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The relationship between perioperative blood transfusion and overall mortality in patients undergoing radical cystectomy for bladder cancer

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Abstract

Objectives—The relationship between perioperative blood transfusion (PBT) and oncologic outcomes is controversial. In patients undergoing surgery for colon cancer and several other solid malignancies, PBT has been associated with an increased risk of mortality. Yet, the urologic literature has a paucity of data addressing this topic. We sought to evaluate whether PBT affects overall survival following radical cystectomy (RC) for patients with bladder cancer.

Methods—The medical records of 777 consecutive patients undergoing RC for urothelial carcinoma of the bladder were reviewed. PBT was defined as transfusion of red blood cells during RC or within the postoperative hospitalization. The primary outcome was overall survival. Clinical and pathologic variables were compared using chi-squared tests, and Cox multivariate survival analyses were performed.

Results—A total of 323 patients (41.6%) underwent PBT. In the univariate analysis, PBT was associated with increased overall mortality (HR 1.40, 95% CI 1.11–1.78). Additionally, an independent association was demonstrated in a nontransformed logistic regression model (HR, 95% CI 1.01–1.36) but not in a model utilizing restricted cubic splines (HR 1.03, 95% CI 0.77–1.38). The c-index was 0.78 for the first model and 0.79 for the second.

Conclusions—In a traditional multivariate model, mirroring those that have been applied to this question in the general surgery literature, we demonstrated an association between PBT and overall mortality after RC. However, this relationship is not observed in a second statistical model. Given the complex nature of adequately controlling for confounding factors in studies of PBT, prospective study will be necessary to fully elucidate the independent risks associated with PBT.

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Keywords

Bladder Cancer; Cystectomy; Transfusion; Blood

Introduction

The risks and benefits of blood transfusions are complex and poorly understood. While the infectious risks of transfusion are rare and well described, other potential complications are still being characterized[1]. For example, transfusion-associated lung injury (TRALI)—the most common cause of transfusion-related mortality in the United States (U.S.)—was recognized relatively recently[2]. In addition, a number of large trials have identified detrimental effects from liberal compared to restrictive transfusion strategies in critically ill patients[3–5]. These and other studies in the critically ill have consistently found blood transfusions to be independently associated with adverse outcomes.

A great deal of attention over the past 30 years has centered on whether perioperative blood transfusion (PBT) in cancer patients impacts survival. Studies have predominantly been focused on general surgery patients, and most have supported an independent association between PBT and worse survival in those with solid tumor malignancies. PBT has been independently associated with mortality in patients undergoing surgery for gastric cancer, hepatocellular carcinoma, lung cancer, and colorectal cancer [6–9]. Despite the frequent use of PBT in patients undergoing radical cystectomy (RC), the impact of PBT on overall survival in these patients has not been well studied. With over 70,000 new diagnoses and an estimated 10,000 radical cystectomies performed annually in the U.S., there is a continued need to identify factors that may affect long-term survival in these patients[10]. In this single-institution study, we sought to evaluate the relationship between PBT and overall survival in patients undergoing RC for bladder cancer.

Patients and Methods

We performed a retrospective cohort study of 905 consecutive patients who underwent RC at Vanderbilt University Medical Center (VUMC) from 2000–2008. High volume Urologic Oncologists performed all surgeries, and pathologic specimens were evaluated by a staff surgical pathologist and staged according to the 2002 AJCC guidelines. Clinical, pathological, and outcome data were collected prospectively and were supplemented by review of the medical records. Institutional Review Board approval was obtained for the creation of a prospective database and for retrospective analysis of this patient population. We excluded patients who underwent cystectomy for non-urothelial carcinoma (n=81) or for salvage therapy after radiation (n=12). There were 12 patients who received intraoperative cell salvage (autologous transfusion) and these patients were also excluded from the present analysis. Complete data were available from 777 of the remaining 800 patients, and these patients represented our analytic cohort.

