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ORIGINAL ARTICLE

The effect of intra- and postoperative allogenic blood transfusion on patients' survival undergoing radical cystectomy for urothelial carcinoma of the bladder

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Abstract
Purpose Radical cystectomy (RC) can be associated with significant blood loss. Allogenic blood transfusion (ABT) may alter disease outcome because of a theoretical immunomodulatory effect. We evaluated the effects of ABT on overall survival (OS) and progression-free survival (PFS) of patients undergoing RC for urothelial carcinoma of the bladder (UCB).
Materials and methods This is a retrospective single-center study of 350 consecutive patients of a university health center with a median follow-up of 70.1 month. All patients underwent RC and pelvic lymph node dissection. The effect of ABT on OS and PFS was analyzed using univariable and multivariable Cox proportional hazards models.
Results The overall ABT rate was 63 % ($n = 219$), with intraoperative blood transfusion and postoperative blood transfusion being performed in 183 patients (52 %) and 99 patients (28 %), respectively. Preoperative anemia was detected in 156 patients (45 %) with median estimated blood loss of 800 ml (IQR: 500–1,200). ABT was associated with significant decrease of OS and PFS in multivariable analyses ($p < 0.001$), whereas patients' prognosis worsened the more packed red blood cells (PRBC) were transfused ($p < 0.001$). The study is limited in part due to its retrospective design.
Conclusions We found that ABT and the number of PRBC transfused are associated with poor prognosis for UCB patients undergoing RC, whereas preoperative anemia had no influence on survival. This emphasizes the importance of surgeon's awareness for a strict indication for ABT. A prospective study will be necessary to evaluate the independent risks associated with ABT during surgical treatments.

Keywords Urothelial carcinoma · Cystectomy · Blood · Transfusion

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Introduction

Radical cystectomy (RC) is associated with prevailing morbidity rate as high as 28–32 %. Blood loss as a specific potential complication of this major surgical procedure leads to a high prevalence of allogenic blood transfusion (ABT) particularly with many patients starting the operation with anemia [1, 2]. Besides, the need for transfusion could be an indicator of other prognostic factors that are difficult to quantify, such as tumor extension and tumor dissection, the surgeons' skill, and the nutritional state of the patient [3].

Allogenic blood transfusion (ABT) is among autologous blood transfusion, preoperative recombinant erythropoietin injection, intraoperative hemodilution, and intraoperative cell salvage, one of the most common methods of blood volume management [4, 5]. Nevertheless, there are risk factors of ABT as transmission of infection, immune reactions, and blood type incompatibility [6]. Additionally in 1981, the nephrologists Clarence C. Gantt hypothesized that allogenic blood transfusion (ABT) may influence the immune system leading to poorer patients' prognosis [7]. Several previous reports attested the effect of blood transfusion in various cancers including breast, lung, colorectal, and prostate cancer [3, 8–10]. But the results have not always been conclusive with other studies not demonstrating a negative influence of blood transfusions [11].

Despite the common use of ABT in patients undergoing RC for bladder cancer, evaluation of the effects of ABT on overall survival (OS) and progression-free survival (PFS) has not been well studied. Therefore, we evaluated this influence on our consecutive patients series by including established histopathological and clinical criteria among others preoperative anemia and patient comorbidities.

Materials and methods

Study group and criteria under investigation

This was an institutional review board approved study providing the necessary institutional data before initiation of the study. A computerized database was compiled for data transfer. In this single-center study, we retrospectively included 350 consecutive patients (82 % men and 18 % women) of a university health center undergoing RC with pelvic lymph node dissection (PLND) for urothelial carcinoma of the bladder (UCB) between March 1995 and April 2010. From all patients, complete data about ABT must be available. Clinical and pathological staging was performed according to the WHO 2002 TNM classification; tumor grade was assessed according to the 1973 WHO/ISUP consensus classification [12, 13]. Genitourinary pathologists also reviewed all histopathologic slides.

In all patients involved, the indication to perform RC was muscle invasive bladder cancer and recurrent high-risk non-muscle invasive bladder cancer. RC was performed by several surgeons according to standard criteria for RC with bilateral PLND. No patient underwent neoadjuvant chemotherapy or radiotherapy prior to surgery. Recent clinical and pathological follow-up data were obtained for retrospective analysis of this patient population. ABT was arranged by transfusing packed red blood cells (PRBC). Differentiation in intraoperative and postoperative blood transfusion (IBT and PBT) was performed, whereas IBT is defined as ABT during the surgical treatment and PBT as time of transfusion up until 10 days after RC.

