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Survival Advantage of Using Autologous Blood Transfusion During Surgery for Esophageal Cancer

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Abstract

Purpose. There is evidence that blood transfusion is associated with an increased rate of tumor recurrence. This study was conducted to assess the survival advantage of giving autologous blood instead of allogeneic blood during surgery for esophageal cancer.

Methods. We retrospectively analyzed 62 patients who underwent esophagectomy for thoracic esophageal cancer between January 1991 and February 1995 and received allogeneic blood transfusion, and 61 patients operated on between March 1995 and February 1998, who received autologous blood transfusion. The clinicopathological factors and survival rates were compared between the two groups.

Results. The clinicopathological factors that influenced prognosis were similar in the two groups; however, a definite survival advantage was evident in the autologous blood transfusion group. According to multivariate analyses, the transfusion of allogeneic blood was an independent prognostic factor ($P = 0.0222$), as was the presence of metastatic lymph nodes. Patients who received allogeneic blood transfusions perioperatively had more than a twofold greater risk (Hazard ration 2.406) of death over patients who received autologous blood transfusions.

Conclusion. Autologous blood transfusion appears to be an independent prognostic factor for the survival of patients with esophageal cancer.

Key words Esophageal cancer · Autologous blood transfusion · Survival

Introduction

There is increasing evidence that blood transfusions may result in transfusion-induced immunosuppression, which in turn leads to increased rates of cancer recurrence and death.[1–11] The first randomized control study to investigate this association in patients with colorectal cancer who had received autologous or allogeneic blood transfusions revealed that the modality of blood transfusion was correlated with tumor recurrence.[12] However, other studies have produced contradictory findings, including two by Busch et al., which revealed that overall survival rates did not significantly differ between patients who received allogeneic and those who received autologous blood during surgery for colorectal cancer.[13,14] No such studies to date have compared survival in patients with esophageal cancer, even though considerable amounts of blood are transfused during esophageal cancer surgery with extended lymph node dissection. As immunosuppression occurs after surgery with blood transfusion and is associated with tumor recurrence, in 1995 we instituted the transfusion of autologous blood as a routine procedure during esophageal cancer surgery in an effort to improve patient survival.[15–17] Here we report the survival advantage of using autologous blood transfusions in surgery for esophageal cancer.

Patients and Methods

Between January 1991 and February 1998, 220 consecutive patients underwent esophagectomy for thoracic esophageal cancer at Akita University Hospital. During the initial period from January 1991 to February 1995, we transfused allogeneic blood; however, from March 1995 we began giving autologous blood transfusions to patients with esophageal cancer in accordance with guidelines established by the Japan Transfusion Soci-

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Table 1. Patient selection for the autologous and allogeneic transfusion groups

	Autologous	Allogeneic	*P* value
Period of surgery	3. 1995–2. 1998	1. 1991–2. 1995	
Total patient number for esophagectomy	108	112	
Patients subjected to analysis	61 (56%)	62 (58%)	
Excluded patients	47 (44%)	50 (42%)	0.9860[a]
Criteria for exclusion			
Neoadjuvant chemoradiotherapy	17 (36%)	21 (42%)	
No transfusion	6 (13%)	1 (2%)	
Anemia (Hb < 11 g/dl)	3 (6%)	2 (4%)	
Heart disease	2 (4%)	3 (6%)	
Use of anticoagulant drug	3 (6%)	1 (2%)	
Hemopathy	2 (4%)	0	
Noncurative (R2) operation	2 (4%)	7 (14%)	
Hospital death	2 (4%)	5 (10%)	
Additional allogeneic blood transfusion	10 (21%)	—	
Over 1100 ml operative blood loss	—	10 (20%)	0.1814[b]

[a] No significant difference between the patients subjected to analysis and the excluded patients
[b] No significant difference among the criteria for exclusion

ety. The requirements for autologous blood donation were set as a hemoglobin level between 11.0 and 15.0 g/dl, an age below 80 years, a body weight of more than 40 kg, a serum protein level of more than 6.5 g/dl, and satisfactory general health. Among the total 108 patients treated during this period, 75 (69%) met these requirements and were given autologous blood transfusions during esophagectomy. The remaining 33 patients were excluded from this study as they did not meet the requirements from the outset for the following reasons: 17 received neoadjuvant chemoradiotherapy; 6 underwent transhiatal esophagectomies and did not require transfusion; 3 had anemia; 2 had heart disease; 3 were taking an anticoagulant drug; and 2 had hemopathy. None of the 75 patients included in this study had severe complications before surgery. Informed consent to undergo surgery and receive a blood transfusion was routinely obtained.

