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Severity of Complications After Gastrectomy in Elderly Patients With Gastric Cancer

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Abstract
Background The risk of surgery for gastric cancer has not been fully evaluated, and this study aimed to assess the severity of postoperative complications after D2 or modified D2 gastrectomy in elderly patients.
Methods Eligible patients were retrospectively selected from the Kanagawa Cancer Center database between 1990 and 2009 based on the following criteria: age ≥80 years and D2 or modified D2 gastrectomy as a primary treatment for gastric cancer. The severity of complications was evaluated using the Clavien–Dindo classification.
Results A total of 83 patients with a median age of 82 years (range 80–88 years) were entered in this study. Sixty (72 %) had at least one co-morbid condition. American Society of Anesthesiologists scores were 2 in 66 patients and 3 in 17 patients. The extent of gastrectomy was distal in 65 (78 %) and total in 18 (22 %) patients. The procedure used for lymphadenectomy was modified D2 in 38 (46 %) and D2 in 45 (54 %) patients. Altogether, 18 complications were observed in 15 patients. The overall morbidity rate was 18 % [95 % confidence interval (CI) 9.7–26.2 %], and the mortality rate was 3.6 % (95 % CI 0–7.6 %). Complications were classified as grade 2 ($n = 9$), grade 3a ($n = 1$), grade 3b ($n = 4$), grade 4 ($n = 1$), and grade 5 ($n = 3$). Severe complications (≥ grade 3) occurred in 8.4 % (95 % CI 2.4–14.4 %).
Conclusions The morbidity rate was acceptable, but that of severe complications was high, suggesting that surgery for gastric cancer in elderly patients is risky and should be limited.

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Introduction

Every year, more than 800,000 patients are newly diagnosed with gastric cancer, which is the second most common cause of cancer-related death in the world [1]. In Japan, 20 % of gastric cancer patients are >80 years old [2]. Therefore, it is not rare in clinical practice for gastric cancer patients over the age of 80 years to undergo gastrectomy. In addition, Phase III trials evaluating surgical treatment that are ongoing in Japan (JCOG0912: UMIN000003319 and JCOG1001:UMIN000003688) have age upper limits of 80 years. In the other words, it would be impossible to provide evidence about surgical treatment for patients >80 years old.

Complete tumor removal is essential to treat gastric cancer, and D2 gastrectomy is the standard surgical procedure in Japan. Morbidity and mortality after D2 surgery were 20.9 and 0.8 %, respectively, in a Japanese Phase III trial [3]. However, patients who entered into the clinical trials were relatively young and had no severe co-morbidities. No prospective data are available to confirm that D2 surgery is safe for elderly patients who are not eligible for inclusion in clinical trials.

Previously, many retrospective analyses have focused on morbidity and mortality in elderly gastric cancer patients [4–14]. Although some authors [6, 9, 13] reported that age was an independent factor that affects mortality and morbidity, others [4, 5, 7, 8, 10–12, 14] described gastrectomy for elderly patients as feasible and safe based

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on a low incidence of morbidity. Elderly cancer patients often have co-morbidities and age-related physiologic problems that may not increase the incidence but could increase the severity of morbidity after gastrectomy. However, no study has reported on the severity of complications. The safety of surgery should be evaluated not only by the overall morbidity rate but also by the rate of severe complications together with mortality.

Recently, Dindo [15] proposed a new classification for surgical complications, called the Clavien–Dindo classification, which categorizes morbidity from grade 1 to grade 5. It was validated in 2009 [16]. Our retrospective study aimed to assess the severity of postoperative complications after D2 or modified D2 gastrectomy in gastric cancer patients >80 years of age using the Clavien–Dindo classification.

Methods

Selection of patients

The patients were selected from the prospective database of the Kanagawa Cancer Center, Department of Gastrointestinal Surgery, Yokohama, Japan, according to the following criteria: (1) histologically proven gastric adenocarcinoma; (2) D2 or modified D2 gastrectomy for gastric cancer as a primary treatment between January 1990 and December 2009; (3) R0 or R1 resection achieved according to surgical and pathologic findings; (4) age ≥80 years.

Indication for surgery

Tumor progression was evaluated by physical examinations, endoscopy, upper gastrointestinal series, chest radiography, and abdominal computed tomography (CT). Surgery was considered when no metastasis to distant organs was apparent. Preoperative risks were assessed by activities of daily life, performance status, medical history, physical status, physical examinations, symptoms of chronic lung or heart disease, chest radiography, electrocardiography, pulmonary function test, and biochemical and hematologic tests. Four staff surgeons and at least one anesthesiologist evaluated the surgical indications. Surgery was selected when all five physicians agreed on the operability of the patients.

Surgical procedure

Extent of lymphadenectomy was according to the Japanese gastric cancer treatment guidelines 2010 [Japanese Gastric Cancer Guidelines (JGCG) version 3] [17]. In this study, D2 lymph node dissection included D2 defined by the JGCG version 3 and D2 with nodal dissection of nodes along the superior mesenteric vein. Thus, splenectomy was necessary for total gastrectomy with D2. On the other hand, modified D2 gastrectomy included D1+ or D1+ plus some nodal dissection which did not reach the definition of D2. Splenectomy was not performed in the modified D2 total gastrectomy.

In principle, D2 gastrectomy was adopted for T2–T4 disease, whereas modified D2 was used for T1 cancer. Because T1 gastric cancer rarely metastasizes to lymph nodes along the splenic or proper hepatic arteries, these lymph nodes are preserved with the modified D2. At present, this type of surgery has been regarded as standard treatment for T1 disease in Japan [18]. Spleen-preserving modified D2 gastrectomy was selected based on the physician's preference, the patient's co-morbidities, and the tumor status.

The depth of tumor and nodal involvement was determined by Japanese Classification of Gastric Carcinoma: 3rd English edition (JCGC 3rd English edition) [19].

Clavien–Dindo classification

The Clavien–Dindo classification categorizes surgical complications from grade 1 to grade 5 based on the invasiveness of the treatment required. Grade 1 requires no treatment; grade 2 needs medical therapy; grade 3a requires surgical, endoscopic, or radiologic intervention but not general anesthesia; grade 3b requires general anesthesia; grade 4 represents life-threatening complications that require intensive care; grade 5 represents the death of the patient.

In this study, we retrospectively determined complications ranging from grade 2 to 5 from patients' records during hospitalization and within 30 days after surgery. Grade 1 was not evaluated to exclude the possibility of description bias in patient records. Severe complications were defined as those graded as >3a. Mortality (grade 5) was defined as hospital death due to any cause after surgery.

This study was reviewed and approved by the institutional review board committee of Kanagawa Cancer Center.

Results

A total of 109 patients underwent D2 or modified D2 gastrectomy for gastric adenocarcinoma. Among them, 83 underwent R0 or R1 resection and were entered into the study. Table 1 summarizes the baseline characteristics of the patients. Among 83 patients, 82 (99 %) scored 0 or 1 for Eastern Cooperative Oncology Group (ECOG)

Table 1 Baseline characteristics of the patients

Characteristics	No. of patients	%
Age (range 80–88 years)		
80–84 years	70	84
≥85 years	13	16
Sex		
Male	49	59
Female	34	41
ECOG-PS		
0	72	87
1	10	12
2	1	1
ASA score		
2	66	80
3	17	20
Co-morbidities		
Heart disease	19	23
Cerebrovascular disease	10	12
Pulmonary disease	26	31
Diabetes mellitus	9	11
Liver disease	1	1
Hypoalbuminemia (<3.5 g/dl)	12	14
Anemia: hemoglobin (<10 g/dl)	12	14
Renal disfunction: (Ccr <30)	8	10
No. of co-morbidities[a]		
0	23	28
1	27	32
2	18	22
3	11	13
≥4	4	5

ECOG-PS Eastern Cooperative Oncology Group performance status, *ASA* American Society of Anesthesiologists, *Ccr* creatinine clearance

[a] Co-morbidities were applied to above eight co-morbidities

Table 2 Surgical procedure and pathologic findings

Parameter	No. of patients	%
Operative procedure		
Distal gastrectomy	65	78
Total gastrectomy	18	22
Extent of lymphadenectomy		
D2	45	54
Modified D2	38	46
Combined resection		
Spleen	4	5
Pancreas	1	1
Liver	1	1
Colon	1	1
Depth of invasion[a]		
T1a (m)	14	17
T1b (sm)	31	37
T2 (mp)	11	13
T3 (ss)	7	9
T4a (se)	16	19
T4b (si)	4	5
Lymph node metastasis[a]		
N0	55	66
N1 (1–2)	14	17
N2 (3–6)	5	6
N3a (7–14)	8	10
N3b (>15)	1	1
Stage[a]		
I	48	58
II	16	19
III	16	19
IV	3	4

[a] Tumor depth, nodal involvement, and staging classification were based on JCGA 3rd English edition

performance status, and 60 (72 %) patients had more than one co-morbidity. The most common co-morbidity was pulmonary disease, which included chronic obstructive pulmonary disease, chronic bronchitis, and interstitial pneumonitis requiring continuous drug therapy. Most patients had an American Society of Anesthesiologists (ASA) score of 2 in this series.