PBT was defined as transfusion of packed red blood cells (PRBCs) either intraoperatively or up until the time of discharge from the hospitalization immediately following RC. Rarely, patients received a transfusion prior to RC, and these were also considered perioperative transfusions if they were administered during the same hospitalization as the RC. The median time to discharge was 6 days (IQR 5–7 days). Transfusion of other blood products, including fresh frozen plasma or platelets, was not included in this analysis. Per routine blood bank protocol, PRBCs were separated from whole blood and stored in anticoagulant solution. Prestorage leukodepletion of PRBCs was standard at VUMC throughout the time period of this study. The decision to administer a blood transfusion was made on a case-by-

case basis by the attending urologist and/or anesthesiologist. During the time period of the study, there were no standardized intra-operative and post-operative transfusion thresholds. All patients received low molecular weight heparin as part of the standard perioperative pathway unless specifically contraindicated.

Covariates, including age, sex, race, smoking status, preoperative hematocrit, Charlson comorbidity index (CCI), pathologic stage, pathologic cell type (pure vs. mixed urothelial carcinoma), margin status, neoadjuvant chemotherapy, estimated blood loss, and lymph node density, were obtained through patient charts. Vital status was ascertained through the VUMC cancer registry, the Social Security Death Index, and patient charts. Patients were censored at the date of last follow-up or death up to August 1, 2009.

Statistical analysis

Baseline and pathologic characteristics were compared across groups (transfused vs. not transfused) using Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables. Overall survival was compared between groups using Kaplan-Meier analysis with log-rank statistics. Estimates of 3-year overall survival with 95% confidence intervals were compared according to the number of units transfused.

To model the relationship between transfusion and survival, we used Cox proportional hazards models, adjusting for factors known to influence survival and/or confound the relationship between transfusion and survival. Specifically, we controlled for age, CCI, gender, race, pathologic stage, node density, surgical margin status (positive urothelial or soft tissue margins), preoperative hematocrit, and estimated blood loss. In the first model, we entered continuous variables without transformation or categorization. This is the most commonly utilized methodology for this type of analysis because of its simplicity and ease of interpretation. However, this method has the limitation of assuming that there is a linear relationship between each continuous independent variable and the outcome and may give more weight to extreme or outlying values. Thus, we also constructed a second model using a technique known as restricted cubic splines[11]. Splines allow for non-linear relationships between continuous variables and the outcome by creating a number of “hinge points” along the continuous variable, where the slope of the line relating the two variables can change. The concordance indices were assessed as a measure of the accuracy of the two models, and bootstrap analysis with 200 resamples was performed for validation. All statistical analyses were conducted using Stata software, Version 11 (Stata, Inc., College Station, TX) and R version 2.10.1 (R Development Core Team, 2008).

Results

Out of the 777 patient cohort, a total of 323 patients (41.6%) underwent PBT. The median overall follow-up was 25.0 months (IQR 11.7–46.5 months). Among those still alive at their last follow-up, there was a significant difference in median follow-up between transfused and non-transfused patients (31.8 vs. 41.0 months, $p=0.001$). The median patient age was 69.5 years (IQR 61.7–75.9 years), and transfused patients were significantly older than non-transfused patients (71.9 vs. 67.4 years, $p<0.001$). Additionally, transfused patients were more likely to be female, have a higher CCI, higher pathologic tumor and nodal stage, and have positive margins at RC (Table 1).

At the time of this analysis, there have been 300 deaths (39%). In the univariable Cox proportional hazards model, patients who underwent PBT had a significantly increased risk of mortality compared to those who did not undergo PBT (HR 1.40 per 2 transfused units, 95%CI 1.11–1.78). The probability of survival at three years was significantly worse with increasing numbers of transfused units ($p<0.001$): 66% (95%CI 61–71%, $n=454$) for 0 units,

60% (37–77%, n=30) for 1 unit, 54% (45–62%, n=155) for 2 units, 49% (30–66%, n=37) for 3 units, 59% (43–72%, n=55) for 4 units, and 38% (22–53%, n=46) for 5 or more units transfused. These results are shown graphically in Figure 1 and Figure 2.