Patients in the autologous blood transfusion group were scheduled to donate 1–2 units of blood (one unit = 200 ml whole blood origin) once a week for 2–3 weeks. The blood obtained was separated and stored as red blood concentrate preserved in mannitol adenine phosphate (RC-MAP) and fresh-frozen plasma (FFP). The RC-MAP was not leukocyte-depleted. Blood cell counts were done before every donation and if the hemoglobin value was found to be under 11 g/dl, no more blood was taken. Iron supplementation was given as 100 mg sodium ferrous citrate orally two times a day over the donation period. Furthermore, 80 mg of saccharated ferric oxide was infused at the time of every donation, and erythropoietin (6000 units) was administered three times a week. None of the patients suffered any severe complications as a result of giving blood.

Study Group

Between March 1995 and February 1998, 75 patients who underwent esophagectomy received an autologous blood transfusion. Two patients had undergone surgery for a macroscopic residual tumor (R2) (according to the International Union Against Cancer: TNM Classification of Malignant Tumors, 5th edition, 1997), two died in hospital, and ten received additional allogeneic blood (4–14 units RC-MAP). Therefore, 61 patients in total were enrolled in the autologous blood transfusion group (Table 1). To investigate the relationship between survival and the modality of transfusion, we compared these 61 patients with 62 of the total 112 patients who had received allogeneic blood transfusions between January 1991 and February 1995. To match the patient backgrounds of the two groups, we excluded from the allogeneic group: 21 patients who had received neoadjuvant chemoradiotherapy; 1 who did not require a transfusion; 2 with anemia; 3 with heart disease; 1 who was taking an anticoagulant drug; 7 who had undergone surgery for a macroscopic residual tumor (R2); 5 who died in hospital; and 10 who had operative blood loss of more than 1100 ml (as the operative blood loss in the ten patients from the original autologous blood transfusion group who received additional allogeneic blood was over 1100 ml) (Table 1).

None of the total 123 patients had received a blood transfusion within 1 year prior to surgery. The period of blood transfusion was defined as when blood was given intraoperatively and up to a maximum of 14 days postoperatively. In the allogeneic group, we transfused allogeneic blood if the hemoglobin value was lower than 10 g/dl, to maintain sufficient tissue levels of oxygen. In the autologous group, donated blood was transfused when the hemoglobin value was lower than 10 g/dl, but additional allogeneic blood transfusion was given if the hemoglobin value dropped below 8 g/dl. None of the patients were given an erythropoietin injection postoperatively. Ultimately, the final decision on the need for intraoperative transfusion was made by the anesthesiologist. Allogeneic blood was collected from healthy volunteers and prepared by the Japanese Red Cross. In 113 patients (92%), we performed right transthoracic esophagectomy and dissection of the mediastinal and abdominal lymph nodes, involving those in the periesophagus region and areas around the trachea and bilateral main bronchus, and those in the perigastric region and areas around the celiac axis, respectively (two-field lymph node dissection). In three patients with upper thoracic esophageal cancer, lymph node dissection was extended to the neck (three-field lymph node dissection). Reconstruction usually involved a subtotal gastric tube pull-up via the posterior mediastinal route.[18] In four patients with a tumor in the cervicothoracic junction of the esophagus, a transhiatal esophagectomy was performed, with cervical and upper mediastinal lymph node dissection via a sternotomy. The extent of lymphadenectomy was the same in both groups during this period. Four senior consultants performed all operations in this study, but 80% were performed by one surgeon (M.K.). Postoperative adjuvant chemotherapy primarily consisted of cisplatin and 5-fluorouracil. None of the patients were lost to follow-up.

Parameters

The clinicopathological profile of each group is based on the International Union Against Cancer: TNM Classification of Malignant Tumors (5th edition, 1997). The autologous and allogeneic groups were compared by age, sex, operative approach, method of reconstruction, duration of surgery, operative blood loss, amount of transfused blood (RC-MAP), tumor location, depth of tumor invasion (pT), tumor size, tumor histology and differentiation, lymph node metastasis (pN), extent of lymph and blood vessel invasion, pathological stage of esophageal cancer, and adjuvant chemotherapy.