Surgical procedure and pathologic findings

More than half of the patients underwent D2 gastrectomy; splenectomy was performed in only 4 patients (5 %); and 18 (22 %) underwent total gastrectomy. In all, 48 patients (58 %) had early-stage disease (Table 2). Thus, 22 patients were candidates for D2 total gastrectomy including splenectomy.

Complications

A total of 18 perioperative complications were observed in 15 patients. Details of these complications are given in Table 3. The overall morbidity rate was 18 % [95 % confidence interval (CI) 9.7–26.2 %]: Anastomotic leakage occurred in 1 % and pancreas-related abscess in 2 %. Complications were classified as grade 2 in nine patients, grade 3a in one, grade 3b in four, grade 4 in one, and grade 5 in three. The rate of severe complications of grade ≥3a was 8.4 % (95 % CI 2.4–14.4 %), and that of severe complications of grade ≥3b was 7.2 % (95 % CI 1.6–12.8 %). There were no significant differences in the proportions of total or severe morbidities between modified D2 (20.0 % and 7.8 %, respectively) and D2 (16.0 % and 8.9 %, respectively). Death (grade 5) occurred in three

Table 3 Postoperative complications according to the Clavien–Dindo classification

Complication	Grade 2		Grade 3a		Grade 3b		Grade 4		Grade 5		≥Grade 3a	
	mD2	D2	mD2	D2	mD2	D2	mD2	D2	mD2	D2	mD2	D2
Surgical												
Pancreas-related abscess	2	0	0	0	0	0	0	0	0	0	4	1
Anastomotic leakage	0	0	0	0	1	0	0	0	0	0		
Ileus	0	0	1	0	0	1	0	0	0	0		
Wound infection	1	1	0	0	2	0	0	0	0	0		
Cholecystitis	0	1	0	0	0	0	0	0	0	0		
Medical												
Pneumonia	1	3	0	0	0	0	0	0	0	1	1	3
Cardiac	0	0	0	0	0	0	0	0	0	1		
Liver	0	0	0	0	0	0	0	0	1	0		
Colitis	0	0	0	0	0	0	0	1	0	0		

mD2 modified D2 lymphadenectomy, *D2* D2 lymphadenectomy

patients, and the mortality rate was 3.6 % (95 % CI 0–7.6 %). Among three patients who developed surgical mortality, one who had liver cirrhosis as a co-morbidity died after surgery owing to hepatic failure; the other two died after surgery owing to cardiac or pulmonary disease even though they had no preoperative co-morbidities.

Discussion

This is the first report to focus on the severity of complications after gastrectomy in elderly patients with gastric cancer. Our results demonstrated that the overall morbidity rate was acceptable but that the rate of severe complications was high, suggesting that surgery for gastric cancer in elderly patients is risky.

In the present study, the overall morbidity rate was 18 %, whereas the rates for patients with ≥grade 3a and ≥grade 3b complications were 8.4 % (7/83) and 7.2 % (6/83), respectively. Previously, morbidity and mortality in nonelderly patients (≤75 years of age) were evaluated in the Japan Clinical Oncology Group (JCOG) 9501 Phase III study [3], which compared D2 with D2 plus paraaortic lymphadenectomy. In that study, the overall morbidity rate was 20.9 % after D2, which is similar to that in the present study. Thus, the safety of D2 for elderly patients may be acceptable when the overall morbidity rate alone is considered. In contrast, the rate of reoperation, which is equal to grade 3b in the Clavien–Dindo classification, was 1.9 % in the Phase III study, so the overall rate of ≥grade 3b complications was considered to be high in elderly patients, as shown in this study. Our results strongly suggest that surgery for gastric cancer was risky when the rate of severe complications was considered. When complications occurred in the elderly patients, they rapidly increased in severity. Moreover, surgical mortality was 3.6 % in the present study, which was also higher than the 0.8 % reported in the JCOG 9501 study. Considering the correlation between preoperative co-morbidities and postoperative mortality, two of three patients died owing to cardiac or pulmonary disease even though they had no preoperative co-morbidities. Thus, elderly patients easily develop severe cardiac or pulmonary morbidity even without the presence of preoperative co-morbidities.

When comparing D2 and modified D2, no significant difference in overall morbidity rate or severity of complications was observed, although the surgical procedures in D2 and modified D2 differ, especially for total gastrectomy. The spleen is resected with total gastrectomy using D2 dissection but is preserved for the modified D2 procedure. Recently, the JCOG 0110 Phase III trial [20] clearly showed a difference in morbidity: 30.3 % after total D2 and 16.7 % after total modified D2, with the difference statistically significant. In the present study, total D2 and total modified D2 were performed in 4 and 14 patients, respectively, being selected according to the physician's preference, the patient's co-morbidities, and tumor status. Only a small number of patients underwent D2 total gastrectomy, which may explain why there was no difference in morbidity between the two procedures. In the patients who underwent D2, rather than modified D2 total gastrectomy, morbidity was greatly increased. In contrast, the difference in morbidity after D2 and modified D2 distal gastrectomy was much smaller. Thus, there was no evidence that D2 increased overall morbidity to a greater extent than modified D2. Among the 65 patients who underwent distal gastrectomy, 41 had the D2 procedure and 24 had the modified D2 operation. Thus, there was no possibility that morbidity and mortality were overestimated.

Because the present study was carried out on a case series from a single center, morbidity may have been affected by surgical indication, and this selection bias is its major limitation. In these cases, the surgical indication was determined by five physicians, including an anesthesiologist, who took into consideration activities of daily living, performance status, medical history, physical examinations, and organ functions, as is done in general community hospitals. However, there is a possibility that only patients with good status were selected because our hospital is a regional cancer center that treats only cancer patients. Elderly patients who have co-morbidities and visit general hospitals often undergo surgery at the same hospital where they were diagnosed with gastric cancer.

Furthermore, surgical skill is an important factor determining surgical morbidity. By reviewing our data of nonelderly patients, overall mortality and morbidity (>grade 2) rates in the nonelderly were 0.3 and 13.0 % (precise data not shown), respectively, which were similar or even low when compared with the data of JCOG-9501 [3], suggesting that our surgical skill seems average for a Japanese high-volume cancer center. Thus, the high severe morbidity rate shown for the elderly patients would not be due to inappropriate surgical skill at our institution but to the patients' ages.

To evaluate the possibility of selection bias in this series, their complications and background characteristics were compared with those in previous reports [4, 5, 7, 8, 10–12, 14] (Table 4). In this study, the rate of co-morbid conditions numbering >1 was 72 % (95 % CI 62.3–81.7 %); and rate of those with an ASA score >3 was 20 % (95 % CI 11.4–29.0 %). The morbidity rate was 18 % (95 % CI 9.7–26.2 %). Among the previous studies, the largest series (sample size 249 patients) was reported by Orsenigo et al. [11]. Their rates of co-morbid conditions >1 and morbidity were both greater than in our series, suggesting that the conditions of their patients were slightly worse than ours. The next largest series (sample size 182 patients) was reported by Eguchi et al. [5]. However, they gave no description of co-morbid conditions or ASA scores. The third largest series (sample size 141 patients) was reported by Katai et al. [7]. In their series, the rate of co-morbid conditions was slightly greater and the morbidity rate higher than our findings; also, their ASA scores were similar to our series, suggesting that the patient conditions were slightly worse than in our series. The fourth largest series (sample size 101 patients) was reported by Jeong et al. [14]. The rate of co-morbid conditions and the morbidity rate were similar to those in our series, whereas their ASA scores were better than in our series, suggesting that the patients conditions were fairly similar in the two series. The other four studies had a sample size of <60. Overall, the background characteristics and morbidity rates in the present series did not differ greatly from those of previous reports [5, 7, 11, 14] with more than 100 patients.

In contrast, mortality ranged from 0 to 17.2 % in previous reports, but some authors [4, 5, 7–12, 14] did not evaluate the severity of surgical morbidity (Table 4). In this study, the mortality rate was 3.6 % and that of severe

Table 4 Comparison for previous studies about postoperative complications and preoperative co-morbidities

Study	Postoperative complications					Preoperative co-morbidities	
	Morbidity rate (%)	Mortality rate (%)	Severe morbidity rate (%)			≥1 Co-morbidity (%)	ASA score ≥3 (%)
			≥Grade 3a	≥Grade 3b	Reoperation		
Our cases ($n = 83$)	18.0 (9.7–26.2)	3.6 (0–7.6)	8.4 (2.4–14.4)	7.2 (1.6–12.8)	4.8 (2.0–9.4)	72.0 (62.3–81.7)	20.0 (11.4–29.0)
Kitamura [4] ($n = 60$)	65.0	1.7	ND	ND	ND	65	ND
Eguchi [5] ($n = 182$)	30.8	2.2	ND	ND	ND	ND	ND
Katai [7] ($n = 141$)	27.0	0	ND	ND	1.4	86.5	19.9
Saidi [8] ($n = 24$)	33.3	8.3	ND	ND	ND	50.0	ND
Gretschel [10] ($n = 48$)	23.0	8.0	ND	ND	10.4	83.0	81.0
Orsenigo [11] ($n = 249$)	20.0	3.0	ND	ND	ND	92.0	ND
Pisanu [12] ($n = 23$)	30.4	17.2	ND	ND	ND	74.0	ND
Jeong [14] ($n = 101$)	23.7	0	ND	ND	ND	65.3	7.9
JCOG9502-D2 [18]	20.9	0.8	ND	ND	1.9	ND	ND

Numbers in parentheses are the 95 % confidence intervals

ND Not described

complications was 8.4 % for ≥grade 3a and 7.2 % for ≥grade 3b. Severe complications easily lead to surgical mortality. Although the point estimate of the mortality rate is important, it is affected by whether patients recover from severe complications. Thus, the proportions of severe complications are more reliable measures to evaluate the safety of surgery with a low mortality rate.

