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Blood Transfusion and Survival for Resected Adrenocortical Carcinoma: A Study from the United States Adrenocortical Carcinoma Group

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Abstract

Perioperative blood transfusion is associated with decreased survival in pancreatic, gastric, and liver cancer. The effect of transfusion in adrenocortical carcinoma (ACC) has not been studied. Patients with available transfusion data undergoing curative-intent resection of ACC from 1993 to 2014 at 13 institutions comprising the United States Adrenocortical Carcinoma Group were included. Factors associated with blood transfusion were determined. Primary and secondary end points were recurrence-free survival (RFS) and overall survival (OS), respectively. Out of 265 patients, 149 were included for analysis. Out of these, 57 patients (38.3%) received perioperative

transfusions. Compared to nontransfused patients, transfused patients more commonly had stage 4 disease (46% vs 24%, $P = 0.01$), larger tumors (15.8 vs 10.2 cm, $P < 0.001$), inferior vena cava involvement (24.6% vs 5.4%, $P = 0.002$), additional organ resection (78.9% vs 36.3%, $P < 0.001$), and major complications (29% vs 2%, $P < 0.001$). Transfusion was associated with decreased RFS (8.9 vs 24.7 months, $P = 0.006$) and OS (22.8 vs 91.0 months, $P < 0.001$). On univariate Cox regression, transfusion, stage IV, hormonal hypersecretion, and adjuvant therapy were associated with decreased RFS. On multivariable analysis, only transfusion [hazard ratio (HR) = 1.7, 95% confidence interval (CI) = 1.0–2.9, $P = 0.04$], stage IV (HR = 3.2, 95% CI = 1.7–5.9, $P < 0.001$), and hormonal hypersecretion (HR = 2.6, 95% CI = 1.5–4.2, $P < 0.001$) were associated with worse RFS. When applying this model to OS, similar associations were seen (transfusion HR = 2.0, 95% CI = 1.1–3.8, $P = 0.02$; stage 4 HR = 6.2, 95% CI = 3.1–12.4, $P < 0.001$; hormonal hypersecretion HR = 3.5, 95% CI = 1.9–6.4, $P < 0.001$). There was no difference in outcomes between patients who received 1 to 2 units versus >2 units of packed red blood cells in median RFS (8.9 vs 8.4 months, $P = 0.95$) or OS (26.5 vs 18.6 months, $P = 0.63$). Perioperative transfusion is associated with earlier recurrence and decreased survival after curative-intent resection of ACC. Strategies and protocols to minimize blood transfusion should be developed and followed.

Adrenocortical carcinoma (ACC) is a rare but aggressive cancer, with an estimated annual incidence of two in every one million and a 5-year overall survival (OS) ranging from 15 to 84 per cent after curative-intent surgical resection.^{1–3} Although some ACC are hormonally functional tumors, leading to an earlier presentation, most are discovered at an advanced stage, and approximately half of the patients have metastatic disease at diagnosis.^{4,5} For such patients, the median survival is less than one year.⁶ Surgical resection remains the mainstay of treatment, even for select patients with advanced and metastatic disease; adjuvant therapy has a limited role.^{7,8}

Because of the aggressive nature and generally poor outcomes of patients with ACC, determining individual prognosis is vital to patient counseling and development of treatment plans. The current American Joint Committee on Cancer (AJCC) staging system for ACC, however, does not reliably predict outcomes for individual patients.^{9,10} Factors including positive surgical margin, large tumor size, older age, poor cell differentiation, high mitotic index, and hormone secretion have all been associated with worse survival.^{1,2,5,11,12} To optimize treatment and outcomes, it is important to fully understand the prognostic factors profile for ACC.

Red blood cell transfusion has been associated with worse oncologic outcomes in a number of different cancers, including pancreatic adenocarcinoma, gastric adenocarcinoma, hepatocellular carcinoma, and colorectal cancer.^{13–18} This relationship is thought to be secondary to transfusion-related immunomodulation, which is thought to interfere with immune system suppression of oncogenesis.^{14,19,20} Some studies suggest that high-volume transfusion has a worse effect than low-volume transfusion, but this finding has not been consistent across studies and disease sites.^{15,21,22} The prognostic value of perioperative transfusion during curative-intent resection of ACC has not been studied and is not known. The aim of this study is to determine whether perioperative blood transfusion is a poor prognostic factor in ACC, as it is in other cancers.

