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ORIGINAL ARTICLE – PANCREATIC TUMORS

Effects of Perioperative Red Blood Cell Transfusion on Disease Recurrence and Survival After Pancreaticoduodenectomy for Ductal Adenocarcinoma

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ABSTRACT

Background. The premise that allogeneic red blood cell transfusion (RBCT) contributes to adverse oncologic outcomes after surgery remains controversial. We examined the effects of RBCT during and after pancreaticoduodenectomy (PD) for pancreatic ductal adenocarcinoma (PDAC) on disease recurrence and survival.

Methods. A prospective database of 220 patients undergoing PD for PDAC from 2000 to 2008 was reviewed and transfusion data collected. Univariate and multivariate analyses were performed for factors influencing RBCT, recurrence-free survival (RFS), and overall survival (OS). The effect of amount and timing (intraoperative vs. postoperative) of RBCT was analyzed.

Results. One hundred forty-seven patients (67%) received RBCT: 70 (32%) received 1 to 2 units, and 77 (35%) received >2 units. Median RFS and OS for the entire cohort was 12 and 16 months, respectively. RBCT of >2 units was associated with reduced RFS (9 vs. 15 months; $P = 0.033$) and OS (14 vs. 20 months; $P = 0.003$). Stratified by timing of transfusion, postoperative RBCT was associated with shortened RFS and OS. Controlling for age, body mass index, comorbidities, tumor factors, and major complications, each incremental unit of postoperative RBCT was associated with reduced RFS (hazard ratio 1.10, 95% confidence interval 1.02–1.18) and OS (hazard ratio 1.08, 95% confidence interval 1.03–1.12). Low hemoglobin and presence of comorbidities were the only preoperative factors independently associated with RBCT.

Conclusions. Allogeneic red blood cell transfusion after PD for PDAC is independently associated with earlier cancer recurrence and reduced survival, in particular when administered postoperatively and in larger quantities. Blood-conservation methods are especially indicated for patients with preoperative anemia and medical comorbidities.

Surgical resection is the only treatment modality that offers a realistic potential for long-term survival for patients with pancreatic ductal adenocarcinoma (PDAC).[1] In large-volume tertiary referral centers, the median survival for patients with resected PDAC remains a mere 15–20 months.[2–4] Along with indicators of aggressive tumor behavior such as large size, poor differentiation, lymph node involvement, and positive resection margins, administration of perioperative blood transfusion has been identified as a poor prognostic factor after pancreaticoduodenectomy (PD) for PDAC.[5–9] Despite a growing experience and refinements in surgical technique, PD remains a challenging procedure with substantial potential for blood loss. Although transfusion rates have decreased in contemporary series compared with previous reports, where nearly all patients undergoing PD received a perioperative transfusion, they still remain high, between 47 and 60% of cases.[10–12]

Allogeneic red blood cell transfusions (RBCT) can induce host immunosuppression by several mechanisms, including transfusion-induced suppression of natural killer cell activity, depression of monocyte phagocytic activity, increase in suppressor T-cell activity with inhibition of interleukin-2 production, and concomitant soluble

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Fas-ligand and HLA-molecule transfusion.[13–16] Burrows and Tartter were the first to report that RBCT was associated with adverse oncologic outcomes, such as early tumor recurrence, in patients who underwent resection of colorectal cancer.[17] However, the premise that RBCT adversely affect outcome after cancer surgery still remains controversial.

There are current studies that both support and refute the idea that RBCT is associated with worse outcomes in patients undergoing PD for PDAC.[11,12,18,19] Recent data also suggest that the timing of transfusion as related to the operation may be critical.[12] Understanding that RBCT may be associated with cancer recurrence, and that most patients will experience recurrence and consequently die of PDAC within 2 years after resection, we sought to further explore the relationship between RBCT and recurrence because of the inconsistency of the available data.[20]

The purpose of this study was to examine the effects of perioperative allogeneic RBCT on disease recurrence and survival in a large cohort of patients undergoing PD for PDAC. By analyzing the effect of number and timing of transfusions, we aim to further clarify the impact of transfusion on disease recurrence and survival.

