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ORIGINAL SCIENTIFIC REPORT

Allogenic Blood Transfusion is Associated with Poor Perioperative and Long-Term Outcome in Esophageal Cancer

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Abstract

Background Esophageal resection for cancer (EC) is still associated with considerable mortality and morbidity rates. Allogenic blood transfusion (aBT) is associated with poor short-term and long-term outcome in surgical oncology. We aimed to evaluate the effect of aBT in a homogeneous population of EC patients undergoing esophagectomy without perioperative treatment.

Methods We analyzed 565 esophagectomies performed due to EC. Allogenic blood transfusion was correlated to clinicopathological parameters, perioperative mortality and morbidity as well as the long-term outcome. Results are presented as adjusted odds ratio (OR) or hazard ratio (HR) with 95 % confidence interval (95 % CI).

Results Patients receiving aBT (aBT(+)) had no higher tumor stages or higher rates of lymph node metastasis ($P = 0.65$ and 0.17, respectively) compared to patients without aBT (aBT(−)). Allogenic blood transfusion was strongly associated with perioperative morbidity (OR 1.9, 95 % CI 1.1–3.5, $P = 0.02$) and mortality (OR 2.9, 95 % CI 1.0–8.6, $P = 0.04$). Tumor recurrence rate was significantly higher in aBT(+) patients ($P = 0.001$). The disease-free and overall survival were significantly longer in aBT(−) compared to aBT(+) patients ($P = 0.016$ and <0.001, respectively). Patients receiving aBT had almost doubled risk for tumor recurrence (HR 1.8, 95 % CI 1.2–2.5, $P = 0.001$) and death (HR 2.2, 95 % CI 1.5–3.2, $P < 0.001$).

Conclusion Allogenic blood transfusion has a significant impact on the natural course of EC after complete resection. The poor short-term and long-term outcome warrants further evaluation of the underlying molecular mechanisms induced by allogenic blood transfusion in cancer patients.

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Abbreviations

aBT	Allogenic blood transfusion
AC	Adenocarcinoma
AJCC	American Joint Committee on Cancer
autoBT	Autologous blood transfusion
CD	Cluster of differentiation
CI	Confidence interval
DFS	Disease-free survival
EC	Esophageal cancer
HR	Hazard ratio
OR	Odds ratio
OS	Overall survival
SCC	Squamous cell carcinoma

TA	Thoracoabdominal
TH	Transhiatal
TRICC	Transfusion requirements in critical care
WBC	White blood cell

Introduction

Incidence of esophageal cancer (EC) is steadily rising worldwide [1]. Despite significant improvement in long-term survival, the perioperative mortality and morbidity associated with esophagectomy for EC, even in high volume centers, remains high [2]. The reported morbidity and mortality rates associated with esophageal resection reach up to 50 and 20 %, respectively [3, 4]. Esophageal resection represents a major operation associated with potentially high blood loss and long intensive care unit stay. Allogenic blood transfusion (aBT) is frequently performed in EC patients even in non-anemic patients [5]. Besides the potential risk of infectious disease transmission and mismatch incompatibility, aBT has recently been identified as an independent risk factor for perioperative outcome in terms of mortality and morbidity [5]. Furthermore, aBT has been associated with higher rates of tumor recurrence and poor survival in various types of cancer. In addition, in several entities, including EC, autologous blood transfusion (autoBT) or transfusion of white blood cell (WBC)-depleted blood has been associated with a more favorable perioperative and long-term outcome compared to patients with aBT [6–11]. Previously, few studies attempted to address the role of aBT on the clinical outcome in EC. These studies were biased by heterogeneity of the study population, especially in terms of applied treatment regimens [7, 12]. To evaluate the effect of aBT on perioperative and long-term outcome, it is of importance to define a homogeneous study population since any type of systemic therapy or radiation will result in immune modulation that is impossible to detach from the effects initiated by aBT. Furthermore, previous studies only focused on either short- or long-term outcome. The aim of this study was to evaluate the effect of aBT on perioperative mortality and morbidity as well as long-term outcome in patients undergoing complete resection for EC without perioperative treatment.