Methods

Patient Population

Patients were selected from the United States Adrenocortical Carcinoma Group (USACC) database, which is composed of patients who underwent resection of ACC from 1993 to 2014 at 13 academic institutions across the United States: Emory University, Stanford University, The Johns Hopkins University, Medical College of Wisconsin, New York University, The Ohio State University, Washington University in St. Louis, University of Wisconsin, University of California San Diego, University of Texas Southwestern, University of California San Francisco, Vanderbilt University, and Wake Forest University. The Institutional Review Boards at all participating centers approved this study, and research was conducted in accordance with the Health Insurance Portability and Accountability Act of 1996.

Only patients who underwent curative-intent resection of ACC, defined as resection without gross residual disease, with available data on transfusion of allogenic packed red blood cells (pRBC) were included. Surviving patients with less than 30-day follow-up and patients who died within 30 days of surgery were excluded from survival analyses. Data were gathered retrospectively by chart review of demographic, radiographic, pathologic, and clinical data. Pathologic staging was based on the 7th AJCC guidelines,²³ and postoperative complications were graded based on the Clavien-Dindo criteria,²⁴ with grades III to V representing major complications. Minimally invasive surgical techniques were defined as laparoscopic, hand-assisted laparoscopic, retro-peritoneoscopic, and robotic. Adjuvant therapy included chemotherapy, mitotane, and radiation. Transfusion was defined as administration of allogenic pRBC during the perioperative period, either intraoperatively or postoperatively during the patient's hospital stay. The total perioperative number of pRBC units was recorded. Recurrence data were determined by chart review, including review of surveillance imaging. Survival data were collected by chart review and verified using the Social Security Death Index database.

Statistical Analysis

Chi-square analyses, Fisher's exact tests, two-tailed student's *t* tests, and Mann-Whitney *U* tests were used for comparison of categorical and continuous, parametric and nonparametric variables, as appropriate, between transfused and nontransfused groups. Kaplan-Meier log-rank tests were performed to assess the relationship of transfusion and the volume of blood transfused with recurrence-free survival (RFS) and OS. Univariate cox regression analysis was used to determine factors associated with RFS. Factors that were statistically significant ($P < 0.05$) on univariate analyses were included in a multivariable Cox regression model, and collinear variables were removed from the model. This model was then applied to OS. The primary and secondary aims were to determine the relationship of transfusion with RFS and OS, respectively, in patients undergoing curative-intent resection of ACC. All statistical analyses were conducted using SPSS version 22.0 (IBM Corp, Armonk, NY). A *P* value less than 0.05 was considered statistically significant.

Results

Study Population

From the USACC database ($n = 265$), patients were excluded who had incomplete or absent transfusion data ($n = 81$), gross residual disease (R2: $n = 13$) or missing resection margin data ($n = 18$), and clinical follow-up for less than 30 days ($n = 4$). A total of 149 patients who underwent curative-intent resection of ACC were included for analysis. Baseline clinicopathologic data of the study population are summarized in Table 1. The mean age was 52 years (standard deviation (SD) = 14.1 years), and 53 patients were male (36%). Less than half of the patients had tumor-associated hormonal hypersecretion ($n = 58$, 40.0%). The average tumor size was 12.4 cm (SD = 5.9 cm); 21.5 per cent of patients ($n = 32$) had metastatic disease at the time of resection. The median blood loss among all patients was 650 mL (range = 0–15,000 mL).

Transfusion Data

A total of 57 patients (38.3%) received a transfusion: 51 (89.5%) intraoperatively, 24 (42.1%) postoperatively, and 18 (31.6%) both intra-and postoperatively. Only six patients (10.5% of those transfused) received an isolated postoperative transfusion. The median amount transfused was five units (range = 1–74 units). Of those transfused, 16 (28.1%) received 1 to 2 units, whereas 41 (71.9%) received >2 units.