Another limitation is that this was a retrospective study performed in a single hospital. Complications were verified retrospectively and graded by examining patient records. To exclude the possibility of description bias, we did not evaluate grade 1 complications. To include the data of patients with grade 1 complications would have two serious problems. One is reliability. Grade 1 complications were defined as "any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions." In other words, grade 1 complications present a deviation from the normal postoperative course but without any additional treatment. Before the Clavien–Dindo classification was developed, we suspect that grade 1 had not been treated as "complications." Thus, retrospective data of grade 1 complications would be unreliable. The other problem is comparability. All retrospective studies [4, 5, 7, 8, 10–12] had no definition of complications. Moreover, they do not know about the Clavien–Dindo classification. We suspect that all retrospective studies had treated complications as >grade 2. In the prospective study, Jeong et al. [14] defined complications as abnormal findings of radiologic tests that had been performed when a complication was clinically suspected, which should mean complications of >grade 2. Thus, when we compare our data with those from other studies, we should treat complications as >grade 2. Thus, the overall incidence of morbidity could be underestimated. However, it is unlikely that severe complications were underestimated because grade 3 requires surgical, endoscopic, or radiologic intervention. To confirm our results, a prospective multicenter trial is needed.

The changes over a long-term period are another concern. Surgical technique, indications, and postoperative care change over time. However, the morbidity and mortality rates did not change during each 5-year period during 1990–2009 (precise data not shown). Thus, high severe morbidity observed in elderly patients may not be prevented even by sophisticated surgical techniques or updated postoperative care.

Conclusions

The overall morbidity rate in this study was acceptable, but the rate of severe complications was high. The latter finding suggests that surgery for gastric cancer in elderly patients is risky and should be limited.

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The Impact of Preoperative Lymph Node Size on Long-Term Outcome Following Curative Gastrectomy for Gastric Cancer

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ABSTRACT

Background. Multidetector-row computed tomography (MDCT) is widely used to predict pathological nodal status. However, an appropriate nodal size cutoff value to predict pathological nodal status has not been determined, and the impact of preoperative lymph node size on long-term outcomes is unclear.

Methods. This study included 137 gastric cancer patients with nodal involvement who underwent R0 gastrectomy between September 2002 and December 2006. Lymph nodes with a short-axis diameter of 10 mm or more as measured by MDCT were regarded as metastasized. An appropriate cutoff value with a high positive predictive value (PPV) and high specificity also was identified, and the subsequent clinicopathological characteristics and long-term outcomes were investigated.

Results. A cutoff value of 15 mm was found to be appropriate for grouping patients into large (≥15 mm) and small (<15 mm) lymph node metastasis (LLNM and SLNM) groups, with a high PPV (98.6 %) and specificity (99.8 %). There were no differences in clinicopathological characteristics between the groups except for pathological nodal status. In the LLNM group, the 5-year survival rate was 55 %, which was significantly lower than in the SLNM group (73.2 %; $P = 0.008$). After stratification by tumor depth, the same trend was observed in patients with pT3 disease (46.8 % vs. 72.7 %; $P = 0.015$) and those with pT4 disease (14.3 % vs. 64.8 %; $P = 0.035$).

Conclusions. Gastric cancer patients with lymph nodes measuring 15 mm or more preoperatively have worse long-term outcomes. These patients would therefore be suitable candidates for future clinical trials investigating the efficacy of neoadjuvant chemotherapies.

Gastric cancer is frequently diagnosed in east Asian countries. Early gastric cancer accounts for more than 50 % of cases in Japan and Korea, and favorable long-term outcomes have been reported following curative surgery.[1,2] Conversely, the long-term outcomes of patients with advanced gastric cancer remain poor, even after curative surgery.[1,2] In western countries, perioperative chemotherapy with or without radiation is a standard treatment for advanced gastric cancer.[3,4] In contrast, the standard treatment for advanced gastric cancer in east Asian countries is curative gastrectomy followed by adjuvant chemotherapy. The feasibility of utilizing neoadjuvant chemotherapy also is under investigation.[5–9]

Before neoadjuvant chemotherapy can become more widely used, it is necessary to determine the tumor stage before treatment begins. It is useful to identify patients who have a poor long-term outcome. Staging laparoscopy would be useful for detecting small peritoneal metastases for accurate staging[10]; however, this procedure is unable to assess nodal status accurately. Currently, multidetector-row computed tomography (MDCT) is widely used to predict pathological nodal status. However, an appropriate nodal size cutoff value to predict the pathological nodal status has not been determined, and the impact of preoperative lymph node size on long-term outcomes remains unclear despite a number of studies.[11–18]

In the present study, we investigated the clinicopathological characteristics of patients with lymph nodes longer than 10 mm in the short-axis diameter, as measured by preoperative MDCT. In addition, the long-term outcomes of patients with large lymph nodes (≥15 mm) were compared to those with smaller lymph nodes (<15 mm). The purpose of the present study was to clarify the impact of

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TABLE 1 Accuracy of predicting pathological lymph node status for each cutoff value

Cutoff value (mm)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
10	39.1 (120/307)	96.9 (528/545)	87.6 (120/137)	73.8 (528/715)	76.1 (648/852)
15	22.5 (69/307)	99.8 (544/545)	98.6 (69/70)	69.6 (544/782)	71.9 (613/852)
20	14.0 (43/307)	100.0 (545/545)	100.0 (43/43)	67.4 (545/809)	69.0 (588/852)
30	2.0 (6/307)	100.0 (545/545)	100.0 (6/6)	64.6 (545/846)	64.8 (552/852)

PPV positive predictive value, *NPV* negative predictive value

preoperative lymph node size on clinicopathological characteristics and long-term outcomes.

PATIENTS AND METHODS

The present study included 137 gastric cancer patients with clinically diagnosed nodal involvement who underwent R0 gastrectomy between September 2002 and December 2006 at the Shizuoka Cancer Center in Japan. Patients who received neoadjuvant or adjuvant chemotherapy, patients who had other cancers simultaneously, or patients who underwent surgery for gastric stump carcinoma were excluded. Patients also were excluded if the primary lesion was not identified as an adenocarcinoma by histology.

Patient characteristics and the pathological and surgical findings were collected from our database records and individual patient electronic medical records. Data collection and analysis was approved by the institutional review board of the Shizuoka Cancer Center.

Pathological tumor depth, nodal status, and curability of surgery were assigned according to the International Union Against Cancer (UICC) classification system.[19] Histological type was classified according to the Japanese Gastric Cancer Association (JGCA) classification system,[20] in which tubular and papillary adenocarcinoma are defined as differentiated adenocarcinoma, whereas poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma are defined as undifferentiated adenocarcinoma.

Preoperative Examinations

Enhanced MDCT scans were performed on all patients before surgery. If patients had severe renal dysfunction or an allergy to the contrast media, a plain MDCT scan was performed instead. The patients were examined in a supine position with their arms stretched above their heads at the end of inspiration using a CT scanner (Aquilion, Toshiba Medical Systems, Tokyo, Japan). Parameters for scanning were: tube voltage, 120 kVp; scan time, 0.5 s; and reconstruction slice thickness, 2 mm. The tube current was automatically determined by the CT automatic exposure control system. The diameter of each lymph node was measured using transverse MDCT images. Lymph nodes with a short-axis diameter of 10 mm or more were regarded as clinically metastasized lymph nodes. Multiplanar reformation (MPR) images were not used in the present study, and the longitudinal diameter of each node was not taken into account.

A second cutoff value was also applied for further classification of the patients. Short-axis diameter cutoff values of 15 mm, 20 mm, and 30 mm were tested. The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of each cutoff value were investigated (Table 1). To calculate the sensitivity and specificity of each cutoff value, 715 clinically node-negative patients (patients who had lymph nodes with a short-axis diameter less than 10 mm as measured by MDCT) who underwent curative gastrectomy during the same study period were recruited. Of these 715 patients, 187 patients were found to have pathologically positive lymph nodes.

