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Infection, thrombosis, and oncologic outcome after interval debulking surgery: Does perioperative blood transfusion matter?

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HIGHLIGHTS

- After interval cytoreduction, thrombosis rates are not affected by transfusion.
- Infection and wound complication rates are similar, regardless of transfusion.
- After interval cytoreduction, transfusion does not impact survival.

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ABSTRACT

Objectives. To determine whether perioperative red blood cell transfusion (PRBCT) affects infection, thrombosis, or survival rates in epithelial ovarian cancer (EOC) patients undergoing neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS).

Methods. Demographics, operative characteristics, and outcome data were abstracted from records of stage IIIC-IV EOC patients managed with NACT-IDS from 01/2010–07/2015. Associations of PRBCT with morbidity and oncologic outcomes were evaluated.

Results. Of 270 patients, 136 (50.4%) received PRBCT. Patients with preoperative anemia and higher estimated blood loss (EBL) were more likely to undergo PRBCT (OR,95%CI 1.80, 1.02–3.17) and (OR,95%CI 1.00, 1.002–1.004), respectively. There were no significant differences in PRBCT based on patient age, Charlson Comorbidity Index, or stage. When compared to low complexity operations, patients with moderate and high complexity surgeries were more likely to receive PRBCT (OR,95%CI 1.81, 1.05–3.09) and (OR,95%CI 2.25, 1.13–4.50), respectively. On univariate analysis, PRBCT was associated with intraabdominal infection (OR,95%CI 8.31, 1.03–67.41), but not wound complications (OR,95%CI 1.57, 0.76–3.23) or venous thromboembolism/pulmonary embolism (VTE/PE) (OR,95%CI 2.02, 0.49–8.23). After adjusting for surgical complexity and preoperative anemia, PRBCT was not independently associated with intraabdominal infection (OR,95%CI 7.66, 0.92–63.66), wound complications (OR,95%CI 1.70, 0.80–3.64), or VTE/PE (OR,95%CI 2.15, 0.51–9.09). When comparing patients undergoing PRBCT versus those who did not, there were no significant differences in median progression-free survival (PFS) or median overall survival (OS) on univariate analysis after adjusting for age, stage and residual disease.

Conclusions. Among patients undergoing NACT-IDS, intraabdominal infection, wound complication and VTE/PE rates are similar, regardless of PRBCT. PRBCT does not impact PFS or OS.

1. Introduction

Surgical debulking is a cornerstone of ovarian cancer treatment and offers patients both progression free and overall survival advantage. Debulking surgery can require extensive surgical effort, and reported rates of perioperative blood transfusion in primary debulking surgery

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(PDS) range from 39% to 56% [1–3]. The use of neoadjuvant chemotherapy (NACT) prior to surgical debulking can decrease the extent of surgical cytoreduction, however reported perioperative red blood cell transfusion (PRBCT) rates in patients undergoing interval debulking surgery (IDS) still range from 21% to 77% [1–3].

Perioperative transfusion is not without risks, and some suggest that blood transfusion may result in immunosuppressive effects and worsened perioperative and survival outcomes via a phenomenon called transfusion related immune modulation [4–10]. In a large multicenter study of over 38,000 patients surgically treated for thoracic, abdominal, or pelvic neoplasms, PRBCT was associated with a worse 30-day mortality after adjusting for covariates [11]. However, it is possible that increased postoperative complications as well as decreased survival and recurrence seen after transfusion may not be due to receiving blood products, but instead due to the circumstances under which blood transfusion becomes necessary.

In patients with epithelial ovarian cancer (EOC), specific outcomes related to PRBCT have been examined. Several studies have demonstrated that patients receiving PRBCT have an increased risk of recurrence and death [3,12,13]. In contrast, other research has not supported such an association [14,15]. Similarly, studies evaluating risk of infection and venous thromboembolism/pulmonary embolism (VTE/PE) associated with PRBCT vary from showing an increased risk to reporting no such association [16–18]. Among women undergoing NACT-IDS for EOC, there are few studies examining these previously-studied associations between blood transfusion and infection, thrombosis, recurrence, or death. This is of particular relevance as blood transfusions are frequently administered in this patient population, likely secondary to worse preoperative anemia due to the bone marrow-suppressive effects of chemotherapy [2,3]. Given prior mixed findings, we hypothesized that confounding factors, including surgical complexity, influenced the association of transfusion with rates of infection, thrombosis, recurrence, and survival outcomes in patients undergoing NACT-IDS.

