The impact of perioperative blood transfusion on survival following radical cystectomy for urothelial carcinoma

Neda Sadeghi, MD, Gina M. Badalato, MD, Gregory Hruby, MD, Max Kates, MD, James M. McKiernan, MD

Department of Urology, Squier Urological Clinic, Columbia University Medical Center, New York, New York, USA

SADEGHI N, BADALATO GM, HRUBY G, KATES M, MCKIERNAN JM. The impact of perioperative blood transfusion on survival following radical cystectomy for urothelial carcinoma. *Can J Urol* 2012; 19(5):6443-6449.

Introduction: *Perioperative blood transfusion (PBT) has been shown to contribute to cancer progression and mortality. This study sought to determine the impact of PBT during radical cystectomy on cancer-specific survival (CSS) and overall survival (OS).*

Materials and methods: *The Columbia University Urologic Oncology Database was reviewed for patients who underwent a RC from 1989 to 2010 (n = 638). PBT was defined as non-autologous packed red blood cells (PRBC) received during the same hospital stay as the radical cystectomy. Clinical and pathological variables were compared between the cohorts and survival analysis was performed with the Kaplan-Meier and Cox-regression methods. The primary outcomes were CSS and OS.*

Results: *Of 638 patients identified, 209 patients (32.8%) underwent PBT with an average of 2.21 ± 1.66 units transfused PRBC. Mean age was 68.1 ± 11.2 years; median follow up was 25.5 months (range 1-164 months). The number of units of PRBC transfused was inversely associated with OS (HR 1.12; p = 0.008) and CSS (HR 1.12; p = 0.049) on univariable analysis. Additionally, Kaplan-Meier analysis demonstrated a significant difference in OS (p = 0.0211) in patients who received more units of PRBC. However, on multivariable analysis, the number of units of PRBC transfused was not an independent predictor of outcome for CSS (p = 0.300) or OS (p = 0.246).*

Conclusions: *Each additional unit of PRBC received during radical cystectomy is associated with a decrease in survival. However, after controlling for clinical and pathologic factors which predict survival, PBT does not have an independent affect upon CSS or OS.*

Key Words: bladder cancer, perioperative blood transfusion, radical cystectomy, survival

Introduction

In 1973, Opelz and colleagues published a pioneering report on the benefit of blood transfusion on renal allograft outcomes.[1] Opelz's continued research on the benefits of transfusion prompted a response by Gantt in 1981 who commented that perhaps the immunosuppressive advantage from blood transfusions in renal allografts has implications in cancer outcomes.[2,3] This subsequently heralded an entire body of research regarding the effects of blood transfusion on cancer recurrence and survival. Perioperative blood transfusion (PBT) is hypothesized to decrease the physiologic immune response, rendering a quasi-immunocompromised state and increasing the susceptibility to cancer progression.[4]

Approximately 30%-83% of all patients undergoing a radical cystectomy receive a perioperative blood transfusion (PBT).[5,6] In contemporary series, the estimated blood loss during radical cystectomy ranges from 400 cc to 1400 cc and with a median of 2-3 units of blood transfused.[5-9] The established risks of blood transfusion include fluid overload, allergic reaction, fever, infection, hemolytic reactions, and acute lung injury.[4,10] In contrast, the debatable risks of blood transfusion include cancer recurrence and progression. Since the advent of minimally invasive surgery for urologic malignancy, the incidence of PBT during radical cystectomy is likely declining. The impact of PBT on mortality in the setting of bladder cancer remains unclear. Therefore, this study sought to explore the correlation of PBT during radical cystectomy on overall survival and bladder cancer-specific survival (CSS).

Accepted for publication May 2012

Address correspondence to Dr. Gina M. Badalato, Department of Urology, Columbia University College of Physicians and Surgeons, 161 Fort Washington Avenue - Herbert Irving Pavilion, 11th Floor, New York, NY 10032, USA

Materials and methods

The IRB-approved Comprehensive Urologic Oncology Database was retrospectively reviewed for all patients who underwent a radical cystectomy from August 1989 to August 2010 (n = 638). PBT was defined as non-autologous packed red blood cells (PRBC) received in the same hospital stay before, during, or after radical cystectomy. The receipt of a PBT was analyzed as both a categorical variable and as a continuous variable: PBT as a categorical variable was defined as whether or not a patient received a PBT (yes or no); PBT as a continuous variable was defined as increasing units of PRBCs (0 units, 1 unit, 2 units, ≥ 3 units).

