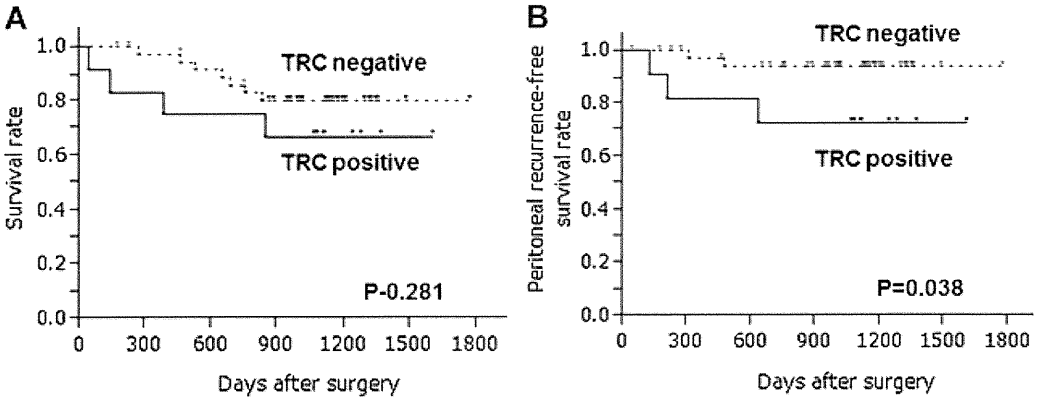

Fig. 3. Survival analysis according to the TRC diagnosis from peritoneal lavage specimens. **A**: Peritoneal recurrence-free survival. **B**: Overall survival.

stable and more accurate with respect to quantification. Another advantage is that this method amplifies RNA directly, avoiding the need for reverse transcription to convert RNA to cDNA prior to amplification. These advantages may allow the establishment of more reliable and practical genetic diagnosis of cancer micrometastasis. We reported previously on TRC using carcinoembryonic antigen (CEA) as a biomarker marker for the early detection of peritoneal recurrence after gastric cancer surgery [23]. However, CEA is not a cancer-specific marker and some regions in gastric tumors show no expression of CEA. Additional markers will therefore improve the sensitivity and specificity of our TRC method for predicting peritoneal recurrence following gastric cancer treatment. Our analyses in this study implicated TRC for REGIV as a potential molecular diagnostic method for predicting peritoneal dissemination in advanced gastric cancer in a simple and rapid manner.

In conclusion, we identified REGIV overexpression in peritoneal dissemination of advanced gastric cancer and that the detection of REGIV mRNA in peritoneal lavage fluid by TRC could be a predictor of peritoneal recurrence after curative gastrectomy. Overexpression of REGIV could become a predictor of peritoneal recurrence, although further studies will be needed in a larger population.

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Neoadjuvant Intraperitoneal and Systemic Chemotherapy for Gastric Cancer Patients with Peritoneal Dissemination

Yoshiyuki Fujiwara, MD, PhD, Shuji Takiguchi, MD, PhD, Kiyokazu Nakajima, MD, PhD, Hiroshi Miyata, MD, PhD, Makoto Yamasaki, MD, PhD, Yukinori Kurokawa, MD, PhD, Kaoru Okada, MD, Masaki Mori, MD, PhD, and Yuichiro Doki, MD, PhD

Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan

ABSTRACT

Background. The present study was designed to assess the feasibility and efficiency of intraperitoneal and intravenous neoadjuvant chemotherapy in gastric cancer patients with peritoneal dissemination.

Methods. The study subjects were 25 treatment-naïve patients with gastric cancer. Patients with positive cytology or with peritoneal carcinomatosis received neoadjuvant intraperitoneal and systemic chemotherapy (NIPS), comprising intraperitoneal (i.p.) mitomycin C (MMC) and cisplatin (CDDP), followed by two cycles of intravenous triplet chemotherapy of docetaxel, 5-fluorouracil (5-FU), and CDDP. Gastrectomy with lymph node dissection was performed after NIPS in patients free of peritoneal deposits, confirmed by staging laparoscopy.

Results. Seventeen patients had measurable lymph node metastases by the RECIST criteria. CT examination showed response to the treatment in ten (59%, 0 complete response, 10 partial response). Of the 25 patients, 14 (56%) showed negative results on peritoneal cytology with no macroscopic peritoneal metastasis, whereas the remaining 11 were cancer cell-positive on peritoneal cytology or macroscopic peritoneal metastasis even after NIPS. The median survival time for all 25 patients was 16.7 months. Prognosis was better in patients who showed negative cytology and disappearance of peritoneal cancer metastases after NIPS than in those with positive cytology or existing peritoneal deposits ($P < 0.0001$). The predominant toxicity was myelosuppression and grade 3–4 leukopenia and neutropenia occurred in 20 (80%) patients, which were manageable. No treatment-related mortality was observed during and after NIPS and surgery.

Conclusions. The results of this prospective phase II study indicated that the newly designed NIPS was highly effective and well tolerated in patients with advanced gastric cancer and peritoneal dissemination.

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Y. Fujiwara, MD, PhD
e-mail: yfujiwara@gesurg.med.osaka-u.ac.jp

The prognosis of patients with advanced gastric cancer, especially those with serosa-invading tumors, remains poor even after curative resection, and in these cases, peritoneal dissemination caused by free cancer cells seeded from a primary gastric tumor is the most common type of recurrence.[1,2] Cytological examination of peritoneal lavage at laparotomy is usually performed to predict peritoneal recurrence.[3–5] Most cases with positive cytology on peritoneal lavage develop peritoneal recurrence even in patients without macroscopic peritoneal dissemination.[4,5]

Recently, a multidisciplinary approach, including chemotherapy, radiation, and surgery for advanced gastric cancer, has been developed and its survival benefit has been investigated worldwide.[6,7] Furthermore, several novel chemotherapeutic agents, including the taxans (paclitaxel and docetaxel), irinotecan, oxaliplatin, S-1, and capecitabine, have shown potent effects in gastric cancer.[8–13]

These advances in chemotherapy for gastric cancer encouraged us to introduce neoadjuvant chemotherapy for gastric cancer patients with poor prognosis, such as those with positive peritoneal lavage cytology. In this study, we performed peritoneal lavage cytology under local anesthesia or staging laparoscopy for patients with T3 or T4 gastric tumors diagnosed using multidetector row computed tomography (CT) and three-dimensional imaging before treatment.[14] Patients with positive cytology on peritoneal lavage specimens or with macroscopic peritoneal metastasis were enrolled in the study.

Intraperitoneal (i.p.) chemotherapy with mitomycin C (MMC) and cisplatin (CDDP) was reported to be safe for

patients with T3 or T4 gastric tumors defined by preoperative staging laparoscopy in our pilot study.[15] In that study, the toxicity of the preoperative i.p. chemotherapy was minimal and no serious postoperative complications were observed. A course of intravenous triplet chemotherapy of docetaxel, 5-fluorouracil (5-FU), and CDDP, which was developed by our group, was given every 4 weeks.[16] The modified triplet regimen had been developed to reduce the severe hematological toxicities commonly encountered in the V325 phase III study used in western countries.[17] We reported that the modified regimen was less toxic and no serious complications were observed during chemotherapy and surgery.[16] After the sequential combination chemotherapy, a second staging laparoscopy was performed to evaluate the therapeutic effect for peritoneal dissemination and to decide on the indication of surgery. The purpose of this prospective study was to investigate the feasibility and efficacy of the newly developed neoadjuvant triplet chemotherapy in the setting for gastric cancer with positive peritoneal lavage cytology and/or macroscopic peritoneal dissemination.

MATERIALS AND METHODS

Patient Selection

The eligibility criteria for entry in this study were as follows: (1) the presence of gastric cancer confirmed by histopathology; (2) presence of positive peritoneal cytology (PPC) or peritoneal deposits confirmed by staging laparoscopy; (3) absence of noncurative factors, such as distant metastasis to liver, lung, or lymph nodes except for the peritoneal dissemination; (4) performance status [Eastern Cooperative Oncology Group (ECOG)] < 2; (5) age younger than 75 years; (6) no prior chemotherapy or surgery for gastric or other cancers; (7) adequate bone marrow function (leukocyte count $> 3{,}000$ ml^{-1} and platelet count $> 100{,}000$ ml^{-1}), (8) adequate liver function (serum bilirubin level < 1.5 mg dl^{-1} and serum transaminase levels less than twice the upper limit of normal); (9) adequate renal function (serum creatinine level < 1.5 mg dl^{-1}; (10) no other severe medical conditions, such as symptomatic infectious disease, intestinal pneumonia, active hemorrhage/bleeding, or obstructive bowel disease; (11) no current pregnancy or lactation; and (12) provision of written informed consent in accordance with government guidelines of each institution or hospital. This study was approved by the ethics committee of Osaka University Hospital.

Treatment Strategy

Figure 1 shows the treatment strategy followed in this study. A staging laparoscopy or peritoneal lavage cytology was performed under local anesthesia in gastric cancer patients with serosa-invading tumors.[14] Neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) were administered to patients with positive cytology and/or peritoneal metastasis. Staging laparoscopy was performed in all patients after chemotherapy, followed by gastrectomy with lymph node dissection in patients free of macroscopic peritoneal deposits of cancer metastasis. MMC was administered by i.p. infusion at a dose of 20 mg/body at day 1 and CDDP also was administered by i.p. infusion at a dose of 20 mg/body at days 1–5.[15] After a 2-week recovery period, we administered a chemotherapy combination of docetaxel at a dose of 60 mg/m^2 on day 1, 5-FU at a dose of 350 mg/m^2 on days 1–5, and CDDP at a dose of 10 mg/m^2 on days 1–5, every 4 weeks. The intravenous chemotherapy was repeated twice unless disease progression was observed after one cycle. All 22 patients who underwent surgery received adjuvant chemotherapy using 5-FU and cisplatin or 5-FU derivative, S-1.