2. Methods

After obtaining institutional review board approval, a retrospective chart review was conducted of all patients undergoing NACT-IDS for advanced-stage (FIGO IIIC-IV) epithelial ovarian/fallopian tube/primary peritoneal carcinomas (referred to as EOC) between January 1, 2010 and July 31, 2015 at Brigham and Women's Hospital and Massachusetts General Hospital. Exclusion criteria included: patients undergoing PDS as well as those with non-epithelial histology or incomplete medical records. Patients were selected for NACT based on provider discretion, with reasons including provider determination of unresectable disease, presence of an acute medical condition at time of diagnosis, or poor baseline performance status. Neoadjuvant chemotherapeutic regimens were platinum and taxane-based and administered per standardized protocols. The intent of neoadjuvant treatment was with 3–4 cycles of chemotherapy prior to IDS. While the majority of patients underwent chemotherapy within our practice, patients who received chemotherapy elsewhere were included in analysis as long as surgery was conducted at Brigham and Women's or Massachusetts General Hospital. After completion of 3–4 cycles of chemotherapy, patients underwent computed tomography scan to determine whether residual disease volume appeared resectable. If deemed unresectable, patients received additional cycles of chemotherapy at that time. Patients with surgical resection of all gross disease were classified as having undergone a complete surgical resection. Patients with any remaining tumor nodule measuring >1 cm in diameter were classified as sub-optimally (SO) debulked. Those with remaining gross disease ≤1 cm (maximal diameter of largest residual tumor nodule) were considered to be optimally debulked.

Preoperative hemoglobin levels included results within one week prior to surgery, and information on estimated blood loss (EBL) as well as intraoperative or postoperative transfusion was obtained from operative, anesthesia, and blood bank records. Anemia was defined as a hemoglobin concentration of ≤11.5 g/dL, consistent with prior studies [2,3]. Across institutions, restrictive transfusion policies were employed during the study period; transfusion was only recommended in cases of active bleeding intra-operatively or post-operatively, active myocardial ischemia, a hematocrit under 21%, or when signs or symptoms of anemia were present. Perioperative transfusion was defined as patients undergoing intraoperative transfusion and/or post-operative transfusion during the admission directly following the patient's index surgery; transfusion did not include patients undergoing PRBCT during a readmission, or those receiving PRBCT as an outpatient prior to chemotherapy. All transfusions consisted of allogenic, pre-storage leukoreduced packed red blood cells; no autologous blood transfusions were given in this patient population.

Surgical procedures were assigned a complexity score reflecting the difficulty and number of procedures performed as described by Aletti et al. [19] The Aletti scoring system is an additive summary of surgical procedures performed, with hysterectomy and bilateral salpingo-oophorectomy, omentectomy, pelvic lymphadenectomy, para-aortic lymphadenectomy, pelvic peritoneum stripping, abdominal peritoneum stripping and small bowel resection each counting as one point; large bowel resection, diaphragm stripping, splenectomy, and liver resection each counting as two points; recto-sigmoid resection with primary anastomosis as three points. In this system, a surgery of less than or equal to 3 points qualifies as low complexity, a surgery of 4–7 points qualifies as intermediate, and a surgery of greater than or equal to 8 points qualifies as a high complexity score. Significant surgical complications evaluated for this study included postoperative intraabdominal infection, wound complications and/or VTE/PE. Wound complications were defined as a disruption of the wound, including wound infection, seroma, and/or wound separation. Intraabdominal infection was defined as an intraabdominal collection requiring intervention and management, including antibiotic treatment and/or source control. A VTE/PE was defined as a thrombosis of the deep venous structures or a pulmonary embolus; included in these is both symptomatic and asymptomatic VTE.

Patients were separated into two groups based on whether they did or did not receive a PRBCT. The two groups were then compared with respect to clinical, operative, and postoperative factors. We performed univariate and multivariate logistic regression analyses with receipt of PRBCT as the outcome. Associations are shown as odds ratios (OR) with 95% confidence intervals (CI).

