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ORIGINAL ARTICLE

Adverse prognostic impact of perioperative allogeneic transfusion on patients with stage II/III gastric cancer

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Abstract
Background Allogeneic blood transfusions (BTFs) are sometimes required for radical gastrectomy with regional lymph node dissection for advanced gastric cancer (GC). The prognostic impact of perioperative BTF in GC is controversial.
Methods Clinical data were collected retrospectively from 250 consecutive patients who underwent curative gastric resection for stage II/III GC. The prognostic impact of BTF on patient survival was evaluated. Subgroup analysis was performed according to units of blood transfused, timing of BTF, type of gastrectomy, splenectomy, intraoperative estimated blood loss, and year of surgery.
Results Fifty-seven (22.8 %) patients underwent perioperative BTF. Patients who received BTF experienced a significantly shorter disease-specific survival after curative surgery, and multivariable analysis identified perioperative BTF as an independent prognostic factor for cancer-related death (hazard ratio, 1.80; 95 % confidence interval, 1.05–3.02; $p = 0.032$). The BTF group experienced significantly lower recurrence-free survival rate and a higher rate of initial peritoneal recurrence. The amount of blood cells transfused had less impact on prognosis. Pre- or postoperative BTF without intraoperative BTF had limited influence on postoperative prognosis. Prognosis of patients was affected by splenectomy. Even when intraoperative blood loss exceeded 800 ml, the prognosis of the non-BTF group was more favorable. The prognostic impact of BTF became less clear after introduction of adjuvant chemotherapy with S-1.
Conclusions BTF was an independent prognostic factor in patients with stage II/III GC after curative gastrectomy. To improve prognosis, BTF should be avoided when possible, particularly during surgery.

Keywords Gastric cancer · Transfusion · Prognosis · Splenectomy

Introduction

Gastric cancer (GC) is the fourth most common malignancy and the second leading cause of cancer-related death worldwide [1]. Radical gastrectomy with regional lymph node dissection is the only available curative treatment for gastric cancer, and D2 gastrectomy is now widely recommended in the guidelines for patients with advanced GC in East Asia, the United States, and Europe [2–4].

Patients with advanced GC are prone to anemia and malnutrition, typically caused by hemorrhage and stenosis [5]. Further, gastrectomy with lymphadenectomy sometimes causes excessive bleeding even when performed at high-volume centers [6]. Allogeneic blood transfusion (BTF) is sometimes required when performing D2 gastrectomy for advanced GC, although the frequency of BTF is declining because of improvements in surgical technique and devices and perioperative management [7, 8]. There are concerns that BTF increases tumor recurrence and decreases overall survival rate [9, 10], although some

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studies demonstrate that BTF does not influence prognosis [11, 12]. Thus, the significance of the timing and the number of BTFs on survival, including its interaction with splenectomy, along with the association of BTF with type of gastrectomy and estimated blood loss (EBL), remain interesting issues.

The aim of the present study was to answer these questions by evaluating the potential impact of BTF on the long-term survival of patients with stage II/III GC after curative surgery.

Patients and methods

Patients

We reviewed the records of 1,078 patients who underwent gastrectomy for GC at the Department of Gastroenterological Surgery, Nagoya University, between January 1999 and July 2014. Stage classification by the Union for International Cancer Control (UICC) was applied to the current study [13]. Two hundred and fifty patients met the eligibility criteria, which included histologically confirmed R0 gastric resection with negative resection margins, UICC stage II/III, and pathological evaluation of the number of resected lymph nodes (>15).

This study conforms to the ethical guidelines of the World Medical Association Declaration of Helsinki–Ethical Principles for Medical Research Involving Human Subjects. All patients granted written informed consent for surgery and use of clinical data as required by the Review Board of Nagoya University (Nagoya, Japan) [14, 15].

Surgical procedures and postoperative treatment

Patients underwent gastrectomy with D2 or further lymphadenectomy in accordance with the Japanese Gastric Cancer Treatment Guidelines 2010 [16]. Splenectomy was performed to completely remove splenic hilar lymph nodes as required for cancers located in the upper-third stomach, or when the tumor invaded the spleen. The method of reconstruction was at the discretion of surgeons. Postoperative adjuvant chemotherapy was administered according to the evidence available at the time of surgery, the patient's physical condition, and with the patient's consent. Since 2007, adjuvant chemotherapy using S-1 (an oral fluoropyrimidine derivative) has been was administered to all UICC stage II–III GC patients, unless contraindicated by the patient's condition, based on the ACTS-GC study [17, 18]. The treating physician determined the chemotherapy protocol after recurrence. Patients were followed once every 3 months for 2 years after surgery and then every 6 months for 5 years or until death. Physical examination, laboratory tests, and enhanced computed tomography (chest and abdominal cavity) were performed at each visit [19].