Patients and methods

The study was approved by the medical ethics committee of the Chamber of Physicians of Hamburg. A total of 714 patients with esophageal cancer underwent esophageal resection at our institution between 1992 and 2010. Only patients with histopathologically proven EC and tumor-free resection margins were included into the study. In total, 565 patients were included in this study. Only patients with local R0 and distant R0 status were included. 24 patients had lung metastases, which were not detected by the preoperative staging. These lung metastases were detected during the thoracic part after completing the abdominal part of the esophagectomy. Thus, these patients underwent R0 lung metastasectomy during esophagectomy. None of the patients received perioperative or postoperative treatment. Informed consent was obtained from all patients before including them in a prospective database. All patients had a detailed preoperative assessment of the general health condition and organ function evaluation. Routine tumor staging included esophago-gastro-duodenoscopy, computed tomography and blood tests. The perioperative mortality was defined as 30-day post-hospital discharge mortality. The perioperative morbidity included only major complications in which further medical or surgical intervention was necessary (Clavien Dindo III–IV) within 30 days after discharge [13]. Clinical follow-up data were obtained by studying the patient clinical charts or by contacting them on an outpatient basis. To evaluate the true impact of aBT on the clinical outcome in EC, we did not define any cutoff points but only compared patients who received (aBT(+)) and who did not receive blood transfusion (aBT(−)) perioperatively. aBT was defined as any aBT in the perioperative in-hospital course. Indication for aBT was primarily based upon patient's condition. The anemia threshold for transfusion in patients with coronary heart disease was 10 g/dl and in patients without heart disease 7 g/dl. In case of acute life-threatening bleeding, the decision for aBT was made by the doctor in charge. In a hemodynamic stable patient, the indication was primarily based upon surgeon's discretion. None of the patients received autoBT. Application of leukocyte-depleted blood due to presence of comorbidities resulted in exclusion of the patient from this study.

Statistical analysis

For statistical analysis, SPSS for Windows (IBM SPSS Statistics for Windows, Version 20.0. Released 2011. Armonk, NY: IBM Corp.) was used. For correlation of clinicopathological parameters and aBT, the Chi-square test was used. For variables with a continuous scale, the Mann–Whitney *U* test was applied. To evaluate the effect of aBT on perioperative morbidity and mortality, univariate and multivariable logistic regression analyses were performed and adjusted odds ratio (OR) with 95 % confidence interval (95 % CI) calculated. Disease-free (DFS) and overall survival (OS) curves of the patients were

Table 1 Correlation between clinicopathological parameters and aBT

Variables	N	aBT(−)	aBT(+)	*P*
Total	565 (100)	93 (16.5)	472 (83.5)	–
Age (years)				
≤60	255 (45.1)	41 (16.1)	214 (83.9)	
>60	310 (54.9)	52 (16.8)	258 (83.2)	0.82
Sex				
Male	446 (78.9)	71 (15.9)	375 (84.1)	
Female	119 (21.1)	22 (18.5)	97 (81.5)	0.50
Tumor size				
pT1	104 (18.4)	18 (17.3)	86 (82.7)	
pT2	167 (29.6)	32 (19.2)	135 (80.8)	
pT3	259 (45.8)	38 (14.7)	221 (85.3)	
pT4	35 (6.2)	5 (14.3)	30 (85.7)	0.65
Nodal status				
pN0	217 (38.4)	31 (14.3)	186 (85.7)	
pN1	130 (23.0)	23 (17.7)	107 (82.3)	
pN2	119 (21.1)	16 (13.4)	103 (86.6)	
pN3	99 (17.5)	23 (23.2)	76 (76.8)	0.17
Distant metastasis				
Negative	541 (95.8)	89 (16.5)	452 (83.5)	
Positive	24 (4.2)	4 (16.7)	20 (83.3)	0.98
Grading				
G1	25 (4.4)	5 (20.0)	20 (80.0)	
G2	294 (52.0)	43 (14.6)	251 (85.4)	
G3	246 (43.5)	45 (18.3)	201 (81.7)	0.46
Tumor type				
SCC	269 (47.6)	21 (7.8)	248 (92.2)	
AC	296 (52.4)	72 (24.3)	224 (75.7)	0.001
Operating technique				
Transhiatal	261 (46.2)	55 (21.1)	206 (78.9)	
Thoracoabdominal	304 (53.8)	38 (12.5)	266 (87.5)	0.006
Recurrence				
No	272 (48.2)	71 (26.3)	201 (73.8)	
Yes	293 (51.8)	37 (12.7)	256 (87.3)	0.001
Perioperative mortality				
No	484 (85.6)	93 (19.3)	391 (80.7)	
Yes	81 (14.6)	5 (5.7)	76 (94.3)	0.001
Perioperative morbidity				
No	371 (65.6)	65 (20.7)	249 (79.3)	
Yes	194 (34.4)	21 (10.8)	173 (89.2)	0.006
Preoperative hemoglobin (g/dl)	–	14.4 (10–17.3)	13.7 (8.7–17)	0.003*
Operating time (min)	–	400 (230–720)	445 (230–845)	0.01*
Blood loss(ml)	–	1000 (200–2800)	1600 (200–3100)	<0.001*