Survival analysis included progression-free survival (PFS), defined as the number of months between the date of initiation of chemotherapy and either disease progression or death from any cause, as well as overall survival (OS), defined as the number of months between the date of initiation of chemotherapy and death from any cause. Patients alive and progression-free or alive with disease were censored for PFS and OS, respectively, at the date of last follow up. Associations are shown as hazard ratios (HR) with 95% confidence intervals. The Kaplan–Meier method was used to estimate survival curves and Cox proportional hazards regressions were used to compare survival data. For all calculations, a p-value < 0.05 was considered statistically significant. MedCalc (version 18.0) statistical software was used for all statistical analyses.

3. Results

A total of 270 patients with FIGO stage IIIC and IV EOC treated between January 1, 2010 and July 31, 2015 were included in this study. Table 1 presents demographic and clinical characteristics of this population. Mean patient age was 63.8 years (±10.5 years). The majority of patients were white (85.6%). Approximately half (55.9%) of patients had stage IIIC disease. Most patients underwent 3–4 cycles of preoperative chemotherapy (Mean 3.7 ± 1.2 cycles). In total, 100.0% (270/270)

Table 1
Demographics and operative characteristics of patients undergoing NACT-IDS.

Characteristic	Number of patients	%
Age (median, range)	65 years	34–89 years
Race		
White	231	85.6%
Black	5	1.8%
Asian	8	3.0%
Hispanic	4	1.5%
Unknown/Other	22	8.1%
BMI (median, range)	25.1	16.1–72.1
Charlson cormorbidity index		
Low (0,1)	28	10.4%
Intermediate (2,3)	133	49.2%
High (≥4)	109	40.4%
Number of chemotherapy cycles preoperatively (median, range)	3.0	2–13
Number of chemotherapy cycles postoperatively (median, range)	3.0	0–10
Stage		
IIIC	151	55.9%
IV	119	44.1%
Tumor grade		
1	1	0.3%
2	6	2.2%
3	262	97.4%
Primary site		
Ovary	217	80.4%
Fallopian tube	35	12.9%
Peritoneum	18	6.7%
Histology		
Serous	250	92.6%
Mucinous	1	0.4%
Endometrioid	2	0.7%
Carcinosarcoma	5	1.9%
Clear cell	4	1.5%
Mixed	8	2.9%
Preoperative hemoglobin (median, range)	10.6 g/dL	(7.1–13.7)
Operative time (median, range)	162 min	50–508 min
EBL in mL (median, range)	300	0–4200
Required intraoperative blood transfusion	47	17.4%
Required postoperative blood transfusion	118	43.7%
Surgical complexity		
Low	160	59.3%
Moderate	93	34.4%
High	17	6.3%
Residual disease		
Complete surgical resection (CSR)	173	64.1%
Optimal (≤1 cm)	81	30.0%
Suboptimal (>1 cm)	16	5.9%
Postoperative complications		
Wound complications	35	13.0%
Post-operative VTE/PE	9	3.3%
Intra-abdominal infection	13	3.3%

patients received first-line platinum and 98.5% (266/270) patients received first-line taxane. Overall, 75.6% of patients were considered anemic (Hgb ≤ 11.5 g/dL). The mean preoperative hemoglobin concentration was 10.4 g/dL (±1.6 g/dL). Most patients had a low surgical complexity score (59.3%), while 34.1% of patients underwent moderate complexity operations and 6.3% underwent high complexity surgeries. The majority of patients (64.1%) had complete surgical resection, while 30.0% had macroscopic gross residual disease ≤1 cm (i.e. "optimal"). Only 16 (5.9%) patients had a suboptimal debulking surgery. Mean operative time was 185.9 min (±89.5 min) and mean EBL was 455.5 mL (±559.4 mL). The median length of stay over a perioperative admission was 7 days (range 4–27 days). Postoperative morbidity included: wound complications in 35 patients (13.0%), intraabdominal infection in 13 patients (4.8%), and post-operative VTE/PE in 9 patients (3.3%). In total, 136 (50.4%) women underwent PRBCT: 47 (17.4%) patients underwent intraoperative blood transfusion, 118 (43.7%) patients required postoperative blood transfusion, and 29 (10.7%) required both.