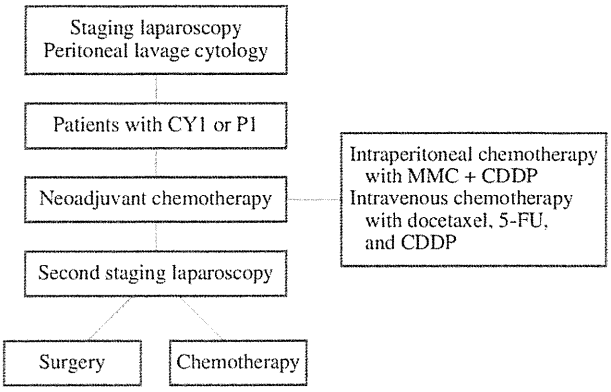

FIG. 1 Flow diagram of the treatment protocol. *CY1* patients with positive peritoneal cytology, *P1* patients positive for macroscopic peritoneal metastasis, *MMC* mitomycin C, *CDDP* cisplatin, *5-FU* 5-fluorouracil

Evaluation of the Disease

Before and after NIPS with i.p. and i.v. infusion of anticancer drugs, conventional examinations, including multidetector row computed tomography and gastric endoscopy were performed to assess the clinical response. A second staging laparoscopy was conducted to evaluate the effect of peritoneal metastasis. The tumor response of measurable metastatic lesions was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[18] A complete response (CR) was defined as the disappearance of all evidence of cancer for more than 4 weeks. A partial response (PR) was defined as more than 50% reduction in the sum of the products of the perpendicular diameters of all lesions without any evidence of new regions or progression on any lesions. Stable disease

(SD) was defined as <50% reduction or <25% increase in the sum of the products of the perpendicular diameters of all lesions, without any evidence of new lesions. Progressive disease (PD) was defined as >25% increase in more than one region or the appearance of new region. The response of the peritoneal metastasis was evaluated by staging laparoscopy or surgery after NIPS.

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 4.0 and recorded.

Statistical Analysis

Survival was calculated by the Kaplan–Meier method from the initial date of the treatment to the occurrence of the event or to the date of the most recent follow-up visit. Univariate analysis was performed using the log-rank test, and multivariate analysis was conducted using the Cox proportional hazards model. $P < 0.05$ was considered statistically significant.

RESULTS

Clinicopathological Characteristics

Between July 2000 and June 2006, a total of 25 patients with gastric cancer with peritoneal dissemination were enrolled in this study. Table 1 shows the clinicopathological characteristics of the enrolled patients treated at the Department of Gastroenterological Surgery, Osaka University Hospital. The patients were 13 men and 12 women with a mean age of 58.9 (range, 31–75) years. Macroscopically, infiltrating-type tumors (type 3 and type 4) accounted for 80% of the cases (20/25). Histopathologically, undifferentiated tumors, including poorly differentiated and signet ring cell carcinoma were dominant (20/25, 80%). Gastrectomy with lymph node dissection was performed in 22 of the 25 patients (88%), who showed no macroscopic peritoneal metastasis at the second staging laparoscopy, whereas surgery was not performed in the remaining 3 patients because of the presence of macroscopic deposits of cancer nests in the abdominal cavity. Eighteen of the 22 patients (82%) underwent total gastrectomy and 14 underwent additional splenectomy. Seventeen of 22 cases (77%) underwent D2 lymphadenectomy and 5 had D2 minus lymph nodes in the region of hilus lienis, which was classified as D1+ alpha.

TABLE 1 Clinicopathological variables of the 25 patients enrolled in the present study

Average age, year (range)	58.9 ± 11.8 (31–75)*
Male/female ratio	13/12
Tumor type	
1	1
2	4
3	8
4	12
Histology	
Diffuse type	20
Differentiated type	5
Distant metastasis except peritoneum	
Present	1 (liver metastasis)
Absent	24
Type of surgery (22 cases)	
Total gastrectomy	18
With splenectomy	14
Without splenectomy	4
Distal gastrectomy	4
Lymph node dissection	
D2	17
D1 + α	5

* Data are mean ± standard deviation

Clinical Response and Toxicity of NIPS

After NIPS, all patients were evaluated for the clinical response and toxicities. Of the 25 patients, 23 (92%) completed the sequence combination chemotherapy, whereas intravenous chemotherapy for the remaining 2 patients was withheld after one cycle due to the appearance of progressive diseases. Seventeen of 25 patients had measurable lymph node metastases by RECIST criteria. As shown in Table 2, the CT scan showed that 10 of 17 (59%) displayed major response (0 CR, 10 PR) to the treatment. Of the 25 patients, 14 (56%) showed negative results on peritoneal cytology and no macroscopic peritoneal metastasis; the remaining 11 patients had positive results on peritoneal cytology or macroscopic peritoneal metastasis after NIPS (Table 2).

Adverse events were graded according to the National Cancer Institute-Common Terminology Criteria for

TABLE 2 Anti-tumor efficacy of neoadjuvant intraperitoneal and systemic chemotherapy (NIPS)

RECIST criteria	*n*	%
Measurable disease	17	
Overall response rate (CR + PR)	10	59
CR	0	0
PR	10	59
SD	6	35
PD	1	6
Nonmeasurable disease	8	
Efficacy for peritoneal disease	25	
CY0 and P0 after NIPS	14	56
CY1 or P1 after NIPS	11	44

TABLE 3 Toxicity profile of neoadjuvant chemotherapy in 25 patients (National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.0: NCI-CTCAE ver. 4.0)

	Grade 1	Grade 2	Grade 3	Grade 4
Nonhematological				
Fatigue	11 (44)	2 (8)	0 (0)	
Nausea	6 (24)	7 (28)	4 (16)	
Diarrhea	2 (8)	2 (8)	0 (0)	
Alopecia	8 (32)	7 (28)	0 (0)	
Hematological				
Leukopenia	0 (0)	2 (8)	17 (68)	3 (12)
Neutropenia	1 (4)	1 (4)	14 (56)	6 (24)
Anemia	10 (40)	11 (44)	0 (0)	0 (0)
Creatinine	4 (16)	0 (0)	0 (0)	0 (0)
ALT elevation	2 (8)	1 (4)	1 (4)	0 (0)

Data are numbers with percentages in parentheses

TABLE 4 Postoperative complications in 22 patients

Complications	*n*	(%)
Bleeding	0	0
Anastomotic insufficiency	2	9.1
Pancreatic fistula	3	13.6
Wound infection	2	9.1
Intra-abdominal abscess	2	9.1
Intestinal occlusion	0	0
Death resulting from complications	0	0
Any postoperative complication	7	31.8

Adverse Events Version 4.0 (Table 3). In 20 (80%) patients, leukopenia and neutropenia were graded as more than grade 3. Four patients (16%) experienced grade 3 gastrointestinal-related toxicities. However, no chemotherapy-related death was observed. Nineteen patients underwent surgery during a month and three patients did between a month and 6 weeks after recovery of NIPS.

Postoperative Complications

Among 22 patients who underwent surgery, postoperative complications occurred in 7 patients (31.8%, Table 4). Pancreatic fistula was the most frequent complication (three patients). Anastomotic leakage, intra-abdominal abscess, and wound infection occurred in two cases each.

Survival Rates

Figure 2a shows the overall survival time after the introduction of NIPS in all 25 patients enrolled in this study. The median survival time (MST) was 16.7 months. Patients with negative cytology and disappearance of peritoneal cancer metastases ($n = 14$) after NIPS had a significantly better prognosis than those with positive results of cytology or peritoneal deposits (MST 27.1 vs. 9.6 months; $P < 0.0001$; Fig. 2b). Patients who showed major response in metastatic lymph nodes ($n = 10$) also had a significantly better prognosis than those without major response ($n = 7$, $P = 0.0173$; Fig. 2c). Figure 2d shows no significant difference between the prognosis of patients with measurable lymph node metastases and those without measurable disease.

DISCUSSION

In this study, we conducted a prospective phase II study to evaluate the feasibility and efficacy of the neoadjuvant intraperitoneal and systemic chemotherapy, named NIPS, for gastric cancer patients with peritoneal dissemination of cancer cells. After NIPS, 14 (56%) of 25 patients showed negative results on peritoneal cytology, no macroscopic peritoneal metastasis, and had a remarkably better prognosis than those with positive results of cytology or peritoneal deposits (Fig. 2b). Although frequent hematotoxicities were observed in NIPS, they were controllable by specialized oncologists. Furthermore, no chemotherapy-related severe morbidity and mortality were observed. Twenty-two (88%) patients underwent gastrectomy with lymphadenectomy. Total gastrectomy (82%) with D2 lymphadenectomy (77%) was the main surgical approach. Postoperative complications were observed in 32%, which is comparable with previous reports of surgery after neoadjuvant chemotherapy, and no surgery-related mortality was observed.[19,20] These results indicate that NIPS is feasible and effective for gastric cancer patients with peritoneal dissemination.

Multicenter phase III trials have been conducted in gastric cancer and the effects of postoperative adjuvant chemoradiotherapy and perioperative chemotherapy have been demonstrated.[6,7] Furthermore, adjuvant chemotherapy with S-1, an oral fluoropyrimidine (Taiho Pharmaceutical), has an affirmative effect on locally advanced gastric cancer.[21] Although the effect of neoadjuvant chemotherapy on gastric cancer has been studied in several phase III trials, definite conclusions have not been made because of insufficient statistical power and high rate of surgical complications.[19,22,23] However, preoperative chemotherapy may have some advantages, such as the delivery of antitumor agents may be more efficient if administered before surgical disruption of the vasculature, tumor down-staging may increase the rate of complete surgical resection, and preoperative chemotherapy can be used to evaluate chemosensitivity of drugs.