In order to assess for an independent association between PBT and overall mortality, two multivariable models were constructed. The first was a standard Cox proportional hazards model, in which continuous variables were assumed to have linear relationships with the outcome and were thus entered without categorization or transformation. This model parallels the current literature on the relationship between PBT and recurrence or survival after cancer surgery. In this model (Table 2), there appeared to be a significant mortality risk associated with PBT after adjusting for age, sex, race, preoperative hematocrit, comorbidity, pathologic stage, node density, margin status, and estimated blood loss (HR 1.17, 1.01–1.36). That is, for every 2 units transfused, there was a 17% increase in the risk of mortality. We then constructed a second Cox proportional hazards model using restricted cubic splines to allow for nonlinear relationships between the continuous independent variables and the outcome (Table 2). The use of restricted cubic splines attenuated the effect of PBT on overall mortality, and PBT was no longer a significant independent predictor of overall mortality (HR 1.03, 0.77–1.38). Evaluation of the fit of each model revealed bootstrap-adjusted c-indices of 0.78 for the nontransformed model and 0.79 for the transformed model.

Discussion

To our knowledge, this is the first large-scale study to address the impact of allogeneic PBT on overall survival in patients with bladder cancer treated with RC. In this study, we found an increased mortality risk associated with PBT in the univariable model and in a multivariable model in which continuous independent variables were included without transformation or splines. The nontransformed model mirrors those that have been applied in the general surgery literature to study the relationship between PBT and outcomes after cancer surgery[6, 12]. These data add support to the literature implicating PBT as an independent predictor of decreased overall survival in patients with solid tumor malignancies. However, a significant association was not observed when restricted cubic splines were used for continuous variables.

The impact of PBT on survival in patients undergoing cancer surgery continues to be controversial. In patients with urologic malignancies, there have been few studies addressing the impact of PBT, and most have addressed outcomes other than overall survival. Several studies have evaluated the association between PBT and biochemical recurrence following radical prostatectomy for prostate cancer. These reports have generally found no increase in recurrence risk secondary to transfusion, although the number of events in these studies implies they may be underpowered for the primary endpoint[13–16]. Studies of PBT in other urologic malignancies are scarce. In a study of patients who underwent nephrectomy for renal cell carcinoma, PBT had no independent impact on overall survival[17]. One prior study in bladder cancer was limited by its methodology and small cohort size and another assessed intraoperative cell salvage, reporting no increased risk of metastasis or death in patients who underwent autologous blood transfusion during RC[18, 19].

In contrast to these studies, the majority of reports in the general surgery literature evaluating patients with solid tumor malignancies undergoing cancer surgery have found an independent adverse effect of PBT on survival. However, a question that is central these studies—as well as our report here—is the ability to adequately and accurately control for relevant confounding variables. A positive univariable association between PBT and mortality may be present in most investigations of surgical outcomes where transfusion rates are high. Increased transfusion rates may be indicative of a number of poor prognostic

features such as increased age, surgical complexity, adverse tumor pathology, and possibly surgical expertise. These factors make a retrospective assessment of the impact of PBT challenging and necessitate the construction of well-controlled multivariable models.

The rationale for a potential relationship between PBT and mortality in cancer patients has been well described[20]. An immunosuppressive effect of PBT, initially appreciated in studies of renal transplantation and also observed in patients with Crohn's disease, may lead to decreased tumor surveillance[21, 22]. Known effects of allogeneic transfusion include down-regulation of antigen presenting cells and T cells as well as impaired macrophage and natural killer cell function[20]. Animal studies have suggested that at least some of the immunosuppressive effect is mediated by donor leukocytes, and the tumor promoting properties of allogeneic blood can be abrogated by leukoreduction of the donor blood[23]. Notably, leukoreduction of donor blood has become commonplace in the U.S. and was standard at our center during the time period of this study. It is impossible to ascertain from the present analysis whether leukoreduction was a contributing factor to the findings here. Another mechanism proposed to explain a negative impact of PBT on overall survival is the delivery of growth factors present within red cells. Vascular endothelial growth factor (VEGF), fibroblastic growth factor (FGF), and epidermal growth factor (EGF) have all been shown to accumulate in stored blood and may promote tumor growth after transfusion[24].

Numerous retrospective studies suggest an association between PBT and mortality in general surgery patients.[7–9, 25–27] Ojima and colleagues found that PBT independently increased the risk of overall mortality by a factor of 2.7 in patients undergoing curative gastrectomy for gastric cancer, and others have reported a 3% increased mortality risk per transfused unit in patients undergoing liver resection for hepatocellular carcinoma[7, 8]. Another study of patients with hepatocellular carcinoma found a 2-fold increased mortality risk associated with PBT[9]. Retrospective studies of PBT in patients with colon cancer are multiple, and hazard ratios for mortality well over two have been reported[26, 27].

