pylorus-preserving gastrectomy for early gastric cancer compared with conventional distal gastrectomy. *Surgery* 1998; **123**: 165–170.
16 Enjoji A, Ura K, Ozeki K, Tsukamoto M, Ikematsu Y, Kanematsu T. Cyclic motor activity of the gallbladder maintained in a pylorus-preserving gastrectomy in dog. *Jpn J Surg* 1996; **26**: 489–495.
17 Zhang D, Shimoyama S, Kaminishi M. Feasibility of pylorus preserving gastrectomy with a wider scope of lymphadenectomy. *Arch Surg* 1998; **133**: 993–997.
18 Nishikawa K, Kawahara H, Yumiba T, Nishida T, Inoue Y, Ito *et al.* Functional characteristics of the pylorus in patients undergoing pylorus-preserving gastrectomy for early gastric cancer. *Surgery* 2002; **131**: 613–624.
19 Tomita R, Fujisaki S, Tanjoh K. Pathophysiological studies on the relationship between postgastrectomy syndrome and gastric emptying function at 5 years after pylorus-preserving distal gastrectomy for early gastric cancer. *World J Surg* 2003; **27**: 725–733.
20 Shiratori T, Hongo M, Ishii M. Interpretation of gastric emptying curve by RI method. *J Smooth Muscle Res* 1994; **30**: 433.
21 Tomita R, Munakata K, Kurosu Y, Aoki N, Tanjoh K, Abe Y. Gastric emptying time after distal subtotal mgastrectomy with or without the pylorus-preserving. *J Smooth Muscle Res* 1994; **20**: 229.
22 Griffith CA. Selective vagotomy plus suprapyloric antrectomy: an alternative antidumping operation. In *Surgery of the Stomach and Duodenum* (4th edn), Nyphus LM, Wastei C (eds). Little, Brown: Boston, 1986; 337–363.
23 Sasaki I, Fukushima K, Naito H, Matsuno S, Shiratori T, Maki T. Long-term results of pylorus-preserving gastrectomy for gastric ulcer. *Tohoku J Exp Med* 1992; **168**: 539–548.
24 Ohashi M, Katai H, Fukagawa T, Gotoda T, Sano T, Sasako M. Cancer of the gastric stump following distal gastrectomy for cancer. *Br J Surg* 2007; **94**: 92–95.
25 Honmyo U, Misumi A, Murakami A, Haga Y, Akagi M. Clinicopathological analysis of synchronous multiple gastric carcinoma. *Eur J Surg Oncol* 1989; **15**: 316–321.
26 Kosaka T, Miwa K, Yonemura Y, Urade M, Ishida T, Takegawa S *et al.* A clinicopathological study on multiple gastric cancers with special reference to distal gastrectomy. *Cancer* 1990; **65**: 2602–2065.
27 Takeda J, Toyonaga A, Koufuji K, Kodama I, Aoyagi K, Yano S *et al.* Early gastric cancer in the remnant stomach. *Hepatogastroenterology* 1998; **45**: 1907–1911.
28 Thorban S, Böttcher K, Etter M, Roder JD, Busch R, Siewert JR. Prognostic factors in gastric stump carcinoma. *Ann Surg* 2000; **231**: 188–194.
29 Ichiyoshi Y, Toda T, Minamisono Y, Nagasaki S, Yakeishi Y, Sugimachi K. Recurrence in early gastric cancer. *Surgery* 1990; **107**: 489–495.
30 Sano T, Sasako M, Kinoshita T, Maruyama K. Recurrence of early gastric cancer. Follow-up of 1475 patients and review of the Japanese literature. *Cancer* 1993; **72**: 3174–3178.
31 Katai H, Maruyama K, Sasako M, Sano T, Okajima K, Kinoshita T *et al.* Mode of recurrence after gastric cancer surgery. *Dis Surg* 1994; **11**: 99–103.

Original article

Treatment strategy after non-curative endoscopic resection of early gastric cancer

I. Oda[1], T. Gotoda[1], M. Sasako[2], T. Sano[2], H. Katai[2], T. Fukagawa[2], T. Shimoda[3], F. Emura[1] and D. Saito[1]

[1]Endoscopy, [2]Gastric Surgery and [3]Pathology, Clinical Laboratory Divisions, National Cancer Centre Hospital, Tokyo, Japan
Correspondence to: Dr I. Oda, Endoscopy Division, National Cancer Centre Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan (e-mail: ioda@ncc.go.jp)

Background: Endoscopic resection (ER) is indicated for patients with early gastric cancer who have a negligible risk of lymph node metastasis (LNM). Histological examination of the resected specimen may indicate a possible risk of LNM or a positive resection margin. These patients are considered to have undergone non-curative ER. The aim of this study was to determine the appropriate treatment strategy for such patients.

Methods: A total of 298 patients who had non-curative ER were classified into those with a positive lateral margin only (group 1; 72 patients) and those with a possible risk of LNM (group 2; 226 patients).

Results: Surgery was performed within 6 months of non-curative ER in 19 patients in group 1 and 144 in group 2. In group 1, nine patients were found to have local residual tumours, all limited to the mucosal layer without LNM. In Group 2, 13 patients had residual disease, including four local tumours without LNM, two local tumours with LNM and seven cases of LNM alone. The rate of LNM after surgery was 6·3 per cent in group 2.

Conclusion: Surgery remains the standard treatment after non-curative ER in patients with a possible risk of LNM.

Paper accepted 24 April 2008
Published online 21 October 2008 in Wiley InterScience (www.bjs.co.uk). **DOI:** 10.1002/bjs.6305

Introduction

The percentage of all gastric cancers diagnosed as early gastric cancer (EGC) varies between countries, reaching nearly 60 per cent in Japan[1–4]. Endoscopic resection (ER) has been accepted as the standard treatment for those patients with EGC who have a negligible risk of lymph node metastasis (LNM)[5,6]. However, endoscopic prediction of EGC in terms of tumour depth or lateral spread is not always accurate even when endoscopic ultrasonography is used[7–10]. The success of ER is subsequently determined histologically. It is considered to have been non-curative if tumours are subsequently diagnosed as having either a possible risk of LNM or a positive lateral margin (*Table 1*)[11–13].

Patients who have undergone non-curative ER generally need additional treatment, but there are only a few published reports of surgical outcomes after non-curative ER in small series[14,15]. The aim of this study was to evaluate additional treatment strategies after non-curative ER based on retrospective analysis of a large series of consecutive patients.

Methods

A total of 1783 EGCs were treated with ER, including 495 endoscopic mucosal resections[5,6] and 1288 endoscopic submucosal dissections (ESDs)[9], with curative intent at the National Cancer Centre Hospital, Tokyo, between March 1989 and December 2003. A total of 298 lesions (16·7 per cent) were subsequently diagnosed as having undergone non-curative ER after histological evaluation.

The medical records of the 298 patients who had non-curative ER were analysed retrospectively with regard to

The Editors are satisfied that all authors have contributed significantly to this publication

Table 1 Histological criteria for curative endoscopic resection

Early gastric cancer with no risk of lymph node metastasis
Differentiated adenocarcinoma
No lymphatic or venous invasion
Intramucosal cancer regardless of tumour size without ulcer finding
or intramucosal cancer ≤ 30 mm in size with ulcer finding
or minute submucosal cancer (sm1) ≤ 30 mm in size
Resection margin
Tumour-free lateral margin
Tumour-free vertical margin

demographics, concomitant disease, endoscopic tumour findings, histological findings in the ER specimen, additional surgical and non-surgical treatment after ER, histology of surgical specimens and clinical outcomes. Tumour location was classified into upper, middle and lower third of the stomach, based on the Japanese Classification of Gastric Carcinoma[16], and macroscopic type as elevated, depressed or mixed.

ER specimens were examined histologically using serial sections 2 mm in width according to recommendations in the Japanese Classification of Gastric Carcinoma[16]. Curability was assessed based on the histological criteria for curative ER (*Table 1*). The procedure was considered non-curative if the EGC criteria for no risk of LNM were not fulfilled or a positive resection margin was demonstrated.

Patients who had non-curative ER were classified into those with a positive lateral margin only (group 1) and those who did not fulfil the histological EGC criteria for no risk of LNM, irrespective of resected margin findings (group 2). Surgical treatment was generally recommended in group 2, whereas in group 1 additional treatment was based on the extent of lateral margin involvement and the time frame of each case. In the early years, surgical treatment was recommended for patients with an extensive positive lateral margin.

Groups 1 and 2 were each further divided into two subgroups: patients who underwent radical gastrectomy with lymph node dissection within 6 months of non-curative ER and those who did not.

Surgical specimens were examined according to the recommendations in the Japanese Classification of Gastric Carcinoma[16]. The entire resected stomach area, including the tumour or ER scar, was divided into slices 5 mm in width and LNMs were evaluated in the central portion of each lymph node. Local residual tumour was defined as any cancer diagnosed histologically at the ER site.

Statistical analysis

Clinical outcomes of patients who had surgery and those treated non-surgically were collected and analysed in January 2006. Disease-specific survival curves were calculated by the Kaplan–Meier method (Statview; Abacus Concepts, Berkeley, California, USA).

Table 2 Demographic and tumour characteristics of 298 patients who had non-curative endoscopic resection

	No. of patients*
Mean(s.d.) age (years)	66(10)
Sex ratio (M : F)	248 : 50
Concomitant disease	35 (11·7)
Other cancer	26
Heart disease	6
Renal failure	3
Gastric tumour location	
Upper third	69 (23·2)
Middle third	126 (42·3)
Lower third	103 (34·6)
Macroscopic type	
Elevated	99 (33·2)
Depressed	171 (57·4)
Elevated and depressed	28 (9·4)

*With parentheses in percentages unless indicated otherwise.