Preoperative blood transfusion (POBT) occurred very rarely (2 patients received 2 PRBC, 3 patients received 3 PRBC). All 5 patients with POBT received either IBT or PBT in the following and were therefore assigned to those subgroups. Intraoperative cell salvage as a blood management strategy was not performed. The decision to administer a blood transfusion was made on a case-by-case basis by the attending urologist and/or anesthesiologist. In all patients, general anesthesia was performed. Preoperative anemia was defined as hemoglobin levels of <13 and <12 g/dl in men and women, respectively [14]. Low molecular weight heparin was administered in weight-adapted dose to every patient as part of the standard perioperative pathway over a period of 4 weeks after operation unless specifically contraindicated. Clinical parameters included in the analysis were age, gender, ASA classification (physical status classification system of the American Society of Anaestesiologists), Charlson comorbidity index (CCI) [15], body mass index (BMI), and blood loss during operation (BL). Within the scope of histopathological parameter, we included pT stage, pN stage, and R status. R1 status equalizes a positive surgical margin (PSM), which was defined as tumor cells at the color stained edge of the RC specimen. R2 status was determined as macroscopic residual tumor mass after RC, whereas R0 status implicates no residual tumor [16].

The median follow-up time for patients was 70.1 months. All patients classified as having died of bladder cancer had progressive and often widely disseminated disease. Patients were censored at the date of last follow-up up to April 2010.

Statistical analysis

Continuous variables are presented as median values and interquartile range (IQR). Categorical variables are presented as absolute numbers and proportions. Median follow-up time was estimated using the reverse Kaplan–Meier method. Overall survival (OS) was calculated from the date of RC to the date of death. Progression-free survival (PFS) was calculated from the date of RC to the date of progression or death of any cause. Patients with no event (death or progression) until end of the study or patients lost to follow-up were classified as censored. Univariable and multivariable analyses (Cox proportional hazards regression model) were performed to assess the influence of several clinical and pathological parameters on the endpoints (PFS and OS). To avoid multicollinearity between predictor variables in the multivariable model, the variance inflation factor (VIF) for each variable was calculated. A VIF > 2.5 was considered as an indicator for multicollinearity problems.

In all models, proportional hazards' (PH) assumptions were verified using the Grambsch-Therneau residual-based test. It was applied by the *R* procedure called *cox.zph* (library: *survival*), while a p value <0.05 counted as a violation. If a covariable violated the PH assumption and seemed to be time-dependent, a time*covariate "interaction" was added to the model. In the case of significance, the interaction was left in the model [17].

Since no imputation methods for missing values were used, the multivariable model contains only patients with full data sets according to the predictive variables. A two-sided p value of less than 0.05 was considered to indicate statistical significance. Hazard ratios (HR) and corresponding 95 % confidence intervals (CI) were calculated and considered statistically significant if CI excluded 1.0. All analyses were performed with the use of *SPSS* 19.0 and *R* (version 2.14.2) using the package *survival*.

Results

In Table 1, the descriptive characteristics of the patients are listed. From 350 patients undergoing RC, 287 (81.7 %) were male and 63 (18.3 %) female, respectively. The overall ABT rate was 63 % ($n = 219$), whereas IBT and PBT were performed in 183 patients (52 %) and 99 patients (28 %), respectively. 63 patients (18 %) sustained both IBT and PBT. The median number of PRBC transfused was 1 (IBT:IQR 0:2; range from 0 to 7 PRBC) and 0 (PBT: IQR 0; 1; range from 0 to 8 PRBC), whereas median estimated blood loss was 800 ml (IQR: 500–1200). Preoperative anemia was detected in 156 patients (45 %).

We found significant differences in patients with pT3 or pT4 stage compared to those of patients with T0, Ta, Tis, and T1 stage receiving less PRBC. Figure 1 presents the corresponding Kaplan–Meier survival curves with correlation of progression-free survival (a) and overall survival (b), and number of PRBC of 350 patients receiving intra- and/or postoperative allogenic blood transfusion. Both OS and PFS decrease by the number of PRBC transfused. This result is confirmed by the univariable Cox regression analysis with highly significant data (Table 2). In the univariable model, age, BMI, ASA score, CCI, pT stage, pN stage, R status, IBT, PBT, and preoperative anemia were associated with worse OS and PFS. Intraoperative blood loss and gender had no influence on OS and PFS.