Statistical Analysis

All values are expressed as mean ± SD. Categorical data were compared by the chi-squared test and Fisher's exact test, and continuous data were compared by the Mann-Whitney *U*-test. The survival rates were estimated by the Kaplan-Meier method and statistical analysis was carried out using the log-rank test for equality of the survival curves. In univariate and multivariate analyses, independent prognostic factors were determined using a Cox proportional hazards model (Stat View J-5.0). Statistical significance was determined at the $P < 0.05$ level.

Results

The amount of blood donated by the 75 patients given an autologous blood transfusion ranged from 400 to 1200 ml (1011 ± 228 ml), collected over 8–29 days (16.7 ± 5.0 days). Before blood donation, the hemoglobin values in the autologous and allogeneic groups were 13.6 ± 1.3 and 13.6 ± 1.3 g/dl, respectively, and the total protein values were 7.1 ± 0.4 and 7.4 ± 0.5 g/dl, respectively. After blood donation, the hemoglobin values fell significantly from 13.6 ± 1.3 to 11.6 ± 1.2 g/dl. Ten patients (13%) from the autologous blood transfusion group received 4–14 units of transfused allogeneic blood; however, successful esophagectomy was carried out without the need for allogeneic blood in 87% of the patients. Some of the stored blood from ten patients (13%) was not used perioperatively. No complications occurred as a result of the autologous blood transfusions.

We evaluated the survival advantage of using autologous blood transfusions over allogeneic blood transfusions. The clinical profile of both groups is shown in Table 2. The surgical methods did not differ significantly, but the duration of surgery was longer in the autologous blood transfusion group than in the allogeneic group ($P < 0.0001$). Although the operative blood loss was significantly greater in the allogeneic blood transfusion group ($P < 0.0001$), the amount of RC-MAP required for transfusion did not differ significantly ($P = 0.2433$). The clinicopathological factors known to influence prognosis, such as tumor location, depth of tumor invasion, tumor size, tumor histology and differentiation, lymph node metastasis, lymph vessel invasion, and pathological staging, were well balanced in the two groups. Only blood vessel invasion differed significantly between the two groups ($P = 0.0009$).

At the time of analysis, on March 1, 2001, 50 patients (82%) had survived for 3 years in the autologous blood transfusion group and 11 (18%) had died; 9 as a direct result of esophageal cancer and 2 from unrelated causes, being pharyngeal cancer in one and suicide in the other. In the allogeneic blood transfusion group, 31 (50%) had survived for 3 years and 31 (50%) had died;

Table 2. Clinicopathological features of patients given autologous transfusions and those given allogeneic blood transfusions

	Autologous ($n = 61$)	Allogeneic ($n = 62$)	P value
Age (years)	61.8 ± 7.2	63.8 ± 6.2	0.2145
Sex			
Male	54 (89%)	57 (92%)	
Female	7 (11%)	5 (8%)	0.5593
Operative approach			
Transthoracic	59 (97%)	57 (92%)	
Transhiatal	2 (3%)	5 (8%)	0.4395
Reconstruction			
Stomach	57 (93%)	56 (90%)	
Colon	4 (7%)	3 (5%)	
Jejunum	0 (0%)	3 (5%)	0.2077
Duration of surgery (min)	528 ± 99	431 ± 71	<0.0001[a]
Operative blood loss (ml)	470 ± 255	642 ± 221	<0.0001[a]
RC-MAP transfusion (units[b])	5.0 ± 1.3	5.9 ± 3.7	0.2433
Tumor location			
Upper	4 (7%)	6 (10%)	
Middle	31 (51%)	28 (45%)	
Lower	26 (43%)	28 (45%)	0.7330
Depth of invasion (pT)			
T1	32 (52%)	19 (31%)	
T2	7 (11%)	13 (21%)	
T3	17 (28%)	21 (34%)	
T4	5 (8%)	9 (14%)	0.0566
Tumor size (mm)	48 ± 26	53 ± 25	0.1701
Tumor histology			
SCC	59 (97%)	60 (97%)	
Other	2 (3%)	2 (3%)	>0.9999
Tumor differentiation (SCC)			
Well	15 (25%)	13 (22%)	
Moderately	33 (56%)	35 (58%)	
Poorly	11 (19%)	12 (20%)	0.8883
Lymph node involvement (pN)	36 (59%)	41 (66%)	0.4592
Number of metastatic lymph nodes	2.2 ± 2.8	2.5 ± 3.1	0.4804
Lymph vessel invasion	43 (70%)	53 (80%)	0.0520
Blood vessel invasion	28 (56%)	47 (76%)	0.0009[a]
pM			
M0	50 (82%)	52 (84%)	
M1 Lym	11 (18%)	10 (16%)	0.8146
pStage			
I	20 (33%)	13 (21%)	
IIa	5 (8%)	6 (10%)	
IIb	15 (25%)	15 (24%)	
III	9 (15%)	18 (29%)	
IV	12 (20%)	10 (16%)	0.3063
Adjuvant chemotherapy	42 (69%)	50 (81%)	0.1502