Table 3 Reasons for risk of lymph node metastasis in group 2

	Surgical treatment	Non-surgical treatment
Predominantly undifferentiated type	33 (73)	12 (27)
Positive lymphatic and/or venous invasion	61 (73)	22 (27)
Submucosal deep invasion (sm2)	93 (77·5)	27 (22·5)
Intramucosal cancer > 30 mm in size with ulcer finding	13 (35)	24 (65)
Minute submucosal cancer (sm1) > 30 mm in size	8 (36)	14 (64)
Positive vertical margin	17 (68)	8 (32)

Values in parentheses are percentages. Some patients had more than one reason.

Results

Patient demographics and endoscopic tumour findings are summarized in *Table 2*. Of 298 patients who had a non-curative ER, 72 with a positive lateral margin only were included in group 1 and 226 with a risk of LNM, regardless of the resection margin findings, were included in group 2. Factors generally considered to be associated with risk of LNM in group 2 are shown in *Table 3*. Patients in groups 1 and 2 represented 4·0 and 12·7 per cent] respectively of all 1783 patients with EGC who were treated by ER.

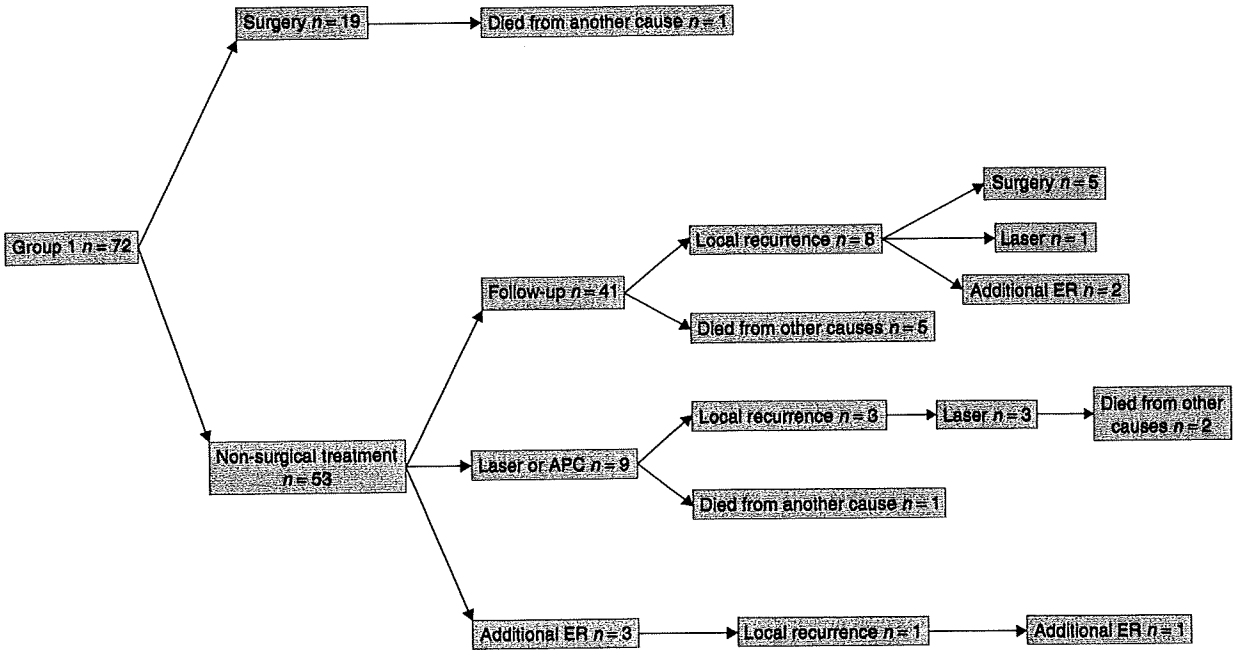

Fig. 1 Clinical courses in group 1 (patients with lateral margin involvement alone). APC, argon plasma coagulation; ER, endoscopic resection

In group 1, 19 patients underwent surgery within 6 months of non-curative ER and 53 had non-surgical treatment (*Fig. 1*). In Group 2, 144 patients had surgery within 6 months (*Fig. 2*). Reasons for not having surgery in the remaining 82 patients in group 2 included patient choice (47 patients), high surgical risk (21 patients; 15 very elderly, two with chronic renal failure, two with ischaemic heart disease and two with autoimmune disease) and concomitant cancer in other organs (14).

The median interval between non-curative ER and gastrectomy was 46 (range 3–170) days and there were no operation-related deaths. In group 1, nine patients had local residual tumours, all of which were limited to the mucosal layer without LNM (*Table 4*). In group 2, 13 patients had residual disease, including four with local tumours without LNM, two with local residual tumours and LNM, and seven with LNM alone. The rate of LNM after surgery was 6·3 per cent in group 2 (*Table 4*).

Clinical courses for patients in group 1 are shown in *Fig. 1*. The median follow-up period was 5·0 (range 0·5–17) years and there were no gastric cancer-related deaths.

Clinical courses for patients in group 2 are summarized in *Fig. 2*, and disease-specific survival curves are shown in *Figs 3* and *4*. The median follow-up time was 4·0 (range 0·5–16) years among those who had surgery. Three of these patients developed distant metastasis and received chemotherapy, but died from gastric cancer 1, 1·5 and 1·7 years after the non-curative ER. The 3- and 5-year disease-specific survival rates were both 97·8 per cent (*Fig. 3*). Patients in group 2 who did not have surgery were followed up for a median of 3·2 (range 0·5–16·9) years. Two patients died from distant metastasis 3·3 and 4·9 years after non-curative ER. The 3- and 5-year disease-specific survival rates were 100 and 91 per cent (*Fig. 4*).

Table 4 Relationship between outcome of endoscopic resection and surgical outcome

		Surgical outcome	
Outcome of endoscopic resection	No. of patients	Local residual tumour	LNM
Group 1 (positive lateral margin)	19 (11·7)	9 (47)	0 (0)
Group 2 (risk of LNM regardless of margin)	144 (88·3)	6 (4·2)	9 (6·3)
Total	163 (100)	15 (9·2)	9 (5·5)

Values in parentheses are percentages. LNM, lymph node metastasis.

Discussion

In this retrospective series, it was anticipated that all 1783 patients might satisfy the criteria for EGC

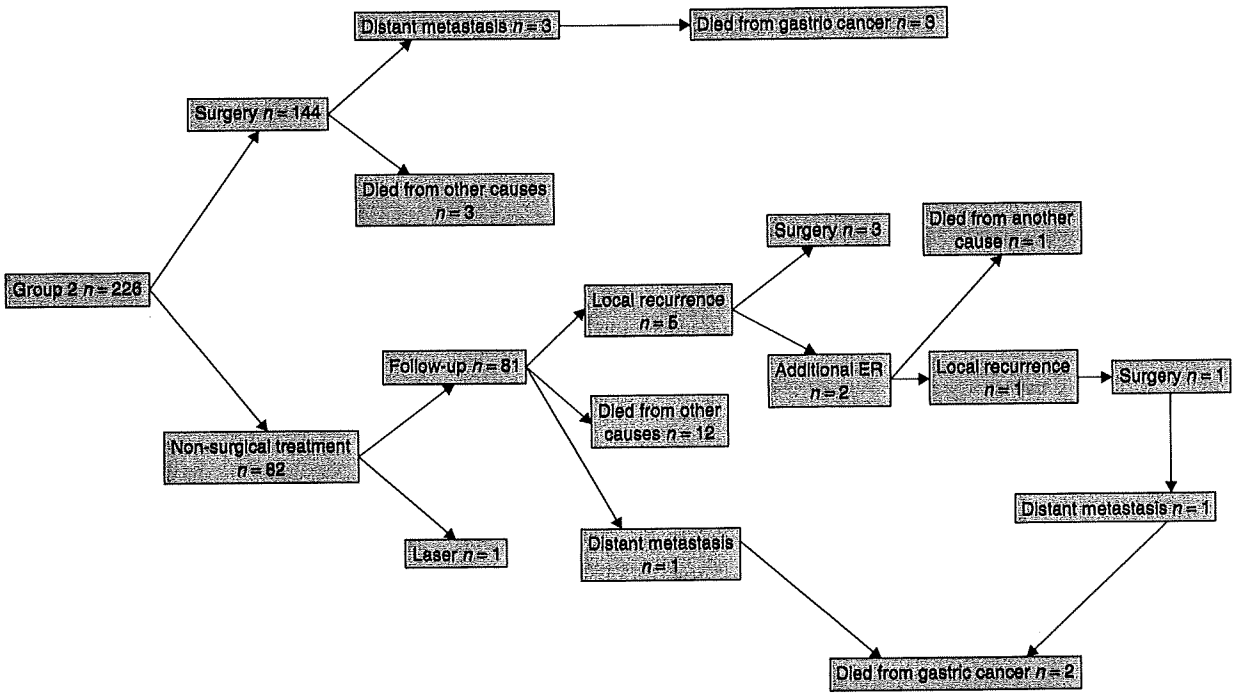

Fig. 2 Clinical courses in group 2 (patients at risk of lymph node metastasis, regardless of lateral margin involvement). ER, endoscopic resection

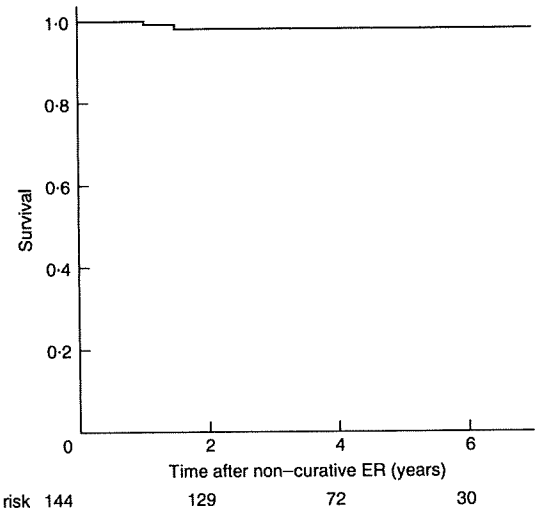

Fig. 3 Disease-specific survival for patients in group 2 who had surgery. ER, endoscopic resection