Statistical Analyses

All continuous variables are presented as the median (range). Statistical analyses were performed by using Fisher's exact test, the Student's t test, and the Mann-Whitney test. Five-year survival rates were calculated by using the Kaplan-Meier method and the log-rank test was used to compare the groups. Independent prognostic factors were identified using the Cox proportional hazards model. In this analysis, each patient's age, sex, histology, type of surgery, tumor depth, and lymph node size measured by MDCT were included as covariates. $P < 0.05$ was considered significant. All statistical analyses were conducted using the R version 2.13.1 statistical package.

RESULTS

Table 1 shows the sensitivity, specificity, accuracy, PPV, and NPV of each cutoff value tested. Both clinically node-positive patients ($n = 137$) and clinically node-negative patients ($n = 715$) were included in these calculations. Specificity and PPV reached a plateau when a cutoff value of 15 mm was used. The specificity and PPV did not increase when higher cutoff values were adopted; however, the sensitivity, NPV, and accuracy decreased. Therefore, a cutoff value of 15 mm was considered suitable for dividing the patients into further groups. Patients who had lymph nodes with a short-axis diameter measuring 15 mm or more were placed into the large lymph node metastasis (LLNM) group. The remaining patients were placed into the small lymph node metastasis (SLNM) group. The clinicopathological characteristics and long-term outcomes were compared between the two groups.

Table 2 shows the clinicopathological characteristics of the patients. There were no differences in sex, age, surgical procedures, degree of lymph node dissection, operation times, intraoperative blood loss, length of postoperative hospital stay, histology, or number of retrieved lymph nodes between the two groups. The pathological nodal status was different between the two groups. In the LLNM group, 98.6 % of patients had pathologically positive lymph nodes, whereas in the SLNM group, 76.1 % of patients had pathologically positive lymph nodes. Consistent with these results, the positive predictive value (PPV) was 98.6 % (69/70) when a short-axis diameter of 15 mm was used as the cutoff value and 87.6 % (120/137) when a short-axis diameter of 10 mm was used as the cutoff value. In addition, the number of patients with N3 disease was higher in the LLNM group than in the SLNM group ($P < 0.001$).

Figure 1 illustrates the survival curves of all patients. The median follow-up period of survivors was 70 months. In the LLNM group, the 5-year survival rate was 55 %, which was significantly lower than that of the SLNM group (73.2 %; $P = 0.008$). Survival curves were stratified by the tumor depth and were not significantly different between the two groups in patients with pT1 ($P = 0.765$) and pT2 ($P = 0.548$) disease. Conversely, the survival rate was significantly worse in the LLNM group than in the SLNM group in patients with pT3 and pT4 disease. The 5-year survival rate for patients with pT3 disease was 46.8 % in the LLNM group and 72.7 % in the SLNM group (Fig. 2a; $P = 0.015$), and for patients with pT4 disease it was 14.3 % in the LLNM group and 64.8 % in the SLNM group (Fig. 2b; $P = 0.035$).

Table 3 shows the results of multivariate analysis. Tumor depth (hazard ratio [HR], 6.570; 95 % confidence interval [CI], 1.585–27.238) and lymph node size (HR, 1.879; 95 % CI, 1.068–3.304) were found to be independent prognostic factors of survival.

Table 4 describes the sites of initial recurrence after curative gastrectomy. Lymph node metastasis was the most frequently observed recurrence pattern in the LLNM group and accounted for 67 % of recurrences. In the SLNM group, blood-borne metastasis (56 %) was the most frequently observed recurrence pattern followed by lymph node metastasis (44 %) and peritoneal metastasis (44 %). There were no significant differences between the two groups in the initial recurrence site.

TABLE 2 Patient characteristics

Characteristics	LLNM group	SLNM group	*P* value
Sex, *n*			
Male	55	46	0.244
Female	15	21	
Age, years			
Median	68.5	66	0.446
Range	38–85	30–86	
Surgical procedure, *n*			
Total gastrectomy	37	29	0.306
Partial gastrectomy	33	38	
Lymph node dissection			
<D2	13	16	0.532
≥D2	57	51	
Operation time, min			
Median	224	211	0.153
Range	99–607	107–562	
Intraoperative blood loss, mg			
Median	447	363	0.238
Range	49–2267	20–2613	
Postoperative hospital stay, days			
Median	14.5	14	0.593
Range	7–78	7–308	
Histology, *n*			
Differentiated	35	31	0.733
Undifferentiated	35	36	
Number of retrieved lymph nodes, *n*			
Median	41.5	41	0.436
Range	16–98	4–75	
Tumor depth, *n*			
T1	11	11	0.437
T2	6	12	
T3	46	35	
T4a	5	7	
T4b	2	2	
Lymph node status, *n*			
N0	1	16	<0.001
N1	12	12	
N2	27	21	
N3	30	18	
Pathological stage, *n*			
I	4	10	0.075
II	17	23	
III	43	32	
IV	6	2	

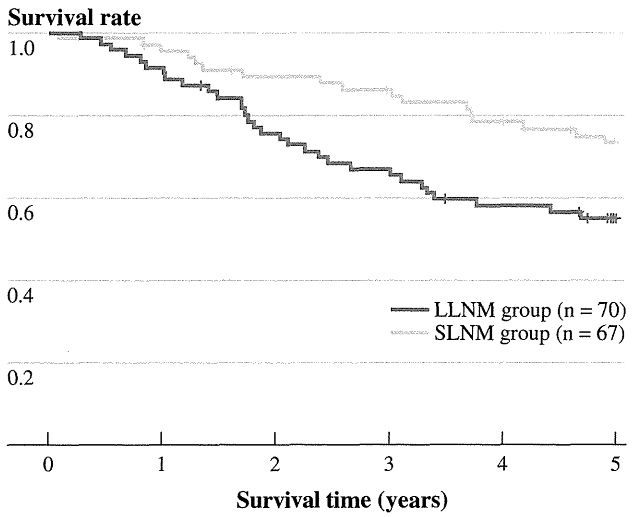

FIG. 1 Overall survival curves of patients in the LLNM group ($n = 70$) and SLNM group ($n = 67$). The 5-year overall survival rate is significantly worse in the LLNM group (55 %) than in the SLNM group (73.2 %; $P = 0.008$)

DISCUSSION

The present study showed that a high positive predictive value (87.6 %) for pathologically positive lymph nodes could be obtained by MDCT if a short-axis diameter of 10 mm was used as the nodal size cutoff value. This study also showed that the positive predictive value increased to 98.6 % if the short-axis diameter cutoff value was increased to 15 mm. In addition, survival analysis revealed that patients in the LLNM group had a worse overall survival rate than those in the SLNM group. Finally, multivariate analysis revealed that clinically measured lymph node size was an independent prognostic factor of survival.

The current standard treatment for advanced gastric cancer in western countries involves perioperative chemotherapy with or without radiation.[3,4] In contrast, curative gastrectomy followed by adjuvant chemotherapy is the standard treatment used in Japan and Korea.[6,8] Recently, the feasibility of neoadjuvant chemotherapy also has been investigated in east Asian countries, particularly for patients with advanced disease.[5,7] However, solid criteria for neoadjuvant chemotherapy do not exist, presumably due to the difficulty in accurate preoperative staging. If candidates can be selected for neoadjuvant chemotherapy appropriately, then the efficacy of neoadjuvant and adjuvant chemotherapy treatments in suitable candidates could be compared in future clinical trials.

There are a number of different criteria and ways to assess nodal status; therefore, no solid criteria exist for detecting metastasized lymph nodes appropriately. The ability of MDCT to detect lymph node metastasis preoperatively is limited, with a reported sensitivity of 62.5–91.9 % and specificity of 50–87.9 %.[21] The definition of metastasized lymph nodes differs between studies using MDCT and various cutoff values have been applied.[11,12,15–17,22] Ahn et al.[18] defined metastasized lymph nodes as having a short-axis diameter of ≥8 mm, and Yan et al.[12] defined regional lymph nodes as metastatic when the short-axis diameter was ≥6 mm, whereas extraperigastric lymph nodes were defined as metastatic when the short-axis diameter was ≥8 mm. In addition, the superiority of multiplanar reformation (MPR) images to transverse images in assessing tumor depth has been reported, although its feasibility for preoperative nodal staging remains controversial.[14,15]

Kim et al.[16] and Yang et al.[17] reported that the sensitivity and specificity of MDCT for gastric cancer staging differed according to the cutoff value used: the nodal size criteria were proportional to the specificity and inversely