In the multivariable Cox regression models (Table 2) with intraoperative and postoperative blood transfusion identified as time-dependent covariables, patients' prognosis worsened the more PRBC were transfused (HRs between 1.52 and 1.82, $p < 0.001$), while the interaction terms (HRs between 0.85 and 0.93, $p < 0.001$) indicate a time decreasing influence of PRBC. There is a significant impact on OS and PFS for IBT and PBT, patients' age, pT stage, pN stage, and ASA score. R status, CCI, and a preoperatively existing anemia could no longer exert their influence.

Discussion

Several published reports of patients with solid tumor malignancies undergo cancer surgery raised concerns about an adverse effect of blood transfusion on outcome and survival including gastrointestinal cancer, head and neck cancer, lung, and breast cancer [18–21]. This is one of the first studies to address this effect of ABT on patients with UCB undergoing RC.

As one of our main findings, we confirm IBT and PBT having an independent influence on PFS and OS. Furthermore anemia was preoperatively detected in approximately half of the patients included in this study, which may raise the question of correcting this anemia before surgery. ASA score and pN stage are discrete risk factors on postoperative outcome after RC.

One prior study by Morgan et al. [22] in bladder cancer patients, which was limited by its methodology, found that perioperative blood transfusion for bladder cancer was associated with an increased mortality risk in the univariable and the multivariable models. But results of studies for other tumor entities applied in surgical literature have been contradicting. For patients with prostate cancer, for example some studies could demonstrate an independent influence of blood transfusion on survival whereas others found no correlation in their patient cohort [18, 21, 23]. That emphasizes the importance of further comparable studies for UCB. Besides, there is always the central question whether a deleterious immunomodulatory effect is, as proposed, present or whether these effects are related to other confounding variables [24]. Therefore, multivariable models including physical status classification (e.g., ASA score, CCI), age, tumor stage, information about preoperatively existing anemia, and intraoperative blood loss are outstanding for studies with retrospective assessment with all these variables being included in our study.

We additionally found a correlation of the number of PRBC transfused and tumor stage. Patients with advanced tumor stage received consequently more PRBC. This leads us to assume that more complex surgical situations and an all in all worse initial situation of the patient goes along with a higher transfusion rate. We draw a distinction between IBT and PBT to overhaul whether there is a different influence on PFS and OS when blood transfusion was performed during operation or during a ten day period after surgery. In this connection, no difference was found with both variables exhibit an influence on PFS and OS. Even

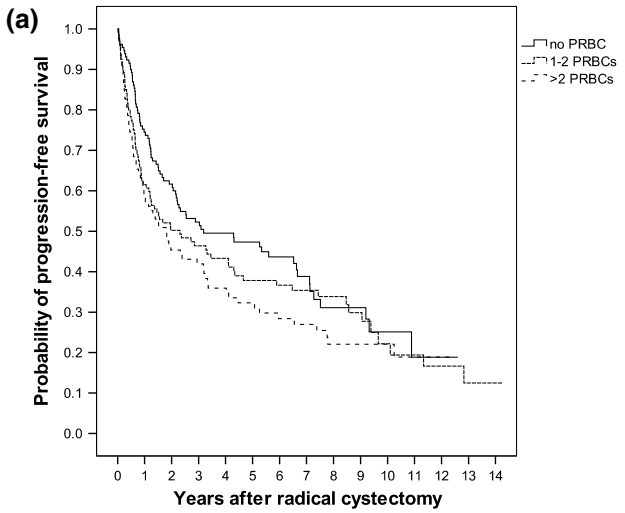
Table 1 Patient characteristics of the 350 patients who were treated with radical cystectomy with lymph node dissection