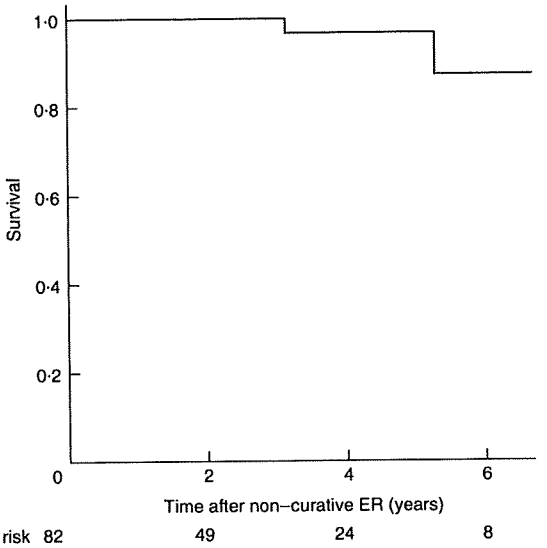

Fig. 4 Disease-specific survival for patients in group 2 who did not have surgery. ER, endoscopic resection

with no risk of LNM, but in fact 12·7 per cent did not. Several other articles have also reported that endoscopic staging of EGC is not always accurate, and is correct only 80–90 per cent of the time, even when using endoscopic ultrasonography[7–10]. Histological staging using resected specimens obtained by ER is

important, therefore, in deciding on the need for any additional treatment.

Differences exist between Japanese and Western pathologists with respect to the diagnostic criteria for determining gastric carcinoma[17]. A lesion diagnosed as non-invasive EGC in Japan could be diagnosed by biopsy as dysplasia in Western countries and might not receive any follow-up treatment. As the present series demonstrated, some EGCs that were considered to be non-invasive were confirmed to be invasive by histological examination after ER. ER is therefore recommended even for lesions diagnosed as high-grade dysplasia by Western pathologists so that histological staging can be carried out[18]. As the number of ER procedures increases in the future, the number of non-curative ERs will undoubtedly increase in Western countries as well.

Patients who had non-curative ER were divided into two groups in this study based on their different risk of LNM. None of the patients with lateral margin involvement only developed LNM, whereas lymph node involvement was confirmed in some patients who fulfilled the criteria for risk of LNM. The results provided valuable information on additional treatment strategy for both groups.

The LNM rate of 6·3 per cent among patients who had surgery in group 2 was lower than the reported incidence of nearly 20 per cent in patients with submucosal invasive cancer[7]. Lesions in the present study, which had been treated with curative intent by ER, had a lower risk of LNM than submucosal invasive cancer overall. Gastrectomy with lymph node dissection has a low operative mortality rate, particularly in Japan (less than 1 per cent), and results in an excellent prognosis for patients with EGC[2,3,19,20]. The LNM rate of 6·3 per cent in the present study cannot therefore be ignored. Similar results were obtained in two small series, in which one of six[14] and four of 24 patients[15] had LNM in surgical specimens after non-curative ER for submucosal invasive cancer.

The authors previously reported a 5-year disease-specific survival rate following gastrectomy of 96·7 per cent for submucosal invasive cancer[20]. A similar rate was found in the present study, even though there were three gastric cancer-related deaths from distant metastasis after salvage surgery in group 2. Additional gastrectomy is strongly recommended, therefore, in such patients.

The 5-year disease-specific survival rate among patients in group 2 who did not have salvage surgery was 91 per cent, a figure that was not markedly different from the rate in group 2 patients who did, or previously reported data[20]. This is probably because there were considerable differences in histological findings after ER between patients who had surgery and those who did not (*Table 3*). Histological findings strongly related to LNM, such as positive lymphatic and/or venous invasion and submucosal deep invasion, were much more frequent in surgical patients than in non-surgical patients. Although this may indicate that there is yet another group with a negligible risk of LNM, additional gastrectomy is recommended until such a group has been identified definitively.

Finally, it is important to note that none of the patients in group 1 had LNM. This suggests that any local residual tumour can be treated locally without lymph node dissection. Previous reports have also indicated in a small number of patients that none of the intramucosal lesions with a positive lateral margin had LNM[14,15]. Until recently, repeat ER of local residual tumour after an initial non-curative procedure was often difficult to perform because extensive fibrosis prevented a solution injected into the submucosa from raising the lesion sufficiently. The newly developed ESD technique has made it possible to treat even EGC associated with ulcerative changes[13] and to resect locally recurrent gastric cancer after non-curative ER[21]. As a result, subsequent ER using ESD has become feasible for certain patients with a positive lateral margin but no risk of LNM.

Surgery remains the standard treatment after non-curative ER because of the possibility of LNM in patients who meet the EGC criteria for risk of nodal metastasis, regardless of whether the resection margin is involved. A second ER may be possible, however, when the initial resection is deemed non-curative only because of a positive lateral margin.

References

1 Everett SM, Axon AT. Early gastric cancer in Europe. *Gut* 1997; **41**: 142–150.

2 Nakamura K, Ueyama T, Yao T, Xuan ZX, Ambe K, Adachi Y *et al.* Pathology and prognosis of gastric carcinoma. Findings in 10000 patients who underwent primary gastrectomy. *Cancer* 1992; **70**: 1030–1037.

3 Shimizu S, Tada M, Kawai K. Early gastric cancer: its surveillance and natural course. *Endoscopy* 1995; **27**: 27–31.

4 Kim JP, Lee JH, Kim SJ, Yu HJ, Yang HK. Clinicopathologic characteristics and prognostic factors in 10783 patients with gastric cancer. *Gastric Cancer* 1998; **1**: 125–133.

5 Rembacken BJ, Gotoda T, Fujii T, Axon AT. Endoscopic mucosal resection. *Endoscopy* 2001; **33**: 709–718.

6 Soetikno RM, Gotoda T, Nakanishi Y, Soehendra N. Endoscopic mucosal resection. *Gastrointest Endosc* 2003; **57**: 567–579.

7 Sano T, Okuyama Y, Kobori O, Shimizu T, Morioka Y. Early gastric cancer. Endoscopic diagnosis of depth of invasion. *Dig Dis Sci* 1990; **35**: 1340–1344.

8 Seto Y, Shimoyama S, Kitayama J, Mafune K, Kaminishi M, Aikou T *et al.* Lymph node metastasis and preoperative diagnosis of depth of invasion in early gastric cancer. *Gastric Cancer* 2001; **4**: 34–38.
9 Yanai H, Matsumoto Y, Harada T, Nishiaki M, Tokiyama H, Shigemitsu T *et al.* Endoscopic ultrasonography and endoscopy for staging depth of invasion in early gastric cancer: a pilot study. *Gastrointest Endosc* 1997; **46**: 212–216.
10 Yanai H, Matsubara Y, Kawano T, Okamoto T, Hirano A, Nakamura Y *et al.* Clinical impact of strip biopsy for early gastric cancer. *Gastrointest Endosc* 2004; **60**: 771–777.
11 Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T *et al.* Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; **3**: 219–225.
12 Eguchi T, Gotoda T, Oda I, Hamanaka H, Hasuike N, Saito D. Is endoscopic one-piece mucosal resection essential for early gastric cancer? *Dig Endosc* 2003; **15**: 113–116.
13 Oda I, Gotoda T, Hamanaka H, Eguchi T, Saito Y, Matsuda T *et al.* Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. *Dig Endosc* 2005; **17**: 54–58.
14 Korenaga D, Orita H, Maekawa S, Maruoka A, Sakai K, Ikeda T *et al.* Pathological appearance of the stomach after endoscopic mucosal resection for early gastric cancer. *Br J Surg* 1997; **84**: 1563–1566.
15 Nagano H, Ohyama S, Fukunaga T, Seto Y, Fujisaki J, Yamaguchi T *et al.* Indications for gastrectomy after incomplete EMR for early gastric cancer. *Gastric Cancer* 2005; **8**: 149–154.
16 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma – 2nd English Edition. *Gastric Cancer* 1998; **1**: 10–24.
17 Schlemper RJ, Itabashi M, Kato Y, Lewin KJ, Riddell RH, Shimoda T *et al.* Differences in diagnostic criteria for gastric carcinoma between Japanese and Western pathologists. *Lancet* 1997; **349**: 1725–1729.
18 Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM *et al.* The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000; **47**: 251–255.
19 Sue-Ling HM, Johnston D, Martin IG, Dixon MF, Lansdown MR, McMahon MJ *et al.* Gastric cancer: a curable disease in Britain. *BMJ* 1993; **307**: 591–596.
20 Sasako M, Kinoshita T, Maruyama K. Prognosis of early gastric cancer. *Stom Intest* 1993; **28**: 139–146.
21 Yokoi C, Gotoda T, Hamanaka H, Oda I. Endoscopic submucosal dissection allows curative resection of local recurrent early gastric cancer after prior endoscopic mucosal resection. *Gastrointest Endosc* 2006; **64**: 212–218.

Original Paper

Prognostic Significance of Peritoneal Washing Cytology in Patients with Potentially Resectable Gastric Cancer

Toshio Nakagohri MD, Yasuo Yoneyama MD, Taira Kinoshita MD, Masaru Konishi MD
Kazuto Inoue MD, Shinichiro Takahashi MD
Department of Surgery, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa
Chiba 277-8577, Japan
Corresponding Author: Toshio Nakagohri MD, PhD, Department of Surgery
National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa 277-8577, Japan
Tel: +81 4 7133 1111, Fax: +81 4 7131 9960, E-mail: tnakagor@east.ncc.go.jp

ABSTRACT
Background/Aims: The prognostic value of cytological examination of intraoperative washings in potentially resectable gastric cancer is controversial.
Methodology: Between February 1993 and August 2001, clinicopathological features and surgical outcome of 26 consecutive patients with gastric cancer with positive cytological findings of peritoneal washings without peritoneal dissemination were retrospectively analyzed.
Results: The overall 1, 2, 3-year survival rates for 26 patients were 69%, 35%, and 0%, respectively. The median survival was 17.5 months. The median survival of patients with curative resection (n=16) and non-curative resection (n=10) was 19 months and 12.5 months, respectively. There was no significant difference in survival between curative resection and non-curative resection (p=0.10). Recurrent disease frequently occurred as peritoneal dissemination (69%). No patient survived for more than 34 months.
Conclusions: Aggressive surgical resections do not provide any survival benefit for gastric cancer with positive cytological findings of peritoneal washings even in the absence of peritoneal dissemination.