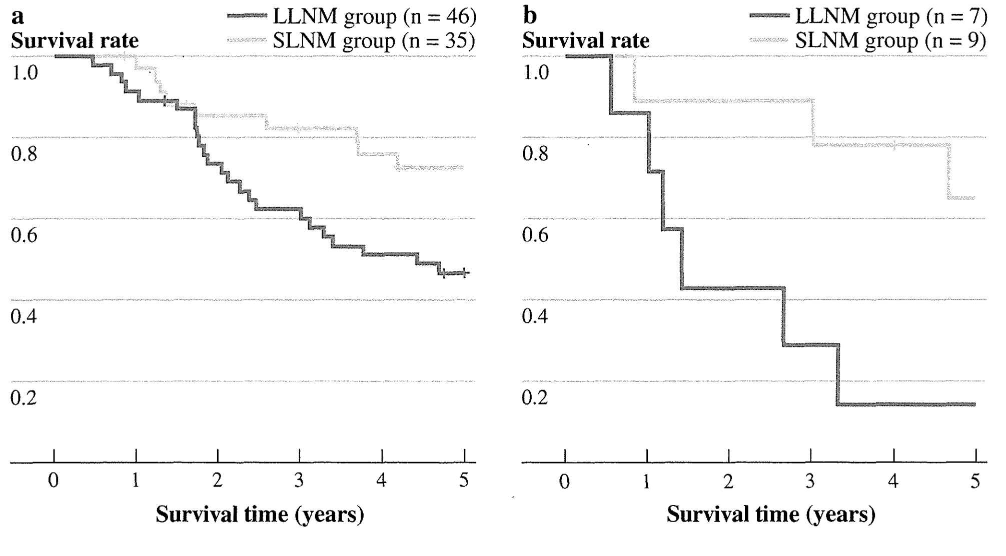

FIG. 2 **a** Overall survival curves of 81 patients with pT3 disease. The 5-year overall survival rate is significantly worse in the LLNM group (46.8 %) than in the SLNM group (72.7 %; $P = 0.015$). **b** Overall survival curves of 16 patients with pT4 disease. The 5-year overall survival rate is significantly worse in the LLNM group (14.3 %) than in the SLNM group (64.8 %; $P = 0.035$)

TABLE 3 Results of multivariate analysis

Covariates	*P* value	Hazard ratio (HR)	95 % CI
Age (≥65 year vs. <65 year)	0.191	1.317	0.871–1.990
Sex (male vs. female)	0.405	1.322	0.686–2.546
Surgery (total gastrectomy vs. partial gastrectomy)	0.635	1.139	0.665–1.951
Histology (undifferentiated vs. differentiated)	0.155	1.488	0.860–2.576
pT (pT2–4 vs. pT1)	0.009	6.570	1.585–27.238
Lymph node size (LLNM vs. SLNM)	0.029	1.879	1.068–3.304

LLNM large lymph node metastasis, lymph node with a short-axis diameter measuring 15 mm or more; *SLNM* small lymph node metastasis, lymph node with a short-axis diameter measuring 10–14 mm

TABLE 4 Site of initial recurrence after surgery

Recurrence site	LLNM group	SLNM group
Peritoneal metastasis	8	7
Locoregional recurrence	3	0
Lymph node metastasis	22	7
Blood-borne metastasis	12	9
Number of cases with recurrence[a]	33	16

[a] Patients with multiple recurrence sites are included at each recurrence site

proportional to the sensitivity of nodal involvement. We believe that high specificity is more important than high sensitivity when selecting candidates for neoadjuvant chemotherapy if the administration of unnecessary toxic regimens to patients with early stage disease is to be avoided. In the present study, a sensitivity and specificity of 39.1 and 96.9 %, respectively, was achieved with a short-axis diameter cutoff value of 10 mm. When the short-axis diameter cutoff value was increased to 15 mm, a sensitivity of 22.5 % and specificity of 99.8 % was achieved. The specificity increased when higher cutoff values were adopted, which is consistent with the results of previous studies.

In the present study, the highest accuracy was obtained using a cutoff value of 10 mm; however, the PPV (87.6 %) was not high enough, meaning that 12.4 % of patients may receive excessive treatment if a cutoff value of 10 mm was adopted. Therefore, other cutoff values were tested, each of which yielded a higher PPV. Of these, a cutoff value of 15 mm yielded a higher sensitivity, NPV, and accuracy than the other cutoff values tested. Therefore, a second cutoff value of 15 mm was adopted. In addition, according to the new response evaluation criteria in solid tumors (RECIST version 1.1), lymph nodes with a short axis of 15 mm are considered measurable and assessable as target lesions.[23]

In this study, the long-term survival rate between the two groups also was compared. Previously, Dhar et al.[24,25] reported that the size of the lymph node, measured from the pathological specimen, was one of the independent prognostic factors following colorectal surgery and esophageal surgery. Dhar et al.[22] reported that this result was also applicable to patients with gastric cancer. Cheong et al.[26] reported that metastatic lymph nodes larger than 20 mm were an independent predictor of poor prognosis. However, in their study, lymph node diameters were measured by using pathologically resected specimens. In contrast, lymph node diameters in the current study were measured preoperatively using MDCT. Thus, the size of the lymph nodes was known before treatment, and this information could be used to select the relevant treatment strategy. By adopting a short-axis diameter cutoff value of 15 mm, node-positive patients could be identified with extremely high specificity. The survival outcome of patients in the LLNM group was poor; thus, these patients would be suitable candidates for much stronger multimodality treatment.

The present study has several limitations. First, the diameter of each node was measured retrospectively, and interobserver differences were not assessed. However, lymph nodes that are 15 mm in diameter were large enough for every investigator to find and assess. Therefore, any interobserver differences would be small compared with previous studies adopting cutoff values less than 10 mm.[15–17] Second, the results of the present study would be less meaningful in western countries where perioperative chemotherapy is already a standard treatment for advanced gastric cancer. However, even in western countries, patients with poor long-term outcomes could be identified with a cutoff value of 15 mm. A much stronger treatment regimen could then be indicated for these patients. Third, although a cutoff value of 15 mm yielded a high specificity (99.8 %) and PPV (98.6 %), the low sensitivity (22.5 %) and NPV (69.6 %) values were lower than desired. However, as stated previously, we believe high specificity is important if the administration of unnecessary toxic regimens is to be avoided if perioperative chemotherapy is planned. Lastly, transverse MDCT images were used to measure the diameter of each node instead of reconstructed MPR images, which were not routinely used during the study period. Although the superiority of MPR images over transverse images in the preoperative assessment of lymph nodes is under debate, these images would enable us to measure the longitudinal diameter of lymph nodes in future trials.[14,15]

CONCLUSIONS

By using a short-axis diameter cutoff value of 15 mm, MDCT was able to predict nodal status with high specificity (99.8 %) and achieve a high positive predictive value. Gastric cancer patients with enlarged lymph nodes, which have a short-axis diameter measuring 15 mm or more preoperatively, were found to have worse long-term outcomes than patients with lymph nodes smaller than 15 mm. These patients would therefore be suitable candidates for future clinical trials investigating the efficacy of neoadjuvant chemotherapies.

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Poor Survival Rate in Patients with Postoperative Intra-Abdominal Infectious Complications Following Curative Gastrectomy for Gastric Cancer

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ABSTRACT

Background. The impact of postoperative complications on recurrence rate and long-term outcome has been reported in patients with colorectal and esophageal cancer, but not in patients with gastric cancer. This study evaluated the impact of postoperative intra-abdominal infectious complications on long-term survival following curative gastrectomy.

Methods. This study included 765 patients who underwent curative gastrectomy for gastric cancer between 2002 and 2006. Patients were divided into 2 groups: with (C-group, $n = 81$) or without (NC-group, $n = 684$) intra-abdominal infectious complications. Survival curves were compared between the groups, and multivariate analysis was conducted to identify independent prognostic factors.

Results. Male patients were dominant, and total gastrectomy was frequently performed in the C-group. The pathological stage was more advanced and D2 lymph node dissection and splenectomy were preferred in the C-group. The 5-year overall survival (OS) rate was better in the NC-group (86.8 %) than in the C-group (66.4 %; $P < .001$). The 5-year relapse-free survival (RFS) rate was also better in the NC-group (84.5 %) than in the C-group (64.9 %; $P < .001$). This trend was still observed in stage II and III patients after stratification by pathological stage. Multivariate analysis identified intra-abdominal infectious complication as an independent prognostic factor for OS (hazard ratio, 2.448; 95 % confidence interval [95 % CI], 1.475–4.060) and RFS (hazard ratio, 2.219; 95 % CI, 1.330–3.409) in patients with advanced disease.

Conclusions. Postoperative intra-abdominal infectious complications adversely affect OS and RFS. Meticulous surgery is needed to decrease the complication rate and improve the long-term outcome of patients following curative gastrectomy.

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Gastrectomy with R0 resection is inevitable to cure patients with gastric cancer.[1,2] However, even after R0 resection, a significant number of patients suffer from recurrence, particularly after surgery for advanced gastric cancer.[3–5] Tumor depth and lymph node status are well-known prognostic factors, and patient age and performance status have also been reported as having an impact on the long-term outcome of patients.[1,2, 6,7]

In Japan, gastrectomy with D2 lymph node dissection has been the standard treatment for advanced gastric cancer.[8–11] However, Western randomized trials have failed to prove the efficacy of D2 lymph node dissection, presumably because of the increased incidence of postoperative morbidity, which results in increased in-hospital deaths following D2 lymph node dissection.[12–14] Moreover, postoperative morbidity may adversely affect long-term, as well as short-term outcomes in patients.

