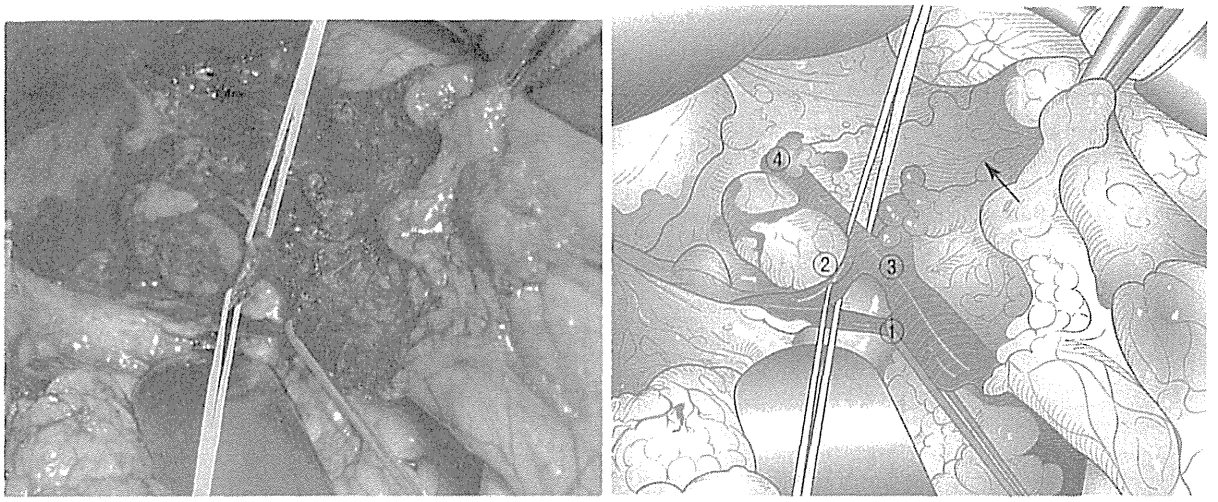

図10　左胃動脈右側からの腹腔枝の同定

右側から左胃動脈（①）を根部から郭清していき，腹腔枝（②）が合流する部を同定したのちに腹腔枝周囲を郭清する。腹腔枝から後胃枝（③）が分岐するが，その周囲を十分剝離すれば後胃枝は鋭的に切離可能である。なお，腹腔枝根部付近（④）は食道に近いので食道胃接合部の位置を確認しながら，この部の郭清範囲を決める。

11．No.1 および No.3 の郭清

あらかじめ胃においた切離線のマークまで胃の後壁，また前壁の脂肪層を正確に除去し，もっとも重要なリンパ節領域である No.1 および No.3 の郭清を終了する。

12．吻合

後壁は 4-0 モノフィラメント吸収糸で一層連続縫合を行う。前壁は層層に吻合するが，粘膜粘膜下層は後壁の糸を連続して用い，漿膜筋層は 4-0 編み糸吸収糸を用いて結節縫合をしている。

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Prognostic Significance of Complications after Curative Surgery for Gastric Cancer

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ABSTRACT

Background. Postoperative complications such as anastomotic leakage were reported to be a major independent prognostic factor for long-term survival in gastrointestinal malignancies. This study sought to clarify the prognostic significance of postoperative inflammatory complications specifically for patients with gastric cancer.

Methods. This study included 1,395 patients who underwent curative resection for gastric cancer from 2005 to 2008. Complications were evaluated according to the Clavien-Dindo classification. Overall survival (OS) and disease-specific mortality (DSM) were compared between complication and no-complication groups. Presence of complications was modeled by the Cox proportional hazard model for OS and the Fine and Gray competing risk regression model for DSM to assess the correlation between complication and prognosis.

Results. The median follow-up time was 3.1 years. Two hundred seven patients (14.8 %) had complications of grade 2 or higher. Of 131 patients who died within this period, 87 died of gastric cancer. The 3-year OS in the complication group was 84.1 % compared to 93.1 % in the no-complication group ($P < 0.0001$). The cumulative incidence of DSM was also significantly worse in patients with complications ($P < 0.0001$). Multivariate analysis identified the same significant increasing risk of complication for both OS (hazard ratio 1.88; 95 % confidence interval 1.26–2.80) and DSM (hazard ratio 1.90; 95 % confidence interval 1.19–3.02).