RC-MAP, red blood concentrate in mannitol adenine phosphate; SCC, squamous cell carcinoma
[a] Significant difference between autologous and allogeneic groups
[b] 200 ml whole blood origin

24 as a direct result of esophageal cancer and 7 from unrelated causes, being pneumonia in 3, heart failure in 1, gastric cancer in 2, and leukemia in 1 (Table 3). There was no significant difference in deaths from esophageal cancer versus unrelated deaths between the autologous and allogeneic groups ($P > 0.9999$). The cumulative 5-year survival rates of the two groups differed significantly (long-rank test, $P = 0.0019$, Fig. 1) as did the esophageal cancer-specific survival (long-rank test, $P = 0.0269$, Fig. 2).

According to the univariate analyses of 3-year survival, the following 12 co-variants were considered: the type of blood transfusion (allogeneic *vs* autologous), the duration of surgery (<460 min *vs* ≧460 min), blood loss during surgery (<540 ml *vs* ≧540 ml), the amount of blood (RC-MAP) transfused (<5 units *vs* ≧5 units),

Table 3. Three-year survival of patients given autologus and those given allogeneic transfusions

	Autologous (n = 61)	Allogeneic (n = 62)	P value
Surviving	50 (82%)	31 (50%)	
Deceased	11 (18%)	31 (50%)	0.0003[a]
Cause of death			
Tumor recurrence	9 (15%)	24 (39%)	
Unrelated	2 (3%)	7 (8%)	>0.9999
Another malignancy	1[b]	3[c]	
Pneumonia	0	3	
Heart failure	0	1	
Suicide	1	0	

[a] Significant difference
[b] Pharyngeal cancer
[c] Two cases of gastric cancer and one of leukemia

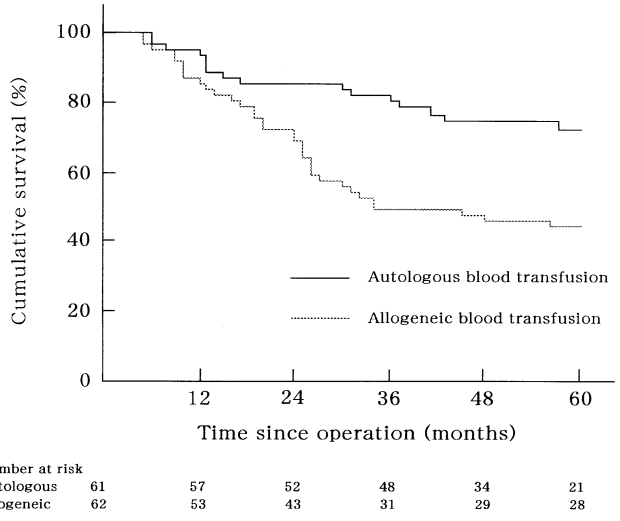

Fig. 1. Overall 5-year survival rates according to transfusion status (autologous *vs* allogeneic) for patients undergoing surgery for thoracic esophageal cancer. There were significant differences in the survival rates of the two groups (log-rank test, P = 0.0019)