On univariate analysis, patients with greater EBL were more likely to undergo PRBCT compared to those who did not (OR, 95% CI 1.00, 1.002–1.004; $p < 0.0001$). Similarly, patients with preoperative anemia were more likely to undergo PRBCT (OR, 95%CI 1.80, 1.02–3.17; $p = 0.042$). Using a standardized surgical complexity score, increasing surgical complexity was associated with receiving PRBCT. Specifically, compared to patients undergoing debulking surgery with a low complexity score, moderate (OR, 95% CI; 1.81, 1.05–3.09; $p = 0.032$), and high (OR, 95% CI; 2.25, 1.13–4.50; $p = 0.022$) surgical complexity scores were associated with PRBCT. Factors that were not found to be associated with PRBCT included: mean age, mean BMI, Charlson Comorbidity Index, stage, or residual disease at the completion of surgery (Table 2).

On univariate analysis, there was no increased risk of wound complications (OR, 95% CI; 1.57, 0.76–3.23; $p = 0.22$) or VTE/PE (OR, 95% CI 2.02, 0.49–8.23; $p = 0.33$) in patients undergoing PRBCT compared to those who did not. In contrast, an increased rate of intraabdominal infection was seen among patients who underwent PRBCT (OR, 95% CI; 8.31, 1.03–67.41; $p = 0.047$).

On multivariate analysis, including surgical complexity, preoperative anemia, and receipt of PRBCT, PRBCT was not associated with increased risk of wound complications (OR, 95% CI; 1.70, 0.80–3.64; $p = 0.17$), VTE/PE (OR, 95% CI; 2.15, 0.51–9.09; $p = 0.30$), or intraabdominal infection (OR, 95% CI; 7.66; 0.92–63.66; $p = 0.06$).

Among all 270 patients undergoing NACT-IDS, there were a total of 240 recurrences (88.9%). The median PFS was similar between patients undergoing PRBCT and those who did not (12.0 vs. 14.8 months, $p = 0.07$). Kaplan-Meier curves for PFS for patients undergoing PRBCT and those who did not are displayed in Fig. 1. Cox proportional hazards regression including age, stage and residual disease status was performed: there was no association between PRBCT and increased risk of disease progression (HR, 95% CI; 1.2, 0.9–1.6; $p = 0.15$).

There were a total of 132 deaths (48.9%) in this patient population. There was no significant difference in median OS in patients undergoing PRBCT versus those who did not (41.9 vs. 52.0 months; $p = 0.10$). Kaplan-Meier curves for OS by receipt of PRBCT are displayed in Fig. 2. Similar to the findings for PFS, Cox proportional hazard regressions including age, stage, and residual disease status was performed: there was no association between PRBCT and increased risk of death (HR, 95% CI; 1.2, 0.9–1.7; $p = 0.25$).

4. Discussion

Although perioperative anemia can lead to increased symptomatology and delays in resumption of chemotherapy, prior studies have proposed more restrictive transfusion policies due to demonstrated associations between PRBCT and worsened outcomes in EOC patients [3,14]. In particular, associations between PRBCT and infection, VTE/PE, and decreased PFS and OS have been reported [3,12,14,21]. It has been proposed that transfusion related immune modulation, via the suppression of cytotoxic cells and alterations in T-lymphocyte activity, may explain worsened outcomes in patients undergoing PRBCT [4–10]. However, few studies have examined the effects of PRBCT in patients who have been exposed to NACT [2]. This is particularly important given the frequent presence of preoperative anemia and subsequent requirement for perioperative PRBCT in patients undergoing NACT-IDS [1–3]. This study sought to compare the association of PRBCT with perioperative infection, thrombosis, and survival outcomes in this NACT-IDS patient population.

Rates of preoperative anemia and perioperative blood transfusion in this study were consistent with prior reports, at 75.6% and 50.4% respectively. When examining the association between PRBCT and perioperative morbidity, this study found no significant differences in wound

Table 2
Patient characteristics and outcomes based on receipt of PRBCT.