KEY WORDS:
Peritoneal washing cytology; Gastric cancer; Peritoneal dissemination; Gastrectomy

INTRODUCTION

Gastric cancer with positive cytological findings of peritoneal washings is generally considered to be an advanced disease, because it is frequently associated with peritoneal dissemination (1-4). However, positive cytological findings of peritoneal washings without definite peritoneal dissemination are sometimes encountered in advanced gastric cancer. The prognostic value of cytological examination of intraoperative washings in potentially resectable gastric cancer is not fully understood (5-7). The efficacy of gastrectomy for gastric cancer with positive cytological findings of peritoneal washings without peritoneal dissemination is also controversial (8-9). In this study, we analyzed our 10-year experience of gastric cancer with positive cytological findings of peritoneal washings in the absence of peritoneal dissemination.

METHODOLOGY

Between February 1993 and August 2001, 26 consecutive patients with gastric cancer with positive cytological findings of peritoneal washings without peritoneal dissemination were retrospectively analyzed in this study. Clinicopathological features of these patients and surgical outcome after gastrectomy (curative or non-curative) were investigated. Patients with liver metastasis were excluded in this study. All 26 patients were followed after the operation. Follow-up of patients ranged from 2 to 34 months (median 17.5 months). The overall survival analysis included all deaths, such as in-hospital death or death of unrelated cause.

Specimens for cytological examination were obtained before manipulation of the tumor at laparotomy. Isotonic saline (100mL) was instilled into the pelvis. After manual agitation, the washings were retrieved by aspiration. After centrifugation for 3 minutes, direct smears were prepared and fixed in 95% ethanol. Two slides were prepared for each patient and were stained using the Papanicolaou method. All slides were reviewed by three cytopathologists.

The clinicopathological features of gastric cancer with positive cytological findings of peritoneal washings without peritoneal dissemination were investigated with regard to age, sex, tumor size, histopathological findings, and outcome.

Statistical analysis was performed by chi-squared test and Student's t-test, when appropriate. Cumulative survival rates were generated by Kaplan-Meier method. The overall survival curve includes all deaths. The survival curves were compared by gener-

Hepato-Gastroenterology 2008; 55:1913-1915

TABLE 1 Characteristics of Patients with Gastric Cancer with Positive Cytological Findings of Peritoneal Washings without Peritoneal Dissemination

	(n=26)
Age year (mean)	61
Gender (male/female)	10/16
Tumor size (cm)	9.9 (range 3.3-19.0)
Histological findings	
Poorly diff. ca.	16
Moderately diff. tubular ca.	7
Well diff. tubular ca.	1
Papillary ca.	1
Mucinous ca.	1
Involved margin (%)	27
Lymph node metastasis (%)	88
Distal/Total gastrectomy	15/11
Curative (R0)/Non-curative (R1 or R2)	16/10

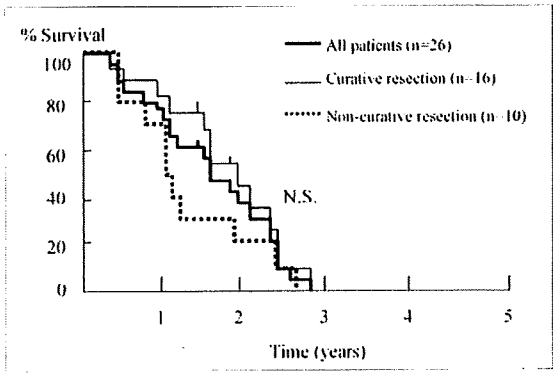

FIGURE 1 Survival rates for the patients with gastric cancer with positive cytological findings of peritoneal washings without peritoneal dissemination.

alized Wilcoxon test. Differences were considered significant at $p<0.05$.

RESULTS

The characteristics of gastric cancer with positive cytological findings of peritoneal washings without peritoneal dissemination (n=26) are shown in **Table 1**. The mean age of patients was 61 years. The mean size of the tumor was 9.9cm (range: 3.3-19.0). Gastric cancers comprised 16 poorly differentiated tubular adenocarcinomas, 7 moderately differentiated tubular adenocarcinomas, 1 well differentiated tubular adenocarcinoma, 1 papillary adenocarcinoma and 1 mucinous adenocarcinoma. Patients were treated by total gastrectomy (n=11) or distal gastrectomy (n=15). None of the 26 patients died within 30 days of operation, and all patients were discharged from hospital after surgery. Histopathological examination revealed that 7 patients had invasion of the surgical margin. The frequency of nodal involvement was 88%. The mean number of metastatic lymph nodes and the mean number of resected lymph nodes were 17 and 48, respectively. Metastasis in para-aortic lymph nodes was observed in 6 patients (23%).

The survival curves following surgical treatment are shown in **Figure 1**. The overall 1, 2, 3-year survival rates for the 26 patients with positive cytological findings of peritoneal washings without peritoneal dissemination were 69%, 35%, and 0%, respectively **(Figure 1)**. The median survival of the 26 patients was 17.5 months. No patient survived for more than 34 months after gastrectomy. Cumulative 1, 2, 3-year survival rates for patients after curative (R0) resection (n=16) and those after non-curative (R1 or R2) resection (n=10) were 81%, 44%, 0% and 50%, 20%, 0%, respectively (10). There was no significant difference in survival between the two groups ($p=0.10$). The median survival of patients with curative resection and non-curative resection was 19 months and 12.5 months, respectively. Numbers of disease recurrence and deaths after surgery are shown in **Table 2**. Recurrent disease occurred in 24 patients. The sites of recurrence were as follows: peritoneum (n=18), lymph nodes (n=11), liver (n=6), ovary (n=4), bone (n=3), lung (n=1), and pancreas (n=1). Two patients are now alive and disease free at 17 and 13 months after surgery.

TABLE 2 Numbers of Disease Recurrence and Death after Surgical Treatment

	Curative (n=16)	Non-curative (n=10)	Total (n=26)
Numbers of death	13	10	23
Death due to recurrence	12	9	21
Death from other causes in patients with recurrence	1	1	2
Alive with recurrence	1	0	1
Alive without recurrence	2	0	2

DISCUSSION

The main conclusion of this single-institute study was that patients with gastric cancer with positive peritoneal washing cytological findings had a very poor prognosis after surgical resection, even in the absence of peritoneal dissemination. It has been reported that the presence of cancer cells in peritoneal washings in patients with gastric cancer indicates a poor prognosis (1-4). Bonenkamp *et al.* reported that survival of those with positive cytological findings of peritoneal washings was significantly lower than that of those with negative findings, irrespective of the procedure employed (1). Kodera *et al.* reported that patients with positive cytological findings of peritoneal washings were confirmed to have a greater risk of recurrence in the form of peritoneal carcinomatosis and hence a significantly worse prognosis (5). These results suggest that positive cytological findings of peritoneal washings in patients with gastric cancer imply invisible microperitoneal dissemination.

Are there any survival benefits of surgical resection for gastric cancer with positive washing cytology in the absence of definite peritoneal dissemination? Fujimoto *et al.* reported a 22.2% 5-year survival rate

for patients with gastric cancer with positive cytological findings of peritoneal washings after curative resection (2). Nekarda *et al.* reported an estimated 5-year survival rate of 8% for patients with free peritoneal tumor cells after complete resection (7). However, several studies reported that positive cytological findings of peritoneal washings contraindicated further surgical treatment. Burke *et al.* concluded that patients with positive lavage cytology had stage IV disease, even in the absence of macroscopic peritoneal dissemination, and cytological examination of laparoscopically obtained lavage fluid was a rapid technique for identifying the subset of M0 patients who are unlikely to benefit from resection alone (4). Kodera *et al.* reported that positive cytological findings may indicate that gastrectomy should be avoided for Borrmann type 4 gastric cancer, because the outcome of patients with positive cytological findings of peritoneal washings and no other residual disease was extremely poor and was equivalent to that of patients undergoing noncurative R2 resection (8). Wu *et al.* reported that when free cancer cells were present in the washing fluid, the gastric cancer was incurable and simply gastrectomy without additional lymphadenectomy was the optimal treatment strategy (9). In this study, there was no significant difference in survival between patients with curative resection and those with non-curative resection (p=0.10). However, there was a tendency for patients with curative resection to show a more favorable outcome than those with non-curative resection. Thus, the efficacy of gastrectomy for gastric cancer with positive cytological findings of peritoneal washings is still controversial. Further confirmatory studies are needed to evaluate the role of gastrectomy for gastric cancer with positive cytological findings of peritoneal washings without peritoneal dissemination.

REFERENCES

1 **Bonenkamp JJ, Songun I, Hermans J, van de Velde CJ:** Prognostic value of positive cytology findings from abdominal washings in patients with gastric cancer. Br J Surg 1996; 83:672-674.

2 **Fujimoto T, Zhang B, Minami S, Wang X, Takahashi Y, Mai M:** Evaluation of intraoperative intraperitoneal cytology for advanced gastric carcinoma. Oncology 2002; 62:201-208.

3 **Bando E, Yonemura Y, Takeshita Y, Taniguchi K, Yasui T, Yoshimitsu Y, Fushida S, Fujimura T, Nishimura G, Miwa K:** Intraoperative lavage for cytological examination in 1,297 patients with gastric carcinoma. Am J Surg 1999; 178:256-262.