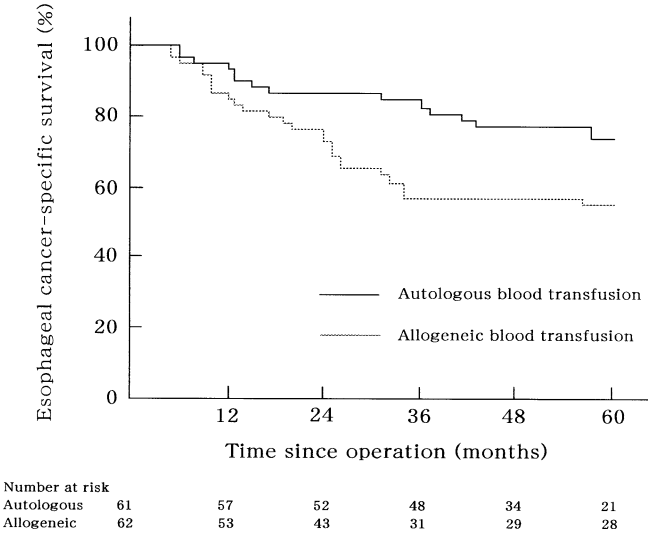

Fig. 2. Esophageal cancer-specific 5-year survival. The survival rate differed significantly between the two groups (log-rank test, P = 0.0269)

tumor size (<50 mm *vs* ≧50 mm), tumor location (upper thoracic *vs* middle and lower thoracic), depth of tumor invasion (T3–4 *vs* T1–2), lymph node metastasis (positive *vs* negative), the number of lymph nodes involved in metastasis (<4 *vs* ≧4), blood vessel invasion (positive *vs* negative), lymph vessel invasion (positive *vs* negative), and histological differentiation of the tumor (well *vs* not well differentiated) (Table 4). The divisions between values were defined as the median values for the duration of surgery (460 min), blood loss (540 ml), amount of blood (RC-MAP) transfused (5 units), and tumor size (50 mm). In the univariate analysis of the 3-year survival, the prognostic factors included the number of lymph nodes involved in metastasis ($P < 0.0001$), the type of blood transfusion (P = 0.0008), lymph node metastasis (P = 0.0018), blood vessel invasion (P = 0.0027), lymph vessel invasion (P = 0.0143), depth of tumor invasion (P = 0.0215), and blood loss (P = 0.0320). Stepwise, we selected these seven covariants for the multivariate analysis of 3-year survival. The independent prognostic factors were found to be the number of lymph nodes involved in metastasis (P = 0.0022) and the modality of blood transfusion (P = 0.0222). Patients who received allogeneic blood transfusions perioperatively had more than a twofold greater risk (Hazard ratio 2.406) of death than those who received autologous blood transfusions (Table 5).

To determine whether the date of surgery and/or allogeneic blood transfusion were independent risk factors, we divided the patients into four groups according to

Table 4. Univariate analysis of the prognostic factors for 3-year survival (Cox proportional hazard model)

Parameter	Coefficient	*P* value	Hazard ratio	95% CI[a]
Number of lymph node metastases (≧4/<4)	1.374	<0.0001[b]	3.951	2.146–7.272
Type of blood transfusion (Allogeneic/autologous)	1.178	0.0008[b]	3.247	1.630–6.470
Lymph node metastasis (+/−)	1.292	0.0018[b]	3.639	1.615–8.198
Blood vessel invasion (+/−)	1.180	0.0027[b]	3.255	1.506–7.037
Lymph vessel invasion (+/−)	1.468	0.0143[b]	4.341	1.341–14.056
Tumor invasion (T3, T4/T2, T1)	0.717	0.0215[b]	2.049	1.111–3.774
Amount of blood loss (≧540 ml/<540 ml)	0.691	0.0320[b]	1.996	1.061–3.753
Tumor size (≧50 mm/<50 mm)	0.341	0.2779	1.407	0.759–2.605
Duration of surgery (≧460 min/<460 min)	0.180	0.3281	1.1919	0.456–1.531
Tumor location (Upper/middle and lower)	0.674	0.3527	1.961	0.474–8.117
Tumor differentiation (Well/not well)	0.105	0.7809	1.110	0.431–1.882
Amount of blood transfusion (≧5 units/<5 units[c])	0.049	0.8932	1.050	0.515–2.140