	All ($n = 350$)	Transfusions		p value
		No ($n = 113$)	Yes ($n = 219$)	
Age (years), median (IQR)	68 (61–74)	68 (58–74)	68 (62–74)	0.10
BMI, median (IQR)	26.6 (24.1–29.1)	26.8 (24.2–29.3)	26.3 (24.1–29.0)	0.58
Sex (*N* %)				
Male	287 (82 %)	118 (90 %)	169 (77 %)	0.002
Female	63 (18 %)	13 (10 %)	50 (23 %)	
ASA classification (*N* %*)				
I	61 (17 %)	23 (18 %)	38 (17 %)	0.21
II	157 (45 %)	66 (50 %)	91 (42 %)	
III	123 (35 %)	40 (31 %)	83 (38 %)	
IV	2 (1 %)	0 (0 %)	2 (1 %)	
pT stage (*N* %*)				
T0, Ta, Tis, T1	122 (35 %)	50 (38 %)	72 (33 %)	0.025
T2	60 (17 %)	29 (22 %)	31 (14 %)	
T3	110 (31 %)	38 (29 %)	72 (33 %)	
T4	58 (17 %)	14 (11 %)	44 (20 %)	
Charlson index (*N* %*)				
2	171 (49 %)	70 (53 %)	101 (46 %)	0.08
3	100 (29 %)	46 (35 %)	54 (25 %)	
4	46 (13 %)	12 (9 %)	34 (16 %)	
≥5	17 (5 %)	2 (2 %)	15 (7 %)	
R status (*N* %)				
*R*0 (no residual tumor)				
*R*1 (microscopic residual tumor, PSM)	304 (87 %)	121 (92 %)	183 (84 %)	0.021
*R*2 (macroscopic residual	40 (11 %)	10 (8 %)	30 (14 %)	
tumor)	5 (1 %)	0 (0 %)	5 (2 %)	
pN stage (*N* %)				
pN0	233 (67 %)	97 (74 %)	136 (62 %)	0.018
pN1	47 (13 %)	15 (12 %)	32 (15 %)	
pN2	52 (15 %)	13 (10 %)	39 (18 %)	
pN3	3 (1 %)	1 (1 %)	2 (1 %)	
Urinary diversion (*N* %*)				
Ileal neobladder	135 (39 %)	69 (53 %)	66 (30 %)	<0.001
Ileal conduit	170 (49 %)	52 (40 %)	118 (54 %)	
Indiana pouch	22 (6 %)	6 (5 %)	16 (7 %)	
Cutaneous ureterostomy	11 (3 %)	1 (1 %)	10 (5 %)	
Preoperative anemia ($m < 13$ g/dl, $w < 12$ g/dl), (*N* %*)				
Blood loss (ml), median (IQR)	156 (45 %)	43 (33 %)	113 (52 %)	0.001
IQR: interquartile range (p25–p75)	800 (500–1,200)	600 (400–1,000)	1,000 (500–1,400)	<0.001

%* Do not add up to 100 % due to occasional missing values

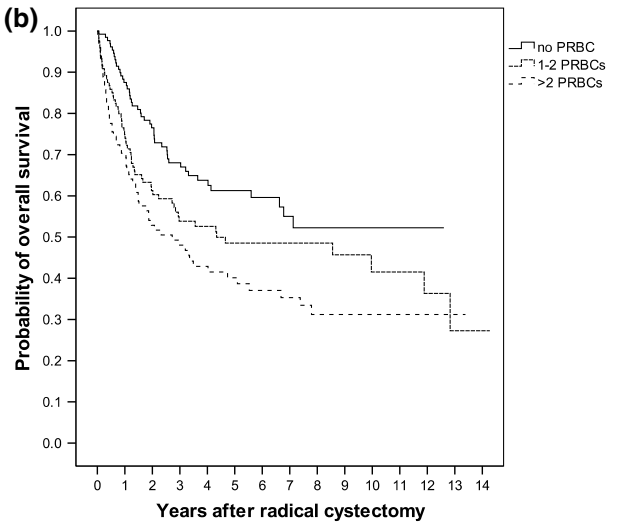
if the median follow-up period of our study is accurate, the possibility remains that patients may have also received blood transfusions prior surgery or after our observation period of ten days post RC with those data not being available. Nevertheless by means of our statistical analysis, we found that patients' prognosis worsened the more PRBC were transfused and that there is a decreasing influence of PRBC on survival the longer the patient was without an event. Thus, the time of transfusion post surgery seems to influence prognosis.