4 **Burke EC, Karpeh MS Jr, Conlon KC, Brennan MF:** Peritoneal lavage cytology in gastric cancer: an independent predictor of outcome. Ann Surg Oncol 1998; 5:411-415.

5 **Kodera Y, Yamamura Y, Shimizu Y, Torii A, Hirai T, Yasui K, Morimoto T, Kato T:** Peritoneal washing cytology: prognostic value of positive findings in patients with gastric carcinoma undergoing a potentially curative resection. J Surg Oncol 1999; 72:60-65.

6 **Hayes N, Wayman J, Wadehra V, Scott DJ, Raimes SA, Griffin SM:** Peritoneal cytology in the surgical evaluation of gastric carcinoma. Br J Cancer 1999; 79:520-524.

7 **Nekarda H, Gess C, Stark M, Mueller JD, Fink U, Schenck U, Siewert JR:** Immunocytochemically detected free peritoneal tumour cells (FPTC) are a strong prognostic factor in gastric carcinoma. Br J Cancer 1999; 79:611-619.

8 **Kodera Y, Yamamura Y, Ito S, Kanemitsu Y, Shimizu Y, Hirai T, Yasui K, Kato T:** Is Borrmann type IV gastric carcinoma a surgical disease? An old problem revisited with reference to the result of peritoneal washing cytology. J Surg Oncol 2001; 78:175-182.

9 **Wu CC, Chen JT, Chang MC, Ho WL, Chen CY, Yeh DC, Liu TJ, P'eng FK:** Optimal surgical strategy for potentially curable serosa-involved gastric carcinoma with intraperitoneal free cancer cells. J Am Coll Surg 1997; 184:611-617.

10 TNM classification of malignant tumours. 6th Edition. New York: Wiley-Liss; 2002.

早期胃癌における術前MDCTの有用性の検討

国立がんセンター東病院上腹部外科
信岡大輔　後藤田直人　小西大
中郡聡夫　高橋進一郎　木下平

DIAGNOSTIC PERFORMANCE OF MDCT FOR EARLY GASTRIC CANCER

Daisuke NOBUOKA, Naoto GOTOHDA, Masaru KONISHI,
Toshio NAKAGOHRI, Shinichiro TAKAHASHI and Taira KINOSHITA
Department of Surgery, National Cancer Center Hospital East

日本臨床外科学会雑誌　第69巻　6号　別刷

(平成20年6月25日発行)

日臨外会誌　69（6），1303—1307，2008

原　著

早期胃癌における術前MDCTの有用性の検討

国立がんセンター東病院上腹部外科
信岡大輔　後藤田直人　小西　大
中郡聡夫　高橋進一郎　木下　平

目的：早期胃癌の術前検査におけるMDCTの有用性を評価し，必須か，あるいは省略可能かにつき検討する．対象および方法：2006年の1年間に当院で行った胃癌手術のうち術前診断T1の144例を対象とし，術前検査所見を手術所見および病理所見と比較検討した．結果：リンパ節転移診断の感度は7％，特異度は97％，正診率は87％であった．術前MDCTにて検出された他疾患には胆嚢結石・肝血管腫・肝嚢胞・腎嚢胞等があるも，胆嚢疾患以外は術式決定に影響を及ぼさず，またその殆どが超音波検査で検出可能であった．考察：MDCTは早期胃癌では腫瘍描出能が悪いうえリンパ節転移診断の正診率も低く，術前stagingとしての有用性は低いと考えられた．MDCTの結果で手術操作の変更・追加を要した事例は認められなかった．結論：早期胃癌の術前検査においてMDCTの有用性は低く超音波検査で代用できる可能性が示唆された．

索引用語：早期胃癌，術前検査，multidetector-row CT，リンパ節転移，超音波検査

緒　言

今日の胃癌治療はガイドラインにより病期ごとに適応となる治療法が明示されている[1]が，治療法選択のためには術前に進行度を正確に診断することが不可欠である．胃癌の術前検査としては，上部消化管内視鏡と生検，上部消化管造影，腹部CT検査，腹部超音波検査，超音波内視鏡などが日常的に行われている．

近年の画像診断の進歩は目覚ましく，なかでもmultidetector-row CT（以下，MDCT）の登場とワークステーションの発達はその画像解析能において従来のCT検査をはるかに凌駕した[2][3]．その結果MDCTは現在，胃癌の術前検査としてstagingと他病変検索の目的で広く用いられている．MDCTはその優れた空間分解能により，進行胃癌の周囲への進展，リンパ節転移，肝転移，腹膜転移の描出に有用とされる[4]~[6]．しかし，一方で早期胃癌における原発巣の深達度およびリンパ節転移診断などについては，満足すべき報告はない[7]~[10]．またMDCTはその検査の低侵襲性・簡便性と得られる情報量の多さから当院では撮影件数が増加の一途を辿っており，現在その飽和したCT検査件数から内科系外科系を問わず，必要性の見直しが迫られている．こうした実情は全国の基幹施設など患者集中のみられる多くの施設で抱える問題ではないかと推測する．

そこでわれわれは，今回早期胃癌の術前検査におけるMDCTの有用性を評価し，MDCTは必須か，あるいは省略可能かどうかにつき検討を行った．

対象および方法

2006年1月より12月までの1年間に当院で行った胃癌手術280例のうち，術前内視鏡および上部消化管造影にてcT1と診断された144例を対象とし（**図1**），術前検査所見を手術所見および切除標本の病理組織学的所見と比較してMDCTの有用性につき検討した．

MDCTは4列もしくは16列検出器CT装置を使用し，画像再構成は5 mmスライス厚を基本とした．造影剤アレルギーなどの特別な理由がない限り非イオン性ヨード系造影剤を使用し，造影前と門脈相（造影剤注入後70秒）とで撮影した．

進行度診断は第13版胃癌取扱い規約[11]に従った．術前リンパ節転移診断に関してはMDCTで短軸径10 mm以上を基本とし，そこに形状・造影効果の所見を加えて総合的に判定した．全症例の術前診断は放射線

2008年2月20日受付　2008年4月8日採用
〈所属施設住所〉
〒277-8577　柏市柏の葉6－5－1

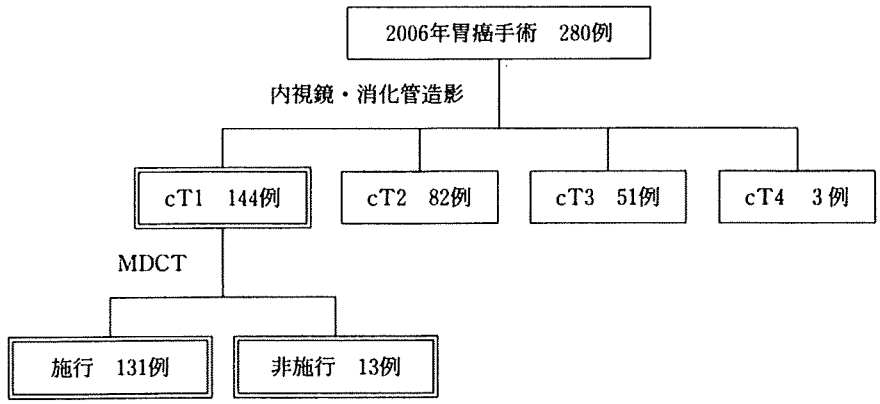

図1　症例の内訳

表1　MDCTによる早期胃癌術前のリンパ節転移診断能

	病理組織診	
	リンパ節転移あり	リンパ節転移なし
術前MDCTにて リンパ節転移あり	1 (pN1)	3
術前MDCTにて リンパ節転移なし	14 (pN1：13例/pN2：1例)	113

感度＝7％
特異度＝97％
陽性適中率＝25％
陰性適中率＝89％
正診率＝87％

科・内科・外科合同の術前カンファレンスにて最終確認した．

結　果

144例全例において，開腹下にリンパ節郭清を伴う根治的手術が行われた．組織学的にpT1であったのは134例で，10例がpT2であった．全144例中MDCTが行われたのは131例で（**図1**），全例に静注造影剤が使用されていた．そのうち4例がMDCTにてリンパ節転移ありと術前診断されたが，この中で実際にリンパ節転移を認めたのは1例のみであった(pN1)．また，術前MDCTでリンパ節転移なしと診断された127例中14例に病理所見でリンパ節転移を認めた（pN1が13例・pN2が1例）．リンパ節転移診断の感度は7％，特異度は97％，陽性適中率25％，陰性適中率89％，正診率87％であった（**表1**）．

ルーチンの術前MDCTにて検出された他疾患は胆嚢疾患（結石・ポリープ・腺筋症），肝疾患（血管腫・嚢胞），膵疾患（嚢胞），腎疾患（嚢胞・結石・血管筋脂肪腫），副腎疾患（腫瘍），骨盤内疾患（子宮筋腫・卵巣嚢腫・総腸骨動脈壁在血栓）であった．MDCTおよび超音波検査が両方施行された102例の検討では，胆嚢結石・胆嚢ポリープで同時に胆嚢摘出術を施行した9例以外は術式決定に影響を及ぼさず，またその多くが超音波検査でも検出可能であった（**表2**）．

この期間内にMDCTの所見を理由に手術を中止・延期した症例は認めず，また術前MDCTを省略した13例には省略したことに起因する術中・術後の問題点は一切認めなかった．

考　察

早期胃癌で起こりうるほとんどの転移形態はリンパ節転移であり[12]，最も重要な予後因子とされている[13]．このため治療法の選択にあたっては術前にリンパ節転移を正確に把握することが重要で，MDCTを術前に行う大きな理由の一つである．胃癌治療ガイドラインにおいても，深達度T1における治療選択はリンパ節転移度に応じて多岐に渡る[1]．しかし大きさ，形状，造影効果に頼った現状の術前リンパ節転移診断には限界があり，過去の報告から早期胃癌におけるリンパ節転移