[a] 95% confidence interval
[b] Significant
[c] 200 ml whole blood origin

Table 5. Multivariate analysis of the prognostic factors for 3-year survival (Cox proportional hazard model)

Parameter	Coefficient	*P* value	Hazard ratio	95% CI[a]
Number of lymph node metastases (≧4/<4)	1.085	0.0022[b]	2.959	1.479–5.921
Type of blood transfusion (Allogeneic/autologous)	0.878	0.0222[b]	2.406	1.133–5.106
Amount of blood loss (≧540 ml/<540 ml)	0.518	0.1311	1.678	0.857–3.288
Lymph node metastasis (+/−)	0.424	0.4406	1.528	0.520–4.487
Tumor invasion (T3, T4/T2, T1)	0.227	0.4894	1.255	0.660–2.386
Lymph vessel invasion (+/−)	0.436	0.5713	1.547	0.342–7.000
Blood vessel invasion (+/−)	0.165	0.7235	1.180	0.472–2.951

[a] 95% confidence interval
[b] Significant

the date of surgery and the type of blood transfusions given: period 1, allogeneic blood transfusions given between January 1991 and October 1992 ($n = 31$); period II, allogeneic blood transfusions given between November 1992 and February 1995 ($n = 31$); period III, autologous transfusions given between March 1995 and April 1996 ($n = 31$); and period IV, autologous transfusions given between May 1996 and March 1998 ($n = 30$). There were no significant differences in survival between periods I and II (log-rank test, $P = 0.98687$), and periods III and IV (log-rank test, $P = 0.7613$). However, there were significant differences in survival between periods I and III (log-rank test, $P = 0.0190$), periods I and IV (log-rank test, $P = 0.0331$), periods II and III (log-rank test, $P = 0.0257$), and periods II and IV (log-rank test, $P = 0.0391$, Fig. 3). The only change in the treatment of esophageal cancer between periods II and III was the use of autologous blood. These data imply that allogeneic blood transfusion was a greater risk factor than the date of the operation.

Finally, we analyzed the survival rates in stage II and III esophageal cancer. The results showed that the cumulative 5-year survival rates differed significantly (log-rank test, $P = 0.0393$, Fig. 4).

Discussion

The findings of our study suggest that patients given autologous blood transfusions for esophageal cancer

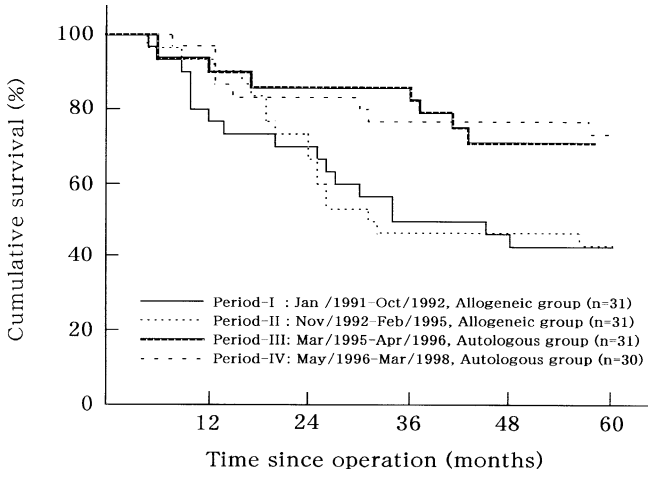

Fig. 3. Overall 5-year survival rates according to the period of operation. There were no significant differences in survival between periods I and II (log-rank test, $P = 0.98687$), or III and IV (log-rank test, $P = 0.7613$). However, there were significant differences in survival between periods II and III (log-rank test, $P = 0.0257$)