Conclusions. Postoperative complications that can cause prolonged inflammation have an obvious impact not only on the OS but also on the DSM of patients with gastric cancer even if the tumor is resected curatively.

Gastric cancer is the fourth most common malignancy and second most common cause of cancer deaths worldwide. Although surgical resection is the sole mainstay of curative treatment for patients with gastric cancer, recurrence and metastasis occur in 20–60 % of patients, and survival remains low even after curative resection.[1–3] Gastric cancer mortality and relapse are largely attributed to tumor aggressiveness and extent of surgery.[4,5] However, various other prognostic factors have been identified. Previous studies on gastrointestinal malignancies, such as colorectal and esophageal cancers, found that postoperative complications could have a significant negative impact on prognosis.[6–9] Few such reports have been published on gastric cancer, but two recent studies demonstrated that anastomotic leakage after surgery for advanced gastric cancer was a major independent prognostic factor for long-term survival.[10,11] Why anastomotic leakage affects prognosis remains open to speculation; however, the authors suggested that prolonged inflammatory response to anastomotic breakdown could promote the metastasis of residual tumor cells.[10,11] We therefore proposed that overall complications including anastomotic leakage could mediate a poor prognosis.

In this study, we investigated the impact of postoperative overall complications that can cause prolonged inflammation on long-term survival.

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PATIENTS AND METHODS

Data Source

From March 2005 to December 2008, a total of 1,395 patients with gastric cancer underwent curative (R0) gastrectomy at the Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan. Patients with distant metastasis were excluded. Gastrectomy and lymph node dissection were carried out according to the recommendations of the Japanese Research Society for Gastric Cancer. Tumor staging was evaluated according to the 7th edition of the International Union Against Cancer tumor, node, metastasis (TNM) classification system.[12] As our policy, patients with clinical stage (cStage) I disease underwent laparoscopic gastrectomy, while patients with cStage II/III disease underwent open gastrectomy with standardized extended lymphadenectomy (D2). Patients with pathological stage (pStage) II/III disease received adjuvant chemotherapy. Information including patient characteristics, surgical records, and pathological data were obtained from the database of our hospital. The dates and causes of death were collected from the follow-up data based on clinical examinations performed every 3–6 months after discharge. Four patients died during the hospital stay; they were excluded from this study. The data collection and analysis were approved by the institutional review board of the Cancer Institute Hospital.

Evaluation of Complications

During the postoperative period, all patients were observed for any complications, and only those occurring within 1 month after surgery were taken as an object. Anastomotic leakage was diagnosed clinically by the presence of saliva or gastrointestinal contents in the drain or during relaparotomy, and radiologically by the contrast swallow test. Drain output of any measurable volume of fluid on or after postoperative day 3 with amylase content three times higher than the serum level was considered to indicate a pancreatic fistula. Prolonged fever-up and/or inflammation with positive findings on computed tomography (fluid collection or abscess) was defined as intra-abdominal infection, while that without positive findings on computed tomography and just requiring antibiotic therapy was defined as "prolonged fever-up/inflammation." Wound infection was diagnosed if purulent discharge from the wound returned a positive result on bacterial culture. We objectively evaluated the presence and severity of these postoperative complications using the Clavien-Dindo classification.[13,14] On that basis, we divided the patients into two groups: a complication group (complications of grade 2 or higher) and a no-complication group (complications of less than grade 2). When two or more complications occurred in one patient, the higher grade was adopted. Additionally, to evaluate postoperative inflammation status, we obtained blood samples of patients on days 1, 3, 5, and 7 after surgery and measured the relevant parameters including white blood cell (WBC) and C-reactive protein (CRP). Body temperature (BT) was measured every day.

Statistical Analysis

The primary interest of this study was to evaluate whether the postoperative complication affected the following two time-to-event end points: (1) overall survival (OS), defined as the duration between the date of surgery and the date of death from any cause or the date of last follow-up in living patients; and (2) disease-specific mortality (DSM), defined as the duration between the date of surgery and the date of death due to gastric cancer.