表2　術前 MDCT にて検出された他疾患の詳細

	検出した検査法			
	MDCT および超音波	MDCT のみ	超音波のみ	
胆嚢疾患（結石・ポリープ・腺筋症）	6	3	6	→ 9例が同時に胆摘を付加
肝疾患（血管腫・嚢胞）	18	18	7	→ 全例経過観察
膵疾患（嚢胞）	0	1	1	
腎疾患（嚢胞・結石・血管筋脂肪腫）	5	6	11	
副腎疾患（腫瘍）	2	1	0	
骨盤内疾患（子宮筋腫・卵巣嚢腫・総腸骨動脈壁在血栓）	0	6	0	

診断についての満足すべき結果は得られていない[6)14)~20)]．診断に multiplanar reformation（MPR）像を組み合わせることによりリンパ節と胃周囲血管の区別がより明瞭になるとの最近の報告があるが，それでも正診率の向上は不十分とされている[21)]．また，今回の検討結果からも早期胃癌におけるリンパ節転移診断の感度は7％と低く，術前 MDCT にてリンパ節転移度を正確に把握することは困難と考えられるため，現時点では術前 MDCT の有用性は示されなかった．特異度が97％と高い割に感度が7％と低い理由としては，リンパ節転移の診断基準が狭すぎる可能性が示唆され，結果的に131例中14例(11％)が understaging に陥っていた．また，MDCT における胃癌の深達度診断については，進行癌では有用だが早期癌では精度が低いとする報告が多く，この点においても早期胃癌に対する術前 MDCT の有用性は示されていない[8)~10)]．

腹腔内に並存する他疾患の検索も，胃癌術前に MDCT を行う目的の重要な一つに挙げられる．高齢化社会においては胃癌手術を受ける患者にも高齢化を認め，それに伴い併存疾患を有する症例の割合は年代を経るごとに増えてきている．術前にこれらの併存疾患を確実に把握し，先行手術や同時手術，あるいは術式の変更など，個々の患者の状況に応じて適切に対応することがテーラーメイド医療として求められる．しかし，今回の検討において検出された併存疾患は胆嚢結石・胆嚢ポリープを手術時に同時切除した症例を9例（9％）認めた以外は治療方針や術式決定に影響を及ぼさず，また胆嚢疾患の殆どが超音波検査でも検出可能であった．この点においても術前にルーチンで行う MDCT の有用性は低いと考えられ，まずは全例に対し超音波検査を行い，何か異常所見を認めた場合にのみ MDCT を行うという検査位置づけが効率的ではないかと思われた．

また，胃周囲の血管走行の詳細な把握により術前シミュレーションに利用できることも MDCT の利点の一つとされる．MDCT により得られたスライスデータをワークステーションに転送して処理することにより，術中のイメージに即したリアルな三次元画像を得ることができる[22)~24)]．徳永ら[25)]は安全で正確な手術のためには血管走行の確実な把握が必須と述べ，MDCT および血管再構築（3D-CT angiography）にて術前診断した Adachi VI型の手術症例を報告している．また Okabayashi ら[26)]は後胃動脈の走行を術前に把握することが外科治療に有用と述べている．確かに血管走行の把握は手術の一助となりうるが，手術症例全例に thin-slice の MDCT および3D-CT angiography を施行するのは人的労力および経費の問題から困難であり，通常は腹腔鏡手術や拡大郭清を予定する症例に限って施行しているのが実状と考えられる．しかし腹腔鏡下手術などに際し術前に行われる thin-slice の MDCT や3D-CT angiography の有用性が期待される一方で，5 mm スライス厚での MDCT で指摘し得なかった血管走行の異常は術中にしばしば経験することがある．開腹下手術に限っては実際に術中初めて血管の走行異常に気付いても慎重かつ臨機応変な対応により安全な D2郭清手術は可能である．

以上，今回の検討では早期胃癌におけるルーチンで行われる術前 MDCT の有用性は低いことが示唆された．近年の著しい普及により広く MDCT が行われている現状があるが，早期胃癌の必要十分な術前検査として，医療費節約の観点，患者への過剰な放射線被爆の問題からもまずは超音波検査を行うことで多くの症

例でMDCTが省略可能ではないかと考えられた．当然ながら全症例に対し超音波検査で代用可能という訳ではなく，肥満など体型的な問題から腹部超音波検査による腹腔内の描出が不良な場合や，また超音波検査で胃壁肥厚や胃周囲リンパ節腫大が疑われた場合などは，躊躇なくMDCTを追加し，さらなる術前評価を行うべきと考える．

結　語

今回の検討から現状では内視鏡検査，上部消化管造影検査を行って胃癌と診断されたときに深達度SM以浅と考えられる早期胃癌の術前検査においてはルーチンで行われるMDCTの有用性は低いことが示唆された．まずは超音波検査を行い，必要と思われる症例に限りMDCTを追加施行することが効率で有効と考えられた．

文　献

1) 日本胃癌学会編：胃癌治療ガイドライン（医師用）．第2版，金原出版，東京，2004
2) Prokop M : General principles of MDCT. Eur J Radiol 45 : S4—S10, 2003
3) Blackshaw GR, Stephens MR, Lewis WG, et al : Progressive CT system technology and experience improve the perceived preoperative stage of gastric cancer. Gastric Cancer 8 : 29—34, 2005
4) Shinohara T, Ohyama S, Yamaguchi T, et al : Preoperative TMN staging of advanced gastric cancer with multi-detector row computed tomography. JMAJ 48 : 175—182, 2005
5) Habermann CR, Weiss F, Riecken R, et al : Preoperative staging of gastric adenocarcinoma : comparison of helical CT and endoscopic US. Radiology 230 : 465—471, 2004
6) Yajima K, Kanda T, Ohashi M, et al : Clinical and diagnostic significance of preoperative computed tomography findings of ascites in patients with advanced gastric cancer. Am J Surg 192 : 185—190, 2006
7) Kim HJ, Kim AY, Oh ST, et al : Gastric cancer staging at multi-detector row CT gastrography : comparison of transverse and volumetric CT scanning. Radiology 236 : 879—885, 2005
8) Minami M, Kawauchi N, Itai Y, et al : Gastric tumors : radiologic-pathologic correlation and accuracy of T staging with dynamic CT. Radiology 185 : 173—178, 1992
9) Fukaya T, Honda H, Kaneko K, et al : Efficacy of helical CT in T-staging of gastric cancer. J Comput Assist Tomogr 21 : 73—81, 1997
10) Kim JH, Eun HW, Hong SS, et al : Early gastric cancer : virtual gastroscopy. Abdom Imaging 31 : 507—513, 2006
11) 日本胃癌学会編：胃癌取扱い規約．第13版，金原出版，東京，1999
12) Katai H, Sano T : Early gastric cancer : concept, diagnosis, and management. Int J Clin Oncol 10 : 375—383, 2005
13) Yamamura Y, Nakajima T, Ohta K, et al : Determining prognostic factors for gastric cancer using the regression tree method. Gastric cancer 5 : 201—207, 2002
14) 安井昌義，小林研二，藤谷和正他：CTによる胃癌の術前リンパ節転移診断の現状．日臨外会誌 61：618—622，2000
15) 藤村　隆，米村　豊，谷口桂三他：術前CTによる胃癌のリンパ節転移診断．北陸外科会誌　16：23—26，1997
16) Davies J, Chalmers AG, Sue-Ling HM, et al : Spiral computed tomography and operative staging of gastric carcinoma : a comparison with histological staging. Gut 41 : 314—319, 1997
17) Fukuya T, Honda H, Hayashi T, et al : Lymph-node metastasis : efficacy for detection with helical CT in patients with gastric cancer. Radiology 197 : 705—711, 1995
18) Kim HS, Han HY, Choi JA, et al : Preoperative evaluation of gastric cancer : value of spiral CT during gastric arteriography (CTGA). Abdom Imaging 26 : 123—130, 2001
19) Kim AY, Kim HJ, Ha HK : Gastric cancer by multidetector row CT : preoperative staging. Abdom Imaging 30 : 465—472, 2005
20) Hur J, Park MS, Lee JH, et al : Diagnostic accuracy of multidetector row computed tomography in T-and N staging of gastric cancer with histopathologic correlation. J Comput Assist Tomogr 30 : 372—377, 2006

21) Chen CY, Hsu JS, Wu DC, et al : Gastric cancer : preoperative local staging with 3D multidetector row CT-correlation with surgical and histopathologic results. Radiology 242 : 472—482, 2007
22) 李　相雄，野村栄治，奥田準二他：術前診断のポイント—マルチスライス CT による術前シミュレーション．手術　60：275—280，2006
23) 松木　充，奥田準二，可児弘行他：腹腔鏡下胃癌，大腸癌手術に対するマルチスライス CT による術前シミュレーション．日独医報　48：235—247，2003
24) Matsuki M, Tanikake M, Kani H, et al : Dual-phase 3D CT angiography during a single breath-hold using 16-MDCT : assessment of vascular anatomy before laparoscopic gastrectomy. AJR 186 : 1079—1085, 2006
25) 徳永正則，大山繁和，比企直樹他：MDCT により術前診断した Adachi VI型の総肝動脈走行異常を伴った胃癌の 5 例．日臨外会誌　67：2604—2608，2006
26) Okabayashi T, Kobayashi M, Morishita S, et al : Confirmation of the posterior gastric artery using multi-detector row computed tomography. Gastric cancer 8 : 209—213, 2005

DIAGNOSTIC PERFORMANCE OF MDCT FOR EARLY GASTRIC CANCER

Daisuke NOBUOKA, Naoto GOTOHDA, Masaru KONISHI,
Toshio NAKAGOHRI, Shinichiro TAKAHASHI and Taira KINOSHITA
Department of Surgery, National Cancer Center Hospital East

Background : To completely remove tumors or to avoid excessive treatments, a precise assessment of cancer spread before surgery is important to determine the best treatment strategy for patients with early gastric cancer (EGC). However, previous results of preoperative staging on EGC have not been satisfactory. Purpose : The purposes of this study were to assess the diagnostic performance of multidetector-row computed tomography (MDCT) and to examine whether routine MDCT was necessary for preoperative diagnosis of EGC. Patients and method : During 1-year period, 280 consecutive patients with gastric cancer underwent surgery in our institution. Among these 280 patients, 144 were diagnosed preoperatively as EGC with gastroscopy and upper gastrointestinal series. MDCT findings were compared with operative findings and histopathologic studies of the resected specimens. Results : Among 144 patients, 131 underwent preoperative MDCT. The sensitivity, specificity and accuracy of MDCT for detection of lymph node metastasis were 7%, 97% AND 87%, respectively. Cholelithiasis, liver hemangioma, liver cyst, renal cyst were detected with routine MDCT. According to the result of MDCT cholecystectomy was added on 9 patients. Conclusions : MDCT was insufficient for assessing regional lymph node metastasis. It is suggested that we could omit MDCT from preoperative examinations for patients with EGC.