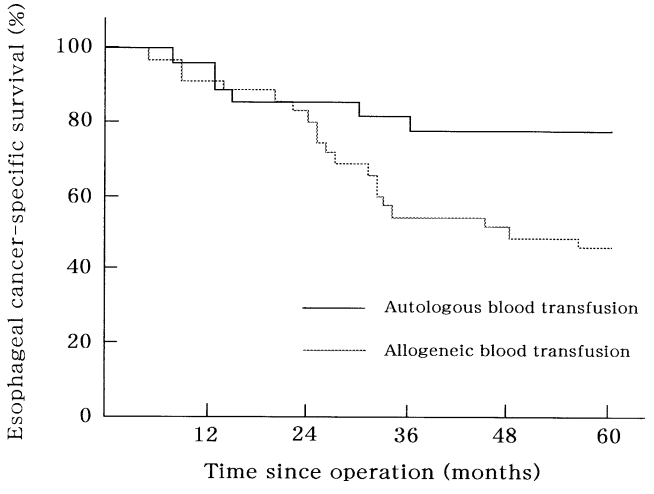

Fig. 4. Overall 5-year survival rates according to transfusion status for patients with stage II and III esophageal cancer. There were significant differences in survival rates between the two groups (log-rank test, $P = 0.0393$)

have a significant survival advantage over those given allogeneic transfusions. This concurs with the results of three previous retrospective meta-analyses concluding that allogeneic blood transfusion increases the risk of cancer recurrence after curative surgical resection.[3–5] These findings are also supported by experimental studies using an animal model in which allogeneic blood transfusions promoted tumor growth and metastasis formation.[1] Interestingly, two independent randomized control trials investigating whether the survival of patients undergoing surgery for colorectal cancer was influenced by autologous or allogeneic blood transfusion, revealed conflicting results. Heiss et al. reported that allogeneic blood transfusion was an independent risk factor for tumor recurrence and associated with poor long-term survival,[12] whereas Busch et al. reported that overall survival rates do not significantly differ among patients who receive allogeneic or autologous blood.[13,14]

We speculated that the relationship could be further clarified by investigating patients who underwent surgery with blood transfusion for esophageal cancer. Esophagectomy with extended lymph node dissection, being the standard surgical procedure for esophageal cancer in Japan,[18] is a lengthy procedure, inflicting much stress on patients. Esophagectomy under anesthesia itself changes immune function, and with extended lymph node dissection, it results in considerable blood loss requiring blood transfusion.[15–17] Signs of immunosuppression become evident after allogeneic blood transfusion. Transfusion-induced immunomodulation, such as a decrease in natural killer cell activity, an imbalance within the lymphocyte subpopulations, and T-lymphocyte proliferative responses to mitogens, has been identified, which in turn influences tumor recurrence.[19–23] Therefore, we avoid giving allogeneic blood transfusions whenever possible. Although our findings do not concur with those of other researchers who performed larger studies on the effect of blood transfusions on the survival of patients with other forms of cancer and vastly different clinical characteristics, we believe that esophagectomy may allow for accurate assessment of autologous blood transfusion.

There is increasing evidence that allogeneic blood transfusion induces an increased rate of tumor recurrence and other negative factors, resulting in a poor prognosis for patients with esophageal cancer. Our results certainly support this notion by showing that patients who received autologous blood transfusions had a survival advantage over those who received allogeneic blood transfusions.[9–11] However, these results for esophageal cancer are the product of nonrandomized, retrospective studies. Furthermore, the clinicopathological features of patients, including the duration of surgery, operative blood loss, and blood vessel invasion differed between the two groups. There are fundamental limitations involved with the retrospective analysis of data concerning a cause and effect relationship. Unfortunately, we are not currently in a position to perform a randomized prospective trial on blood transfusions, but nonetheless, we do believe that this retrospective analysis of data can provide useful information to clinicians, when variables are correctly accounted for in the study design and statistical analysis. We were unable to determine whether the date of the operation and/or alloge-

neic blood transfusion were independent risk factors, because there was a strong association between the date of surgery and the type of blood transfusion given. Therefore, we could not use both factors as covariants in the multivariable statistical analysis, and divided the patients into four groups according to the date of surgery and the type of blood transfusions given. Statistical analysis then revealed that allogeneic blood transfusion, and not the date of the operation, acts indirectly as a risk factor for survival.

Despite the potential limitations imposed by our study design, the multi-regression analysis of our retrospective data clearly indicated that autologous blood transfusion, as well as the number of lymph node metastases, were significant independent prognostic factors in esophageal cancer. As considerable blood loss is expected during esophagectomy with extensive lymph node dissection, and augmentative allogeneic blood transfusion is associated with tumor recurrence after surgery for esophageal cancer, surgeons should exercise caution to minimize intraoperative blood loss that could necessitate allogeneic blood transfusion.

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