Round parentheses indicate percentages

P indicates significance according to Chi-square test

* *P* indicates significance according to Mann–Whitney *U* test comparing the median values, and parentheses represent range

plotted using the Kaplan–Meier method and analyzed using the log-rank test. The OS was computed as the time period from the date of surgery to either the date of death or last follow-up, whichever occurred first. The DFS was defined as the time period from the date of surgery to the date of recurrence, last follow-up or date of death, whichever

Table 2 Multivariable logistic regression analysis for perioperative (a) morbidity, (b) mortality

Variables	OR	95 % CI	*P*
(*a*)			
Age	1.3	0.8–1.9	0.22
Sex	0.7	0.4–1.1	0.11
Preoperative hemoglobin	0.9	0.8–1.1	0.09
Operating time	1.0	–	0.89
Blood loss	1.0	–	0.7
Tumor size (T1,2 vs. T3,4)	1.3	1.1–1.7	0.03
Nodal status	0.7	0.4–1.1	0.12
Distant metastasis	0.7	0.4–1.2	0.21
Tumor type	0.9	0.6–1.3	0.48
Operative technique	1.1	0.9–1.3	0.14
Allogenic transfusion	1.9	1.1–3.5	0.02
(*b*)			
Age	1.9	1.1–3.4	0.02
Sex	1.1	0.5–2.0	0.87
Preoperative hemoglobin	0.9	0.8–1.1	0.51
Operating time	1.0	–	0.11
Blood loss	1.0	–	0.44
Tumor size (T1,2 vs. T3,4)	1.4	0.9–1.9	0.06
Nodal status	1.3	0.7–2.4	0.38
Distant metastasis	0.8	0.4–1.8	0.60
Tumor type	0.6	0.4–1.1	0.12
Operative technique	1.2	1.0–1.5	0.04
Allogenic transfusion	2.9	1.0–8.6	0.04

OR indicates adjusted odds ratio with 95 % confidence interval

occurred first. Univariate and multivariate Cox regression analyses were performed to determine the adjusted hazard ratio (HR) for tumor recurrence and overall survival. Significant statements refer to P values of two-tailed tests that were <0.05.

Results

Characterization of the study population

Out of 714 patients with esophageal resection at our institution between 1992 and 2010, 103 patients had positive resection margins, 13 patients were resected for diseases different from EC, and 33 patients were lost to follow-up or had incomplete data and were therefore excluded from this study. Complete data and follow-up were available from 565 patients. All 565 patients had histopathologically proven EC. None of the patients received neoadjuvant therapy. Distribution according to tumor type (SCC or AC) and operating technique (TH or TA) was balanced among the study population. Median age of the study population was 63.2 years (range 34.5–85.2). Table 1 depicts patient characteristics of the entire study population. Out of 565 patients, 93 (16.5 %) did not receive aBT. Overall perioperative mortality accounted for 14.6 % ($N = 81$) and perioperative morbidity for 34.4 % ($N = 194$) in the entire study population.

Correlation of aBT with clinicopathological parameters and perioperative outcome

Table 1 depicts the result of the correlation of aBT with clinicopathological parameters. Patients requiring aBT had lower median preoperative hemoglobin level and displayed higher intraoperative median blood loss ($P = 0.003$ and <0.001). The median operating time in aBT(+) patients was significantly longer ($P = 0.01$). Interestingly, aBT(+) had not significantly more advanced disease as reflected by tumor size, presence of lymph node metastasis and tumor grading compared to aBT(−) patients ($P = 0.65$, $P = 0.17$ and $P = 0.46$, respectively). However, patients with aBT(+) had significant higher rates of tumor recurrence ($P = 0.001$).