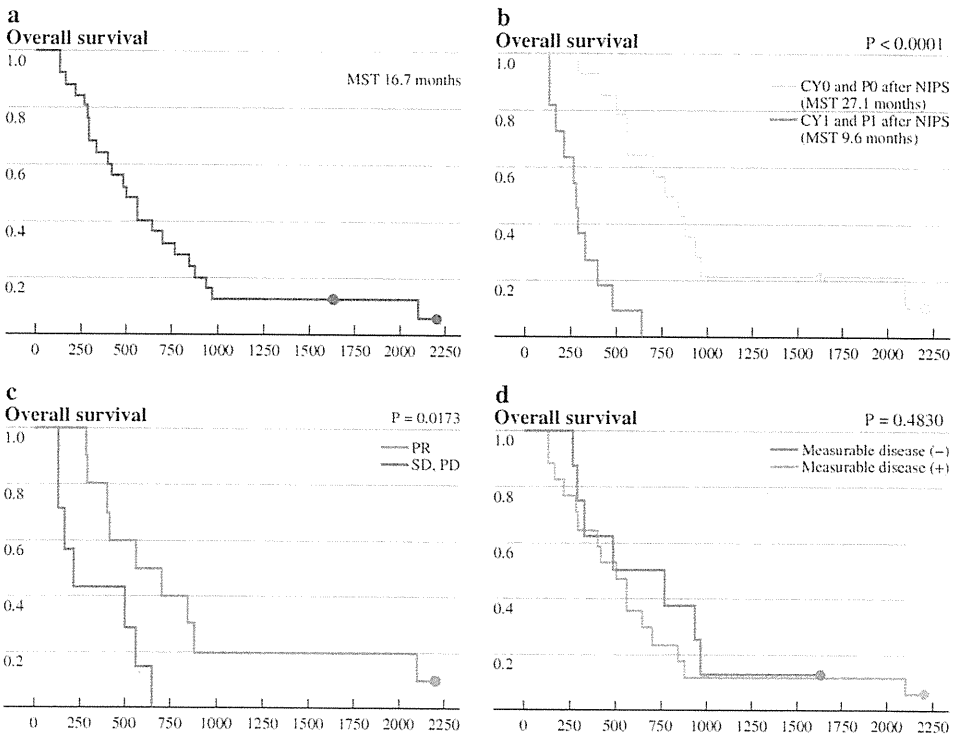

FIG. 2 **a** Overall survival of 25 patients enrolled in this study. *MST* mean survival time. **b** Overall survival according to the effect of NIPS on peritoneal disease. *CY0* negative peritoneal cytology, *CY1* positive peritoneal cytology, *P0* no macroscopic peritoneal metastasis, *P1* presence of macroscopic peritoneal metastasis. **c** Overall survival according to the clinical response evaluated by the RECIST. *PR* partial response, *SD* stable disease, *PD* progressive disease. **d** Overall survival according to the presence or absence of measurable lymph node metastases

Because the prognosis of patients with gastric cancer and peritoneal dissemination is very poor, surgery is not the standard therapy except for patients who require palliative surgery for related symptoms, such as bleeding and obstruction. Several recent retrospective studies have analyzed the effects of neoadjuvant chemotherapy in gastric cancer patients with peritoneal seedlings and/or PPC. Badgwell et al. retrospectively analyzed and concluded that the prognosis of gastric cancer patients with PPC without gross peritoneal diseases was almost similar to that of patients with gross peritoneal disease at preoperative staging laparoscopy.[24] They also reported improvement of prognosis in patients with PCC but without gross peritoneal disease after neoadjuvant chemotherapy compared with a palliative approach. Lorenzen et al. assessed peritoneal cytology before and after neoadjuvant chemotherapy (NAC) and its relation to prognosis.[25] They concluded that some patients with PPC show negative peritoneal cytology after NAC and subsequent improvement of prognosis, although almost 25% of the patients with negative cytology became positive after NAC, which might be a risky strategy. Okabe et al. retrospectively analyzed the effect of induction chemotherapy with S-1 plus cisplatin, which is the standard chemotherapy in Japan, for patients with peritoneal dissemination.[20,26] In that study, 19 (46 %) of 41 patients treated with induction chemotherapy showed disappearance of peritoneal dissemination and negativity of peritoneal cytology and had a curative operation. Furthermore, the prognosis of patients with R0 resection was significantly better than that of patients who underwent noncurative resection.[20]

To our knowledge, our study is the first prospective phase II study on neoadjuvant chemotherapy for gastric cancer with peritoneal disease. We introduced i.p. administration of antitumor drugs combined with systemic chemotherapy. The i.p. chemotherapy was selected to enhance antitumor activity against peritoneal metastasis by maintaining a high concentration of the drug in the peritoneal cavity during a long period of time, and its clinical effects have been verified by a number of convincing clinical trials in ovarian cancer.[27,28] Recent studies also have examined the effects of i.p. administration of taxans, such as paclitaxel and docetaxel, in patients with gastric cancer and peritoneal dissemination because long-term high concentrations of taxans in the peritoneal cavity could be achieved.[29,30] Further studies are needed to define the most suitable regimen for NIPS. Furthermore, the utility of NAC and i.p. chemotherapy for gastric cancer with peritoneal dissemination should be examined by phase III randomized clinical trial.

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Gastric Cancer
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ORIGINAL ARTICLE

Survival benefit of bursectomy in patients with resectable gastric cancer: interim analysis results of a randomized controlled trial

Junya Fujita · Yukinori Kurokawa · Tomoyuki Sugimoto · Isao Miyashiro · Shohei Iijima · Yutaka Kimura · Shuji Takiguchi · Yoshiyuki Fujiwara · Masaki Mori · Yuichiro Doki

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Abstract
Background Bursectomy is regarded as a standard surgical procedure during gastrectomy for serosa-positive gastric cancer in Japan. There is little evidence, however, that bursectomy has clinical benefit. We conducted a randomized controlled trial to demonstrate non-inferiority of treatment with the omission of bursectomy.
Methods Between July 2002 and January 2007, 210 patients with cT2–T3 gastric adenocarcinoma were intraoperatively randomized to radical gastrectomy and D2 lymphadenectomy with or without bursectomy. The primary endpoint was overall survival (OS). Secondary endpoints were recurrence-free survival, operative morbidity, and levels of amylase in drainage fluid on postoperative day 1. Two interim analyses were performed, in September 2008 and August 2010.
Results Overall morbidity (14.3%) and mortality (0.95%) rates were the same in the two groups. The median levels of amylase in drainage fluid on postoperative day 1 were similar in the two groups ($P = 0.543$). In the second interim analysis, the 3-year OS rates were 85.6% in the bursectomy group and 79.6% in the non-bursectomy group. The hazard ratio for death without bursectomy was 1.44 (95% confidence interval [CI] 0.79–2.61; $P = 0.443$ for non-inferiority). Among 48 serosa-positive (pT3–T4) patients, the 3-year OS was 69.8% for the bursectomy group and 50.2% for the non-bursectomy group, conferring a hazard ratio for death of 2.16 (95% CI 0.89–5.22; $P = 0.791$ for non-inferiority). More patients in the non-bursectomy group had peritoneal recurrences than in the bursectomy group (13.2 vs. 8.7%).
Conclusions The interim analyses suggest that bursectomy may improve survival and should not be abandoned as a futile procedure until more definitive data can be obtained.

Keywords Omental bursectomy · Bursa omentalis · Interim analysis · Gastric cancer

J. Fujita
Department of Surgery, Toyonaka Municipal Hospital, Toyonaka, Japan

Y. Kurokawa (✉) · S. Takiguchi · Y. Fujiwara · M. Mori · Y. Doki
Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Osaka, Japan
e-mail: ykurokawa@gesurg.med.osaka-u.ac.jp

T. Sugimoto
Department of Biomedical Statistics, Osaka University Graduate School of Medicine, Osaka, Japan

I. Miyashiro
Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, Japan

S. Iijima
Department of Surgery, Minoh City Hospital, Minoh, Japan

Y. Kimura
Department of Surgery, NTT West Osaka Hospital, Osaka, Japan

Introduction

To accomplish the cure of gastric cancer by surgical treatment it is of prime importance to eliminate all cancer cells from the patient. Total resection of the bursa omentalis has developed as an essential part of radical gastrectomy with extended lymphadenectomy as treatment for advanced gastric cancer in Japan [1, 2]. The operative procedure of bursectomy includes removal of the anterior

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membrane of the transverse mesocolon as well as the pancreatic capsule after total omentectomy. The rationale for this procedure is that en-bloc resection of the post-gastric cavity lining, which includes free cancer cells or micrometastases, may reduce the incidence of cancer recurrence [3–5]. According to the Japanese Gastric Cancer Association *Gastric cancer treatment guidelines*, bursectomy is recommended for tumors with invasion of the serosa [6]. In the past few decades, most Japanese surgeons have continued to perform D2 lymphadenectomy with bursectomy as the conventional operation for advanced gastric cancer.

It is apparent, however, that removing the mesocolon and pancreatic capsule is physically detrimental to patients and increases the risk of intraoperative and/or postoperative complications. Some researchers have remained skeptical about prophylactic bursectomy [7–9], as no prospective clinical trial has clarified the benefits or effectiveness of this surgical procedure.

We have conducted a prospective randomized controlled trial with a non-inferiority design to evaluate prophylactic bursectomy for gastric cancer patients. Previously we reported short-term results for the study, which detailed that experienced surgeons could safely perform bursectomy without increasing major surgical complications [10]. Here, we provide a preliminary report on the results of the first and second interim analyses.