Transfusion, Pathology, and Perioperative Outcomes

Table 1 summarizes the clinicopathologic and perioperative data for transfused *versus* nontransfused patients. Both groups were similar in baseline characteristics including sex, race, body mass index, age, and American Society of Anesthesiologists (ASA) class. There was a similar proportion of patients with hormonally hypersecreting tumors in each group and no difference in laterality of tumor or receipt of pre- or postoperative therapy. The groups were also similar with regard to margin status, with both having 20 to 30 per cent margin-positive resections.

Transfusion was associated with more advanced stage disease (stage IV: 45.6% *vs* 24.4%, $P = 0.007$), and transfused patients compared to nontransfused were more likely to have an open surgical approach (98.2% *vs* 68.5%, $P < 0.001$), other organs resected during surgery (78.9% *vs* 36.3%, $P < 0.001$), inferior vena cava involvement or thrombus (24.6% *vs* 5.4%, $P = 0.002$), intraoperative tumor rupture (20.0% *vs* 6.0%, $P = 0.03$), and larger tumor size (15.8 *vs* 10.2 cm, $P < 0.001$). Additionally, transfused patients had higher operative blood loss (2000 *vs* 250 mL, $P < 0.001$), longer operative time (312 *vs* 181 minutes, $P < 0.001$), and longer hospital stay (8 *vs* 5 days, $P < 0.001$). Transfused patients had more major complications (28.6% *vs* 2.3%, $P < 0.001$), and there was one mortality within 30 days of surgery in a patient who received five total units of blood, although this was not statistically significant (1.8% *vs* 0%, $P = 0.38$).

Transfusion and Survival

After exclusion of the single patient who died within 30 days of surgery, 148 patients were included in survival analyses. The median follow-up period among survivors was 23.2

months (interquartile range = 6.9–61.8 months). Recurrence occurred in 78 patients (56.5%), with 21 (26.9%) having locoregional recurrence only, 39 (50.0%) distant recurrence only, and 15 (19.2%) both distant and locoregional recurrence. There were a total of 59 deaths (39.9%) in the study population.

On log-rank analysis, transfusion was associated with decreased RFS (8.9 vs 24.7 months, $P = 0.006$; Fig. 1A) and OS (22.8 vs 91.0 months, $P < 0.001$; Fig. 1B) compared to no transfusion. On univariate Cox regression, transfusion, stage IV disease, hormonal hypersecretion, and postoperative therapy were found to be associated with decreased RFS (Table 2). In the multivariable model, transfusion [hazard ratio (HR) = 1.74, 1.03–2.92, $P = 0.037$], stage IV disease (HR = 3.17, 1.71–5.86, $P < 0.001$), and hormonal hypersecretion (HR = 2.56, 1.55–4.22, $P < 0.001$) were independently associated with decreased RFS, whereas adjuvant therapy (HR = 1.23, 0.70–2.18, $P = 0.47$) was not (Table 3). When applying this model to OS transfusion (HR = 2.05, 1.14–3.78, $P = 0.016$), stage IV disease (HR = 6.20, 3.10–12.40, $P < 0.001$), and hormonal hypersecretion (HR = 3.49, 1.91–6.39, $P < 0.001$) persisted as independent factors associated with decreased OS (Table 4).

When categorized as receiving 1 to 2 units pRBCs or >2 units pRBCs, the volume of transfusion was not associated with RFS (median 8.9 vs 8.4 months, $P = 0.95$; Fig. 2A) or OS (median 26.5 vs 18.6 months, $P = 0.63$; Fig. 2B).

Discussion

To the authors' knowledge, this is the first and only study to assess the relationship of perioperative allogenic pRBC transfusion with recurrence and survival outcomes for patients undergoing curative-intent resection of ACC. Receipt of transfusion was associated with advanced stage and with increased risk of major complications. Survival analysis demonstrated that transfusion is a negative prognostic factor for RFS and OS, and this association persisted in multivariable analysis taking into account tumor stage, hormonal hypersecretion status, and delivery of adjuvant therapy. There was no discernible difference in RFS or OS based on volume of transfusion. These data corroborate other studies that have reported transfusion to be associated with worse oncological outcomes in a number of other cancers.^{13–16, 21, 25, 26}