METHODS

We conducted a retrospective review of data for 220 patients who underwent PD for PDAC at Emory University Hospital between 2000 and 2008. Permission from Emory's institutional review board was obtained before data review, and compliance with the Health Insurance Portability and Accountability Act of 1996 was ensured.

Demographic data examined included patients' age, sex, and body mass index. Preoperative laboratory values, such as serum albumin, total bilirubin, and hemoglobin, were assessed. Comorbid conditions were identified and graded with the Charlson comorbidity score.[21] Operative records were reviewed to record estimated blood loss and operation time, and to determine whether a portal vein resection was performed. Pathology reports were reviewed to record tumor size and grade, to record margin and node status, and to determine the presence or absence of perineural and lymphovascular invasion.

Postoperative complications were defined and graded according to the validated Clavien classification system.[22] Accordingly, grade 3–5 complications were categorized as major complications. Length of hospital stay was recorded. Postoperative mortality was defined as death within 30 days of operation.

Red blood cell transfusion data for each patient were collected from anesthesia and computerized hospital blood bank records. RBCT was defined as any allogeneic red blood cell transfusion administered from the time of operation until hospital discharge. RBCT was further categorized by timing (intraoperative vs. postoperative) and the number of units transfused (none, 1–2 units, and >2 units). Intraoperative RBCT included all transfusions initiated in the operating room, even if completed postoperatively.

Recurrence-free survival was determined as the time from operation to either biopsy-proven or radiologic evidence of disease recurrence. Overall survival was calculated from the date of operation to last follow-up time or death.

Statistical Analysis

Recurrence-free survival (RFS) and overall survival (OS) were estimated by the Kaplan-Meier technique and compared by log rank test. Patients who died within 30 days of surgery were excluded from survival analysis. The Cox proportional hazard regression model was used for multivariate modeling of RFS and OS. A significance level of $P < 0.05$ in the univariate analysis was used as criterion for inclusion in the multivariate model. Continuous variables were dichotomized around the median value or categorized by an existing definition, if available. The association of variables with transfusion was tested by Fisher's exact test to compare two groups of categorical variables, and Pearson's χ^2 test for more than two groups. Student's *t*-test was used to compare continuous variables. Variables demonstrating a statistically significant association with RBCT on univariate analysis were entered into a multivariate logistic regression model. Statistical significance was defined as a two-tailed P value of <0.05. All data analyses were performed by SPSS version 17.0 for Microsoft Windows (LEAD Technologies, Chicago, IL) statistical software package.

RESULTS

A total of 220 patients underwent PD for PDAC between 2000 and 2008. Median age was 65 (range 37–86) years, and 109 (50%) were women. Median follow-up time for the entire cohort was 13 (range 0–76) months. Fifty-one patients (23%) were considered obese, defined by a body mass index of $\geq$30 kg/m^2, and 92 patients (42%) had at least one comorbid condition. Median length of operation was 266 (range 117–751) min, and median estimated blood loss was 400 (range 50–5700) mL. Portal vein resection was performed in 33 cases (15%). Median tumor size was 3.0 (range 0.7–7.0) cm. One hundred thirty-seven patients (62%) had lymph node involvement, 87 (40%) had lymphovascular invasion, and 190 (86%) had tumors with perineural invasion detected on histopathologic analysis.