Our data to patients with preoperative anemia are comparable to other studies [2]. But still estimated blood loss does frequently not reflect the factual blood loss, and operative blood loss can influence possible effects of blood transfusion on survival. In our multivariable model, preoperative anemia does not adversely effect patients'



No PRBC vs 1-2 PRBCs: p=0.225
No PRBC vs >2 PRBCs: p=0.035
1-2 PRBCs vs >2 PRBCs: p=0.387

OS	Patients under risk / cumulative events						
	0y	2y	4y	6y	8y	10y	12y
No PRBC	131/0	74/49	50/63	30/68	14/75	8/77	2/78
1-2 PRBC	120/0	55/59	40/66	29/72	22/74	8/79	6/81
>3 PRBC	99/0	41/53	30/61	20/67	13/71	7/71	2/72



No PRBC vs 1-2 PRBCs: p=0.037
No PRBC vs >2 PRBCs: p<0.001
1-2 PRBCs vs >2 PRBCs: p=0.128

OS	Patients under risk / cumulative events						
	0y	2y	4y	6y	8y	10y	12y
No PRBC	131/0	84/29	53/42	30/45	15/48	10/48	3/48
1-2 PRBC	120/0	62/45	41/53	30/56	23/56	10/58	7/59
>3 PRBC	99/0	45/45	32/53	22/57	14/60	8/60	3/60

Fig. 1 Kaplan–Meier survival functions, log rank test and patients under risk/cumulative events. Correlation of progression-free survival **a** and overall survival **b**, and number of PRBC of 350 patients receiving intra- and/or postoperative allogenic blood transfusion

outcome. Moreover red blood cell resources can be saved without increasing the patients' risk of postoperative cardiac events [26]. This has a lot to comment for restrictive indications for blood transfusions even in patients with anemia.

As is generally known, static risk factors associated with postoperative morbidity after RC include for example increasing patient age and an ASA score of 3 or greater [25]. Furthermore a higher ASA score is associated with an increased overall hospital stay and more in-hospital complications [26]. We confirm patient age and high ASA score classification as discrete risk factors on postoperative outcome after RC. Still, ASA score as a validated approach for classifying comorbid conditions and as a predictor of postoperative mortality is limited and can be adulterated by leaving the possibility that other unheeded variables may bias the results. The CCI improves the prediction of perioperative mortality <90 days after RC. Nevertheless, the ASA score is superior to the CCI for estimating perioperative mortality [27]. In a study population of 1,121 patients, Koppie et al. [28] showed that OS, but not PFS, is significantly associated with the age-adjusted CCI, whereas CCI in our study could exert its influence on OS and PFS only in the univariable model.

There are a number of other limitations in our study. Due to the retrospective study design, unidentified confounding variables may have been present but not accounted for in multivariable analyses. Adjuvant chemotherapy and postoperative complications were not considered. Besides, estimated blood loss at surgery has a key role in the transfusion requirement but still has to be improved [2]. Therefore, it does not fully disassociate the potential effect of transfusion on survival from any potential effect due to operative

Table 2 Univariable ($n = 350$) and multivariable ($n = 279$) Cox regression of PFS and OS of patients treated with radical cystectomy with pelvic lymph node dissection