ACC is often discovered at an advanced stage, frequently with metastasis or local extension of the tumor into surrounding structures.¹¹ In the current study, 58 per cent of patients undergoing curative-intent resection presented with stage III or IV, locally invasive, or metastatic disease. The mainstay of treatment is complete surgical resection, and although its efficacy is minimal, current practice guidelines recommend adjuvant mitotane therapy for high-risk disease: defined as increased tumor size, positive margins, high grade, and capsular rupture.^{3, 5, 7} Thus, even with advanced and metastatic disease, complete resection of the entire tumor burden is indicated for well-selected patients when technically possible, with the aim of complete tumor extirpation.^{1–3} Given their tendency to locally invade vital structures, resection of large ACC tumors often places patients at high risk of blood loss necessitating transfusion. It is of vital importance to understand the association of

transfusion with tumor recurrence and patient survival so that appropriate transfusion protocols and guidelines can be developed to optimize patient outcomes.

Perioperative transfusion has been associated with worse oncologic outcomes in a number of malignancies. These include lung cancer, hepatocellular carcinoma, gastric adenocarcinoma, pancreatic adenocarcinoma, renal cell carcinoma, and colorectal cancer.^{13–18, 25, 26} However, some of these findings have been conflicting, as there have also been negative studies regarding transfusion and oncologic outcomes in gastric cancer, colorectal cancer, breast cancer, and lung cancer, demonstrating no relationship between the two.^{27–31} Thus, the association of blood transfusion with RFS and OS cannot be generalized to all malignancies, and disease-specific studies are warranted. The current study demonstrated a clear association between RFS, OS, and transfusion. The median RFS for patients who received a blood transfusion was 9 months compared to 25 months for patients who did not receive a transfusion. Similarly, the OS was decreased in the transfused group (23 months) compared to the nontransfused group (91 months). Univariate analysis revealed that transfusion, stage IV disease, hormonal hypersecretion, and adjuvant therapy were all risk factors for worse RFS. All of these, except adjuvant therapy, remained significantly associated with worse RFS and OS in a multivariable model. These data support previous reports that have shown advanced stage and hormonal hypersecretion to be associated with worse RFS and OS in ACC.^{2, 5, 7, 9, 10} This study, however, is the first to demonstrate the independent negative prognostic value of blood transfusion in patients undergoing resection of ACC, even when taking into account stage and hormone secretion.

Several previous studies have examined whether timing or volume of transfusion affect recurrence and survival outcomes in patients undergoing resection of various malignancies and have presented conflicting data. Linder et al.²⁶ recently demonstrated that increased volume of transfusion in patients undergoing nephrectomy for renal cell carcinoma was associated with decreased OS. A study by Kneuert et al.¹⁴ in a population of patients undergoing pancreaticoduodenectomy for pancreatic ductal adenocarcinoma showed a similar association of increased volume of transfusion with decreased RFS and OS, but this effect applied to postoperative transfusion only while intraoperative transfusion had no association with RFS or OS. Another study on pancreatic adenocarcinoma demonstrated that postoperative transfusion and >2 units of intraoperative transfusion were independent predictors of decreased disease-free survival, further supporting a possible role of timing and volume.¹³ Squires et al.¹⁵, on the other hand, did not identify any difference in RFS or OS based on timing or volume of transfusion in patients undergoing resection of gastric adenocarcinoma. In the current study, there was no difference between patients who received 1 to 2 units *versus* >2 units in median RFS (9 *vs* 8 months, $P=0.95$) or OS (26 *vs* 19 months, $P=0.63$). In this study population, nearly all patients who received a postoperative transfusion (24 patients) also received an intraoperative transfusion. Given that there were only six patients who received an isolated postoperative transfusion, the current study could not effectively assess whether there was an association of transfusion timing with outcomes.