The transfusion of allogenic blood was associated with perioperative outcome in terms of morbidity and mortality. Table 2 depicts the results of the multivariable analysis for perioperative morbidity and mortality. Patients with aBT had an adjusted OR of 1.9 (95 % CI 1.1–3.5, $P = 0.02$) for perioperative morbidity and 2.9 and 95 % CI 1.0–8.6, $P = 0.04$ for perioperative mortality.

aBT and clinical outcome

To verify that our study group was representative for patients with EC, we calculated the OS according to the seventh edition of the Union International Contre le Cancer (UICC). The OS was found to be dependent upon AJCC stage and comparable to the published data by other groups. The median OS was 21.6 months (95 % CI 18.1–25.1). The stage-specific OS for stage I to IV was 47.7, 39.3, 29.1, 20.5 and 7.4 months, respectively. Patients, who died perioperatively, were excluded from the survival analysis. During the observation period, 212 (51.7 %) patients experienced a relapse of the disease and 258 (62.9 %) patients died. Kaplan–Meier curves plotted for DFS and OS showed a marked decrease in survival between aBT(−) and aBT(+) patients (Fig. 1; Table 3).

A stratified sub-analysis for tumor type, nodal status, operating technique and aBT was performed. Table 3 depicts the results of the stratified sub-analyses. Interestingly, throughout all sub-analyses aBT(−) patients displayed a significant better DFS and OS compared to aBT(+) patients.

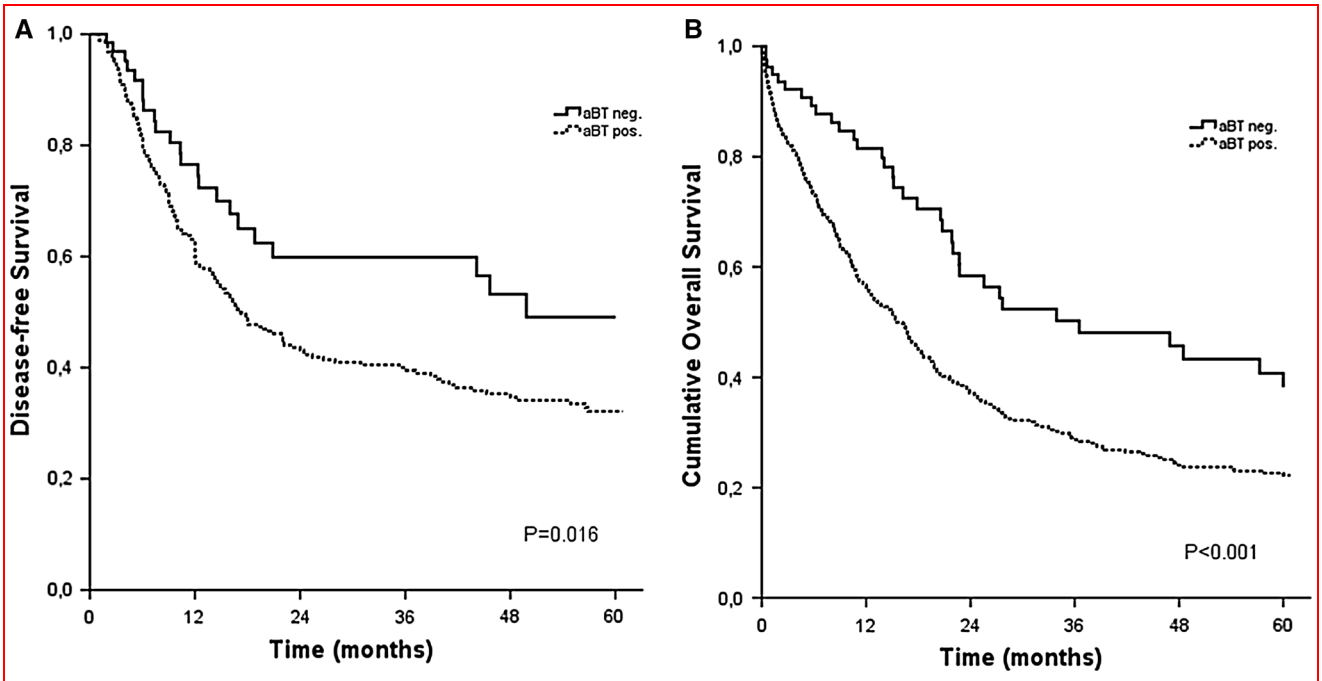

Fig. 1 Kaplan–Meier plots of disease-free (**a**) and overall survival (**b**) in relation to allogenic blood transfusion (aBT). Time period refers to months after surgery

aBT a prognostic factor for recurrence and survival

Multivariable analysis according to the Cox regression hazard model using age, sex, tumor size, presence of lymph node and distant metastasis, tumor grading, tumor type, operating technique and aBT for tumor recurrence and overall survival were performed. Allogenic blood transfusion was strongly associated with recurrence (adjusted HR 1.8, 95 % CI 1.2–2.5, $P = 0.001$) and death (HR 2.2, 95 % CI 1.5–3.2, $P < 0.001$) (Table 4).