BTFs

The general indication for blood transfusions was a hemoglobin (Hb) concentration <8 g/dl, although transfusions were performed at the discretion of the anesthesiologist and the surgical team responsible for perioperative care [20]. Packed blood cells were stored in citrate-phosphate-dextrose-adenine anticoagulant solution without leukodepletion. Perioperative blood transfusion was defined as the administration of blood cells within 14 days before surgery, during surgery, or 7 days after surgery.

Evaluation of clinicopathological factors and survival after curative gastrectomy

The clinicopathological features studied included sex, age, tumor location, tumor size, surgical procedure (type of gastrectomy and splenectomy), operative time, estimated intraoperative blood loss (EBL), and perioperative BTF. The prognostic impact of BTF was evaluated by analyzing patient survival, which included comparisons of disease-specific and recurrence-free survival between patients who were or were not administered perioperative BTF. Further, subgroup analysis categorized patients according to the volume of blood cells transfused, timing of BTF, type of gastrectomy, splenectomy, amount of EBL, and the year of surgery.

Statistical analysis

Survival was estimated using the Kaplan–Meier method, and the overall differences between survival curves were compared using the log-rank test. When calculating disease-specific survival, only gastric cancer-related deaths were counted, and subjects who died of some other cause were censored. Recurrence-free survival was defined as the period between the day of curative gastrectomy and the detection of disease recurrence. We performed multivariable regression analysis to detect prognostic factors using the Cox proportional hazards model, and variables with $p < 0.05$ were entered into the final model. The chi-square test was used to evaluate associations between levels of markers and clinicopathological parameters. We compared values of each marker in different patient groups using the Mann–Whitney test. Statistical analysis was performed using JMP 10 software (SAS Institute, Cary, NC, USA). A statistically significant difference is indicated by $p < 0.05$.

Table 1 Demographics and perioperative clinical characteristics

Variables	Total ($n = 250$)	Without transfusion ($n = 193$)	With transfusion ($n = 57$)	p value
Age, median (range) (years)	65 (20–96)	64 (20–96)	69 (33–87)	0.008
Sex				0.022
Male	182	134	48	
Female	68	59	9	
Cardiopulmonary comorbidity				0.501
Absent	205	160	45	
Present	45	33	12	
Preoperative symptom				<0.001
Absent	93	83	10	
Present	157	110	47	
Preoperative body mass index, mean ± SD	22.3 ± 3.5	22.4 ± 3.3	21.6 ± 4.2	0.040
Preoperative hemoglobin (g/dl), mean ± SD	12.3 ± 2.2	12.9 ± 1.8	10.3 ± 2.0	<0.001
Preoperative anemia				<0.001
Absent	190	164	20	
Present	60	23	37	
Tumor location				0.391
Entire	7	6	1	
Upper third	66	49	17	
Middle third	87	72	15	
Lower third	90	66	24	
Multifocal lesions				0.966
Absent	241	186	55	
Present	9	7	2	
Tumor size (mm)				0.003
<50	117	100	17	
≥50	133	93	40	
Type of gastrectomy				0.375
Total gastrectomy	97	72	25	
Partial gastrectomy	153	121	32	
Splenectomy				0.600
Absent	178	139	39	
Present	72	54	18	
Dissected lymph nodes, mean ± SD	37.8 ± 17.9	37.8 ± 17.8	38.0 ± 18.6	0.907
Operative time (min), mean ± SD	250 ± 83	242 ± 65	278 ± 124	0.244
Estimated blood loss (ml), median (range)	318 (0–7,876)	300 (0–1,285)	527 (20–7,876)	0.002
Postoperative complication[a]				0.007
Absent	217	174	43	
Present	33	19	14	
UICC T factor				0.007
pT1	15	15	0	
pT2	40	33	7	
pT3	90	72	18	
pT4	105	73	32	
Differentiation				0.025
Differentiated	87	60	27	
Undifferentiated	163	133	30	