Ann Surg Oncol
DOI 10.1245/s10434-008-0290-7

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

The Prognostic Impact of Isolated Tumor Cells in Lymph Nodes of T2N0 Gastric Cancer: Comparison of American and Japanese Gastric Cancer Patients

T. Fukagawa[1], M. Sasako[1], T. Shimoda[2], T. Sano[1], H. Katai[1], M. Saka[1], G. B. Mann[3], M. Karpeh[4] D. G. Coit[5], and M. F. Brennan[5]

[1]Gastric Surgery Division, National Cancer Center Hospital, Tokyo, Japan; [2]Clinical Laboratory Division, National Cancer Center Hospital, Tokyo, Japan; [3]Department of Surgery, The Royal Melbourne Hospital, Parkville, VIC, Australia; [4]Surgical Oncology, Beth Israel Medical Center, New York, NY; [5]Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

ABSTRACT

Background. The clinical significance of immunohistochemically detected isolated tumor cells (ITC) in lymph nodes of gastric cancer patients is controversial. This study examined the prognostic impact of ITC on patients with early-stage gastric cancer in two large volume centers in the United States and Japan.

Methods. Fifty-seven patients with T2N0M0 gastric carcinoma who underwent gastric resection between January 1987 and January 1997 at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York and 107 patients resected at National Cancer Center Hospital (NCCH) in Tokyo between January 1984 and December 1990 were studied. The sections were newly prepared from each lymph node for immunohistochemical staining for cytokeratin. Lymph nodes and original specimens from MSKCC were examined by pathologists in NCCH. The prognostic significance of the presence of ITC in lymph nodes was investigated in patients of both institutions.

Results. ITC were identified in 30 of 57 patients (52.6%) at MSKCC and in 38 of 107 patients (35.5%) at NCCH. In both institutions, there was no significant difference in the prognosis of the studied patients with or without ITC ($P = .22$, .86 respectively).

Conclusions. The presence of ITC detected by immunohistochemistry in the regional lymph nodes did not affect the prognosis of American and Japanese patients with T2N0M0 gastric carcinoma who underwent gastrectomy with D2 lymph node dissection.

The complete removal of tumor is the only potentially curative treatment for patients with gastric cancer. Locally advanced gastric cancer frequently recurs after curative operation and even early gastric cancer relapse.[1] In patients with recurrent disease, there must have been residual tumor cells in the form of occult micrometastases that were left behind at the time of apparently curative surgery.

Recent advances in immunohistochemistry (IHC) and molecular biology allow the identification of discrete and occult tumor cells in the lymph nodes of the patients with malignant disease, which remain undetected by standard hematoxylin and eosin (H&E) staining.[2] After some debate regarding the terminology of occult tumor cells, micrometastases (MM) are defined as deposits of tumor cells of 2 mm or less, but those larger than 0.2 mm and isolated tumor cells (ITC) are defined as single or clusters of tumor cells of 0.2 mm or less.[3,4]

The aim of this study is to analyze whether the presence of ITC in lymph nodes originally considered tumor-negative from curatively resected gastric cancer patients led to worse prognosis in two large-volume centers in the United States and Japan. This comparison would also address the hypothesis that gastric cancer in the West and Japan are different.[5]

First Received: 4 November 2008

T. Fukagawa
e-mail: tfukagaw@ncc.go.jp

Published online: 10 January 2009

MATERIALS AND METHODS

Patients Source

MSKCC Between January 1987 and December 1997, 1,028 patients underwent gastric resection for gastric carcinoma at Memorial Sloan Kettering Cancer Center (MSKCC) in New York. During this period, 102 consecutive patients were classified with pT2N0M0 disease in the database maintained in the Gastric and Mixed Tumour Department. Two newly prepared sections from each lymph node for H&E staining and IHC and original specimens of resected primary gastric carcinoma were transported to National Cancer Center Hospital (NCCH), Tokyo. Of the 102 cases, 74 were available for pathological evaluation of both lymph nodes and primary tumors by Japanese investigators. In some cases, T stage (depth of tumor invasion) was revised at this review: 11 to T1, 61 to T2, and 2 to T3. In 4 of 61 T2 cases, definite nodal involvement was found by H&E staining at this review. The remaining 57 patients were included in this study.

NCCH Between January 1984 and December 1990, 1,757 patients underwent gastrectomy for gastric carcinoma at the NCCH. During this period, 118 patients were classified with pT2N0M0 disease on the database maintained in the Gastric Surgery Division. Five patients whose paraffin blocks were lost, two patients whose T stage was wrongly recorded, and another two patients who were completely lost to follow-up were excluded from the analysis. In two of 109 patients whose paraffin blocks were available for newly cut, definite nodal involvement was found at this review by H&E. The remaining 107 patients, already analyzed in a previous report,[6] were also evaluated in comparison and combination with the cases of MSKCC.

All patients of both institutions underwent partial or total gastrectomy with systematic lymphadenectomy including the complete dissection of perigastric lymph nodes and partial or complete removal of the second-tier lymph nodes along common hepatic, proper hepatic, celiac, and splenic arteries.

Pathology and Immunohistochemistry

All specimens were formalin fixed and paraffin embedded. Lymph nodes were examined by one cross section through the center of each lymph node. Tumors were classified histologically into differentiated and undifferentiated types according to the World Health Organization tumor classification system.[7] The differentiated type includes well or moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma, whereas the undifferentiated type includes poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma. Two consecutive sections measuring 4 μm thick were newly cut for H&E staining and IHC.

IHC was performed using AE1/AE3 (Boehringer Mannheim, Indianapolis, IN), a monoclonal antibody that is reactive with a broad spectrum of human cytokeratins. The details of procedures were previously reported.[6] ITC were defined as single or cluster of tumor cells of 0.2 mm or less detected by cytokeratin-specific IHC that could not be detected by ordinary H&E staining.

Statistical Analysis

Statistical analysis was carried out using SPSS software, version 11.5 (SPSS Inc, Chicago, IL). The clinicopathological features of studied cases (United States vs Japan or ITC + vs −) were compared by a chi-square test or a *t*-test. The Kaplan–Meier method was used for making survival curves, and the log-rank test for evaluating the statistical difference between survival curves.

RESULTS

MSKCC

The mean age of studied patients was 67.8 ± SD 12.0 (range, 35–93).

In total, 1,144 lymph nodes of 57 patients were studied (median, 19; range, 1–61).

The patients had 22 and 35 differentiated and undifferentiated type of gastric carcinoma, respectively.

ITC were identified in 30 patients (52.6%) and in 97 lymph nodes (8.48%). The median number of involved lymph nodes with ITC was 3 (range, 1–13) per patient. Seventeen patients had ITC of single-cell type, and 13 had cluster type. The presence of ITC was not correlated with the subtype of gastric carcinoma (10 of 22 patients with differentiated carcinoma vs. 20 of 35 patients with undifferentiated carcinoma. $P = .39$).

The median follow-up for surviving patients was 113 months (range, 8–205). Disease recurrence was observed in 9 of 57 patients; 3 patients had ITC, and 6 patients did not. Twenty patients died of other causes. There were 3 of 30 patients with ITC and 6 of 27 patients without ITC who developed tumor recurrence. The incidence of recurrent disease did not correlate with the presence of ITC ($P = .21$).

The 5-year and 10-year survival rates of patients with or without ITC were 82%, 69% and 64%, 42%, respectively. There was no significant difference between survivals of patients with or without ITC ($P = .22$) (Fig. 1). The type of ITC did not affect survival of patients.

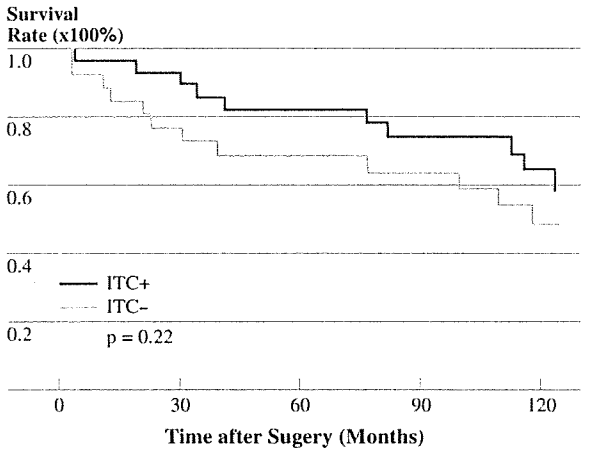

FIG. 1 No significant difference between survivals of patients with or without ITC ($P = .22$) in MSKCC

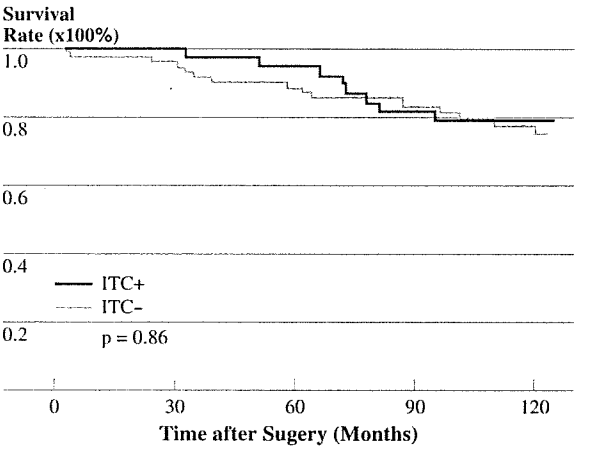

FIG. 2 No significant difference between survivals of patients with or without ITC ($P = .87$) in NCCH

NCCH

The mean age of studied patients was 58.3 ± SD 11.3 (range, 34–88). In total, 4,484 lymph nodes of 107 patients were studied (median, 33; range, 6–173); 55 had differentiated, and 52 had undifferentiated type.