Characteristic	No PRBCT	PRBCT	Crude OR	p-value
	N = 134	N = 136	(95% CI)	
Mean patient age (±SD)	64.7 (±10.6)	62.9 (±10.2)	1.85 (0.65–4.35)	0.15
Age				
<70	44.74%	55.26%	1.00	
≥70	61.25%	38.75%	0.51 (0.30–0.87)	0.013
Mean BMI (±SD)	25.5 (±5.7)	26.8 (±6.5)	1.32 (0.15–2.78)	0.078
Charlson comorbidity index				
Low (0,1)	46.43%	53.57%	1.00	
Intermediate (2,3)	45.11%	54.89%	1.05 (0.46–2.39)	0.90
High (≥4)	55.96%	44.04%	0.68 (0.30–1.57)	0.71
Mean preoperative hemoglobin (±SD)	10.6 (±2.0)	10.3 (±1.2)	0.91 (0.78–1.06)	0.24
Preoperative anemia				
No (Hgb > 11.5)	29.85%	19.12%	1.00	
Yes (Hgb ≤ 11.5)	46.08%	53.92%	1.80 (1.02–3.17)	0.042
Mean EBL (±SD)	272.1 (±273.4)	636.1 (±695.4)	1.00 (1.002–1.004)	<0.0001
Stage				
IIIC	56.72%	55.15%	1.00	
IV	43.28%	44.85%	1.07 (0.66–1.72)	0.8
Surgical complexity				
Low	59.63%	40.37%	1.00	
Moderate	38.04%	61.96%	1.81 (1.05–3.09)	0.032
High	17.65%	82.35%	2.25 (1.13–4.50)	0.022
Residual disease				
Complete surgical resection	68.66%	59.56%	1.00	
Optimal (≤1 cm)	24.63%	35.29%	1.65 (0.97–2.82)	0.066
Suboptimal (>1 cm)	6.72%	5.15%	0.88 (0.31–2.48)	0.081
Wound complications	10.45%	15.44%	1.57 (0.76–3.23)	0.22
Post-operative DVT/PE	2.24%	4.41%	2.02 (0.49–8.23)	0.33
Intra-abdominal infection	0.75%	5.88%	8.31 (1.03–67.41)	0.047

complications, intraabdominal infection, or VTE/PE after controlling for surgical complexity and preoperative anemia. This finding differs from previously-published studies demonstrating worse perioperative infection and thrombotic rates in EOC patients undergoing PRBCT around the time of PDS [14]. A separate report in a population of gynecologic oncology patients including those with ovarian, endometrial, cervical, and other cancers, found no difference in infectious rates when comparing restrictive to liberal use of PRBCT [16]. This same study in gynecologic cancer patients found no difference in VTE/PE rates in restrictive versus liberal transfusion groups, however an additional study on VTE/PE risk in EOC patients after PDS found postoperative VTE/PE in 5/46 (11%) patients undergoing transfusion compared to 3/122 (2.5%) of patients who were not transfused. This finding was statistically significant on univariate analysis, however multivariate analysis was not performed [16,21]. Multivariate analysis is important in this context, given that age and stage have been reported to impact risk of VTE/PE in EOC patients [22,23]. The present report did not find a risk of VTE/PE in NACT-IDS EOC patients on univariate or multivariate analysis.

Reports on the effect of PRBCT on survival in EOC patients also vary, in part due to differences in study methodology [3,12,14,15,18]. While some studies cite an association between PRBCT and decreased survival, it is possible that poor outcomes after transfusion may be due to the circumstances under which blood transfusions become necessary, such as high initial tumor burden requiring complex surgery or preoperative anemia. In fact, several studies have demonstrated worsened overall survival in the setting of pretreatment anemia, with one report finding a 38.5% 5-year overall survival in anemic EOC patients compared to 52.3% in EOC patients without pretreatment anemia [23,24]. Nevertheless, there remains debate regarding whether PRBCT impacts oncologic outcomes. One of the first studies examining the effects of PRBCT on survival reported a 6-month decreased median PFS and 18-month

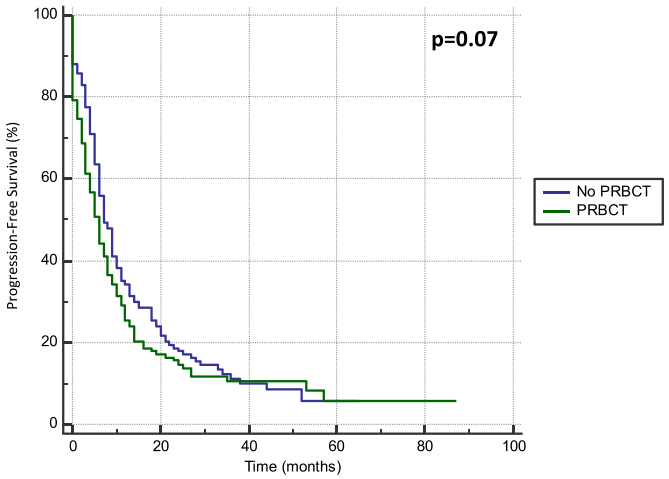

Fig. 1. Progression-Free Survival based on perioperative PRBCT.