Similarly, we found an increased overall mortality risk associated with PBT in both the univariable analysis and a multivariable model in which continuous independent variables were included without transformation. However, the effect we detected was attenuated when restricted cubic splines were utilized. Entering continuous independent variables into a multivariable model without transformation or splines results in the assumption that the relationship between the variable and the outcome is linear. In other words, a rise in age of two years is presumed to be associated with the same increase in risk of mortality, regardless of whether that rise is from 56 to 58 or 86 to 88. Splines effectively split the continuous variable into several categories, allowing each category to have a different relationship with the outcome, thus providing for non-linear relationships between continuous variables and the outcome. In this particular situation, the assumption of linear relationships between continuous independent variables (namely, age, CCI, node density, preoperative hematocrit, estimated blood loss, and number of units transfused) and survival suggested that there was an independent association between PBT and overall survival. In the second model, PBT was not associated with any change in survival, suggesting that the differences observed in the univariable analysis may be due to confounding factors. A comparison of the fit of the two models revealed c-indices of 0.78 for the first model and 0.79 for the second model. Thus, the apparent negative impact of PBT on overall survival that has been collectively reported previously and now observed in our cystectomy cohort may ultimately be refuted as more sophisticated statistical models are used to analyze this and other data. In addition, the apparent attenuation of the association observed when cubic splines were used may suggest that any impact of PBT on overall survival is driven by those patients receiving higher numbers of transfused units.

Our study also lends additional insight into the use of PBT in patients undergoing RC. The 41.6% transfusion rate is in line with other studies, which have reported PBT rates ranging from 22% to 66% [28, 29]. As has been previously described, we found that women are significantly more likely than men to undergo PBT. Other factors associated with the administration of PBT included age, CCI, and stage. Given the high transfusion rate in patients undergoing RC, there is a continued need to develop strategies to reduce the use of blood products in these patients. An appreciation of the importance of these factors in determining the need for PBT may help guide the use of pre-operative erythropoietin or intravenous iron as well as the potential use of minimally invasive surgical techniques to reduce PBT. While post-operative anemia may be associated with an increased risk of myocardial infarction, there is increasing evidence that more restrictive transfusion strategies may be utilized without increasing the risk of post-operative cardiac events [30].

There are a number of limitations to this study. Median follow-up was only 25 months, and unidentified confounding variables may have been present but not accounted for in the multivariable analyses. Specifically, we were not able to control for performance status, albumin, administration of other blood products such as fresh frozen plasma, post-operative hematocrit, or post-operative complications, and data on adjuvant chemotherapy was not available. Additionally, estimated blood loss is an inexact measure of blood loss; therefore, it is not possible to fully disassociate the potential effect of transfusion on survival from any potential effect due to operative blood loss. In addition, while CCI is a validated approach for classifying comorbid conditions and is a predictor of post-operative mortality, it incorporates a specific set of comorbidities leaving the possibility that other conditions may bias the results.

The issue of confounding by indication and its associated endogeneity bias is an important limitation of an observational study of this nature. We have addressed this issue by controlling for potentially confounding variables and applying two disparate statistical models. However, experimental study design—as in a randomized clinical trial—or alternative non-standard observational methods, such as econometric methods designed to address endogeneity and confounding (eg. instrumental variable analysis), will be necessary to better understand the association between PBT and survival. Furthermore, due to lack of racial diversity in this cohort it is not possible to assess whether race influences survival or whether there is an interaction between race and transfusion in terms of survival. Patients may have also received a transfusion sometime prior to their hospitalization for surgery, however this data is not available for analysis. The decision to administer a PBT was made on a case-by-case basis without uniform transfusion guidelines, and information on the indication for transfusion was not available. Finally, we assess only overall, and not cancer-specific, survival due to difficulties in accurately attributing cause of death. Overall survival is a more accurate outcome than disease-specific survival and, therefore, was used as the primary endpoint in this study.