Prognostic factor	Progression-free survival				Overall survival			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Age (per decade)	1.40 (1.20; 1.62)	<0.001	1.31 (1.07; 1.60)	0.008	1.74 (1.45; 2.08)	<0.001	1.64 (1.28; 2.10)	<0.001
BMI	0.96 (0.93; 0.99)	0.016	0.99 (0.96; 1.02)	0.54	0.96 (0.93; 1.00)	0.047	0.99 (0.95; 1.03)	0.61
pT stage								
T0, Ta, Tis, T1	Referent							
T2	1.38 (0.90; 2.13)	0.14	1.28 (0.79; 2.07)	0.31	1.40 (0.81; 2.45)	0.23	1.29 (0.69; 2.38)	0.42
T3	4.26 (3.03; 5.99)	<0.001	2.45 (1.60; 3.76)	<0.001	4.75 (3.12; 7.24)	<0.001	2.68 (1.59, 4.50)	<0.001
T4	5.98 (3.99; 8.95)	<0.001	2.07 (1.11; 3.86)	0.023	8.18 (5.08; 13.16)	<0.001	1.80 (0.81; 4.00)	0.15
ASA score								
I and II	Referent							
III and IV	1.59 (1.21; 2.08)	0.001	1.45 (1.03; 2.05)	0.035	2.22 (1.63; 3.03)	<0.001	1.70 (1.13; 2.56)	0.01
CCI								
2	Referent							
3	1.10 (0.81; 1.49)	0.55	0.71 (0.49; 1.03)	0.07	1.38 (0.96; 1.98)	0.09	0.71 (0.45; 1.12)	0.71
4	1.26 (0.85; 1.89)	0.25	0.97 (0.59; 1.59)	0.90	1.84 (1.18; 2.87)	0.007	1.15 (0.66; 2.03)	0.62
≥5	1.78 (1.02; 3.12)	0.043	1.07 (0.50; 2.29)	0.86	2.06 (1.06; 4.01)	0.034	1.12 (0.47; 2.66)	0.81
Blood transfusions (no vs. yes)	1.30 (0.99; 1.71)	0.059			1.71 (1.23; 2.40)	0.002		
IBT								
Number of PRBC	1.86 (1.67; 2.06)	<0.001	1.50 (1.27; 1.77)	<0.001	2.11 (1.87; 2.38)	<0.001	1.77 (1.47; 2.13)	<0.001
Number of PRBC*time (years)	0.84 (0.81; 0.87)	<0.001	0.90 (0.87; 0.94)	<0.001	0.80 (0.75; 0.84)	<0.001	0.85 (0.80; 0.90)	<0.001
PBT								
Number of PRBC	1.65 (1.49; 1.83)	<0.001	1.56 (1.30; 1.88)	<0.001	1.80 (1.60; 2.02)	<0.001	1.76 (1.41; 2.21)	<0.001
Number of PRBC*time (years)	0.84 (0.79; 0.88)	<0.001	0.88 (0.84; 0.94)	<0.001	0.83 (0.78; 0.88)	<0.001	0.86 (0.79; 0.93)	<0.001
R status								
R0	Referent							
R1 or R2	3.34 (2.36; 4.72)	<0.001	1.72 (0.98; 3.01)	0.06	3.94 (2.69; 5.77)	<0.001	1.84 (0.94; 3.61)	0.078
Pathological N Stage								
pN0	Referent							
pN1	2.69 (1.89; 3.82)	<0.001	1.60 (1.04; 2.46)	0.034	2.89 (1.92; 4.35)	<0.001	1.72 (1.04; 2.87)	0.036
pN2	3.90 (2.74; 5.56)	<0.001	1.67 (1.04; 2.68)	0.034	4.98 (3.35; 7.40)	<0.001	1.95 (1.13; 3.37)	0.017
pN3	5.04 (1.59; 15.95)	0.006	2.45 (0.74; 8.12)	0.14	2.80 (0.69; 11.41)	0.15	1.23 (0.28; 5.38)	0.79
Lymph node density (per 10 %)	1.26 (1.19; 1.33)	<0.001			1.31 (1.24; 1.39)	<0.001		
Lymphovascular invasion	3.63 (2.74; 4.80)	<0.001			4.08 (2.92; 5.70)	<0.001		
Urinary diversion								
Ileal neobladder	Referent							
Ileal conduit	2.30 (1.71; 3.08)	<0.001	1.03 (0.69; 1.53)	0.90	3.81 (2.59; 5.61)	<0.001	1.14 (0.69; 1.88)	0.61
Indiana pouch	0.97 (0.53; 1.76)	0.92	1.34 (0.64; 2.81)	0.44	1.31 (0.60; 2.83)	0.50	1.84 (0.74; 4.56)	0.19
Cutaneous ureterostomy	2.04 (1.01; 4.09)	0.046	–	–	4.14 (1.91; 8.96)	<0.001	–	–
Preoperative anemia	1.58 (1.21; 2.07)	0.001	1.05 (0.76; 1.46)	0.76	1.85 (1.35; 2.53)	<0.001	1.15 (0.77; 1.70)	0.49

HR hazard ratio, *95 % CI* 95 % confidence interval

blood loss. Furthermore, blood transfusion may have been performed prior to operation with no available data for analyses. No uniform transfusion guidelines were applied for indication of blood transfusion. Of course, it is possible that additional statistical modeling and further scrutiny could confute or reinforce our results.

Conclusions

Considering the surgical literature influence of allogenic blood transfusion on mortality of patients with solid tumor malignancies remains contradicting. Nevertheless, in long-term follow-up, we found an apparent worse prognosis for patients who received allogenic blood transfusion undergoing radical cystectomy. This emphasizes the importance of surgeons' and anesthesiologists' awareness for a strict indication for allogenic blood transfusion. Only a prospective study could evaluate the independent risks associated with allogenic blood transfusion during surgical treatments.

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Conflict of interest All authors declare that no conflict of interest exists.

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