Table 1 continued

Variables	Total ($n = 250$)	Without transfusion ($n = 193$)	With transfusion ($n = 57$)	p value
Lymph node metastasis				0.749
Absent	61	48	13	
Present	189	145	44	
UICC stage				0.018
IIA	65	57	8	
IIB	64	53	11	
IIIA	34	24	10	
IIIB	48	35	13	
IIIC	39	24	15	
Adjuvant chemotherapy				0.124
Absent	118	86	32	
Present	132	107	25	

SD standard deviation, *UICC* Union for International Cancer Control. [a] Grade III or IV in the Clavien–Dindo classification

Results

Characteristics of patients with and without perioperative BTF

The characteristics of the 250 patients are shown in Table 1. The median length of follow-up was 36.3 months (range, 3.5–176 months). Fifty-seven patients (22.8 %) received perioperative BTF. The median amount of blood cells administered to patients was 4 units (range, 1–18 units). Patients who were administered BTF were significantly older, more often suffered from preoperative symptoms, had lower preoperative hemoglobin levels, had greater intraoperative EBL, and had greater incidence of postoperative complications compared with patients not administered BTF. Further, tumors in the BTF group were larger, more deeply invasive (UICC T factor), and at a higher pathological UICC stage compared with patients not administered a BTF. In contrast, there was no significant difference between patients who received a BTF and those who did not in the prevalence of cardiopulmonary comorbidity, tumor location, type of gastrectomy, incidence of splenectomy, operative time, lymph node metastasis, and administration of adjuvant chemotherapy.

Overall prognostic impact of perioperative BTFs

Patients administered a BTF had a significantly shorter disease-specific survival after curative surgery compared with those who had not received a BTF (5-year survival rates of 43 % and 70 %, respectively, $p < 0.001$) (Fig. 1a). Because the patient data were collected over a period of 15 years during which there were some changes in the standard of care, relative risk for some variables may not remain constant over the study period. The proportional hazards assumption in the Cox model was assessed with models including time-by-covariate interactions. Thus, we confirmed that no significant violations were found in the model. Multivariate analysis using a stepwise regression model identified perioperative BTF as an independent prognostic factor for mortality (hazard ratio, 1.80; 95 % confidence interval, 1.05–3.02; $p = 0.032$) along with tumor size $\geq$50 mm, pT4, and lymph node metastasis (Table 2).

Subgroup analyses

The prognosis of patients who received $\leq$4 units of blood cells during perioperative BTF was similar to that of those administered >4 units, and the survival of both groups was shorter compared with the group not administered BTF (Fig. 1b). The postoperative outcomes of patients who received intraoperative BTF were less favorable than those who did not. There were no significant differences in the outcome between patients who underwent pre- or postoperative BTF and those who did not receive any BTF (Fig. 1c). Patients who received a BTF had significantly shorter disease-specific survival whether they underwent total or partial gastrectomy (distal gastrectomy and proximal gastrectomy) (Fig. 2a).

Next, we evaluated how splenectomy interacted with BTF to influence patient survival. The prognosis of the BTF group was significantly worse compared with that of the non-BTF group, independent of whether the splenectomy was performed. Moreover, patients who underwent splenectomy were more liable to have a worse prognosis regardless of whether BTF was performed,