This study demonstrated an association between transfusion and decreased RFS and OS for patients undergoing resection of ACC even when accounting for other known poor prognostic factors. A number of studies have investigated the physiologic basis of this

finding, emphasizing the immunosuppressive effect of allogenic pRBC transfusion.^{32–34} The initial interest in transfusion-related immunomodulation was sparked by the observation that renal allograft recipients who underwent preoperative transfusion had decreased rates of rejection.³⁵ In 2007, Chen et al.³² studied a population of patients with gastric cancer to examine the immunosuppressive effects of transfusion by directly comparing allogenic with autologous transfusion. They reported that the expected and normal reduction in serum levels of cytokines and T-lymphocytes that are observed was exaggerated and more sustained in patients who received an allogeneic *versus* an autologous transfusion. There have been a number of other studies examining the immunological effects of transfusion that have established suppression of natural killer cell activity, increase in suppressor T-cell and macrophage activity, and Fas-ligand and HLA-molecule transcription as some of the possible immunosuppressive mechanisms underlying the clinical observations.^{14, 33, 34}

The results of this study are limited by the retrospective nature of its design, which precludes us from establishing a causal relationship between transfusion and oncologic outcomes. However, the formation of the USACC 13-institution study group, creating one of the largest ACC database in the United States, offers a unique opportunity to study this rare disease and to gain a better understanding of whether transfusion is associated with worse prognosis. The data for the USACC database were collected over a span of two decades at 13 different institutions. Thus, some variation in institutional treatment protocols could be expected over time, particularly since a standard transfusion protocol was not followed across all institutions. A 2008 study by Bilimoria et al.¹¹, however, concluded that there has been minimal change in both outcomes and management strategies for ACC in the two decades in which these data were collected. Thus, the findings of this study are applicable and relevant to current clinical practice.

In conclusion, allogenic red blood cell transfusion is independently associated with decreased RFS and OS in patients undergoing curative-intent resection for ACC, even after accounting for other adverse clinico-pathologic factors. The volume of transfusion, however, does not seem to exert any added effect. Given the already poor prognosis of patients with ACC, efforts should be directed to development of and adherence to standardized transfusion protocols.

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Fig. 1. Kaplan-Meier analysis of (A) RFS and (B) OS in non-transfused versus transfused groups. RFS: median 24.7 versus 8.9 months, $P = 0.006$; OS: median 91.0 versus 22.8 months, $P < 0.001$.

Fig. 2. Kaplan-Meier analysis of (A) RFS and (B) OS in patients who received 1 to 2 or >2 units of pRBCs. RFS: median 8.9 *versus* 8.4 months, $P=0.95$; OS: median 26.5 *versus* 18.6 months, $P=0.63$.

Table 1.

Clinicopathologic Features of All Patients Stratified by Receipt of pRBC Transfusion

Variable	Data Available (n)	All Patients (n = 149)	No Transfusion (n = 92)	Transfusion (n = 57)	P Value*
Male gender, n (%)	149	53 (36)	29 (31)	24 (42)	0.26
Race, number (%)					0.31
White	147	119 (81)	70 (78)	49 (86)	
Other		28 (19)	20 (22)	8(14)	
Age (years), mean $\pm$ SD	149	52 $\pm$ 14	52 $\pm$ 14	52 $\pm$ 15	0.11
BMI (kg/m ²), mean $\pm$ SD	124	29 $\pm$ 9	28 $\pm$ 8	31 $\pm$ 10	0.76
ASA Class, n (%)					0.13
1	115	20 (17)	10(15)	10 (20)	
2		29 (25)	22 (33)	7(14)	
3		57 (50)	30 (45)	27 (55)	
4		9(8)	4 (6)	5(10)	
Hormonal hypersecretion, number (%)	145	58 (40)	35 (38)	23 (43)	0.75
Laterality: right sided, n (%)	148	70 (47)	38 (42)	32 (56)	0.12
Preoperative therapy, n (%)					
Systemic therapy	149	3 (2)	1(1)	2 (3)	0.56
Radiation		0 (0)	0 (0)	0 (0)	-
Open approach, n (%)	148	118 (80)	63 (68)	55 (98)	<0.001
Other organs resected, n (%)	148	78 (53)	33 (36)	45 (79)	<0.001
Intraoperative tumor rupture, n (%)	133	15 (11)	5 (6)	10 (20)	0.03
IVC involvement or thrombus, n (%)	149	19 (13)	5 (5)	14 (25)	0.002
Operative time (minute), median (range)	111	231 (71–900)	181 (71–350)	312 (93–900)	<0.001
Operative blood loss (mL), median (range)	128	650 (0–15,000)	250 (0–1,300)	2,000 (100–15,000)	<0.001
Margin status, n (%)					0.09
R0	149	112 (75)	74 (80)	38 (67)	
R1		37 (25)	18 (20)	19 (33)	
Tumor size (cm), mean $\pm$ SD	147	12 $\pm$ 6	10 $\pm$ 5	16 $\pm$ 6	<0.001
T stage, n (%)					0.003
T1	147	9 (6)	9(10)	0(0)	
T2		62 (42)	42 (47)	20 (35)	
T3		53 (36)	31 (34)	22 (39)	
T4		23 (16)	8 (9)	15 (26)	
N stage, n (%)					1.00
N0	52	35 (67)	21 (68)	14 (67)	
N1		17 (33)	10 (32)	7 (33)	