Methods

Patients

Eligibility criteria for the study included: (1) histologically proven primary adenocarcinoma of the stomach, (2) a preoperative and intraoperative classification of T2N0, T3N0, T2N1, or T3N1 according to the *Japanese classification of gastric carcinoma, second English edition* [11], (3) a lack of non-curative surgical factors except for positive lavage cytology, (4) no Borrmann type 4 (linitis plastica) cases, (5) no prior chemotherapy or radiation therapy, (6) age 20–80 years with a performance status of 0–2 according to the Eastern Cooperative Oncology Group (ECOG) scale, (7) no history of gastrectomy or other malignancy during the previous 5 years. All patients gave written informed consent before undergoing randomization. The surgeon confirmed the eligibility criteria during surgery and phoned the data center to receive a randomly generated assignment. Patients were then randomized to either the bursectomy group (a D2 gastrectomy with bursectomy) or the non-bursectomy group (a D2 gastrectomy without bursectomy), using the minimization method, according to gender, clinical T stage (cT2 vs. cT3), and gastrectomy (total vs. distal subtotal gastrectomy). The study protocol was approved by the institutional review board at each of the participating hospitals.

Surgery

The surgeons performed a total or distal subtotal gastrectomy and a D2 lymph node dissection as standard treatment for advanced gastric cancers in both groups. In total gastrectomy for T2 or deeper tumor in the proximal third of the stomach, the spleen was removed, in principle, for splenic hilar lymphadenectomy. Pancreatectomy was confined to those patients whose pancreas was involved by tumor. The type of reconstruction and the indication for prophylactic cholecystectomy were not specified in the protocol.

The details of the surgical procedure for bursectomy were described previously [10]. In brief, in the bursectomy group, the peritoneal lining of the bursa omentalis was removed en bloc as much as possible from the anterior plane of the transverse mesocolon and the pancreas. As complete removal of the left side of the bursa omentalis did not allow for a distal subtotal gastrectomy, the pancreatic serosa was removed up to the proximal half of the splenic artery. For the transverse colon mesentery, the peritoneum was removed up to the left gastroepiploic artery. In the non-bursectomy group, only a minimal amount of peritoneum could be removed for lymph node dissection. An omentectomy was performed for both groups in this study.

Patients were enrolled from 11 hospitals belonging to the Osaka University Clinical Research Group for Gastroenterological Surgery. More than 50 gastrectomies were performed every year in these 11 hospitals. All operations were performed or supervised by senior surgeons who were members of the Japanese Gastric Cancer Association. During the planning of the study, all participating surgeons reached an agreement concerning the technical details of bursectomy.

Endpoint evaluations

The primary endpoint was overall survival (OS), defined as the time from randomization to death. Secondary endpoints were recurrence-free survival (RFS), operative morbidity, and levels of amylase in drainage fluid on postoperative day 1. RFS was defined as the time from randomization to either the first event of recurrence or death from any cause. Operative methods and pathology results were recorded according to the *Japanese classification of gastric carcinoma, second English edition* [11]. Hospital mortality was defined as postoperative death of any cause within 30 days, or death within the same hospitalization period as that for the operation. Patients were followed every 3 months until

five years postoperatively. Adjuvant therapy was not permitted before the recurrence of cancer.

Statistical considerations

For the non-inferiority design, one-sided log-rank test with a non-inferiority margin was used in order to show statistically that the hazard rate of the non-bursectomy group was no less than that of the bursectomy group. We planned initially to recruit 200 patients, with an α error of 0.1 and statistical power of 80%. This allowed for detecting a hazard ratio with a non-inferiority margin of 1.56 in the non-bursectomy group with the estimation of a 60% 5-year OS in the bursectomy group. The projected accrual period and follow-up period were 3 and 5 years, respectively. The required sample size was calculated by a simulated-based approach with 100,000 replications to obtain a reasonable size, because a more conventional approach (for example, Freedman's formula) tends to overestimate the sample size as the hazard ratio margin is more greatly separated from one when there is a high censoring rate. After the registration of 204 patients, we amended the sample size and analysis to correct the estimation of 5-year OS in the bursectomy group as 75% and to reduce the α error. The amended sample size was 464, with an α error of 0.05, statistical power of 80%, and a hazard ratio non-inferiority margin of 1.50, with a 8-year accrual period (in total) and 5-year follow-up. The hazard ratio margin was designed as corresponding to a non-inferiority margin of 10% in 5-year OS.

Differences in proportions between the two groups were evaluated using Fisher's exact test or the χ^2 test. Differences in continuous variables, including age and tumor size, between the two groups were tested with the Mann–Whitney *U*-test. Data from all eligible patients were analyzed for OS and RFS on an intention-to-treat basis. Survival curves were estimated by the Kaplan–Meier method and compared using the log-rank test. Hazard ratios were calculated by Cox regression analysis without adjustment for stratification factors. Two-sided *P* values were used for testing superiority, because our interest in superiority was whether the two groups were different regardless of the direction of the difference, and hence two-sided tests were used as usual. However, one-sided *P* values were used for testing non-inferiority, because one-sided tests were performed following the study design for non-inferiority. All non-inferiority tests were conducted using the handicap log-rank test setting the hazard ratio non-inferiority margin of 1.50. All *P* values were reported as statistically significant if $P < 0.05$, to provide conventional interpretation of results. Statistical analysis was performed using SPSS Statistics software, version 17.0 (SPSS, Chicago, IL, USA) and the R programming language.

Interim analysis

In January 2007, a large-scale randomized controlled trial evaluating the efficacy of adjuvant S-1 chemotherapy for stage II/III gastric cancer patients reported positive results [12]. Since then, adjuvant S-1 chemotherapy has been the new standard treatment for stage II/III gastric cancer in Japan. As our study did not permit adjuvant treatment, including S-1 chemotherapy, we decided to close accrual of our study in January 2007.

Although the interim analysis was not initially planned, the steering committee of this study proposed interim analyses to examine survival and to provide early release of the results, because the time to definitive analysis (5 years) was very long. The data and safety monitoring committee of the Osaka University Clinical Research Group for Gastroenterological Surgery approved the interim analyses with the conditions of Korn's criteria for preliminary data release in randomized clinical trials of non-inferiority [13]. After confirmation of all conditions in Korn's criteria, interim analyses were performed in September 2008 and August 2010. The final analysis of survival data is scheduled for 2012.

Results

Between July 2002 and January 2007, 210 patients were randomized to either bursectomy (104 patients) or non-bursectomy (106 patients) (Fig. 1). Patient characteristics were well balanced between the two groups (Table 1). Total gastrectomy was performed for 22 patients (21.2%) in the bursectomy group and 27 patients (25.5%) in the non-bursectomy group, while 12 bursectomy (11.5%) and 14 non-bursectomy (13.2%) patients underwent splenectomy. Only one (0.9%) non-bursectomy patient underwent distal pancreatectomy. The reasons for R1 resection were positive lavage cytology, except in one non-bursectomy patient with a positive proximal margin.

As reported previously [10], bursectomy required a longer operative time, with a median added time of 27 min in patients with combined resection and 26 min in patients without combined resection. Intraoperative blood loss was also greater in the bursectomy group (median 475 mL) than in the non-bursectomy group (median 350 mL) ($P = 0.047$), while other surgical factors did not vary significantly. The overall morbidity rate was 14.3% for both groups. The median amylase levels in drainage fluid on postoperative day 1 were similar in the two groups ($P = 0.543$). The hospital mortality rate was 0.95%, with one patient death in each group.

At the time of the first interim analysis in September 2008, 3-year OS was 86.4% for the bursectomy group and

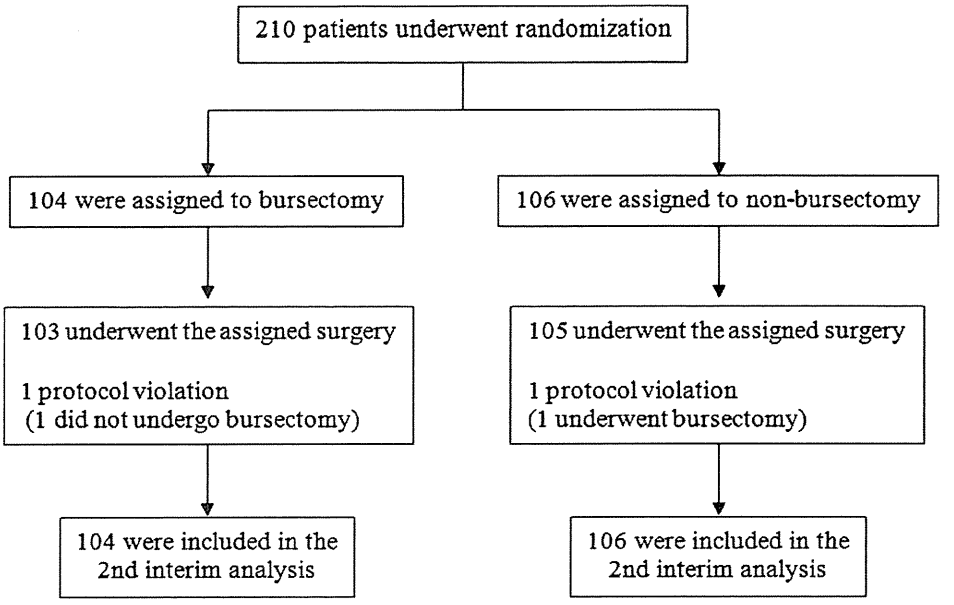

Fig. 1 Distribution of the patients

79.1% for the non-bursectomy group [14]. The hazard ratio for death in the non-bursectomy group was 1.55 (95% CI 0.84–2.84; $P = 0.155$ for superiority; $P = 0.540$ for non-inferiority). By the time of the second interim analysis in August 2010, the median patient follow-up was 46 months; there had been 19 deaths in the bursectomy group and 25 deaths in the non-bursectomy group. The 3-year OS remained better in the bursectomy group (85.6%) than in the non-bursectomy group (79.6%) (Fig. 2). The hazard ratio for death in the non-bursectomy group was 1.44 (95% CI 0.79–2.61; $P = 0.232$ for superiority; $P = 0.443$ for non-inferiority).