Previously, the impact of postoperative complications on recurrence rate and long-term outcome has been reported in patients with colorectal cancer and esophageal or esophagogastric junction cancer.[15–23] In the case of colorectal cancer, anastomotic leakage is generally associated with a high local recurrence rate, as well as a poor long-term survival rate.[15–18] Additionally, a strong correlation between postoperative complications and poor long-term outcome has been reported for esophageal and esophagogastric junction cancer.[19,21,23] However, contradictory studies have also been published. Branagan and Finnis [15] reported that anastomotic leakage does not result in poor survival following colorectal surgery. After esophagogastrectomy, Junemann-Ramirez et al.[22] reported that anastomotic leakage does not correlate with poor survival, and Ancona et al.[20] reported that surgical complications themselves do not affect patients' long-term outcomes although survival of patients with both surgical and medical complications was poor.

In patients with gastric cancer, there have been limited reports assessing the relationship between postoperative complications and long-term outcome. Sierzega et al.[7] reported that anastomotic leakage as well as deeper tumor depth, lymph node metastasis, distant metastasis, and poor performance status were found to be independent prognostic factors following total gastrectomy for gastric adenocarcinoma. Their study included 690 patients from 7 university surgical centers in Poland. However, the impact of other postoperative complications on long-term outcome was not investigated, and their study included patients whose surgery was not curative. Moreover, it is unclear whether their results can be adopted by East-Asian countries where the incidence of gastric cancer is high and the reported incidence of postoperative complications is low compared with Western countries.[13,24–26]

The aim of the present study was to clarify the impact of postoperative intra-abdominal infectious complications on the long-term survival rate of patients undergoing curative gastrectomy in one of the highest-volume centers in Japan.

PATIENTS AND METHODS

A total of 765 patients who underwent curative gastrectomy (R0 resection) for gastric cancer at the Shizuoka Cancer Center between September 2002 and October 2006 were included in the present study. Patients who received neoadjuvant or adjuvant chemotherapy, patients who had other cancers and patients who underwent surgery for gastric stump carcinoma were excluded. Patients were also excluded if the histology of the primary lesion was not adenocarcinoma.

The patients' characteristics and pathological and surgical findings were collected from our database records and individual patient electronic medical records. The postoperative clinical course of each patient, including the incidence and severity of intra-abdominal infectious complications, was collected from individual electronic medical records. The data collection and analysis were approved by the institutional review board of the Shizuoka Cancer Center.

Pathological tumor depth, nodal status, and curability of surgery were assigned according to the International Union Against Cancer (UICC) classification, Seventh edition.[27]

Histological type was classified according to the Japanese Gastric Cancer Association (JGCA) classification system, in which tubular and papillary adenocarcinoma are defined as differentiated adenocarcinoma, while poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma are defined as undifferentiated adenocarcinoma.[28]

Definition of Postoperative Intra-abdominal Complications

In this study, the Clavien–Dindo (CD) classification was adopted to classify each patient's postoperative intra-abdominal complication.[29,30] According to the CD classification, patients were classified as having grade II complications if antibiotics were administered. They were classified as grade IIIa or IIIb if surgical intervention was indicated. If patients required admission to the intensive care unit, they were regarded as having grade IVa or IVb complications. Postoperative mortality was defined as a grade V complication. If multiple complications occurred in a single patient, the highest grade was used.

Comparison Between Patients With and Without Complications

Clinicopathological characteristics were compared between patients with postoperative intra-abdominal infectious complications (C-group, $n = 81$) and those without complications (NC-group, $n = 684$). Overall survival time and relapse-free survival time were also compared between the groups.

Statistical Analyses

All continuous variables are presented as the median (range). Statistical analyses were performed using the Fisher exact test, t test, and Mann–Whitney test. The 5-year survival rates were calculated using the Kaplan–Meier method, and the log-rank test was used to compare the groups. Independent prognostic factors were identified using the Cox proportional hazards model. In the analysis, each patient's age, sex, histology, type of surgery, degree of lymph node dissection, intraoperative blood loss, operation time, pathological stage, and postoperative intra-abdominal infectious complication were included as covariates. $P < .05$ was considered significant. All statistical analyses were conducted using R Statistics version 2.13.1.

RESULTS

The clinicopathological characteristics of all the patients are shown in Table 1. There was no difference in age between the C-group and NC-group. Male patients

TABLE 1 Clinicopathological characteristics of patients in both groups

	C-group	NC-group	*P* value
Sex (*n*)			.001
Male	68	452	
Female	13	232	
Age (years)			.061
Median	66	64	
Range	31–83	24–88	
Performance status (ECOG)			.545
0 or 1	80	678	
2 or 3	1	6	
Hemoglobin (g/dL)			.577
Median	13.7	13.7	
Range	7.5–16.4	6.3–17.5	
Albumin (g/dL)			.090
Median	4.3	4.3	
Range	2.4–5.0	1.8–5.3	
Lymphocyte count[a]			.352
Median	1920	1700	
Range	870–3450	620–3960	
Surgical procedure (*n*)			<.001
Total gastrectomy	44	142	
Partial gastrectomy	37	542	
Splenectomy (*n*)			<.001
Performed	38	67	
Not performed	43	617	
Lymph node dissection			<.001
<D2	25	431	
≥D2	56	253	
Operation time (min)			<.001
Median	244	186	
Range	125–733	50–725	
Intraoperative blood loss (mg)			<.001
Median	454	250	
Range	50–2650	0–1800	
Postoperative hospital stay (days)			<.001
Median	23	11	
Range	12–308	7–56	
Histology (*n*)			.347
Differentiated	47	355	
Undifferentiated	34	329	
Tumor depth (*n*)			<.001
T1	29	430	
T2	10	70	
T3	29	150	
T4a	11	31	
T4b	2	3	
Lymph node status (*n*)			.004
N0	39	449	
N1	10	88	
N2	17	77	
N3	15	70	
Pathological stage (*n*)			<.001
I	29	440	
II	27	120	
III	21	115	
IV	4	9	

ECOG Eastern Cooperative Oncology Group

[a] Lymphocyte count was measured in 27 patients in the C-group and 189 patients in the NC-group

predominated in both groups and total gastrectomy was frequently performed in the C-group. Preoperative serum albumin level, hemoglobin level, and lymphocyte count were not different between the groups. D2 lymph node dissection and splenectomy were also preferred in the C-group. Operation time was longer and intraoperative blood loss was higher in the C-group than in the NC-group ($P < .001$). More advanced gastric cancer was observed in the C-group than in the NC-group ($P < .001$).

The type and severity of complications are shown in Table 2. Intra-abdominal infectious complications were observed in 11 % (81 of 765) of patients. Pancreas-related infections were the most frequently observed intra-abdominal infectious complication, followed by intra-abdominal abscess and anastomotic leakage. We found 33 % of patients recovered well with medication (grade II), and surgical intervention with local or general anesthesia was required in 62 and 1 % of patients, respectively. One patient died following deterioration of a postoperative intra-abdominal infectious complication. In every pathological stage, grade IIIa complications were the most frequently observed, followed by grade II complications.

We also investigated the number of patients who required readmission because of postgastrectomy syndromes, which included bowel obstruction, cholecystitis, and insufficient oral intake. If patients had a recurrence, admission after the recurrence was not counted. In the C-group, 7 of 81 patients (9 %) required readmission because of a postgastrectomy syndrome. In the NC-group, readmission was required in 32 of 684 patients (5 %; $P = .174$). The most frequent reason for readmission was bowel obstruction in both groups (4 patients in the C-group, and 20 patients in the NC-group; $P = .308$). We investigated serum albumin levels of patients without recurrence 1 year after the surgery to assess nutritional status. There was no difference in the serum albumin level change between the groups ($P = .330$).

Details of the initial recurrence site following gastrectomy are listed in Table 3. Recurrence was observed in 21 of 81 patients (26 %) in the C-group, and 83 of 684 patients (12 %) in the NC-group ($P = .002$). In the NC-group, peritoneal metastasis was the most frequent recurrence pattern followed by lymph node metastasis and liver metastasis. In the C-group, lymph node metastasis was the most frequently observed site of recurrence. Locoregional recurrence was not observed in any of the patients in the C-group even after anastomotic leakage. The pattern of recurrence was not different between the 2 groups ($P = .401$).

In the median follow-up period of survivors of 63 months, the 5-years overall survival rate was better in the NC-group (86.8 %) than in the C-group (66.4 %; $P < .001$). The 5-years relapse-free survival rate was also better in the NC-group (84.5 %) than in the C-group (64.9 %; $P < .001$).