Discussion

This study, consisting of 565 homogeneously, surgically, treated patients revealed that aBT is strongly associated with perioperative and long-term outcome in EC patients.

Over the last two decades, aBT has moved into the limelight of being an independent risk factor for morbidity and mortality in non-oncological and oncological patients [5, 14]. Although the attitude toward transfusion has changed, it remains an individual decision. The landmark transfusion requirements in critical care trial (TRICC trial) is the only prospective randomized study reporting on adverse outcome associated with aBT in the liberal group (hemoglobin <10 g/dl) compared to the restrictive group (hemoglobin <7 g/dl) [15]. Importantly, in patients under 55 years a significant association between increased mortality and liberal transfusion attitude was reported. In addition, a recent study demonstrated an association between aBT at young age and increased risk of developing non-Hodgkin lymphoma [16]. These findings not only pinpoint toward the severity of the impact of aBT on short-term outcome but also imply to a long-lasting immune modulatory effect of aBT. These long-lasting effects result in poor clinical outcomes as it has been shown for cardiac and oncological patients [17–20].

Majority of our patients did not suffer of anemia which has been linked to increased morbidity and mortality [21, 22]. Interestingly, Corwin et al. [23] analyzing anemia and blood transfusion in the critically ill reported that anemia only predicted the probability of transfusion but did not correlate with the outcome. Kulier et al. [24] identified preoperative hemoglobin and aBT as independent risk factors for adverse clinical outcome. At the same hemoglobin level, however, risk of adverse outcome increased out of proportion with the number of blood units. In particular, increased risk of infection, prolonged ventilation, cardiovascular events and renal failure have been linked to aBT(+) [25]. These findings support our data, especially as aBT was besides the tumor size the only significant prognostic factor for prediction of perioperative morbidity.

Several studies suggest association between aBT and tumor recurrence and survival in various tumor types [26–29]. The impact of the immune modulation initiated by aBT has first been shown in transplantation where patients

Table 3 Allogenic blood transfusion and survival

	Disease-free survival			Overall survival		
	Median	95 % CI	*P*	Median	95 % CI	*P*
All patients						
Total	14.5	12.6–16.4	<0.001	21.6	18.1–25.1	<0.001
aBT(−)	43.9	25.9–62.0		42.4	37.6–47.2	
aBT(+)	12.0	9.8–14.2		18.0	15.9–20.0	
Lymph node negative patients (N0–M0)						
Total	38.8*	35.2–42.6	0.002	43.3*	39.8–46.8	0.001
aBT(−)	49.5*	43.9–55.2		53.5*	48.9–57.9	
aBT(+)	35.1*	30.7–39.5		39.7*	39.5–46.8	
Lymph node positive patients (N+–M0)						
Total	12.0	9.3–14.7	0.12	17.7	14.5–20.9	0.008
aBT(−)	20.8	13.4–28.4		33.1	23.0–43.0	
aBT(+)	11.0	8.9–13.4		15.4	12.3–18.4	
Transhiatal resection group						
Total	13.6	9.2–18.1	0.04	20.2	16.2–24.2	0.005
aBT(−)	39.9	15.2–64.9		46.9	6.4–87.4	
aBT(+)	11.9	8.5–15.3		16.8	13.6–20.1	
Thoracoabdominal resection group						
Total	15.0	12.1–17.9	<0.001	23.9	18.7–28.9	<0.001
aBT(−)	38.3	31.4–45.2		43.5	37.4–49.6	
aBT(+)	12.3	10.4–14.3		19.5	15.9–23.1	
Squamous cell carcinoma group						
Total	13.2	9.6–16.7	0.002	20.2	16.2–24.3	<0.001
aBT(−)	43.9	27.4–60.5		43.7*	37.3–50.2	
aBT(+)	10.0	8.1–11.9		16.4	12.9–19.7	
Adenocarcinoma group						
Total	15.4	12.3–18.5	0.006	22.9	17.8–28.1	0.006
aBT(−)	35.6*	27.9–43.2		40.9*	3–48.1	
aBT(+)	14.0	11.5–16.6		201	1–23.9	