At the second interim analysis, 24 and 27 recurrences had been recorded in the bursectomy and non-bursectomy groups, respectively. The 3-year RFSs were 77.5 and 75.6% in the bursectomy and non-bursectomy groups, respectively (Fig. 3). The hazard ratio for recurrence in the non-bursectomy group was 1.18 (95% CI 0.68–2.04; $P = 0.563$ for superiority; $P = 0.192$ for non-inferiority). The most frequent site of first tumor recurrence was the peritoneum, as seen in nine patients in the bursectomy group and 14 patients in the non-bursectomy group (Table 2).

We performed a subgroup analysis examining pathological T stage. Among the 162 serosa-negative (pT1–T2) patients, 3-year OS was 90.5 and 88.1% for the bursectomy and non-bursectomy groups, respectively (Fig. 4a). In contrast, among the 48 serosa-positive (pT3–T4) patients, 3-year OS was 69.8% for the bursectomy patients, in contrast to 50.2% for the non-bursectomy group (Fig. 4b). The hazard ratios for death in the non-bursectomy group by pathological stage were 1.15 (95% CI 0.51–2.61; $P = 0.734$ for superiority; $P = 0.263$ for non-inferiority) for serosa-negative patients and 2.16 (95% CI 0.89–5.22; $P = 0.081$ for superiority; $P = 0.791$ for non-inferiority) for serosa-positive patients. Regarding RFS, serosa-negative patients showed similar results in the two groups ($P = 0.673$ for superiority) (Fig. 5a), while serosa-positive patients showed distinct differences in survival between the two groups ($P = 0.086$ for superiority) (Fig. 5b).

Discussion

It has been proposed that prophylactic bursectomy prevents peritoneal recurrences by eliminating cancer cells scattered on the lining of the post-gastric cavity; however, the clinical value of bursectomy has not been demonstrated previously. In our randomized controlled trial, experienced surgeons safely performed D2 gastrectomy with bursectomy without increasing major surgical complications, despite longer operative times and increased intraoperative blood loss [10]. The first and second interim analyses revealed that the bursectomy group had better OS than the non-bursectomy group, although these differences were not statistically significant.

The cavity of the bursa omentalis is not a closed chamber, but opens to the abdominal space through the foramen of Winslow. Yamamura et al. [8] reported that carcinoembryonic antigen or cytokeratin 20 mRNA was detected in peritoneal washes from the bursa omentalis, as well as from the Douglas pouch and the left subphrenic cavity. Resection of the bursa omentalis, the most frequent site of peritoneal seeding from the stomach, may eliminate the majority of cancer cells seeded within the peritoneum [15]. In our study, serosa-positive patients, who have the

Table 1 Patient characteristics

	Bursectomy ($n = 104$)	Non-bursectomy ($n = 106$)	P value
Age (years)			
Median	65	63	0.099
Range	31–79	34–78	
Gender			
Male	73	77	0.761
Female	31	29	
Tumor size (cm)			
Median	4.3	4.5	0.311
Range	0.9–11.0	1.5–12.0	
Clinical T stage			
cT2	61	67	0.572
cT3	43	39	
Clinical N stage			
cN0	59	61	1.000
cN1	45	45	
Pathological T stage			
pT1	17	19	0.902
pT2	62	64	
pT3–4	25	23	
Pathological N stage			
pN0	49	60	0.119
pN1	37	24	
pN2–3	18	22	
Residual tumor			
R0	101	102	1.000
R1	3	4	

The P values for gender, clinical T stage, clinical N stage, and residual tumor were calculated by Fisher's exact test; those for pathological T stage and pathological N stage were calculated by the χ^2 test; and those for age and tumor size were calculated by the Mann–Whitney U-test

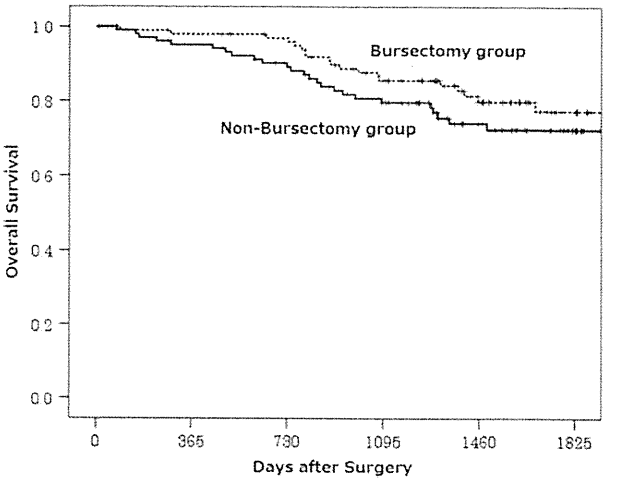

Fig. 2 Overall survival in all patients by treatment group

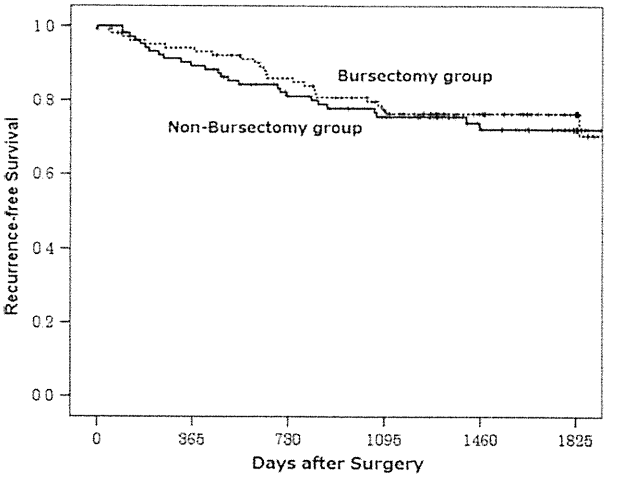

Fig. 3 Recurrence-free survival in all patients by treatment group

highest probability of peritoneal recurrence, displayed differences in 3-year OS of approximately 20% between the two groups. The bursectomy group showed a decreased frequency of peritoneal recurrence, while nodal recurrence occurred at similar rates in the two groups. The total numbers of dissected lymph nodes were similar in the two groups, with a median of 38 (range 11–98) in the bursectomy group and 37 (range 7–97) in the non-bursectomy group [10]. Even those lymph nodes dissected in the operative field of bursectomy, such as No. 6 (infrapyloric), No.14v (along the superior mesenteric vein), and No.8a (along the common hepatic artery), were similar in the two groups (data not shown). These results suggested that the survival benefit of bursectomy was attributable not to more accurate lymphadenectomy, but to the en-bloc removal of free cancer cells or micrometastases contained in the bursa omentalis.

As randomized controlled trials preserve type I and II error rates, the interim results of the trial must be powerful for a data-monitoring committee to stop a trial. The public cannot access data from the interim analyses unless the data meet the criteria for early termination of the study. Because non-inferiority trials often require a long follow-up period for definitive analysis, the early release of the data would be potentially useful to patients who face a treatment decision. Korn et al. [13] suggested that the early release of outcome data could only be done under specific conditions without harming the future conduct of the trial and without being misleading. As the present study satisfied all Korn's conditions, the study steering committee and the data and safety monitoring committee approved the early release of the interim analysis results to the public.

The difference in RFS between the two study groups in our trial was not clear in comparison to that for OS.

Table 2 Site of first tumor recurrence

	Bursectomy ($n = 104$)	Non-bursectomy ($n = 106$)
Any site of recurrence	24	26
Peritoneum	9	14
Lymph nodes	7	5
Liver	4	6
Others	4	2

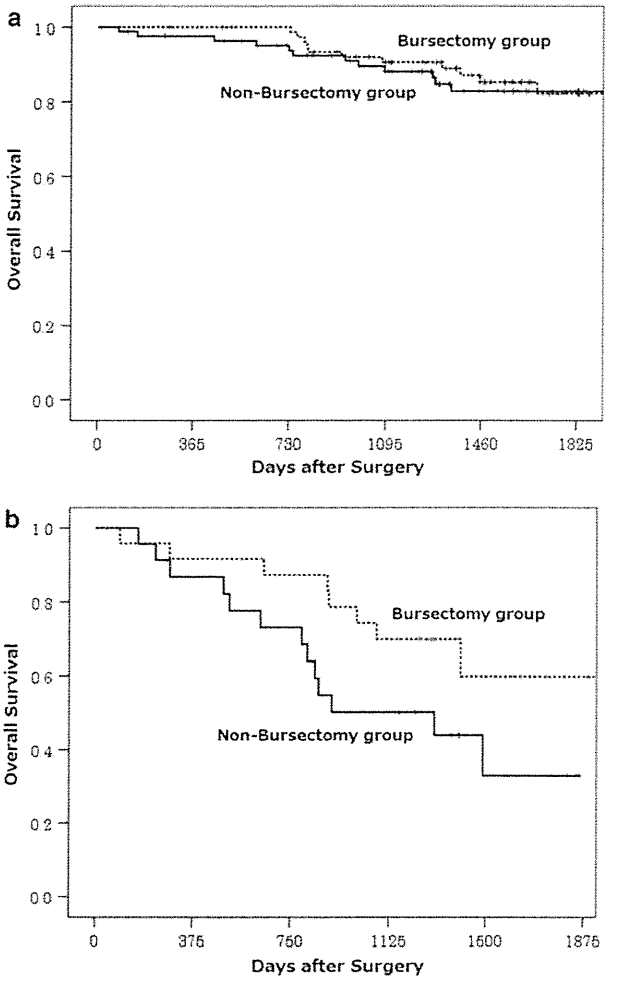

Fig. 4 Overall survival in patients with serosa-negative tumors (**a**) and those with serosa-positive tumors (**b**) by treatment group

In clinical trials of gastric cancer treatments, it is difficult to examine peritoneal recurrence, which is the most frequent pattern of relapse. We therefore focused on the endpoint of OS, not on RFS, in the interim analyses. The number of recurrence events (51 events) was smaller than expected, while the number of deaths (44 events) was similar in frequency to that reported in previous studies. The immature results on recurrence for the interim