Demographic characteristics and laboratory data were compared between the complication and no-complication groups using the χ^2 test for categorical variables and the Mann-Whitney U test for continuous variables. We used Kaplan-Meier method to estimate survival rates and the Cox proportional hazard model to assess the effects of covariates on OS for both univariate and multivariate analyses with the categorical covariates listed in Table 3.[15] Patients with missing covariate values were excluded. Standard clinical thresholds were used, dividing the continuous variables into no more than three categories. To alleviate the multicollinearity, one of the covariates showing a statistical correlation was excluded from the clinical perspective. A stepwise Cox regression analysis was then performed, with two covariates (albumin and body mass index) forcibly retained on the grounds that nutrition was our main concern before the selection of covariates.

Fine and Gray's regression model was used to assess the effects of remaining covariates by stepwise Cox regression in the presence of competing risks; this was especially important for the DSM analysis.[16] The nonparametric cumulative incidence function was also estimated.[17] Survival rate and cumulative incidence function were plotted for both the analysis set and for subgroups stratified by pStage.

All statistical analyses were performed by SAS release 9.3 (SAS, Cary, NCNC) and R version 2.14.1. All P values resulted from a two-sided statistical test, setting the significance level to 0.05.

RESULTS

Patients and Baseline Characteristics

Table 1 summarizes the baseline characteristics of the 1,395 patients who underwent curative resection for gastric cancer according to complication severity level. Two hundred seven (14.8 %) patients developed postoperative complication of grade 2 or higher (anastomotic leakage 2.4 %, pancreatic fistula 2.2 %, intra-abdominal infection 2.9 %), and of these, 126 (7.5 %) had grade 3 complications requiring surgical, endoscopic, or radiological intervention. The incidence of complication was significantly associated with age, gender, and body mass index, but not with preoperative albumin, a parameter indicating nutritional status before surgery. With regard to surgical and tumor factors, the complication rate was significantly higher in patients with tumor in the upper stomach or with more advanced tumor. Such cases would thus require total gastrectomy with extended lymph node dissection, resulting in longer operation time and greater blood loss.

Survival Outcomes

The remainder of this analysis was based on the 1,341 patients who had no missing data in 11 candidate covariates for multivariate analyses. OS and DSM results are represented graphically in Fig. 1a, b, respectively, and the resultant curves stratified by pStage are shown in Fig. 2. The median follow-up time for the 1,341 patients was 3.1 years. Of 131 patients who died within this period, 87 died of gastric cancer. OS was significantly worse in the complication group (84.1 %) than in the no-complication group (93.1), with an unadjusted hazard ratio (HR) for complications of 2.69 (95 % confidence interval [CI] 1.83–3.96; $P < 0.0001$). The cumulative incidence of DSM was also significantly worse in patients with complications (unadjusted HR by Fine and Gray model 2.65; 95 % CI 1.68–4.21; $P < 0.0001$). The pattern remained the same as pStage progressed. However, there was no difference of the effect on OS and DSM between grade 2 and grade 3 (data not shown).

Tables 2 and 3 summarize the univariate and multivariate analyses of 11 candidate covariates. Before multivariate analysis, surgical procedure (instead of tumor location) and pStage (instead of T and N factors) were excluded to alleviate the multicollinearity. Subsequent stepwise Cox regression analysis retained the eight covariates listed in Table 3. These eight variables were then used to assess the correlation between complication and DSM using the Fine and Gray model, revealing the same significant increasing risk of complication for both OS (HR 1.88; 95 % CI 1.26–2.80, $P = 0.002$) and DSM (HR 1.90; 95 % CI 1.19–3.02; $P = 0.007$).