Data were reviewed for patient demographics, clinical traits, presurgical hematocrit, postsurgical hematocrit, surgical pathology, receipt of perioperative PRBC, and survival. Presurgical hematocrit was defined as the hematocrit value up to 30 days prior to surgery; postsurgical hematocrit was defined as the nadir value before hospital discharge.

Clinical and pathological variables were compared between cohorts using chi-square analysis and student's t-test. The primary outcomes were CSS and

TABLE 1. **Patient baseline characteristics**

	No transfusion	Transfusion	p value
Total cohort	429	209	
Clinical data			
Age, yr, (mean ± SD)	67.6 ± 11.1	69.3 ± 11.4	0.077
Follow up, mo, (mean ± SD)	48.2 ± 52.4	42.3 ± 44.7	0.168
Gender (%)			< 0.001
Male	334 (77.9)	135 (64.6)	
Female	95 (22.1)	74 (35.4)	
Race (%)			0.474
Caucasian	319 (74.4)	164 (78.5)	
African-American	25 (5.8)	14 (6.7)	
Hispanic	30 (7.0)	12 (5.7)	
Other	55 (12.8)	19 (9.1)	
Presurgical hematocrit (%)	38.9 ± 5.6	37.4 ± 4.8	0.001
Postsurgical hematocrit (%)	25.6 ± 4.5	24.3 ± 4.3	0.001
Neoadjuant chemo (%)	43 (10.0)	22 (10.5)	0.844
Adjuvant chemo (%)	54 (12.6)	24 (11.5)	0.689
Pathologic data			
Pathologic stage			0.013
pTa	32 (7.5)	8 (3.9)	
pTis	55 (12.8)	28 (13.4)	
pT1	48 (11.2)	35 (16.7)	
pT2	78 (18.2)	20 (9.6)	
pT3	135 (31.5)	82 (39.2)	
pT4	54 (12.6)	23 (11.0)	
Nodes (%)			0.266
pNx	48 (11.2)	15 (7.2)	
pN0	298 (69.5)	154 (73.7)	
pN+	48 (11.2)	15 (7.2)	
Positive margins (%)	28 (6.5)	19 (9.1)	0.245
CIS (%)	309 (72.0)	157 (75.1)	0.409
LVI (%)	154 (35.9)	79 (37.8)	0.640
High grade (%)	335 (78.1)	168 (80.4)	0.505

OS. Bladder cancer-specific survival was defined as death attributed to bladder cancer; within this rubric of bladder cancer-related death, perioperative death was defined as demise within 90 days of radical cystectomy. Survival analysis was performed with the Kaplan-Meier and Cox-regression methods.

The use of only leukoreduced blood at our institution began in 1999. Since there is level I evidence demonstrating that non-leukocyte reduced blood may negatively impact perioperative mortality, we accounted for the use of non-leukocyte reduced blood by performing a Cox regression analysis to compare the survival outcome of patients who received non-leukocyte reduced blood (1989-1998) versus leukocyte-reduced blood (1999-2010).[11-14]

Statistical significance was set at $\alpha = 0.05$. A retrospective power calculation was performed and demonstrated that this study had a 92% power to detect a 30% increase in the risk of death due to PBT. All statistical analysis was done using Stata 11.0 (StataCorp., College Station, TX, USA).

Results

The patients' clinical and pathological characteristics are listed in Table 1. Of 638 patients identified, a total of 209 patients (32.8%) underwent PBT with an average of 2.21 ± 1.66 units transfused. The mean age was 68.1 ± 11.2 years and the median follow up was 25.5 months (range 1-164 months). The majority of the patients in this cohort were male (135/209, 64.6%) and Caucasian (164/209, 78.5%). A total of 143/638 (22.4%) patients received systemic chemotherapy (neoadjuvant or adjuvant). The patients in the transfused group had lower pre and postsurgical hematocrit values compared to the patients in the non-transfused group ($p = 0.001$ for both). Patients also differed with respect to gender and pathologic stage, with more transfused patients being female ($p < 0.001$) and having pT3 disease ($p = 0.013$). Between the two cohorts, there was no significant difference in age, race, follow up time, or systemic chemotherapy use ($p > 0.05$). Groups also did not differ with respect to most pathological attributes including nodal involvement, margin status, concomitant carcinoma in-situ, or lymphovascular invasion. In the total cohort, there were 136/638 (21.3%) cancer-related deaths. Within the first 30 days of surgery, a total of 9/638 (1.41%) patients expired; extending this interval to the first 90 days after surgery, there were a total of 24 (3.7%) deaths noted.