TABLE 1 Demographics and treatment details analyzed by transfusion status at any time

Characteristic	All ($n = 220$)	Univariate			Multivariate	
		No transfusion ($n = 73$)	Transfusion ($n = 147$)	P	Odds ratio (95% confidence interval)	P
Age at operation (y), mean	64	62.9	64.9	0.19		
Sex, *n* (%)						
Female	109 (50)	30 (41)	79 (54)	0.087		
Male	111 (50)	43 (59)	68 (46)			
Body mass index (kg/m^2), mean	27	27	27	0.777		
Charlson comorbidity score, *n* (%)						
0	128 (58)	53 (73)	75 (51)	0.004*	Reference group	
1–2	71 (32)	18 (25)	53 (36)		2.42 (1.03–5.70)	0.042*
>2	21 (10)	2 (3)	19 (13)		9.29 (1.09–79.5)	0.042*
Preoperative albumin (g/dl), mean	3	3.2	2.9	0.007*	1.32 (0.62–2.81)	0.5
Preoperative hemoglobin (g/dl), mean	12.1	12.8	11.8	<0.001*	1.39 (1.17–1.56)	0.002*
Peak total bilirubin (mg/dl), mean	7.4	5.4	8.4	0.003*	1.05 (0.98–1.11)	0.15
Preoperative international normalized ratio of prothrombin time, mean	1.05	1.03	1.07	0.021*	1.93 (0.66–56.3)	0.7
Operation time (min), mean	307	239	342	<0.001*	1.00 (0.99–1.01)	0.21
Estimated blood loss (ml), mean	572	275	718	<0.001*	1.03 (1.01–1.05)	0.001*
Portal vein resection, *n* (%)	33 (15)	7 (10)	26 (18)	0.16		
T size (cm), mean	3.3	3.1	3.3	0.23		
Node involvement, *n* (%)	137 (62)	48 (66)	89 (61)	0.56		
Negative margin, *n* (%)	160 (73)	58 (79)	102 (69)	0.15		
Major complication, *n* (%)	57 (26)	7 (10)	50 (34)	<0.001*	3.75 (1.28–10.9)	0.016*
Days in hospital, mean	14	9.5	16.2	<0.001*	1.06 (0.99–1.13)	0.13
Postoperative deaths, *n* (%)	4 (2)	1 (1)	3 (2)	1		

* $P < 0.05$

Microscopic negative resection margin (R0) was achieved in 160 patients (73%). Postoperatively, 57 patients (26%) developed major complications, and 4 patients (2%) died within 30 days after surgery. The median length of hospital stay was 11 (range 4–74) days.

Red Blood Cell Transfusion

Of the 220 patients who underwent PD, 147 patients (67%) received RBCT. Seventy patients (32%) received 1 or 2 units of red blood cells, while 77 patients (35%) received >2 units. Nine percent of the transfused units were older than 30 days. Timing of transfusion was distributed evenly between intraoperative (47%, $n = 103$) and postoperative (46%, $n = 102$) RBCT. Among these, 58 patients received both intraoperative and postoperative transfusions, 45 patients received only intraoperative transfusions, and 44 patients received only postoperative transfusions. No patients received blood preoperatively. More units of blood were provided in the postoperative period than were given in the operating room, with an average of 3.8 units and 2.2 units, respectively.

RBCT was more frequently administered to patients with greater comorbidities, as depicted by the Charlson comorbidity score (score of 0: 59% vs. score of 1–2: 75% vs. score of > 2: 90%, $P = 0.004$, Table 1). Patients who received RBCT at any time also had longer operation times (mean 342 vs. 239 min, $P = 0.001$), higher estimated blood loss (mean 718 vs. 275 ml, $P = 0.001$), more major postoperative complications (34% vs. 10%, $P = 0.001$), and longer hospital stays (mean 16.2 vs. 9.5 days, $P = 0.001$). These patients also had lower preoperative albumin (mean 2.9 vs. 3.2 g/dl, $P = 0.007$) and hemoglobin levels (mean 11.8 vs. 12.8 g/dl, $P = 0.001$), as well as a higher preoperative international normalized ratio of prothrombin time (1.07 vs. 1.03, $P = 0.02$) and peak total bilirubin level (8.4 vs. 5.4 mg/dl, $P = 0.003$). By multivariate analysis, only the Charlson comorbidity score, preoperative hemoglobin levels, estimated blood loss, and major complications were independently associated with transfusion given at any time (Table 1).