TABLE 1 Patient characteristics

Variable	Complication ($n = 207$)	No complication ($n = 1,188$)	P value
Age, year	64.6	62.5	0.0203
Gender			<0.0001
Male	158 (17.8 %)	728 (82.2 %)	
Female	49 (9.6 %)	460 (90.4 %)	
Body mass index, kg/m^2	22.1	21.6	0.0311
Preoperative albumin[a]			0.8443
≥35 g/L	13 (15.7 %)	70 (84.3 %)	
<35 g/L	189 (14.9 %)	1082 (85.1 %)	
Tumor location[b]			<0.0001
Upper	79 (23.4 %)	259 (76.6 %)	
Middle	72 (11.2 %)	572 (88.8 %)	
Lower	56 (13.6 %)	357 (86.4 %)	
Surgical procedure [laparoscopic surgery]			<0.0001
Total gastrectomy	79 [16] (5.7 %)	234 [40] (94.3 %)	
Distal gastrectomy	109 [50] (7.8 %)	913 [505] (92.2 %)	
Proximal gastrectomy	19 [11] (1.4 %)	41 [26] (98.6 %)	
Operation time, min	256.9	222.5	<0.0001
Blood loss, ml	306.2	165.5	<0.0001
Maximum tumor diameter, cm	5.0	4.5	0.0031
Tumor depth[b]			<0.0001
T1	101 (12.3 %)	719 (87.7 %)	
T2	20 (11.4 %)	155 (88.6 %)	
T3	46 (24.0 %)	145 (76.0 %)	
T4	40 (19.1 %)	169 (80.9 %)	
Lymph node metastasis[b]			0.1199
N0	127 (13.6 %)	806 (86.4 %)	
N1	27 (14.4 %)	160 (85.6 %)	
N2	27 (18.0 %)	123 (82.0 %)	
N3	26 (20.8 %)	99 (79.2 %)	
Pathological stage[b]			0.0061
I	110 (12.4 %)	779 (87.6 %)	
II	44 (18.0 %)	200 (82.0 %)	
III	53 (20.2 %)	209 (79.8 %)	

[a] Data for preoperative albumin were missing in 41 patients

[b] According to the 7th edition of the International Union Against Cancer tumor, node, metastasis classification system

Postoperative Changes in WBC, CRP, and BT

Figure 3 shows changes of clinical and laboratory data relevant to inflammation status during the postoperative

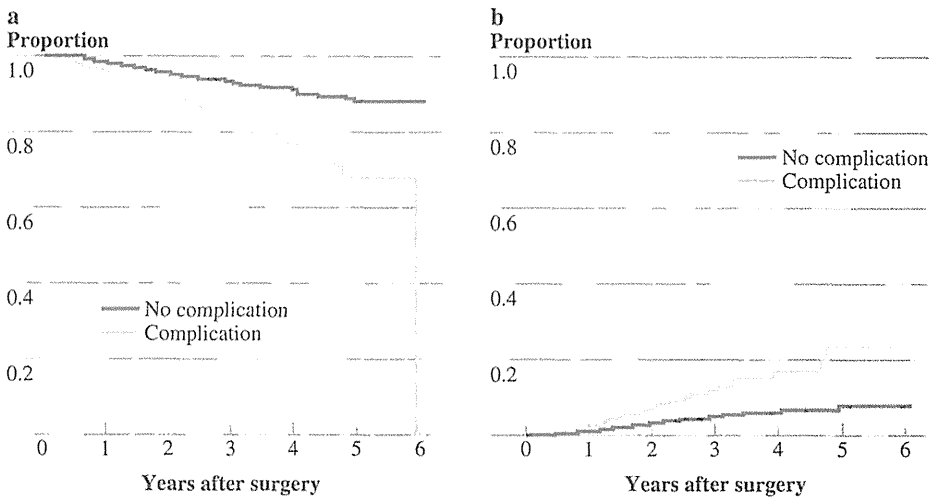

FIG. 1 Overall survival (OS) (**a**) and disease-specific mortality (DSM) (**b**) in patients with and without complications after gastrectomy. The Kaplan-Meier method was used to obtain the OS curve. The cumulative incidence approach considering competing risk was used to obtain the DSM curve. Patients with noncurative gastrectomy, distant metastasis, or death during hospital stay were excluded

days. The mean WBC and BT peaked on day 1, then declined. The mean CRP peaked on day 3, then declined. The mean WBC, CRP, and BT in patients with complication were all significantly higher than those without complications. These in patients with complications were over the normal value even on day 7; especially CRP greatly exceeded it.

DISCUSSION

The present study revealed a correlation between the incidence of postoperative complication and a decreased OS and DSM of patients undergoing curative resection for gastric cancer. Previous studies revealed an association between postoperative complication, especially anastomotic leakage, and an increased risk of relapse and worse prognosis in patients with colorectal and esophageal cancers, and similar results were obtained in patients with gastric cancer.[6–11] In the present study, we adopted the Clavien-Dindo classification, which focuses mainly on the therapeutic consequences of complications, to evaluate the presence and severity of postoperative complications objectively.[8,13,14] Complications of grade 2 or higher include not only infectious complications, but also other inflammatory complications that could possibly delay recovery. Furthermore, multi-institutional studies have now made large data sets available, which is necessary for meaningful analyses because the number of patients with complications after gastrectomy is at most 10–20 %.[10,18–20] Therefore, previous reports on postoperative complication incidence may have introduced some bias, such as surgical technique, diagnosis, or complication evaluation method. We minimized these biases by analyzing a large series of patients at a single institute within a relatively short period.