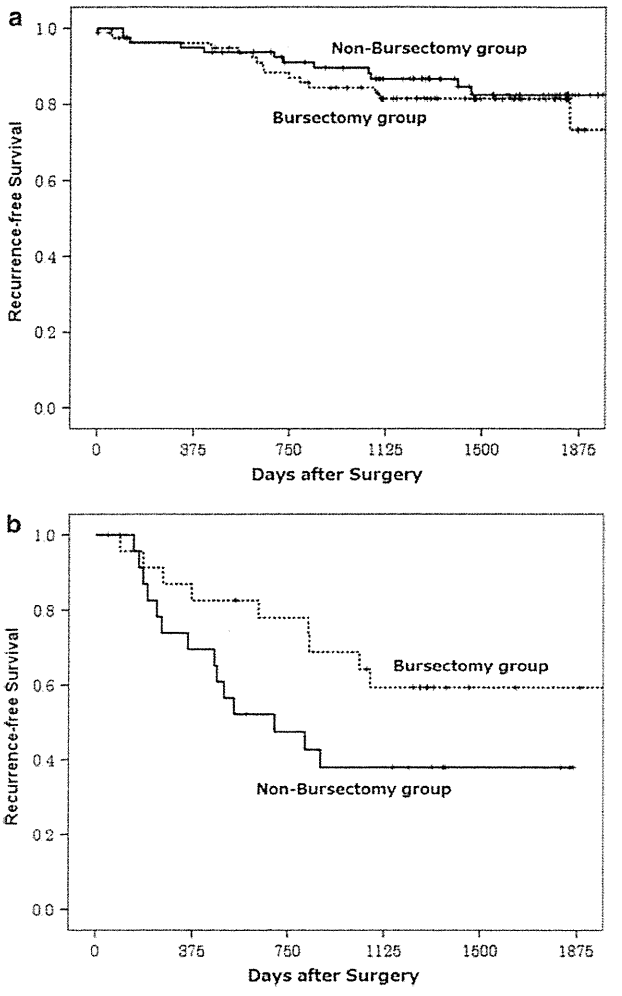

Fig. 5 Recurrence-free survival in patients with serosa-negative tumors (**a**) and those with serosa-positive tumors (**b**) by treatment group

analysis may have provided only small differences in RFS between the two groups. More accurate results concerning RFS will be provided in the final analysis.

This study is the first randomized controlled trial to evaluate omental bursectomy in gastric cancer surgery, although it may be under-powered to provide a definitive conclusion. The interim analyses suggest that bursectomy may improve survival in gastric cancer patients and should not be abandoned as a futile procedure until more definitive data can be obtained. The Japan Clinical Oncology Group (JCOG) is now conducting a large-scale randomized controlled trial (JCOG1001) with the recruitment of 1000 patients with cT3–T4 tumors to confirm the superiority of bursectomy in terms of overall survival.

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Preoperative T staging of gastric cancer by multi-detector row computed tomography

Tomoki Makino, MD,[a] Yoshiyuki Fujiwara, MD,[a] Shuji Takiguchi, MD,[a] Takahiro Tsuboyama, MD,[b] Tonsok Kim, MD,[b] Youichirou Nushijima, MD,[c] Makoto Yamasaki, MD,[a] Hiroshi Miyata, MD,[a] Kiyokazu Nakajima, MD,[a] Masaki Mori, MD,[a] *and* Yuichiro Doki, MD,[a] *Osaka and Hyogo, Japan*

Background and Purpose. *Preoperative T staging demands high accuracy, because it greatly influences subsequent therapies in advanced gastric cancer.*
Patients and Methods. *616 patients with gastric cancer underwent multi-detector row computed tomography (MDCT) before operation. The results were compared with operative and pathologic findings. Especially, we evaluated the correlations among the diagnostic accuracy of T staging and various clinicopathologic parameters by focusing on 276 patients who had detectable lesions by MDCT.*
Results. *The overall diagnostic accuracy of preoperative T staging by MDCT was 90.9% (560/616). For each pathologic T stage, the accuracy was 95% for pT1, 76% for pT2-3, 92% for pT4a, and 75% for pT4b, respectively. Among the 276 patients, 239 (87%) were correctly staged by MDCT whereas 29 (11%) and 8 (3%) were over- or under-staged, respectively. Antral tumors (P = .045), and Borrmann type 1 tumors (P = .0001) were incorrectly T staged by MDCT, whereas differentiated type tumors tended to be over-staged. All patients with positive cytology (n = 12 cases) and peritoneal metastasis (n = 7 cases) diagnosed at laparotomy had been diagnosed as T4a or deeper by MDCT. The 5-year overall survival rates classified by preoperative T staging by MDCT (T1/T2-3/T4a/T4b) were 100%, 89%, 59%, and 31%, respectively, whereas those for each pT stage were 100%, 84%, 59%, and 19%.*
Conclusion. *Preoperative T staging of gastric cancer by MDCT is highly accurate and could contribute to treatment strategies, particularly in advanced disease. (Surgery 2011;149:672-9.)*

From the Departments of Gastroenterological Surgery,[a] and Radiology,[b] Graduate School of Medicine, Osaka University, Osaka, and Department of Surgery,[c] Kawanishi Municipal Hospital, Hyogo, Japan

GASTRIC CANCER is one of the major causes of cancer-related deaths worldwide.[1] Especially in Japan, the incidence of this disease is high and it is the leading cause of death among all malignancies.[2] Accurate preoperative staging is important for the selection of the optimal therapeutic strategy, especially for advanced disease, because preoperative therapies, including chemotherapy or chemo-radiotherapy, have been performed recently more frequently to down-stage the tumor and to extend survival.[3-5]

Double-contrast barium examination and endoscopy are used to evaluate gastric cancer and allow the detection of small lesions earlier in the course of the disease.[6] These procedures, however, are based exclusively on imaging abnormalities in the gastric mucosa and are limited by their inability to evaluate transmural and extraserosal extension of the disease; thus, both have limitations in preoperative T staging and cannot determine whether the metastases are present or not. Similarly, endoscopic ultrasonography (EUS), the most commonly used method for evaluating T stage,[7] is invasive and operator-dependent, and has limitations in the depth of view that can be achieved. In addition, it is not able to evaluate the gastric wall distal to a stenosis caused by the neoplasm. Therefore, EUS is not part of the routine examination for some gastric cancer patients.

The recent development of multi-detector row computed tomography (MDCT) scanners has allowed imaging with a thinner section collimation, translating into increased quality on transverse computed tomography (CT) scans and multiplanar reconstructions (MPR).[8,9]

Moreover, administration of a contrast material permits precise evaluation of any enhanced lesion. Although others have reported the diagnostic

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Reprint requests: Tomoki Makino, MD, Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, 2-2-E2, Yamada-oka, Suita, Osaka, 565-0871, Japan. E-mail: tmakino@gesurg.med.osaka-u.ac.jp.

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utility of MDCT for gastric cancer, the number of patients in their studies was relatively small and the clinical association of MDCT was not elucidated adequately.[8,10,11] In the present study, we assessed the diagnostic accuracy of preoperative T staging by MDCT in a large number of patients according to various clinicopathologic parameters. To our knowledge, this is the first report that examines the relationship between T staging by MDCT and the prognosis to elucidate the accuracy of this modality in clinical use.

PATIENTS AND METHODS

Patients and treatment protocol. The inclusion criteria of this study were the following: (1) histopathologically confirmed gastric adenocarcinoma based on endoscopic gastric biopsies; (2) MDCT performed within 14 days before gastrectomy; (3) absence of any preoperative therapies; (4) appropriate scan conditions of MDCT as described below. Between January 2001 and June 2009, 781 patients with histopathologically confirmed gastric adenocarcinoma received gastrectomy in our hospital. Among them, 88 patients received neoadjuvant chemotherapy and 41 patients did not undergo CT. Therefore, 652 patients were referred for MDCT for preoperative staging. Excluding 36 patients whose MDCT was inappropriate for the protocol, 616 patients were evaluated in this retrospective study.

The 276 patients who had detectable tumors by MDCT included 80 females and 196 males with a mean age of 64.7 years (range 30–92). Patient characteristics were the following: tumor region (fundus/body/antrum; 78/91/107), tumor location (anterior/posterior/greater/lesser/circumferential; 57/60/47/98/14), morphology[12] (Gross type 0/1/2/3/4/5; 102/17/71/73/13/0), histology[12] (papillary adenocarcinoma/well differentiated adenocarcinoma/moderately differentiated adenocarcinoma/poorly differentiated adenocarcinoma/signet-ring cell carcinoma/mucinous adenocarcinoma; 4/28/94/131/13/6), mean tumor area; 24.5 cm^2 (SD, 28.4 cm^2), pT (0/1/2/3/4; 0/75/41/47/113), pN (0/1/2/3; 125/114/34/3), and pStage (0/I/II/III/IV; 0/88/63/103/22) classified according to the 7th edition of TNM classification.[13] Distal and total gastrectomies were performed in 188 and 88 patients, respectively, whereas 253 patients underwent curative and 23 noncurative resection.

Our treatment strategy in gastric cancer was the following: patients with advanced lymph node metastases, peritoneal dissemination, or distant metastasis received chemotherapy whereas patients without these findings underwent gastrectomy if the general condition permitted. Postoperative adjuvant chemotherapy mainly for pStage II/III patients with curative resection used an S-1 alone regimen, uracil/tegafur or 5′-deoxy-5-fluorouridine regimen. Patients were surveyed postoperatively or post-chemotherapy every 3 months by physical examination and serum tumor markers, every 6 months by CT and abdominal ultrasonography, and every year by endoscopy.

The study protocol was approved by the Human Ethics Review Committee of Osaka University School of Medicine, and a signed consent form was obtained from each subject.