ITC were identified in 38 patients (35.5%) and in 87 lymph nodes (1.94%). The median number of involved lymph nodes with ITC was 1.5 (range, 1–10) per patient. There were 17 patients with ITC of single-cell type and 21 with cluster type. The presence of ITC was not correlated with the subtype of gastric carcinoma (16 of 55 patients with differentiated carcinoma vs. 22 of 52 patients with undifferentiated carcinoma. $P = .15$).

The median follow-up was 120 months (range, 71–185). Disease recurrence was observed in 6 of 107 patients. Two patients had ITC, and four patients did not. Twelve patients died of other causes. There were 2 of 38 patients with ITC and 6 of 69 patients without ITC who developed tumor recurrence. The incidence of recurrent disease did not correlate with the presence of ITC ($P = .91$).

The 5-year and 10-year survival rates of patients with or without ITC were 94%, 89% and 79%, 74%, respectively. There was no significant difference between survivals of patients with or without ITC ($P = .87$) (Fig. 2). The type of ITC did not affect the survival of patients.

DISCUSSION

The current results suggest that the presence of ITC detected by IHC in the lymph nodes of patients with T2N0 gastric carcinoma did not affect their prognosis and that such ITC does not imply systemic disease that is beyond cure with local treatment.

The clinical significance of occult tumor cells in the lymph nodes of gastric cancer patients has been controversial. A negative impact on prognosis was reported by some authors,[8–11] but not by others.[6,12–15] In general, the studies including a majority of early gastric cancer patients have a problem of less disease specific death for prognostic evaluation. If many cases of locally advanced gastric cancer that invades to the serosal surface of the stomach are included, the prognostic significance of occult tumor cells in lymph nodes is easily confounded by frequent peritoneal dissemination.[16] For this reason, patients with early-stage disease staged as T2N0 by postoperative examination were analyzed. Analysis of a large group of uniform tumors allows more definitive conclusions to be drawn regarding the prognostic impact.

Occult tumor cells have recently been classified into ITC, which are single cells or a small cluster that is no larger than 0.2 mm, and MM, which are tumor cells of 2 mm or less but larger than 0.2 mm according to UICC. ITC do not show morphological evidence of metastatic activity such as penetration of a vascular or lymph sinus wall, tumor cell growth, and stromal reaction.[17,18] In some reports, ITC do not become metastatic and will be presumably erased by host immune response.[19] In others, tumorigenicity of a single tumor cell is reported.[20] Does ITC have malignant metastatic potential?[21]

'We cannot answer whether a lymph node including ITC should be dissected, because all of the studied patients underwent standard lymph node dissection.[22] Our adequate lymph node dissection could have caused the outcomes to be the same for patients with or without ITC, but on the other hand ITC in the lymph nodes could be ignored without dissection. If ITC in the lymph nodes has malignant metastatic potential, our data suggest they did not travel beyond the surgical field. In our previous report,

most of ITC were found in perigastric nodes.[6] This may be caused by the good prognosis of T2N0. In more advanced-stage gastric cancer, it is possible ITC can reach further stations or distant organs and lead to poor prognosis. The previous reports[11,23] including advanced-stage gastric cancer patients show the negative prognostic impact of occult tumor cells, but the importance of ITC in clinical outcome is an area of debate.[24–26]

Doekhie et al. reported a similar result to this study, that the presence of occult tumor cells in the lymph nodes in gastric cancer patients did not predict disease recurrence.[14] Patients with fewer than five lymph nodes examined or with many lymph nodes involved by occult tumor cells did not have a worse prognosis if those patients had undergone a D2 dissection in the Dutch trial.[27] Presumably, ITC include both malignant cells that have metastatic potential, and those that do not.

Whether the additional information of ITC can be adopted for clinical practice is an important issue. The strategies of adjuvant therapy for gastric cancer patients have been recently standardized. In the United States, node-positive patients are the indication of adjuvant chemoradiotherapy based on the result of INT0116.[28] In Japan, pt2n0 patients are not the indication of adjuvant chemotherapy, but pt2n1 or pt3 patients are the indication of adjuvant chemotherapy based on a randomized control clinical study.[29] The studied group of pt2n0 patients may be applicants for adjuvant therapy in the United States where complete D2 dissection is not popular except for large-volume centers such as MSKCC. The biological malignant potential of ITC cannot be evaluated from this study, so the clinical application of ITC must be argued carefully.

Our study has the additional value of comparing gastric cancer patients in the United States and Japan from the view of prevalence of ITC. Geographic difference of gastric carcinoma in the West and Japan has been argued.[30–34] The similarity of expression of some oncogenes and the discrepancy of microsatellite instability were previously reported.[35,36] In this study, American patients were significantly more likely to have ITC (30 of 57, 52.6% vs. 38 of 107, 35.5%; $P = .03$), and the incidence of undifferentiated gastric carcinoma was more frequent in American patients, but not significant (35 of 57, 61.4% vs. 52 of 107, 48.6%; $P = .12$). American patients were older than Japanese patients ($P < .0001$). These findings may be accounted for by the biological difference of gastric cancer in the two regions, but they are not connected to the relative worse prognosis of American patients. It may well be that the greater number of lymph nodes resected and examined in Japan makes the diagnosis of T2N0 more accurate in Japan prior to examining for ITC.

In conclusion, the presence of ITC in the lymph nodes of patients with T2N0 gastric carcinoma did not have any prognostic impact, and ITC did not imply the systemic disease in the United States as in Japan.

REFERENCES

1. Sano T, Sasako M, Kinoshita T, Maruyama K. Recurrence of early gastric cancer. Follow-up of 1475 patients and review of the Japanese literature. *Cancer.* 1993;72:3174–8.
2. Hayashi N, Arakawa H, Nagase H, Yanagisawa A, Kato Y, Ohta H, et al. Genetic diagnosis identifies occult lymph node metastases undetectable by the histopathological method. *Cancer Res.* 1994;54:3853–6.
3. Hermanek P, Hutter RV, Sobin LH, Wittekind C. International Union Against Cancer. Classification of isolated tumor cells and micrometastasis. *Cancer.* 1999;86:2668–73.
4. Sobin LH. TNM, sixth edition: new developments in general concepts and rules. *Semin Surg Oncol* 2003;21:19–22.
5. Fielding JW. Gastric cancer: different diseases. *Br J Surg.* 1989;76:1227.
6. Fukagawa T, Sasako M, Mann GB, Sano T, Katai H, Maruyama K, et al. Immunohistochemically detected micrometastases of the lymph nodes in patients with gastric carcinoma. *Cancer.* 2001;92:753–60.
7. Hamilton SR, Aaltonen LA. WHO classification of tumors: pathology and genetics of the digestive system. Lyon, France: IARC Press; 2000.
8. Siewert JR, Kestlmeier R, Busch R, Böttcher K, Roder JD, Müller J, et al. Benefits of D2 lymph node dissection for patients with gastric cancer and pN0 and pN1 lymph node metastases. *Br J Surg.* 1996;83:1144–7.
9. Lee E, Chae Y, Kim I, Choi J, Yeom B, Leong AS. Prognostic relevance of immunohistochemically detected lymph node micrometastasis in patients with gastric carcinoma. *Cancer.* 2002;94:2867–73.
10. Ishigami S, Natsugoe S, Tokuda K, Nakajo A, Higashi H, Watanabe T, et al. Clinical impact of micrometastasis of the lymph node in gastric cancer. *Am Surg.* 2003;69:573–7.
11. Cai J, Ikeguchi M, Maeta M, Kaibara N, Sakatani T. Clinicopathological value of immunohistochemical detection of occult involvement in pT3N0 gastric cancer. *Gastric Cancer.* 1999; 2:95–100.
12. Choi HJ, Kim YK, Kim YH, Kim SS, Hong SH. Occurrence and prognostic implications of micrometastases in lymph nodes from patients with submucosal gastric carcinoma. *Ann Surg Oncol.* 2002;9:13–9.
13. Morgagni P, Saragoni L, Scarpi E, Zattini PS, Zaccaroni A, Morgagni D, et al. Lymph node micrometastases in early gastric cancer and their impact on prognosis. *World J Surg.* 2003;27: 558–61.
14. Doekhie FS, Mesker WE, van Krieken JH, Kok NF, Hartgrink HH, Kranenbarg EK, et al. Clinical relevance of occult tumor cells in lymph nodes from gastric cancer patients. *Am J Surg Pathol.* 2005;29:1135–44.
15. Kikuchi Y, Tsuchiya A, Ando Y, Yoshida T, Takenosita S. Immunohistochemical detection of lymph node microinvolvement in node-negative gastric cancer. *Gastric Cancer.* 1999;2:173–8.
16. Yoshikawa T, Tsuburaya A, Kobayashi O, Sairenji M, Motohashi H, Noguchi Y. Peritoneal cytology in patients with gastric cancer exposed to the serosa—a proposed new classification based on the local and distant cytology. *Hepato-gastroenterology.* 2003;50:1183–6.
17. Cserni G, Bianchi S, Boecker W, Decker T, Lacerda M, Rank F, et al. Improving the reproducibility of diagnosing micrometastases and isolated tumor cells. *Cancer.* 2005;103:358–67.