Variable	Data Available (n)	All Patients (n = 149)	No Transfusion (n = 92)	Transfusion (n = 57)	P Value *
M stage, n (%)					0.08
M0	149	117 (78)	77 (84)	40 (70)	
M1		32 (21)	15 (16)	17 (30)	
AJCC stage, n (%)					0.007
I	147	9(6)	9(10)	0(0)	
II		53 (36)	37 (41)	16 (28)	
III		37 (25)	22 (24)	15 (26)	
IV		48 (33)	22 (24)	26 (46)	
Major complications, n (%)	144	18 (12)	2 (2)	16 (29)	<0.001
Reoperation, number (%)	148	7(5)	1(1)	6(10)	0.01
Length of stay (days), median (range)	147	6 (1–50)	5 (1–20)	8 (4–50)	<0.001
30-Day mortality, n (%)	149	1 (1)	0 (0)	1 (2)	0.38
Adjuvant therapy, n (%)					
Systemic therapy	140	62 (44)	37 (42)	25 (49)	0.50
Radiation	128	13 (10)	8(10)	5(11)	1.00

BMI, body mass index; ASA, American Society of Anesthesiologists; IVC, inferior vena cava; SD, standard deviation; AJCC, American Joint Committee on Cancer.

* P value derived from χ^2 , Fisher's exact, independent samples t test, and Mann-Whitney U test as appropriate. Bold text denotes significant P value.

Table 2.

Univariate Cox Regression Analysis for RFS

Variable	HR	95% CI	P Value
Male gender	1.29	0.82–2.03	0.27
Age	0.99	0.97–1.00	0.14
ASA Class			
1	Ref	Ref	-
2	0.38	0.16–0.88	0.02
3	0.72	0.37–1.41	0.34
4	0.87	0.34–2.25	0.78
Hormonal hypersecretion	2.25	1.42–3.57	0.001
Laterality: right sided	1.38	0.88–2.17	0.16
Transfusion	1.88	1.19–2.97	0.007
Open approach	1.82	0.96–3.45	0.07
Operative time > median (231 minutes)	1.52	0.90–2.54	0.11
Positive resection margin	1.36	0.80–2.31	0.26
AJCC stage IV	3.60	2.17–5.99	<0.001
Major complications	0.85	0.37–1.97	0.71
Length of hospital stay (days)	1.02	0.99–1.05	0.19
Adjuvant therapy	2.27	1.40–3.67	0.001

Table 3.

Multivariable Cox Regression Analysis for RF

Variable	HR	95% CI	P Value
Transfusion	1.74	1.03–2.92	0.04
AJCC stage IV	3.17	1.71–5.86	<0.001
Hormonal hypersecretion	2.56	1.55–4.22	<0.001
Adjuvant therapy	1.23	0.70–2.18	0.47

Table 4.

Multivariable Cox Regression Analysis for OS RFS model applied to OS

Variable	HR	95% CI	P Value
Transfusion	2.05	1.14–3.78	0.02
AJCC stage IV	6.20	3.10–12.40	<0.001
Hormonal hypersecretion	3.49	1.91–6.39	<0.001
Adjuvant therapy	0.81	0.43–1.54	0.52