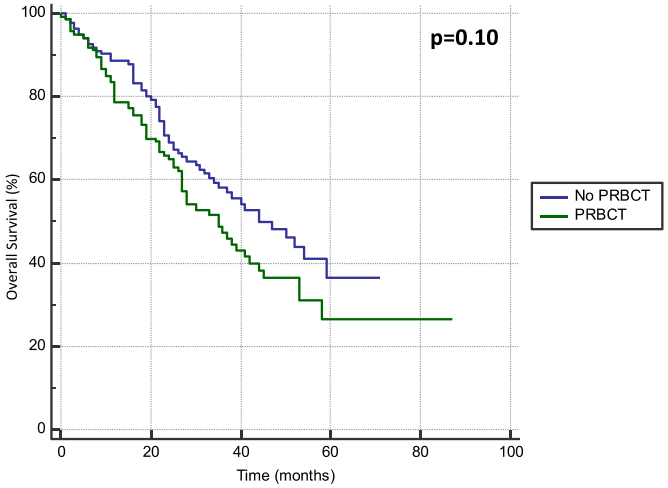

Fig. 2. Overall Survival based on perioperative PRBCT.

decreased OS when comparing EOC patients undergoing transfusion versus those who did not [12]. It is important to note that this often-cited study included only PDS patients and did not control for residual disease volume in its outcome analysis. In a model adjusting for residual disease status, presence of anemia, and use of NACT, only PRBCT (transfused versus not transfused, $p = 0.03$) and debulking status (optimal versus sub-optimal, $p = 0.03$) remained significant negative predictors of survival [3]. On the other hand, another adjusted model found no difference in survival outcomes for EOC patients undergoing PDS after controlling for factors found to be associated with PRBCT, including age, stage, residual disease status, and higher surgical complexity [20].

Our study demonstrated no significant association between PRBCT and PFS or OS after adjusting for age, stage, and residual disease status. Of note, this study is the first to report exclusively on patients undergoing NACT-IDS while also adjusting for additional risk factors, including age, stage, and residual disease status. As in other retrospective analyses, limitations include dependency on the accuracy and completeness of the medical records reviewed as well as variation among physicians on transfusion thresholds. Further, the relatively small numbers of patients in this analysis limit the power and confidence to be able to make any definitive conclusions, however this study sought to add to the body of knowledge. A larger, prospective study could address many of these limitations including standardization of transfusion thresholds and prospective documentation of patients' symptoms.

The decision to transfuse requires balancing risks of transfusion with benefits of improved symptomatology, coagulation, and resumption of chemotherapy. There are disadvantages to unnecessary PRBCT, including risks of transfusion reactions and isoimmunization, as well as significant cost, with some estimating $1600–$2400 per transfusion event [25]. Recent reports have called into question whether PRBCT is also associated with risks of infection, thrombosis, and worsened survival outcomes. The findings reported here suggest that in the NACT-IDS patient population, there is no significant increase in rates of wound complication, intraabdominal infection, VTE/PE, or worsened PFS or OS associated with PRBCT.

Author contributions

Beryl L. Manning-Geist: This author conceived the project and participated in design of the study, abstraction of data, analysis of results, authoring of the manuscript, and review and editing of the manuscript.

Stephanie Alimena: This author participated in the abstraction of data, authoring of the manuscript, as well as review and editing of the manuscript.

Marcela G. Del Carmen: This author participated in review and editing of the manuscript.

AK Goodman: This author participated in design of the study as well as review and editing of the manuscript.

Rachel M. Clark: This author participated in the review and editing of the manuscript.

Whitfield B. Growdon: This author participated in review and editing of the manuscript.

Neil S. Horowitz: This author participated in design of the study as well as review and editing of the manuscript.

Ross S. Berkowitz: This author participated in review and editing of the manuscript.

Michael G. Muto: This author participated in review and editing of the manuscript.

Michael J. Worley Jr.: This author participated in the design of the study, abstraction of data, analysis of results, authoring of the manuscript, and review and editing of the manuscript.

All authors approved this final version of the manuscript.

Conflicts of interest

All authors report no conflicts of interest.

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