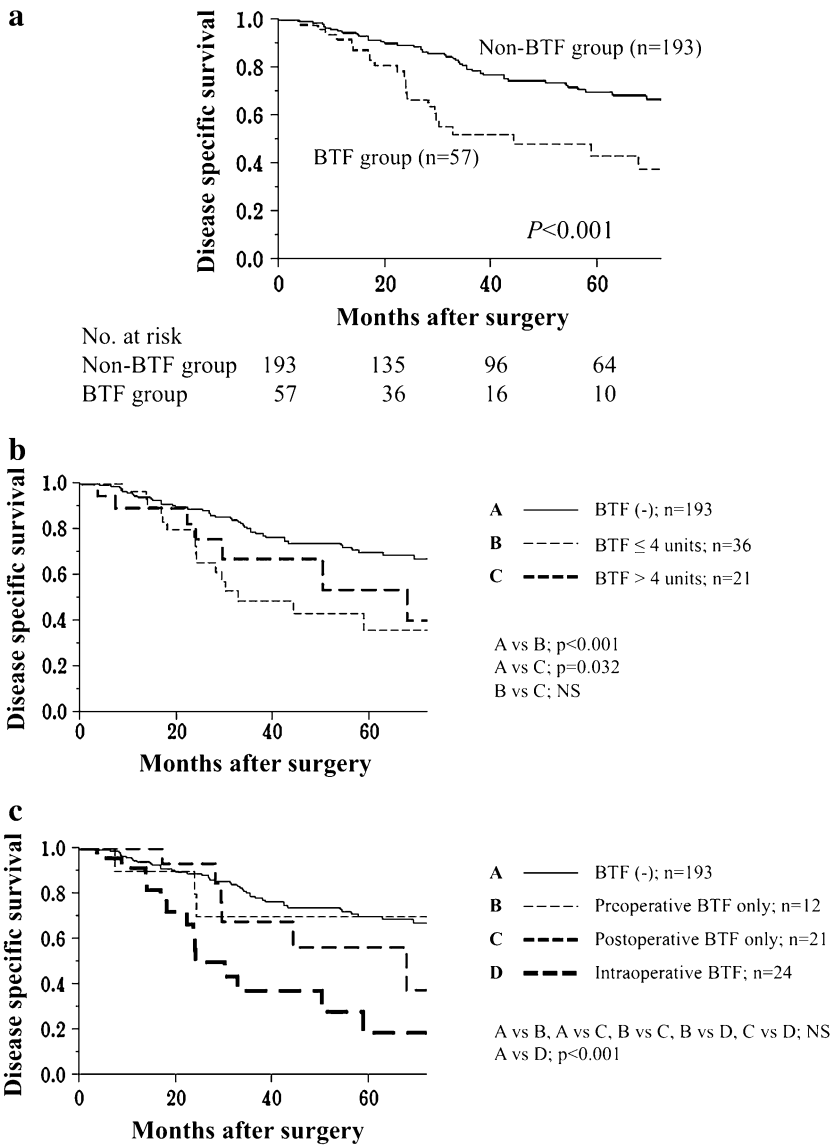

Fig. 1 Prognostic impact of perioperative blood transfusions (*BTF*) on patients with stage II/III gastric cancer (GC). **a** The BTF group experienced significantly shorter disease-specific survival than the non-BTF group. **b**, **c** Subgroup analyses. Patients were categorized according to the total units transfused (**b**) and the timing of BTF (**c**). *BTF* blood transfusion

although the difference was not statistically significant (Fig. 2b).

The amount of intraoperative EBL is generally the most important reason for implementing BTF. Intraoperative EBL ≥800 ml did not affect prognosis as much as BTF. Among the subset of patients with intraoperative EBL < 800 ml and the subset of those with intraoperative EBL ≥800 ml, prognosis of the non-BTF group was better than that of the BTF group (Fig. 2c). After 2007, S-1 (80 mg/m^2) was administrated to all patients as adjuvant chemotherapy, reflecting the results of a pivotal phase III study, unless contraindicated or found intolerable by the patients. When patients were classified according to the year that they underwent surgery (up to 2006, or after 2007), the influence of BTF on patient prognosis was somewhat reduced after 2007 (Fig. 3a).

Associations between perioperative BTF and recurrences of GC after curative gastrectomy

The BTF group experienced significantly lower recurrence-free survival compared with that of the non-BTF group (2-year survival, 52 % and 74 %, respectively; $p < 0.001$) (Fig. 3b). The BTF group had a higher prevalence of peritoneal disease as a type of initial recurrence compared with that of the non-BTF group (22.8 % and 9.3 %, respectively), whereas the frequencies of liver, lymph node, and lung metastases were equivalent (Fig. 3c).