Survival Analysis

Four patients died within the first 30 days of surgery and were excluded from survival analysis. Median RFS and OS for the entire cohort were 12 and 16 months, respectively. Patients who received RBCT at any time had reduced OS after PD for PDAC compared with patients who never received RBCT ($P = 0.015$; Table 2). When stratified by the timing of transfusion, patients who received an RBCT in the postoperative period had earlier recurrence of disease (8 vs. 15 months, $P = 0.002$; Fig. 1) and a reduced OS (14 vs. 18 months, $P = 0.001$; Fig. 2). Intraoperative RBCT had no statistically significant influence on either RFS or OS (Table 2).

The number of units transfused was also associated with survival outcomes. When comparing patients who received no transfusion, 1 to 2 units, or >2 units at any time, both RFS (15 vs. 14 vs. 10 months, $P = 0.033$) and OS (20 vs. 16 vs. 14 months, $P = 0.003$; Table 2) declined significantly with more transfusions. This effect was most evident for postoperative transfusions (Fig. 3). Patients who received a postoperative transfusion of 1–2 units of blood had a shortened OS compared to patients who received no postoperative transfusion (15 vs. 18 months, $P = 0.05$). Patients who received >2 units of RBCT postoperatively had the shortest median OS of 10 months compared to the other two groups ($P = 0.009$; Fig. 3).

Univariate log-rank analysis was performed to determine which factors were predictive of early recurrence. The administration of a postoperative transfusion ($P = 0.002$, Fig. 1), >2 units transfused at any time, positive resection margin, and lymphovascular invasion were all identified as being associated with an earlier recurrence of disease (Table 2). For OS, we found that along with a postoperative transfusion and >2 units transfused at any time, obesity, the presence of comorbidities, and major postoperative complications were associated with reduced OS (Table 2). Tumor factors including increased tumor size, poor differentiation, lymphovascular and perineural invasion, lymph node involvement, and positive resection margins, were also associated with reduced OS by univariate log rank analysis (Table 2).

On multivariate analysis, the administration of a postoperative blood transfusion, when analyzed as a continuous variable by each incremental unit transfused, was an independent prognostic factor for both reduced RFS and OS (Table 3). Other independent predictors of decreased OS included patient comorbidities, increased tumor size, lymph node involvement, and perineural invasion (Table 3).

TABLE 2 Recurrence-free and overall survival excluding patients with 30-day mortality

Characteristic	No. of patients ($n = 216$)	RFS		OS	
		Median (mo)	P	Median (mo)	P
Age at operation			1.0		0.123
<65 y	109	14		19	
≥65 y	107	9		15	
Sex			0.685		0.599
Female	106	12		16	
Male	110	12		16	
Body mass index			0.130		0.017*
<30 kg/m^2	166	12		16	
≥30 kg/m^2	50	10		14	
Comorbidities			0.951		0.011*
None	128	14		18	
Any	88	12		14	
Operation time			0.227		0.561
<4.5 h	110	15		16	
≥4.5 h	106	10		15	
Estimated blood loss			0.404		0.409
<400 ml	102	15		17	
≥400 ml	114	10		15	
Any transfusion			0.347		0.015*
None	72	15		20	
Any	144	10		15	
Amount of transfusion			0.033*		0.003*
None	72	15		20	
1–2 units	69	14		16	
>2 units	75	9		14	
Intraoperative transfusion			0.927		0.289
None	114	14		17	
Any	102	12		15	
Postoperative transfusion			0.002*		0.001*
None	117	15		18	
Any	99	8		14	
Tumor size			0.239		0.006*
<3 cm	84	15		18	
≥3 cm	132	10		14	
Poor differentiation			0.133		0.033*
No	152	13		18	
Yes	64	12		14	
Lymphovascular invasion			0.036*		0.021*
Negative	130	14		18	
Positive	86	10		12	
Perineural invasion			0.569		0.023*
Negative	29	14		24	
Positive	187	12		15	