In this study, the stratified analysis by pStage could resolve some problems. For example, many patients undergoing laparoscopic gastrectomy, known as a less invasive procedure, were included in our series. In general, laparoscopic gastrectomy has several advantages, including less blood loss, less postoperative pain, earlier recovery after surgery, and shorter hospital stay.[21–25] These should contribute to reduce postoperative inflammatory response and immunosuppression. However, as is our policy, laparoscopic gastrectomy was performed in patients with cStage I disease, and most patients undergoing laparoscopic gastrectomy are included in pStage I group. On the other hand, most patients with pStage II/III disease underwent open gastrectomy with standardized extended lymphadenectomy (D2) and received adjuvant chemotherapy. There have also been some reports indicating an association between extended resection or lymph node dissection and significantly higher postoperative mortality, morbidity, and reoperation rates.[26–29] In our study, the incidence of complication in pStage II/III (19.1 %) was indeed significantly more than that in pStage I (13.4 %, $P = 0.0008$) (unpublished data).

The present study demonstrated that postoperative complications also affected DSM, meaning that the incidence of such events could affect a patient's oncologic prognosis, although the underlying mechanism for this specific effect on DSM remains to be elucidated. It is possible that death due to gastric cancer in the complication group studied here was influenced by the prolonged inflammatory response resulting from the complication. Even after pathologically curative resection, tumor cells may remain to cause relapse several years later.[30,31] On the other hand, it is also well established that inflammatory responses to severe postoperative complications are associated with host immunosuppression.[32,33] Consequently, the residual tumor cells may become clinically significant for developing relapse under that circumstance.[8] Indeed, in our series, postoperative inflammatory response was