Discussion

Although many studies attempted to evaluate the influence of perioperative BTF on the prognosis of patients with GC,

Table 2 Prognostic factors for disease-specific survival in 250 patients with stage II/III gastric cancer

Variables	*n*	Univariate			Multivariate		
		Hazard ratio	95 % CI	*p* value	Hazard ratio	95 % CI	*p* value
Age ≥65 years	134	1.07	0.67–1.72	0.768			
Male sex	182	1.13	0.67–1.98	0.659			
Cardiopulmonary comorbidity	45	1.02	0.54–1.80	0.943			
Preoperative symptom	157	1.07	0.66–1.77	0.788			
Preoperative body mass index ≥22	122	1.21	0.76–1.94	0.419			
Preoperative anemia	60	1.60	0.91–2.70	0.099			
Tumor location (lower third)	90	0.94	0.57–1.52	0.803			
Multifocal lesions	9	0.93	0.15–2.99	0.925			
Tumor size ≥50 mm	133	2.13	1.30–3.59	0.002	1.84	1.08–3.23	0.024*
Total gastrectomy	97	1.66	1.04–2.66	0.034	1.14	0.49–2.37	0.752
Splenectomy	72	1.74	1.06–2.79	0.028	1.11	0.53–2.56	0.790
Operative time ≥240 min	127	1.84	1.15–3.01	0.011	1.51	0.89–2.62	0.130
Estimated blood loss ≥800 ml	28	2.29	1.23–4.00	0.011	1.42	0.73–2.63	0.289
Perioperative transfusion	57	2.44	1.46–3.98	<0.001	1.80	1.05–3.02	0.032*
Postoperative complication	33	1.52	0.76–2.79	0.224			
pT4	105	2.21	1.39–3.58	<0.001	1.89	1.16–3.11	0.011*
Undifferentiated tumor	163	1.02	0.62–1.71	0.954			
Lymph node metastasis	189	1.80	1.02–3.43	0.043	2.23	1.24–4.33	0.007*
Adjuvant chemotherapy	132	0.90	0.56–1.44	0.659			

CI confidence interval. * Statistically significant in multivariate analysis

the results had been varied. Thus, BTF has either adverse [18–20] or limited [9, 10, 21] effects. Ojima et al. [7] explored prognostic factors in 856 patients with stage I–IV GC and identified perioperative BTF as an independent unfavorable prognostic factor. In contrast, Zhou et al. [8] evaluated the prognostic impact of perioperative BTF in patients with stage I–III GC and found that BTF is not an independent prognostic factor for long-term survival. Pacelli et al. [21] conducted a multicenter retrospective study of a large cohort and reported no significant difference in survival of patients with stage I–IV GC depending on whether they did or did not receive a BTF. Inconsistency in the criteria for patient inclusion were cited as a possible cause of the conflicting data.

The prognostic influence of perioperative BTF may be difficult to discern when patients with stage I GC, who experience few primary outcome events, and patients with stage IV GC, who harbor widespread metastases, are included in the analyses. Therefore, we evaluated the influence of perioperative BTF on the prognosis of patients diagnosed histopathologically as stage II/III GC. In this study, disease-specific survival was employed instead of overall survival because that endpoint was considered to reflect more genuinely the oncological influence of BTF, although it may leave room for other biases. Our results demonstrate that BTF correlated with significantly worse prognosis and was an independent prognostic factor.

BTF may cause dysfunction of the immune system and malignant transformation of neoplastic cells that adversely affect patients with malignancies [22–24]. The mechanism of the inhibition of cellular immunity by BTF involves decreased cutaneous delayed-type hypersensitivity, T-cell proliferation, and natural killer cell function, and may drive the immune system from a T-helper 1 response toward a T-helper 2 response [7, 25]. Moreover, $CD4^{+}CD25^{+}$ regulatory T cells are implicated in immunosuppression caused by BTF [26, 27]. Moreover, BTF may promote tumor proliferation by inducing angiogenesis [8]. For example, Nielsen et al. [28] detected vascular endothelial growth factor in various components of packed blood cells used for transfusion, which accumulated significantly depending on the storage time. Patel et al. [29] reported that BTF promotes endothelial cell proliferation and angiogenesis.

Our result that BTF is an independent prognostic factor may not be helpful in the clinical setting because BTF will have to be performed nevertheless in the event of massive bleeding during surgery. However, there could be some room for consideration such as minimalizing the amount of blood administered or performing BTF preoperatively for patients who suffer from anemia. To answer these questions, we conducted subgroup analyses but found no correlation between the long-term outcome and the amount of blood transfused. The negative prognostic impact of BTF