TABLE 2 continued

Characteristic	No. of patients ($n = 216$)	RFS		OS	
		Median (mo)	P	Median (mo)	P
Node status			0.094		0.003*
N0	80	12		18	
N1	136	12		15	
Margin status			0.012*		0.002*
R0	157	14		18	
R1–2	59	9		13	
Major complication			0.517		
No	163	14		17	
Yes	53	9		11	0.049*

* $P < 0.05$

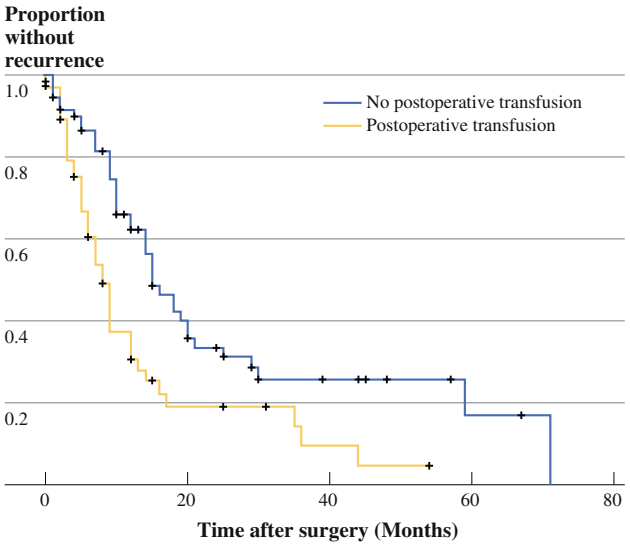

FIG. 1 Recurrence-free survival of patients undergoing pancreaticoduodenectomy for pancreatic ductal adenocarcinoma stratified by postoperative transfusions status. Median time to recurrence of 15 months with no transfusion vs. 8 months with transfusion, $P = 0.002$

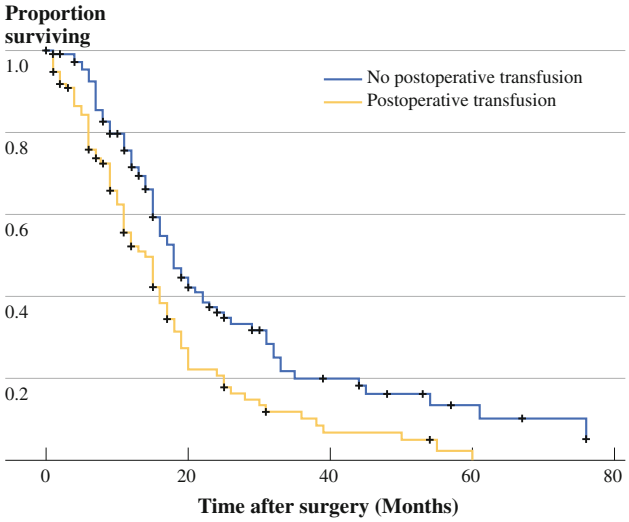

FIG. 2 Overall survival (OS) of patients undergoing pancreaticoduodenectomy for pancreatic ductal adenocarcinoma stratified by postoperative transfusions status. Median OS of 18 months with no transfusion vs. 14 months with transfusion, $P = 0.001$