MDCT protocol. The MDCT protocol has been described in detail previously.[8] Briefly, all 616 patients underwent CT after overnight fasting with a MDCT scanner (LightSpeed QX/I Ultra; GE Medical Systems, Milwaukee, WI) using a high-speed mode. Five minutes before the CT, 20 mg of scopolamine (Buscopan; Boehringer Ingelheim Japan, Tokyo) was injected intramuscularly to relax the bowel wall and decrease peristalsis. To distend the gastric wall, each patient drank 600 mL of tap water or effervescent granules before CT. The patient was positioned prone on the scanning table to avoid artifacts caused by air in the stomach.[14] Patients with gastric cardia or fundal lesion, as determined on a barium swallow examination and endoscopy, were placed supine. Pre-contrast scanning was not performed. A total of 100 mL of nonionic contrast material (iopromide; Proscope, Tanabe Seiyaku, Osaka, Japan) containing 300 mg of iodine per mL was administered intravenously at 3 mL/sec using a power injector (Autoenhance A-50; Nemoto Kyorindou, Tokyo). Scanning was performed 70 sec after initiation of contrast material injection, which corresponded to the venous phase. Scanning began at the level of the dome of the right hemidiaphragm and ended at the caudal edge of the stomach so as to include the entire liver. CT parameters were as follows: 4 detector rows; section thickness, 1.25 mm; pitch, 6; reconstruction interval, 0.63 mm; 200 mA; 120 kV; and tube rotation time, 0.8 sec.

Transverse images with section thickness of 2.5 mm and obtained at 2.5-mm intervals were created by using volumetric data obtained at MDCT. To make interpretation easier, all images were printed as if the patient were in the supine position. MPR images were reconstructed on a workstation (Advantage Windows; GE Medical Systems, Miluwaukee, WI). After confirming the tumor location, oblique coronal and oblique MPR images that were obtained perpendicular to the stomach wall including the tumor were reconstructed in all

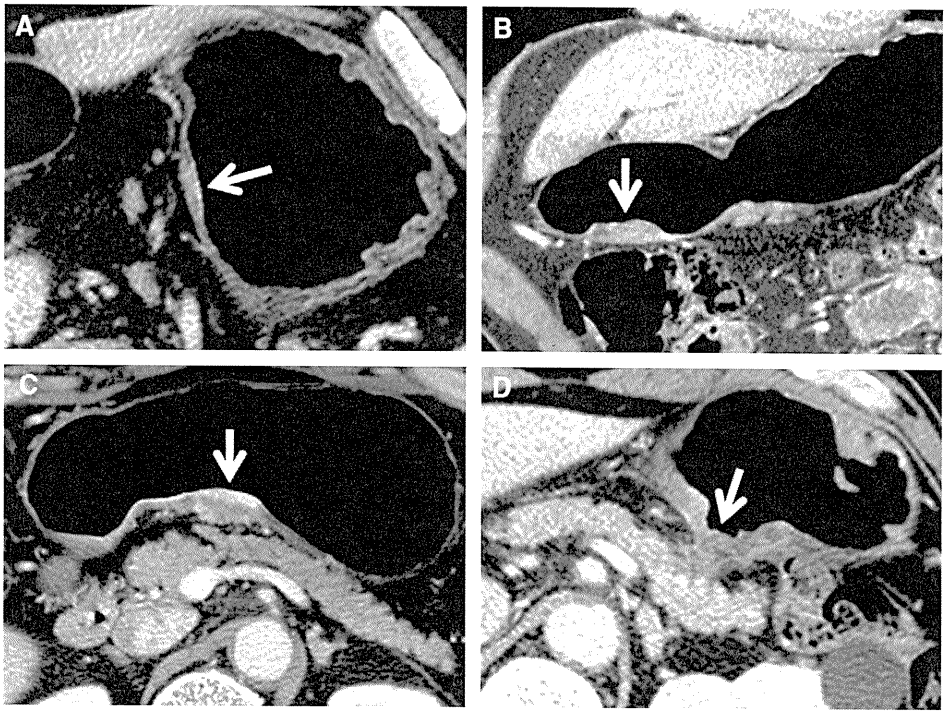

Fig 1. The representative CT images of each T1, T2-3, T4a, and T4b tumors. (*A*) T1 detectable tumor; transverse CT showed enhancement with focal thickening (*arrow*) in inner and middle layers, but the outer layer was intact. (*B*) T2-3 tumor; irregularly enhancing wall thickening (*arrow*) in entire stomach wall without perigastric fatty infiltration. (*C*) T4a tumor; irregularly enhancing wall thickening (*arrow*) with irregular outer border. (*D*) T4b tumor; extension of tumors to adjacent pancreas.

patients by a study coordinator. These MPR images (section thickness, 2.5 mm; intervals, 2.5 mm) were printed subsequently as hard copies.

Preoperative T staging of gastric cancer with MDCT. MDCT of the stomach demonstrates that the normal gastric wall is a 3-layered structure. The inner layer with high attenuation corresponds to the mucosa and the muscularis mucosa, the middle layer with low attenuation to the submucosal layer consisting of coarse tissues and containing fatty tissues, and the outer layer with slightly high attenuation corresponds to the muscularis propria and serosa.[14,15]

The depth of tumor invasion in the gastric wall visualized by CT was classified according to the 7th edition of TNM classification.[13] Based on the assumption that undetectable tumors by MDCT would be pT1, we recognized the following 2 categories together as T1 tumors; the T1 stage represented (a) T1: enhancement with or without focal thickening in the inner and/or middle layer (Fig 1, *A*), but the outer layer showed no enhancement; (b) T0, ie, undetectable: no abnormal enhancement in the entire stomach wall. The T2-3 stage represented thickening of the gastric wall with loss or disruption of the low-attenuation stripe, but the surface of the outer layer in contact with the fatty layer surrounding the stomach was smooth with a clear, perigastric fat plane (Fig 1, *B*). The T4a stage represented a nodular and irregular outer border of the thickened gastric wall or infiltration of the perigastric fat (Fig 1, *C*). The T4b stage represented the changes described for T4a staging extending into adjacent contiguous organs or structures (Fig 1, *D*).[8,11,14,16]

Transverse and MPR images were evaluated simultaneously by 2 experienced radiologists (T.K. and T.T., with 10 and 20 years of experience in abdominal CT, respectively). They interpreted the images independent of each other, and disagreement on diagnosis was resolved by consensus. The radiologists were blinded to the results of other preoperative examinations, including the upper gastrointestinal series or endoscopic examination, and operative and pathologic findings.

Statistical analysis. The correlations among the diagnostic accuracy by MDCT and various clinicopathologic parameters were evaluated by the chi-square test and the Fisher exact probability test. Differences in continuous variables between groups were evaluated by the Mann-Whitney *U* test. Prognostic variables were assessed by the

log-rank test, and overall survival was analyzed by the Kaplan-Meier method. In this study, survival time was defined as time from the day of diagnosis to the day of death. These analyses were carried out using SPSS for Windows release 10 (SPSS, Inc, Chicago, IL). A P value less than .05 was accepted as statistically significant.

RESULTS

Diagnostic accuracy of preoperative T staging determined by MDCT. The overall detection rate of primary tumors by MDCT was 45% (276/616) [pT1 19% (75/396), pT2-3 83% (88/106), pT4a 99% (105/106), and pT4b 100% (8/8), respectively]. Table I provides a summary of preoperative T staging by MDCT. The overall diagnostic accuracy of preoperative T staging by MDCT was 91% (560/616) and for each pathologic T stage, it was 95% (377/396) in pT1, 76% (80/106) in pT2-3, 92% (97/106) in pT4a, and 75% (6/8) in pT4b, respectively. The positive predictive value (PPV), and negative predictive value for each pathologic stage were 95, 91% for pT1, 78, 96% for pT2-3, 89, 98% for pT4a, and 75, 99% for pT4b. With regard to serosal invasion (pT4a or deeper) by MDCT, the accuracy was 94% (107/114). The diagnosis of T staging by MDCT was almost identical by the 2 radiologists, with inter-observer variation of less than 10%. There was no specific pattern for inter-observer variation.

Among the 276 patients who had tumors detectable by MDCT, 239 (87%) patients were staged correctly by MDCT whereas 29 (11%) and 8 (3%) patients were over- or under-staged, respectively. The PPV of preoperative T staging by MDCT were 100% (56/56) for T1, 78% (80/103) for T2-3, 89% (97/109) for T4a, and 75% (6/8) for T4b.

Correlations among preoperative T staging by MDCT and various clinicopathologic parameters. Among the 276 patients who had lesions detectable by MDCT, the percentage of over-staging was greater for antral tumors than other regions (16 vs 7%, P = .045, Table II). Borrmann type 1 tumors tended to be staged incorrectly; the rates of over- and under-staging for these tumors and other types were 35 and 9%, and 12 and 2%, respectively (P = .0001). In this context, differentiated type tumors tended to be over-staged compared with undifferentiated types, (P = .16). For incorrectly staged cases, the tumor area tended to be less for over-staged tumors than for under-staged ones (17.8 vs 26.2 cm^2, respectively, P = .15). Other parameters, including age, sex, and tumor location, did not correlate with the diagnostic accuracy in the present population (Table II).

Table I. Correlation between MDCT-T staging and pathologic T staging

	Pathological T staging				
	T1	*T2-3*	*T4a*	*T4b*	*Total*
MDCT T staging					
T0	321†	18	1	0	340
T1	56†	0	0	0	56
T2-3	17	80†	6	0	103
T4a	2	8	97†	2	109
T4b	0	0	2	6†	8
Total	396	106	106	8	616

MDCT, multi-detector row computed tomography.
†Preoperative T staging by MDCT was concordant with pathological T staging.