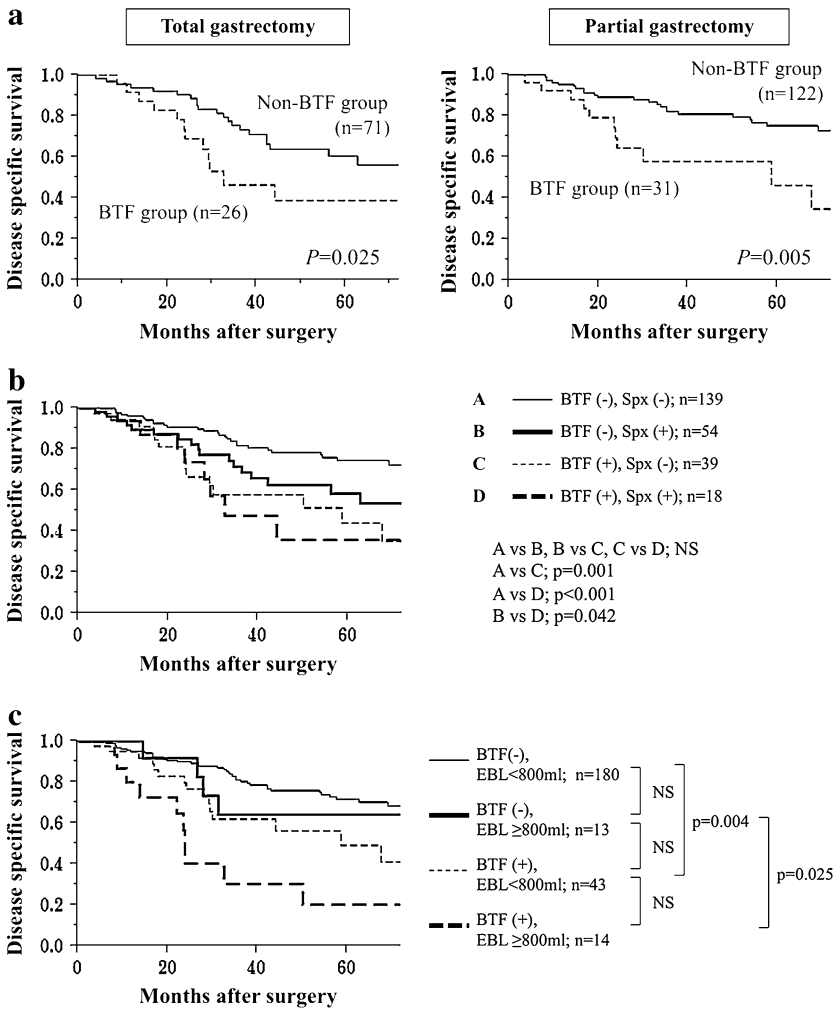

Fig. 2 Subgroup analyses of the prognostic impact of perioperative BTF. Patients were categorized by the type of gastrectomy (**a**), splenectomy (**b**), and intraoperative EBL (**c**). *EBL* estimated blood loss

was observed even among patients who received a small number of units of blood cells, which is consistent with reports that BTF-related immunosuppression occurs regardless of the amount of transfused blood [25, 27]. Surgical stress inhibits the immune system as well, leading to the hypothesis that intraoperative BTF acts synergistically with surgical stress to induce immunosuppression [30].

On the other hand, although intraoperative BTF had significant negative impact on prognosis, pre- or postoperative BTF had less impact, suggesting that efforts should be made to deliver BTF pre- or postoperatively. Splenectomy had been a part of D2 dissection to achieve curative resection of advanced GC in the upper-third stomach [31], but could at the same time have positive impact from the immunological point of view. For example, Shelby et al. [32] demonstrated that the immunosuppressive effects of transfusion were abrogated by splenectomy in experiments involving organ transplantation of animals. Further, Pacelli et al. [21] reported that splenectomy reversed the negative prognostic impact of BTF on overall survival of patients who underwent total gastrectomy. However, we show here that splenectomy and BTF were adverse prognostic factors for patients with stage II/III GC, and that prognosis was least favorable for patients who underwent splenectomy and BTF.