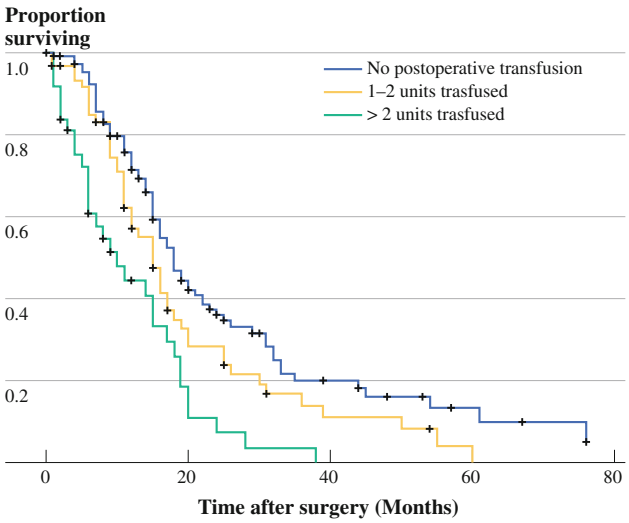

FIG. 3 Overall survival of patients undergoing pancreaticoduodenectomy for pancreatic ductal adenocarcinoma with and without postoperative transfusion, stratified by number of units transfused. Median survival of 18 months without postoperative transfusion ($n = 117$), 15 months with 1–2 units transfused ($n = 62$), 10 months with >2 units transfused ($n = 37$). $P = 0.001$ comparing all three curves; $P = 0.051$, none vs. 1–2 units transfused; $P = 0.001$, none vs. >2 units transfused; $P = 0.009$, 1–2 vs. >2 units transfused

DISCUSSION

The purpose of this study was to evaluate the effects of allogeneic red blood cell transfusion on disease recurrence and survival after resection for pancreatic cancer. Our results indicate that RBCT is an independent poor prognostic factor for survival after resection after PD for PDAC.

Allogeneic blood transfusions are thought to induce a state of relative host immunosuppression. Clinical evidence was first found in the beneficial effect of prolonged graft survival after renal transplantation in conjunction with RBCT, and a reduced relapse rate in patients with Crohn disease.[23,24] In the oncologic setting, however, transfusion acquired immunomodulation has been attributed as a potential cause of earlier cancer recurrence, which has been best described after resection for colorectal and hepatocellular cancer.[25,26] Our data support this theory; we demonstrated statistically significantly shorter recurrence-free time intervals after PD for

TABLE 3 Multivariate predictors of reduced recurrence-free and overall survival for patients undergoing pancreaticoduodenectomy for pancreatic ductal adenocarcinoma excluding patients with 30-day mortality

Variable	Hazard ratio	95% confidence interval	*P*
Recurrence-free survival			
Postoperative transfusion (each unit)	1.10	1.02–1.18	0.01
Overall survival			
Postoperative transfusion (each unit)	1.08	1.03–1.12	0.001
Tumor size $\geq$ 3 cm	1.18	1.02–1.39	0.042
Perineural invasion	1.93	1.05–3.54	0.034
Node involvement	1.49	1.01–2.21	0.044

Variables included were: body mass index; Charlson comorbidity score; intraoperative and postoperative transfusions by units transfused; tumor size (cm); poor differentiation, and lymphovascular and perineural invasion; margin status; node involvement; major complications

PDAC for patients who were transfused in the perioperative period. These effects of transfusion-acquired immunomodulation could potentially be exaggerated in those patients with immunosuppression at baseline. In this study, none of the patients were found to have any underlying immune disorder or on chronic corticosteroid therapy.

Previously, the largest study that examined the effects of RBCT in patients who underwent PD for pancreatic malignancy was reported from the Memorial Sloan-Kettering Cancer Center.[12] This study found that postoperative, but not intraoperative, blood transfusion was associated with decreased OS. Our study confirms this finding, and we also found that postoperative RBCT was associated with earlier recurrence of disease after complete resection. Given the lack of effective salvage therapy, it stands to reason that early recurrence of disease is the explanation for reduced OS in this patient population.