Median refers to median survival in months with 95 % confidence interval

* Mean survival in months since median was not reached

P indicates significance according to log-rank test

with aBT-induced immunosuppression presented prolonged graft-survival [30]. Allogenic blood transfusion is known to reduce natural killer cell activities and T lymphocyte blastogenesis and increase suppressor T lymphocyte activities [31]. These cells do not only prevent dissemination of circulating and quiescent cancer cells but are also important for resistance toward infection [5]. The aBT-related immune modulation is a sum of preexistent patient characteristics and transfused factors [5]. Interestingly, studies comparing aBT and autoBT underline the association between aBT and poor clinical outcome since patients receiving autoBT have been reported to present significantly better perioperative and long-term outcome in EC compared to patients receiving aBT [8, 12]. The reported role of aBT on perioperative outcome and long-term survival is heterogeneous in EC. Melis et al. [32] correlated the clinical outcome with regard to neoadjuvant treatment, anemia and perioperative complications in patients undergoing esophagectomy for cancer. This study excluded anemia as an independent factor and verified the significance of aBT for prediction of postoperative complications. Infectious complications are more likely in the postoperative course in patients with aBT in contrast to patients receiving autoBT [33]. Furthermore, autoBT is superior over aBT comparing immune response by quantification of circulating immune-competent cells in neoadjuvantly treated patients undergoing resection for EC [12]. Motoyama et al. [8] reported on prolonged DFS in autoBT group in recurrent EC. In contrast to these studies, Nozoe et al. did not identify aBT as an independent

Table 4 Multivariable analysis for recurrence and overall survival

Variables	Recurrence			Overall survival		
	HR	95 % CI	P	HR	95 % CI	P
Age (years)						
≤60 versus >60	1.1	0.9–1.5	0.30	1.1	0.8–1.4	0.54
Sex						
Male versus female	0.8	0.6–1.2	0.30	0.9	0.6–1.2	0.44
Preoperative hemoglobin	1.0	0.9–1.1	0.71	1.0	0.9–1.1	0.36
Tumor size						
pT1 versus pT2	1.6	1.1–2.4	0.02	1.6	1.0–2.4	0.05
pT1 versus pT3	2.2	1.5–3.3	<0.001	2.0	1.3–3.1	0.001
pT1 versus pT4	3.9	2.2–7.1	<0.001	3.4	1.8–6.2	<0.001
Nodal status						
Negative versus positive	2.1	1.5–2.7	<0.001	2.4	1.8–3.3	<0.001
Distant metastasis						
Negative versus positive	2.2	1.6–3.1	<0.001	2.0	1.5–2.9	<0.001
Grading						
G1 versus G2	1.3	0.7–2.5	0.41	1.6	0.8–3.2	0.23
G1 versus G3	1.6	0.8–3.2	0.15	1.9	0.9–4.1	0.08
Tumor type						
SCC versus AC	0.7	0.5–0.9	0.008	0.6	0.5–0.9	0.005
Operative technique						
TH versus TA	1.3	0.9–1.7	0.07	1.2	0.9–1.7	0.15
Allogenic blood transfusion						
Negative versus positive	1.8	1.2–2.5	0.001	2.2	1.5–3.2	<0.001

HR refers to adjusted hazard ratio with 95 % confidence interval

P indicates significance according to Cox regression analysis

prognosticator of survival in EC patients and Ling et al. demonstrated that aBT resulted in poorer survival but white blood cell-depleted blood transfusion did not improve the outcome [7, 34]. Furthermore, Kader et al. [35] were able to demonstrate that aBT had a survival benefit in EC patients treated by radio-chemotherapy only.

In our study, aBT(+) patients demonstrated throughout a poorer outcome compared to aBT(−) patients. This effect remained apparent even after stratification of the study population to the underlying tumor type, disease stage and operating technique. Taken together, these findings indicate an early aBT initiated immune modulatory effect that lasts long. Furthermore, we have been able to demonstrate a prognostic significance of aBT as a marker for perioperative morbidity, mortality and oncological outcome in one large homogenous EC population. Limitation of our study is the retrospective nature and lack of determination of immuno modulatory mediators like CD4, CD8 and natural killer cells or interleukin levels and incorporation of these factors in our comparative analysis.

In conclusion, we were able to demonstrate an association between aBT and morbidity, mortality, tumor recurrence and overall survival in a homogeneously, only surgically, treated EC population. The findings warrant an urgent re-evaluation of the current attitude toward aBT to improve the unsatisfying perioperative and long-term outcome in EC patients.

Compliance with ethical standards

Conflict of interest None.

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