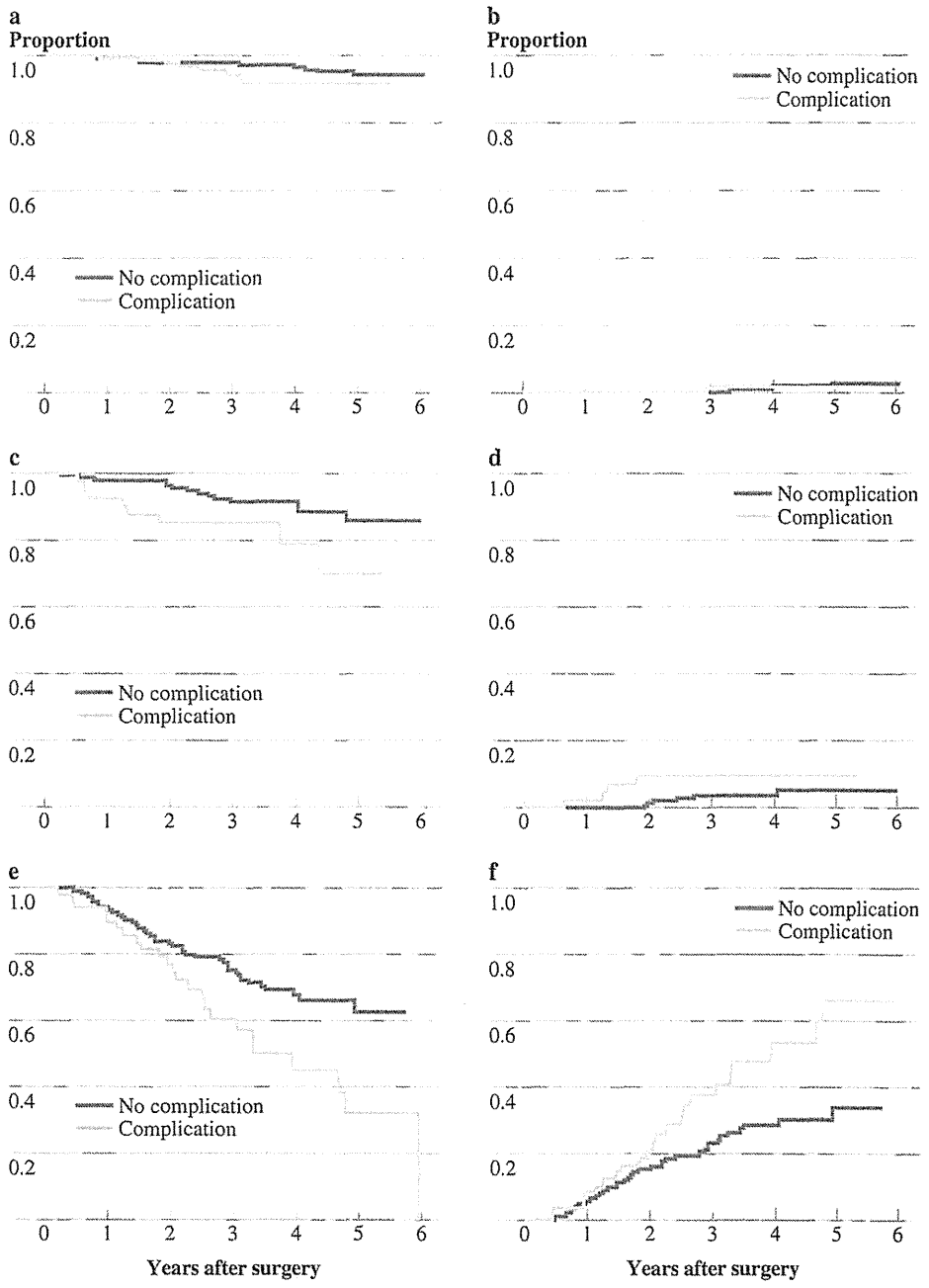

FIG. 2 Overall survival (**a, c, e**) and disease-specific mortality (**b, d, f**) in patients with and without complication after gastrectomy by tumor pathological stage. (**a, b**) Pathological stage I. (**c, d**) Pathological stage II. (**e, f**) Pathological stage III

increased and prolonged in the complication group. Furthermore, our result of a difference in DSM between patients with and without complications that was especially remarkable at pStage III probably reflects the probability or quantity of residual tumor cells.

On the other hand, the OS rate of patients with complications was significantly worse than that in patients without complications in pStage II (similar trend in pStage I), while the difference disappeared in DSM. The definite difference between OS and DSM reflects the deaths due to other causes. The results of OS analysis in pStage II (and pStage I) are also explainable by the above-mentioned mechanism, and stress and immunosuppression after a postoperative complication are certainly a possibility, underlying the worsened comorbidity and subsequent prognosis of patients. In fact, when we assessed the cause of death in pStage I/II, the majority were cardiovascular diseases, cerebrovascular disorders, and pulmonary diseases except cancers (data not shown). Furthermore, when we compared the characteristics of patients who died in the

TABLE 2 Univariate analysis of prognostic factors for OS ($n = 1,341$)

Characteristic	*n*	Death	3-year OS	HR	95 % CI	*P* value
Age						
<75 year	1,130	98	92.6	1.00	–	
≥75 year	211	26	87.4	1.71	1.11–2.63	0.015
Gender						
Male	886	84	90.9	1.00	–	
Female	509	40	93.4	0.76	0.52–1.11	0.156
Body mass index						
<25 kg/m^2	1,123	117	90.9	1.00	–	
≥25 kg/m^2	218	7	96.5	0.34	0.15–0.78	0.010
Preoperative albumin						
<35 g/L	83	21	69.4	1.00	–	
≥35 g/L	1,258	103	93.1	0.22	0.14–0.35	<0.0001
Tumor location						
Upper	329	43	88.5	1.00	–	
Middle/Lower	1,012	81	92.9	0.57	0.39–0.83	0.003
Tumor depth[a]						
T1/2	948	34	96.9	1.00	–	
T3/4	393	90	79.4	7.36	4.96–10.93	<0.0001
Lymph node metastasis[a]						
N0/1	1,069	51	95.8	1.00	–	
N2/3	272	73	76.0	6.55	4.58–9.37	<0.0001
Tumor maximum diameter						
<4 cm	671	24	96.9	1.00	–	
≥4 cm, < 8 cm	493	54	90.5	3.28	2.03–5.31	<0.0001
≥8 cm	177	46	75.5	8.84	5.39–14.48	<0.0001
Operation time						
<240 min	852	56	94.4	1.00	–	
≥240 min	489	68	87.4	2.14	1.50–3.05	<0.0001
Blood transfusion						
No	1,307	111	92.7	1.00	–	
Yes	34	13	56.0	6.90	3.88–12.28	<0.0001
Complication grade 2 or higher						
No	1,139	87	93.2	1.00	–	
Yes	202	37	83.7	2.69	1.83–3.96	<0.0001

