]	Localized	33	4	
	Diffuse	74	17	0.280
Histology	Diff.[2]	76	11	
	Undiff.[3]	31	10	0.094
Size (mm)	< 40	81	11	
	⩾ 40	26	10	0.024
	Unknown	3	1	

[1]Macroscopic: Macroscopic findings; [2]Diff.: Differentiated adenocarcinoma; [3]Undiff.: Undifferentiated adenocarcinoma.

RESULTS

Clinicopathological features of clinical T1 GC in the upper-third stomach

The mean patient age was 63.4 years (range, 28-89 years), and the male: female ratio was 1.79:1. The median tumor size was 29.3 mm (range, 5-145 mm). The clinicopathological characteristics of patients and tumors in the upper-third stomach (U group) and middle- and lower-third of the stomach (ML group) are shown in Table 1. Patients in the U group were older, had a higher ratio of males to females, and had more histologically differentiated tumors than patients in the ML group. The number of pathological T2 or deeper tumors that had been clinically under-diagnosed was significantly higher in the U group than in the ML group. Therefore, the rates of lymph node metastasis and lymphatic invasion were slightly higher in the U group than in the ML group.

Factors affecting the accuracy of a preoperative diagnosis of tumor depth

A clinical under-diagnosis occurred in 57 out of 683 patients (8.3%) and was more frequent in the U group than in the ML group (16.4% *vs* 6.3%). The clinicopathological features of patients in the U group with an accurate-diagnosis and under-diagnosis are listed in Table 2. Although an under-diagnosis was more frequent in large and histologically undifferentiated tumors, the histological difference was not significant.

Long-term prognosis of clinical T1 GC in the upper-third stomach

The median follow-up period after surgery was 56 mo (range, 1-186 mo). Thirty-four deaths, including 10

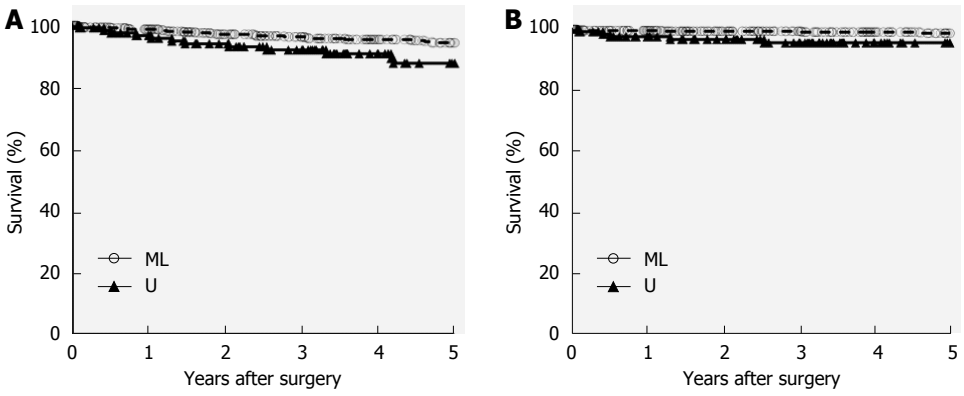

Figure 1 Comparison of survival curves in patients with clinically early gastric cancer in the upper-third stomach (U group) and in the more distal stomach (ML group). A: Overall survival (OS); B: Disease-specific survival (DSS). OS and DSS rates were significantly lower in the U group than in the ML group (P = 0.016 and 0.020, respectively).

disease-related deaths, occurred during the follow-up period. Recurrence was noted in six patients (two and four patients in the U and ML groups, respectively), while four patients (three and one patients in U and ML groups, respectively) died of postoperative complications. Recurrence patterns were peritoneal dissemination in two patients, para-aortic lymph node metastasis in two, and hematogenous metastasis in two. OS and DSS rates were significantly lower in the U group than in the ML group (Figure 1). However, limited operation-related cancer recurrence was not detected in the U group in the present study.

DISCUSSION

The present study clearly showed that clinical T1 GC in the upper-third stomach has features that distinguish it from GC in other regions of the stomach, including older patients, a higher ratio of males to females, and more histologically differentiated tumors. Regarding the histological type, Kunisaki *et al*[16] also reported that patients with tumors in the upper-third stomach more frequently had differentiated tumors. However, the frequency of tumor differentiation may vary markedly between different countries, as previously reported[17].