Overall and relapse-free survival curves stratified by pathological stage were compared between the groups (Figs. 1a, b, 2a, b). In patients with stage I early gastric cancer, there were no differences between the groups. Conversely, in patients with stage II and III gastric cancer, overall and relapse-free survival rates were significantly better in the NC-group than in the C-group, except for relapse-free survival time in patients with stage III gastric cancer. In patients with stage III gastric cancer, the 5-years relapse-free survival rate still tended to be better in the NC-group (55.1 %) than in the C-group (41.3 %); however, the difference did not reach significance ($P = .11$).

Table 4 shows the results of the Cox-proportional hazards model used to identify independent prognostic factors for overall survival. In this analysis, only patients with stage II or more advanced disease were included because the survival analysis did not show a survival difference between the 2 groups in patients with pathological stage I disease. Pathological stage (hazard ratio [HR], 2.564; 95 % CI, 1.681–3.912) and intra-abdominal infectious complications (HR, 2.448; 95 % CI, 1.475–4.060) were found to be independent prognostic factors. The same independent prognostic factors were identified for relapse-free survival (pathological stage [HR, 2.657; 95 % CI, 1.782–3.962], and intra-abdominal infectious complications [HR, 2.219; 95 % CI, 1.330–3.409], Table 5).

Figure 3 shows hazard ratio for death among subgroups. The overall survival was analyzed according to sex, age, type of surgery, splenectomy, degree of lymph node dissection, intraoperative blood loss, operation time, histology, pathological tumor depth, and pathological nodal status.

TABLE 2 Details of postoperative intra-abdominal complications

	Grade of CD classification						Total
	II	IIIa	IIIb	IVa	IVb	V	
Type of complication							
Pancreas-related complication	15	27	0	0	0	0	42
Anastomotic leakage	1	14	1	1	1	0	18
Intra-abdominal abscess	11	9	0	0	0	1	21
Pathological stage							
I	11	17	0	1	0	0	29
II	10	17	0	0	0	0	27
III	6	12	1	0	1	1	21
IV	0	4	0	0	0	0	4
Total	27	50	1	1	1	1	81

CD Clavien–Dindo

TABLE 3 Site of initial recurrence after surgery

	C-group			C-group total	NC-group
	Pancreas-related infection	Anastomotic leakage	Intra-abdominal abscess		
Peritoneal metastasis	4	1	1	6	35
Liver metastasis	5	0	1	6	19
Locoregional recurrence	0	0	0	0	5
Lymph node metastasis	8	1	4	13	31
Lung	1	1	0	2	6
Bone	0	0	0	0	5
Other	0	0	0	0	3
Unknown	0	0	0	0	1
Number of cases with recurrence[a]	12	3	6	21	83

[a] Patients with multiple recurrence sites are included for each recurrence site

DISCUSSION

The present study revealed that postoperative complications were strongly associated with poor overall survival time and relapse-free survival time. This trend was also observed even after stratification by pathological stage.

To investigate the prognostic value of postoperative complications, appropriate assessment of the incidence and severity of complications is mandatory. In 2004, Clavien and Dindo proposed the CD classification, which is a treatment-oriented, objective criteria for postoperative complications.[29,30] Recently, a number of reports, including those concerning postgastrectomy morbidities, have

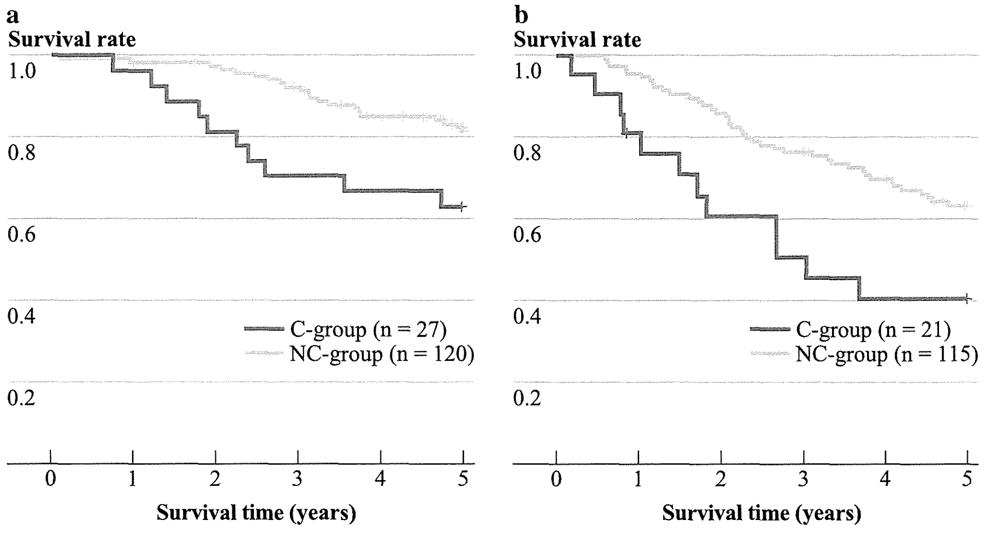

FIG. 1 **a** Overall survival curves of 147 stage II patients who underwent curative gastrectomy for gastric cancer. The 5-year overall survival rate is significantly better in the group of patients without postoperative intra-abdominal infectious complications (NC-group, 81.1 %) than in the group with complications (C-group, 63.0 %; $P = .02$). **b** Overall survival curves of 136 stage III patients who underwent curative gastrectomy for gastric cancer. The 5-year overall survival rate is significantly better in the NC-group (63.3 %) than in the C-group (40.5 %; $P = .03$)

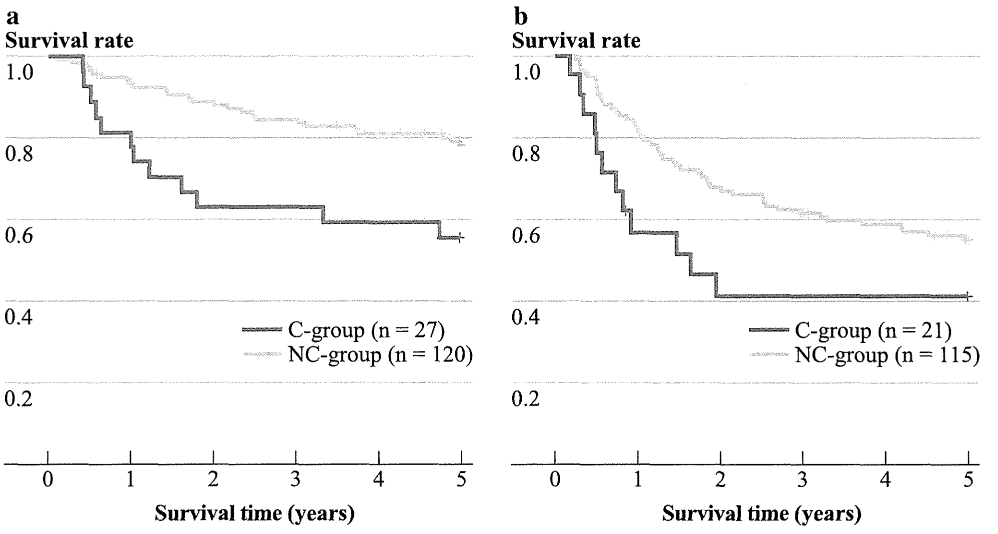

FIG. 2 **a** Relapse-free survival curves of 147 stage II patients who underwent curative gastrectomy for gastric cancer. The 5-year relapse-free survival rate is significantly better in the group of patients without postoperative intra-abdominal infectious complications (NC-group, 78.0 %) than in the group with complications (C-group, 55.6 %; $P = .02$). **b** Relapse-free survival curves of 136 stage III patients who underwent curative gastrectomy for gastric cancer. The 5-year relapse-free survival rate tends to be better in the NC-group (55.1 %) than in the C-group (41.3 %), although the difference is not significant ($P = .11$)

adopted the CD classification to evaluate postoperative problems.[31,32] In contrast, previous studies that investigated the effect of complications on long-term outcomes following surgeries generally used their own criteria to grade the severity of the complications, making it difficult to evaluate the results of the study[15–23] In the present study, to overcome this potential problem, we used the CD classification to assess the severity of complications. In the present study, patients with grade II or more severe intra-abdominal infection were regarded as having complications since we considered these complications to cause systemic inflammatory response syndrome, resulting in excess surgical trauma and tissue damage.

Administration of perioperative chemotherapies has been accepted as it increases the survival rate of patients with advanced gastric cancer.[33–36] In Japan, postoperative administration of S-1 for 1 year after curative surgery has been a standard treatment in patients with advanced gastric cancer since the results of a prospective randomized controlled trial were reported in October 2006.[33] Therefore, in the present study, we only included patients who underwent surgery before 2006 and excluded patients who received neoadjuvant chemotherapy to eliminate the effects of perioperative chemotherapies.