The prognosis of the BTF group was significantly worse both before and after the standardization in 2007 of adjuvant chemotherapy using S-1. Interestingly, the difference in survival between the BTF and non-BTF groups was less marked after 2007, indicating that S-1 may abrogate the adverse effect of BTF on postoperative prognosis. This suggestion is evident in the finding that patients who underwent BTF experienced a significant increase in the incidence of peritoneal recurrence; a tendency that declined after the introduction of postoperative adjuvant chemotherapy with S-1 [18]. Taken together, our findings and those of others described here lead us to conclude that intraoperative BTF should be avoided so long as permitted by the patient's hemodynamic stability. We recommend

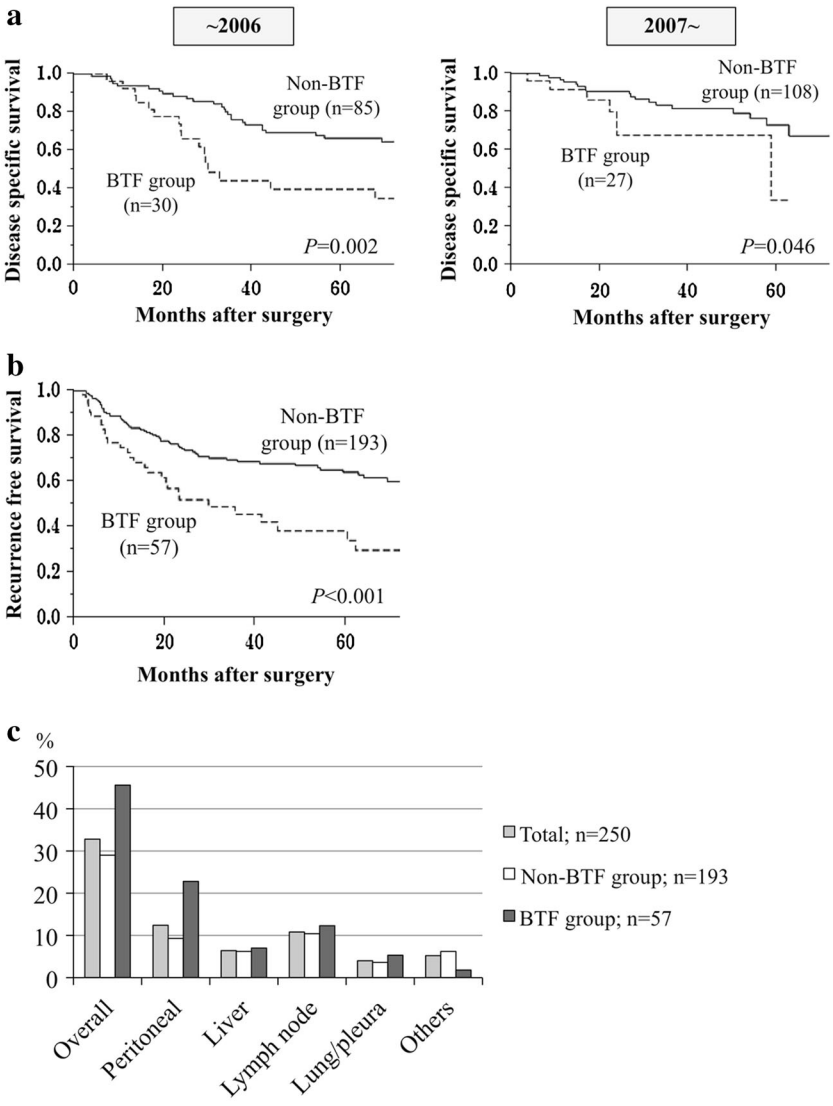

Fig. 3 **a** Prognostic impact of perioperative BTF before and after S-1 adjuvant chemotherapy was standardized. **b** Recurrence-free survival of patients with stage II/III GC. **c** Prevalence of the site of initial recurrence in each group. The BTF group had a high frequency of peritoneal recurrence compared with the non-BTF group

that the use of autologous blood transfusion and artificial blood substitutes should be considered as practical alternatives [33, 34].

The limitations of the present study include its retrospective nature, analysis of a limited number patients, the long period of study at 15 years, and insufficient data on immune function. For example, knowledge of the perioperative levels of cytokines and the population of peripheral blood T-cell subsets may illuminate the mechanism of immunosuppression of perioperative BTF. As for the issue that relative risk for some of the variables may not have remained constant over the 15 years, we used the proportional hazards assumption in the Cox model to confirm that no serious violations were found in the model.

In conclusion, we show here that BTF was an independent prognostic factor for shorter long-term survival in patients with stage II/III GC after curative gastrectomy. Therefore, efforts should be undertaken to minimize blood loss during surgery to possibly reduce the requirement for BTF.

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