The results of the present study revealed that clinical T1 GC in the U group was associated with a higher incidence of under-diagnosis of advanced GC (T2 or higher) in pathological examinations compared to the ML group. Since the extent of gastric resection and lymph node dissection is slightly narrower in such limited treatment options, accurate preoperative diagnoses are crucial for determining individualized treatment strategies. Early GC, which is confined to the mucosa and/or submucosa, has been diagnosed preoperatively based on the findings of upper barium contrast examinations and gastroscopy[11,12]. Endoscopic ultrasonography and multi-detector computed tomography have recently been utilized for more accurate diagnoses; however, preoperative under-diagnoses represent a frequent problem in the clinical staging of early GC[18-20]. The major drawback of this study was that endoscopic ultrasonography was not performed on all of the study patients. However, several recent studies indicated that endoscopic ultrasonography did not impact pretreatment staging of tumor depth, especially in patients with early GC[21-24]. The diagnostic accuracy of the depth of tumor invasion is considered to be affected by several factors[25,26]. Kim *et al*[26] reported that histologically undifferentiated-type tumors were associated with lower diagnostic accuracy of endoscopic assessments in preoperatively predicted tumor invasion, and the probability of a clinical under-diagnosis was significantly high. However, the number of histologically differentiated-type tumors was significantly higher in the U group than in the ML group in this study; therefore, the histological type was not involved in the under-diagnosis of clinical T1 in the U group. Other possible explanations for the predisposition toward an under-diagnosis are anatomy-related factors. Muscle bundles of the lamina muscularis mucosae are separated by wide spaces, are relatively sparse, and have a reticular arrangement in the cardia. In the more distal stomach, the spaces between the muscle bundles are narrower with a more dense reticular arrangement and a linear arrangement[27]. Therefore, superficial cancer may be vulnerable to infiltration to the muscle layer of the gastric wall. Another explanation is that fixation of the gastric wall to the diaphragm and retroperitoneum *via* a bare area of the stomach may reduce changes in the luminal face, which may play a role in the discrepancy observed between clinical and pathological diagnoses of tumor infiltration. Further investigations are needed in order to elucidate the exact reasons why tumors in the upper-third stomach are predisposed to clinical under-diagnosis.

Functional preservation operations, such as proximal gastrectomy and/or limited lymph node dissection, are now more likely to be performed on patients with clinically early GC in the upper-third stomach[6-8]. Previous studies demonstrated that

proximal gastrectomy with regional lymphadenectomy was satisfactory for early GC in the upper-third stomach[6,8,28,29]; however, populations were collected based on pathological examinations in most of these studies. In these conservative operations, clinical under-diagnoses carry the potential risk of incomplete treatments. This study clearly demonstrated that a clinical under-diagnosis correlated with the presence of large and undifferentiated tumors; therefore, the potential risk of clinical underestimations needs to be considered in patients with these tumors.

The present study also investigated the long-term outcomes of clinical T1 GC in the upper-third stomach and compared them with those of patients who had GC in the more distal stomach. Patients with clinical T1 GC in the ML group had significantly better OS and DSS rates than those in the U group; however, the older mean age and higher rates of fatal complications in the U group appeared to be associated with decreased survival rates.

In conclusion, clinically early GC in the upper-third stomach has distinguishable characteristics from the more distal stomach, and the risk of a clinical under-diagnosis is greater in GC in the upper-third stomach, especially in patients with undifferentiated tumors or those larger than 4 cm. Particular attention is needed for the indication of limited operations in patients with those tumors.

COMMENTS

Background

Although the incidence of gastric cancer has recently plateaued, the frequency of gastric cancer in the upper-third stomach has increased. In Asian countries, the detection of early gastric cancer in the upper-third stomach has also been increasing.

Research frontiers

The authors herein investigated the clinicopathological characteristics of early gastric cancer in the upper-third of the stomach and also determined treatment precautions for patients with clinical early gastric cancer in the upper-third stomach.

Innovations and breakthroughs

Treatment strategies are generally selected based on the preoperative findings of several examinations; therefore, the authors focused on patients with clinical early gastric cancer diagnosed preoperatively in this retrospective study.

Applications

Clinically early gastric cancer in the upper-third stomach has distinguishable characteristics from the more distal stomach, and the risk of a clinical under-diagnosis is greater in upper-third stomach cancer, especially in patients with undifferentiated tumors or those larger than 4 cm.

Terminology

Clinically early gastric cancer was diagnosed preoperatively based on the findings of a double contrast barium examination, endoscopy, and computed tomography.

Peer-review

The authors clearly demonstrated that clinically early gastric cancer in the upper-third stomach has distinguishable characteristics from the distal stomach that increase the risk for clinical under-diagnosis. Therefore, particular attention is needed for the indication of limited operations in patients with these tumors.

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P- Reviewer: Osawa S, Reshetnyak VI **S- Editor**: Yu J
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ISSN 1007-9327