OS overall survival, *HR* hazard ratio, *CI* confidence interval

[a] According to the 7th edition of the International Union Against Cancer tumor, node, metastasis classification system

follow-up time between the complication and the no-complication groups in pStage I/II, there was no significant difference but patients with comorbidity, male sex, and older age (these factors are mutually strongly related) showed a tendency to be in the complication group. We guessed that this difference was reflected in the survival curve of pStage I, in which almost none of patient died of gastric cancer, while the difference of the number of DSM with advancing pStage became remarkable in pStage II and III. However, our discussion about the relationship between inflammation and poor prognosis is only a guess drawn from previous reports. It is unknown how much it has influenced the prognosis, and more detailed investigation will be required. What we can say from our results is that postoperative complications have an impact on prognosis; therefore, patients who developed complications should be followed prudently, not only for recurrence of cancer but also comorbidity.

Delays in or lack of compliance with adjuvant chemotherapy is another possible mechanism by which survival of patients with complications might be worsened. In Japan, adjuvant chemotherapy with S-1 is recommended for patients with pStage II or III gastric cancer (according to the 13th edition of Japanese Gastric Cancer Classification, although this is identical to pStage II and III in the 7th edition of the TNM staging system after curative D2 gastrectomy).[34,35] Therefore, when we compared the compliance with adjuvant chemotherapy between pStage II/III patients with and without complications, we found that adjuvant chemotherapy was initiated at a median of 7 weeks after surgery in patients with complications and at 6 weeks in patients without complications (unpublished data). In addition, the planned number of treatment cycles was completed in 62.5 % of the patients with complications but in 66.4 % of the patients without complications (dose modification was permitted) (unpublished data). Thus, it seems improbable that the difference in survival could be affected by these treatment-associated issues.

Finally, it is difficult to accurately evaluate the impact of complications on prognosis as a result of their adventitious nature. With this background, we were forced to analyze this impact by retrospective analysis, and it remains unclear from this study that postoperative complications did not occur as a consequence of other factors not measured in this study data set. We therefore suspect that unclear causal pathways may exist that could not be adjusted for with regard to both complications and survival end points in the present study. Hence, all we can declare from this study is that careful attention to surgical detail would lead to better prognosis.

In conclusion, postoperative complications have an obvious impact not only on OS but also on the DSM of patients with gastric cancer, even if the tumor is resected curatively. Complications could occur not only as a result of surgical factors but also by other factors, including patient's status. Surgeons need to manage perioperative care from various aspects to minimize postoperative complication. Furthermore, patients who developed postoperative complications should be followed prudently for cancer recurrence and comorbidity over a long-term period.

TABLE 3 Multivariate analysis of prognostic factors for OS and DSM

Covariate	OS			DSM		
	HR	95 % CI	*P* value	HR	95 % CI	*P* value
Age						
<75 year	1.00	–		1.00	–	
≥75 year	1.90	1.19–3.03	0.0073	1.37	0.73–2.58	0.3200
Body mass index						
<25 kg/m^2	1.00	–		1.00	–	
≥25 kg/m^2	0.58	0.25–1.33	0.1969	0.49	0.17–1.42	0.1900
Preoperative albumin						
<35 g/L	1.00	–		1.00	–	
≥35 g/L	0.66	0.40–1.10	0.1122	0.88	0.46–1.70	0.7100
Tumor depth[a]						
T1/2	1.00	–		1.00	–	
T3/4	2.98	1.78–5.01	< 0.0001	5.73	2.72–12.07	<0.0001
Lymph node metastasis[a]						
N0/1	1.00	–		1.00	–	
N2/3	2.57	1.65–3.99	< 0.0001	4.06	2.11–7.80	<0.0001
Tumor maximum diameter						
<4 cm	1.00	–		1.00	–	
≥4 cm, <8 cm	1.26	0.72–2.19	0.4174	1.22	0.57–2.61	0.3896
≥8 cm	1.96	1.06–3.62	0.0310	2.37	1.06–5.33	0.0360
Operation time						
<240 min	1.00	–		1.00	–	
≥240 min	1.88	1.30–2.73	0.0008	1.77	1.14–2.77	0.0120
Complication grade 2 or higher						
No	1.00	–		1.00	–	
Yes	1.88	1.26–2.80	0.0018	1.90	1.19–3.02	0.0069