Currently, there is no definitive explanation for the association between postoperative RBCT and early disease recurrence and reduced survival. It has been reported that disseminated tumor cells can be detected in several locations, including blood and peritoneal washings, after patients undergo potentially curative resections of pancreatic tumors.[27] It is possible that with the assistance of RBCT-induced immunosuppression, these tumor cells could escape immunologic surveillance and disseminate, thus predisposing the patient to an earlier recurrence of disease. Interestingly, it seems that only RBCT provided in the postoperative period, and not intraoperatively, exerts a negative effect. The minimal impact of intraoperative transfusion on recurrence and survival perhaps may be explained by the fact that the immunomodulatory factors that accompany RBCT are removed with ongoing blood loss in the operating room. Of note, in our study, the average number of units transfused in the operating room was lower than transfused in the postoperative setting, which could also have influenced these findings. Yeh et al., from Memorial Sloan-Kettering Cancer Center, proposed that postoperative transfusion is reflective of patient long-term comorbidities and clinical status, whereas intraoperative transfusion is an indicator of technical operative requirement.[12] Given the retrospective nature of this study, we cannot accurately determine the cause of transfusion on outcome but instead merely provide possible hypotheses.

An association between transfusion quantity and long-term survival after resection of PDAC has not been established previously. Prior studies have only considered RBCT when $\geq$2 units were transfused.[6,18] The study by Yeh et al., which also analyzed the relationship of quantity of transfusion and survival, did not find a statistically significant association between the two.[12] In our study, we found that indeed the number of units transfused in the postoperative period had an independent impact on survival. Patients who received >2 units of blood postoperatively had the shortest median OS.

Almost a third of all patients in our series only received a limited amount of 1 or 2 units of blood, which was still associated with shortened survival compared to not receiving any postoperative transfusion. In a retrospective review, it is difficult to determine how many of the administered transfusions could potentially have been avoided. In light of these findings, however, it seems that even these patients would benefit from a restrictive approach toward perioperative blood transfusions and blood-conservation techniques. On multivariate analysis, we found that the number of comorbidities and low preoperative hemoglobin levels were associated with an increased likelihood of perioperative blood transfusion. Considering the potential positive impact on survival, blood-conservation techniques may be especially indicated for high-risk patients with multiple comorbidities and preoperative anemia as they prepare to undergo PD for PDAC. Use of hemodilution techniques, pharmacologic substitutions such as recombinant human erythropoietin, folic acid, vitamin B12, and the use of cell-salvage devices have shown to be effective in minimizing blood transfusions in patients undergoing major abdominal surgery for cancer.[28] Although erythropoietin was not administered to

patients in this study, preoperative administration before PD could potentially be a model for future prospective randomized trials.

The impact of RBCT on long term survival is intrinsically difficult to assess because there are a number of potentially confounding factors to consider. For example, it is conceivable that more technically challenging operations are associated with greater blood loss and higher transfusion rates as a result of bulkier and more advanced tumors. Additionally, postoperative complications that are more frequently seen after a challenging operation often result in a blood transfusion. As a group, these patients may reflect the most compromised and vulnerable population, and thus it becomes difficult to ascribe poor outcomes to a blood transfusion independently of all other factors unless accounted for in a multivariate analysis. In fact, some of these assumptions were confirmed in this study, as we found that a RBCT was associated with severity of comorbidities, a higher estimated intraoperative blood loss, and more major postoperative complications. Even though major postoperative complications were associated with transfusion status, no statistically significant association was found in the subset of patients who had infectious complications.

Given the retrospective and observational nature of this study, we cannot infer a causative effect of postoperative RBCT on early recurrence and shortened survival after resection. However, this study includes a large subset of patients, which enabled us to use multivariate analytical techniques to adjust for confounding factors. After controlling for the usual poor prognostic factors, we still found that each unit of RBCT given in the postoperative period is an independent risk factor for early recurrence and reduced survival, and this effect seems to be related to the quantity of units transfused.

In conclusion, allogeneic red blood cell transfusion is independently associated with earlier disease recurrence and decreased OS in patients undergoing PD for PDAC. This association is most evident when transfusions are administered in the postoperative setting and in larger quantities. Blood-conservation methods may be indicated for high-risk patients, especially those with comorbidities and preoperative anemia.

CONFLICT OF INTEREST The authors declare no conflict of interest.

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