Conclusions

The relationship between transfusion and its influence on overall survival in patients with solid tumor malignancies, including bladder cancer, is complex and remains controversial. There are numerous factors that go into the decision to administer a transfusion and controlling for each potentially confounding variable is difficult. While many studies, including ours, have found an association between PBT and mortality in cancer patients, the possibility exists that with additional statistical modeling and further scrutiny the inverse association between PBT and overall survival may be refuted. Only through experimental study design or non-standard observational methods will it be possible to gain a thorough

understanding of the risks and benefits of PBT and to use this limited resource in an evidence-based fashion.

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Figure 1.
Kaplan-Meier analysis of overall survival by receipt of PBT.

Figure 2.
Kaplan-Meier analysis of overall survival by number of transfused units.

Table 1

Distribution of patients by clinical and pathological variables according to receipt of perioperative blood transfusion.

Characteristic	All	Transfusion				p*
		n	%	No	Yes	
All		777		454	323	42%
Age						
<50 years	50	6%	33	7%	17	5%
50-59	121	16%	89	20%	32	10%
60-69	230	30%	145	32%	85	26%
70-79	296	38%	151	33%	145	45%
80	80	10%	36	8%	44	14%
Sex						<0.001
Female	167	21%	67	15%	100	31%
Male	610	79%	387	85%	223	69%
Race						<0.0001
White	727	94%	428	94%	299	93%
Non-white	38	5%	18	4%	20	6%
Charlson Index						0.31
0	287	37%	186	41%	101	31%
1-2	319	41%	189	42%	130	40%
3-4	142	18%	66	15%	76	24%
5	29	4%	13	3%	16	5%
ASA class						0.001
1	4	1%	4	1%	0	0%
2	209	27%	141	31%	68	21%
3	520	67%	286	63%	234	72%
4	44	6%	23	5%	21	7%
Neoadjuvant chemotherapy						0.003**
Yes	20	3%	9	2%	11	3%
No	757	97%	445	98%	312	97%
pTstage						0.253**

Characteristic	Transfusion						p [*]
	All		No		Yes		
	n	%	n	%	n	%	
T0, Ta, Tis, T1	250	32%	177	39%	73	23%	<0.0001
T2	196	25%	111	24%	85	26%	
T3	228	29%	132	29%	96	30%	
T4	103	13%	34	7%	69	21%	
N stage							
N0	516	66%	322	71%	194	60%	0.028
N1	67	9%	39	9%	28	9%	
N2-3	94	12%	45	10%	49	15%	
Nx	72	9%	35	8%	37	11%	
Margins							
Negative	693	89%	417	92%	276	85%	0.018
Urothelial only	27	3%	12	3%	15	5%	
Soft tissue	57	7%	25	6%	32	10%	

* All p values from chi-squared test except where noted.

Table 2

Cox multivariable regression analysis without transformation and with restricted cubic splines added for continuous variables

Characteristic	Non-transformed model			Restricted cubic splines model		
	HR	CI	P	HR	CI	P
Gender						
Male	referent			referent		
Female	0.99	0.74–1.32	0.93	1.03	0.77–1.38	0.83
Age (61.5, 75.7)	1.05	0.73–1.51	0.10	1.07	0.75–1.54	0.09
Charlson comorbidity index (1–2)	1.09	0.88–1.36	0.99	1.30	0.94–1.81	0.96
Race						
Other	referent			referent		
White	1.20	0.75–1.92	0.46	1.19	0.74–1.90	0.48
Node density (0–1)	1.28	1.15–1.42	<0.001	1.28	1.15–1.42	<0.001
pT stage						
T0, Ta, Tis, T1	referent			referent		
T2	1.58	1.10–2.27	<0.001	1.59	1.10–2.28	<0.001
T3	2.84	2.04–3.95	<0.001	2.85	2.05–3.97	<0.001
T4	3.63	2.41–5.46	<0.001	3.70	2.45–5.59	<0.001
Margin						
Negative	referent			referent		
Positive	2.00	1.45–2.74	<0.001	1.99	1.45–2.73	<0.001
Pre-op Hct (38–45)	0.80	0.59–1.10	0.54	0.78	0.57–1.07	0.48
EBL (400–900)	1.19	0.90–1.57	0.16	1.25	0.93–1.67	0.09
Transfusion (per 2 Units)	1.17	1.01–1.36	0.04	1.03	0.77–1.37	0.29

* For continuous variables (age, CCI, preop Hct, EBL), the HR compares the 75th percentile value to the 25th percentile value, as shown in parentheses.