Forcibly retained covariates from a clinical perspective

DSM disease-specific mortality, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval

[a] According to the 7th edition of the International Union Against Cancer tumor, node, metastasis classification system

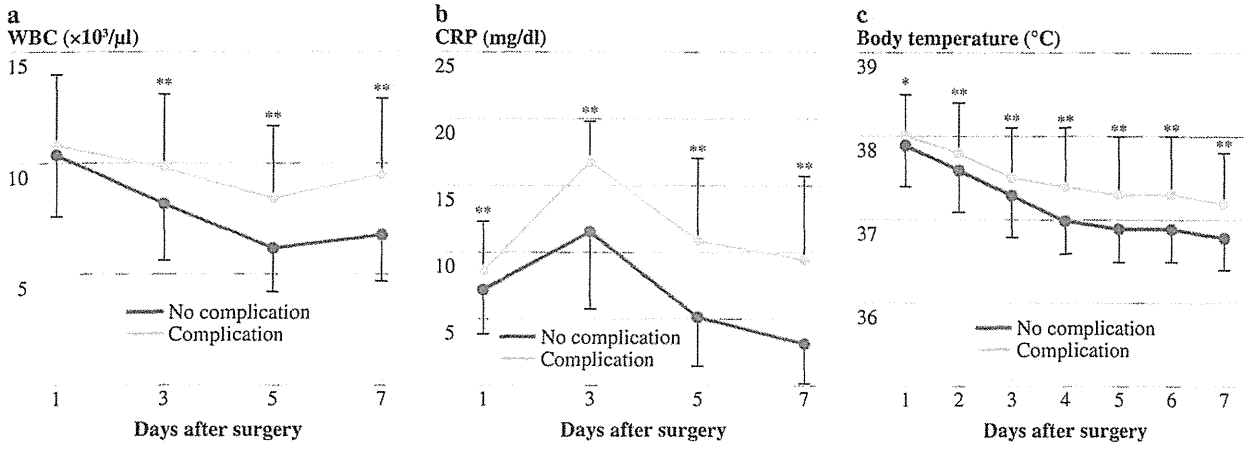

FIG. 3 Changes in white blood cell (a), C-reactive protein (b), and body temperature (c) in patients with and without complication after gastrectomy. For analysis, we used the peak body temperature for the day. *Bars* show standard error. *$P < 0.005$, **$P < 0.0001$

DISCLOSURE The authors declare no conflict of interest.

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Long-term Survival Outcomes of Advanced Gastric Cancer Patients Who Achieved a Pathological Complete Response with Neoadjuvant Chemotherapy: A Systematic Review of the Literature

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ABSTRACT

Background. A pathologic complete response (pCR) can sometimes be induced by intensive or long-term neoadjuvant chemotherapy (NAC). This prognostic research study based on a systematic review of the literature evaluated the impact of a pCR on the long-term survival of gastric cancer (GC) patients.

Methods. Articles were extracted from PubMed and the Japanese medical search engine "Ichu-shi," using the terms "GC," "NAC," and "pCR." Articles were selected based on the following criteria: (1) full-text case report, (2) R0 resection following NAC for locally advanced GC, and (3) pathological complete response in both the primary stomach and in the lymph nodes. A questionnaire regarding the patients' prognoses was sent to the corresponding authors of the articles selected in July 2013.

Results. Twenty-four articles met the criteria. Twenty authors responded to the questionnaire. Finally, 22 patients from 20 articles were entered into the present study. The median follow-up time (range) of the survivors was 76 (range 13–161) months. Tumors that were stage III/IV (86 %: 19/22) and of an undifferentiated histology (61.9 %: 13/21) were dominant. An S1-based regimen was frequently selected for the NAC. All patients underwent R0 resection and D2/D3 lymphadenectomy. The overall survival and recurrence-free survival rates at 3 and 5 years were 96 % and 85 % and 91 % and 75 %, respectively.

Conclusions. Although a pCR was a relatively rare event, a high pCR rate would be helpful to select the regimen and courses of NAC, especially when the pathological response rates are similar.

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