With respect to the association with operative findings, abdominal lavage cytology at laparotomy was performed in 182 of 276 patients.; 12 (7%) patients had positive cytology and all were diagnosed preoperatively as T4a (11 patients) or deeper (1 patient) by MDCT. Similarly, 7 (4%) patients had peritoneal metastasis diagnosed incidentally at laparotomy, and all were preoperatively diagnosed as T4a by MDCT.

Preoperative T staging by MDCT and survival. The median follow-up period was 38 months. The mean survival time for all 276 patients was 55 months. The 5-year overall survival rates classified according to preoperative T stage by MDCT (T1/2-3/4a/4b = 56/103/109/8) were 100, 8, 59, and 31%, respectively, whereas those for each pathologic T stage (T1/2-3/4a/4b = 56/106/106/8) were 100, 84, 59, and 19%, respectively (Fig 2, *A* and *B*).

DISCUSSION

In our analysis of 616 patients with gastric cancer, the overall diagnostic accuracy of preoperative T staging by MDCT was 91% and, for each pathologic T stage, it was 95% for pT1, 76% for pT2-3, 92% for pT4a, and 75% for pT4b. The accuracy of serosal invasion was extremely high (94%). In the 276 patients who had detectable lesions by MDCT, 87% of patients were correctly staged by MDCT whereas 11% and 3% of patients were over- and under-staged, respectively. The factors that contributed negatively to diagnostic accuracy were antral tumors and Borrmann type 1 tumors. T staging by MDCT correlated well with the results of CY and P parameters determined at laparotomy and with the patient's prognosis.

The results of previous reports on the usefulness of CT for T staging of gastric cancer have been

Table II. Correlation among the diagnosis of preoperative T staging by MDCT and various clinicopathologic parameters in detectable tumors by MDCT (n = 276)

Parameters	*Correctly staged* (n = 239) n (%)	*Incorrectly staged*		P *value*
		Over-staged (n = 29) n (%)	*Under-staged* (n = 8) n (%)	
Age				
<65	100 (84)	14 (12)	5 (4)	.43
>65	139 (89)	15 (10)	3 (2)	
Gender				
Male	168 (86)	21 (11)	7 (4)	.56
Female	71 (89)	8 (10)	1 (13)	
Tumor region				
Antrum	91 (81)	18 (16)	3 (3)	.045
Fundus, body	148 (90)	11 (7)	5 (3)	
Tumor location				
Lesser curvature	83 (84.7)	11 (11.2)	4 (4.1)	.65
Other	156 (88)	18 (10)	4 (2)	
Morphology				
Borrmann type 1	9 (53)	6 (35)	2 (12)	.0001
Other	230 (89)	23 (9)	6 (2)	
Histology				
Differentiated*	105 (83)	18 (14)	3 (2)	.16
Undifferentiated†	134 (89)	11 (7)	5 (3)	
Tumor area (cm^2)‡	25.19 ± 29.71	17.83 ± 16.76	26.22 ± 17.12	–

*Papillary adenocarcinoma and well/moderately differentiated adenocarcinoma.
†Poorly differentiated adenocarcinoma, mucinous adenocarcinoma, and signet-ring cell carcinoma.
‡Data are mean ± SD, or otherwise number (%) of patients.

somewhat controversial (overall accuracy rates of 43–82%[14,15,17-22]). Because these studies used a single-detector row CT and applied section thicknesses of 5–10 mm, their results could be influenced by partial volume effects or breathing artifacts. In this respect, MDCT and MPR images overcome such problems by their ability to provide thinner sections in less time and to reduce partial volume effects, with better diagnostic performance. The advantage of MDCT over EUS lies in its ability to image the immediate vicinity of the stomach as well as distant regions. Furthermore, in the preoperative setting, MDCT can also map the arteries and veins around the stomach by using 3D CT angiography,[23] although exposure to radiation is a disadvantage of MDCT.[24] Radiation doses to organs from CT depend on several factors, such as the number of scans, the tube current and scanning time, the size of patient, the axial scan range, the scan pitch, the tube voltage, and the type of scanner used.[25] Although, unfortunately, we have no accurate data about radiation doses for all patients enrolled in this study, our MDCT protocol as described in the text was a standard one which might not increase radiation exposure substantially.[26] Another point related to MDCT is the influence of body mass index on the diagnostic accuracy of T staging. Such an influence of obesity is based on the use of a similar dose of contrast agent in all patients. Alternatively, obesity may increase the contrast between organs/gut and fat tissue with excess visceral fat, thereby increasing the accuracy of MDCT. Further studies are needed to investigate this issue in more detail.

In the present study, the overall tumor detection rate was 45%, which was little lower than previous reports.[27-29] This reason appears to be due in part to the high proportion of early tumors (64%) in this study. With respect to the detectability of T1 tumors by MDCT, there was no difference in tumor area between T1 detectable and T1 undetectable (ie, T0) tumors. This lack of difference appears to be due to the fact that a large proportion of T1 undetectable tumors were superficial (especially 0-IIc) that spread within the mucosal layer and were not detected by MDCT regardless of the tumor area (data not shown). In contrast, most of the T1 detectable tumors showed submucosal invasion, in agreement with the findings described by other investigators.[27] Furthermore, most of the pT1 tumors (321/396, 81%) could not be detected by MDCT, whereas the detection rate of advanced tumors (T2 or deeper) was 91%, suggesting that the depth of tumor invasion

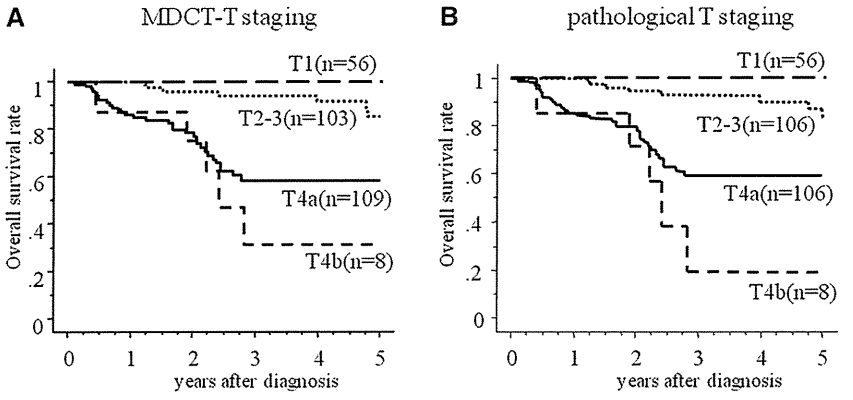

Fig 2. Overall survival classified by preoperative T staging by MDCT and pathologic T staging. Overall survival curves classified by preoperative T staging by (*A*) MDCT and (*B*) pathologic T staging were plotted by the Kaplan-Meier method.

is an important factor in detection of gastric cancer by MDCT. The overall accuracy rate of T staging by MDCT was relatively high (91%) compared with previous studies,[7,27,30] also due to the high proportion of T1 tumors. In respect to T1 tumor diagnosis, 94% of MDCT undetectable tumors and 100% of 'T1 detectable' by MDCT were pT1. Taken together, we considered both T1 detectable and undetectable tumors (T0) as 'T1' diagnosed by MDCT. Using this criterion,[8] diagnostic accuracy in pT1 tumors was very high (95%). Although a high overall diagnostic accuracy was achieved, the accuracy of T2-3 lesions (76%) was relatively low, which was in agreement with the previous report of Moschetta et al.[28] One of the reasons for understaging a T2-3 tumor as a T1 tumor, as in the case with our study, may be related to the poor enhancement of gastric cancer; indeed, complete enhancement of the entire stomach wall was rarely observed.[8] Alternatively, Woo et al[31] reported that it may be difficult to differentiate between a T2-3 cancer and a T1 cancer with massive submucosal invasion using CT, because the hypoattenuating stripe corresponding to the intact submucosal layer could be obliterated for T1 cancer with submucosal invasion.[21] Considering that only EUS could differentiate between mucosal and submucosal tumors,[32] MDCT did not surpass EUS in accuracy of T staging in relatively early-stage tumors, especially for the T1 and T2-3 lesions.

When we focused on advanced cases (T2 and deeper), 83% of patients were staged correctly by MDCT, a performance similar to that of EUS (65–92%).[7] Furthermore, with regard to the diagnosis of serosal invasion (T4a), which implies free cancer cells in abdominal cavity, our diagnostic accuracy was extremely high (94%) compared to a previous report.[33] One possible reason for this finding might be the criteria for T staging by MDCT; some authors[29,33,34] used a stricter criterion for the MDCT diagnosis of serosal invasion than ours. In the present study, the thinner scans of MDCT (1.25 or 0.63 mm), which could depict the outer line (ie, the serosa) adjacent to epigastric fat,[8] also contributed to the high accuracy of serosal invasion. Nevertheless, there appear to be some limitations for MDCT diagnosis of T staging, as reported previously, in distinguishing T3 from T2 tumors, because only a small proportion of the tumor exists in the subserosa in T3, in T2-3 cancers (especially cancers with subserosal invasion) in the presence of perigastric inflammation or vascular/lymphatic engorgement,[33] or in T4a cancers with minimal infiltration of cancer cells into the perigastric adipose tissue.[35]

In this analysis, we identified 2 parameters that influenced misdiagnosis of T staging by MDCT; first elevated type tumors (eg, Borrmann type 1) tended to be over-staged because, as Yan et al[27] estimated, the elevated mass seemed to be accompanied by thickening of the entire gastric wall or by irregularities in the serosal surface. Second, concerning the relation between diagnostic accuracy of T staging by MDCT and tumor location, the previous study[36] reported that there is a tendency that tumors located in the upper third of the stomach are misdiagnosed in T staging by MDCT due to the poor distension of the stomach in cardia tumors. In contrast, in our series, the over-staging of antral tumors was probably related to the thickness of the gastric wall in that area, especially the muscle layer, as well as to the active peristalsis in the antrum.[37] Although minimal infiltration of cancer cells into the deeper layer, observed often in poorly differentiated type tumors, is beyond