It is unclear why postoperative intra-abdominal infectious complications affect the long-term outcome of

TABLE 4 Results of multivariate analysis to identify independent prognostic factors for overall survival

Covariates	*P* value	Hazard ratio (HR)	95 % CI
Age (≥ 65 vs < 65 years)	.138	1.241	.933–1.651
Sex (male vs female)	.683	1.099	.700–1.725
Surgery (total gastrectomy vs partial gastrectomy)	.496	1.165	.751–1.806
Histology (differentiated vs undifferentiated)	.162	1.340	.889–2.022
pStage (III, IV vs II)	<.001	2.564	1.681–3.912
Duration of surgery (≥ 200 vs < 200 min)	.773	.949	.666–1.353
Intraoperative blood loss (≥ 300 vs < 300 mL)	.057	.726	.523–1.009
Intra-abdominal infectious complications (yes vs no)	<.001	2.448	1.475–4.060
Lymph node dissection (≥ D2 vs < D2)	.248	.761	.478–1.210

CI confidence interval

TABLE 5 Results of multivariate analysis to identify independent prognostic factors for relapse-free survival

Covariates	*P* value	Hazard ratio (HR)	95 % CI
Age (≥ 65 vs < 65 years)	.213	1.187	.906–1.555
Sex (male vs female)	.590	1.127	.729–1.743
Surgery (total gastrectomy vs partial gastrectomy)	.747	.933	.614–1.419
Histology (differentiated vs undifferentiated)	.375	1.191	.810–1.751
pStage (III, IV vs II)	<.001	2.657	1.782–3.962
Duration of surgery (≥ 200 vs < 200 min)	.492	1.123	.807–1.562
Intraoperative blood loss (≥ 300 vs < 300 mL)	.140	.795	.586–.178
Intra-abdominal infectious complications (yes vs no)	.002	2.219	1.330–3.409
Lymph node dissection (≥ D2 vs < D2)	.135	.716	.462–1.110

CI confidence interval

patients. Following colorectal surgery, it was reported that anastomotic leakage increased the rate of local recurrence presumably due to viable colorectal cancer cells being deposited extraluminally into the pelvis.[16–18] However, in the present study the incidence of local recurrence did not increase even after anastomotic leakage; thus, we consider implantation of cancer cells into the abdominal cavity not a contributing factor in the present series.

Another possible factor promoting metastatic growth and early recurrence is immune suppression.[37,38] Specifically, cell-mediated immunity, in particular natural killer cells and cytotoxic T lymphocytes, is compromised, and the degree of suppression is considered to be related to the extent of surgical trauma and tissue damage. Goldfarb et al. reported treatment aimed at perioperative enhancement of cell-mediated immunity with simultaneous inhibition of excessive catecholamine and prostaglandin responses could be successful in limiting postoperative immune suppression and metastatic progression.[38] In the C-group, postoperative intra-abdominal infectious complications increased surgical stress and caused severe tissue damage due to local and generalized inflammatory reactions, resulting in more severe immune suppression than in the NC-group. We consider, therefore, that the difference in the degree of immune suppression between the groups is a possible contributing factor to the survival difference between the groups.

The present retrospective study has limitations. Firstly, backgrounds were different between patients with and without complications. Of different backgrounds, pathological stage is assumed to be the strongest prognostic factor for gastric cancer following curative gastrectomy.[1,2,6] Therefore, we stratified patients by their pathological stage, and multivariate analysis was conducted. Even after stratification, the same trend, better survival outcomes in patients without intra-abdominal infectious complications, was still observed in stage II and III patients. Multivariate analysis also identified intra-abdominal infectious complications as an independent prognostic factor. In addition, we investigated hazard ratio for death among subgroups. In each subgroup, long-term outcome tended to be better in the NC-group than in the C-group. Secondly, the degree of immune suppression was not assessed in this study. This should be examined in a future trial to clarify whether our hypothesis, that patients with intra-abdominal infectious complications have severe immune suppression resulting in high recurrence rates and poor overall and relapse-free survival rates, is correct or not.

D2 lymph node dissection and splenectomy were frequently performed in the C-group, and these procedures were thought to increase the incidence of intra-abdominal infectious complications. We also investigated the effect of D2 lymph node dissection on long-term survival rate by

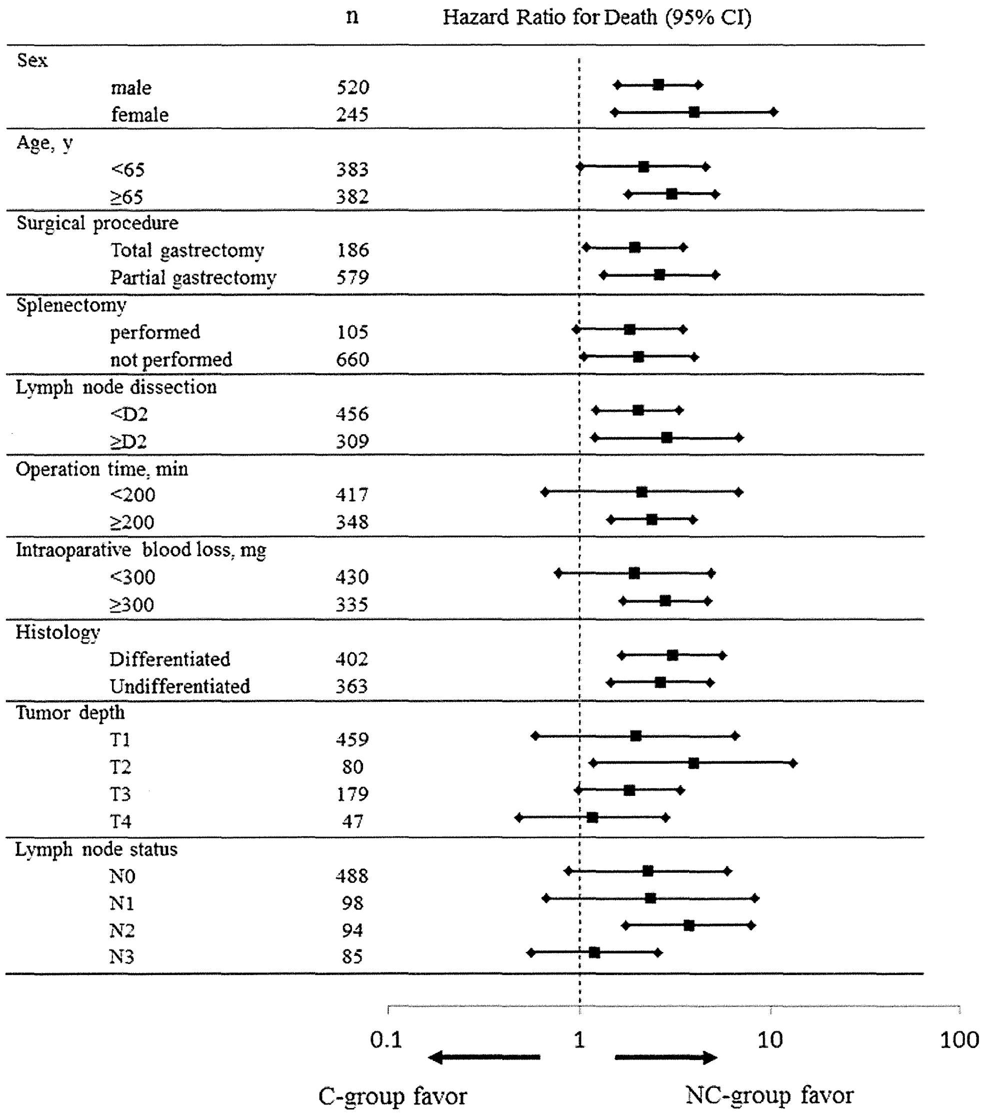

FIG. 3 Hazard ratio for death among subgroups. Long-term survival is better in NC-group than in C-group in most subgroups

multivariate analysis, and it was not identified as an independent prognostic factor. In addition, splenectomy was not identified as an independent prognostic factor even when we included it as a covariate instead of D2 lymph node dissection (data not shown). In Western countries, the most recent European Society for Medical Oncology clinical practice guidelines recommend a D2 gastrectomy as the standard procedure for curable advanced gastric cancer.[39,40] However, in their guidelines, splenectomy is only indicated if there is direct invasion, presumably due to the increased morbidity and mortality seen in 2 European randomized controlled trials.[12–14] In Japan, splenectomy is still a standard treatment for patients with upper-third advanced gastric cancer, although early results from a randomized clinical trial investigating the efficacy of splenectomy showed an increased incidence of postoperative pancreas-related infections. The effect of splenectomy on the long-term survival rate is still unclear even in Japan, and we have to wait for the final results of the randomized clinical trial.[41]

Perhaps surgeons have the urge to decrease postoperative complications in order to improve early surgical outcomes. However, the results of the present study show there are also poor long-term outcomes in patients with postoperative intra-abdominal infections. Therefore, surgeons must perform the surgery with extreme precision, not only to decrease postoperative complications, but also to improve long-term outcomes for patients.

In conclusion, postoperative intra-abdominal infectious complications adversely affect the overall and relapse-free survival of patients with stage II and III advanced gastric cancer. Surgeons have to perform the surgery with meticulous care in order to decrease the complication rate and improve the long-term outcome of patients following curative gastrectomy.