Clinicopathological variables and PBT, both as a categorical and continuous variable, were evaluated to determine their ability to predict bladder cancer-specific survival and overall survival. On univariable analysis, PBT as a categorical variable had no impact on CSS ($p = 0.352$) or OS ($p = 0.183$) (not shown). When PBT was analyzed as a continuous variable, however, accounting for the number of units received, it was then associated with OS (HR 1.12, CI 1.03-1.22; $p = 0.008$) and with CSS (HR 1.12, CI 1.00-1.25; $p = 0.049$), Table 2; this means that each additional unit of PRBC during a transfusion was associated with an increased risk of death. Nevertheless, when this continuous variable was evaluated in multivariable analysis, controlling for age, chemotherapy use, pathological stage, and

TABLE 2. **Cox regression analysis-disease-specific survival**

Variable	Univariable regression analysis			Multivariable regression analysis		
	HR	p value	95% CI	HR	p value	95% CI
Transfusion	1.12	0.049	1.00-1.25	1.20	0.300	0.85-1.69
Age	1.02	0.007	1.01-1.04	1.02	0.024	1.00-1.03
Neoadjuvant	2.35	< 0.001	1.53-3.63	2.34	< 0.001	1.49-3.68
Path stage						
T0	1.39	0.621	0.38-5.14	1.22	0.762	0.33-4.56
T1	2.37	0.046	1.01-5.55	3.04	0.012	1.27-7.24
T2	3.59	0.002	1.62-7.94	3.88	0.001	1.74-8.67
T3	5.53	< 0.001	2.75-11.14	5.68	< 0.001	2.74-11.75
T4	13.62	< 0.001	6.58-28.22	10.14	< 0.001	4.72-21.75
Lymph nodes						
N+	4.23	< 0.001	2.96-6.04	2.61	< 0.001	1.78-3.83
Nx	1.88	0.014	1.13-3.12	1.89	0.019	1.11-3.21

TABLE 3. **Cox regression analysis-overall survival**

Variable	Univariable regression analysis			Multivariable regression analysis		
	HR	p value	95% CI	HR	p value	95% CI
Transfusion	1.12	0.008	1.03-1.22	1.15	0.246	0.91-1.45
Age	1.05	< 0.001	1.04-1.06	1.05	< 0.001	1.03-1.06
Neoadjuvant	1.95	< 0.001	1.38-2.74	2.11	< 0.001	1.49-2.98
Path stage						
T0	0.95	0.884	0.46-1.93	0.83	0.578	0.43-1.60
T1	0.94	0.796	0.58-1.52	1.11	0.664	0.70-1.74
T2	1.59	0.026	1.06-2.39	1.33	0.162	0.89-2.00
T3	2.45	< 0.001	2.54-5.74	2.01	< 0.001	1.45-2.79
T4	3.82	< 0.001	6.58-28.22	2.58	< 0.001	1.72-3.88
Lymph nodes						
N+	2.82	< 0.001	2.16-3.69	2.41	< 0.001	1.83-3.18
Nx	1.16	0.434	0.80-1.67	1.48	0.020	1.06-2.05

nodal status, PBT was not found to be an independent predictor of outcome for either CSS (p = 0.300) or OS (p = 0.246), Table 3.

Kaplan-Meier survival analysis was also performed with PBT as a categorical variable and as a continuous variable. When studied as a categorical variable, Kaplan-Meier analysis revealed no difference between the transfused and non-transfused groups in disease specific survival (p = 0.350) or OS (p = 0.181) after 5 years, (not shown). The 5 year CSS rates were 73% for the non-transfused cohort and 69% for the transfused cohort. The 5 year OS rates were 60% for the non-transfused cohort and 50% for the transfused cohort. When studied as a continuous variable, accounting for the number of units of PRBC, Kaplan-Meier analysis showed a decrease in the OS as each additional unit of PRBC was transfused (p = 0.021); however, there was no difference in disease-specific survival DSS (p = 0.124), Figure 1.

Discussion

This study investigated the impact of perioperative blood transfusion on bladder cancer-specific survival and overall survival in the setting of radical cystectomy for urothelial carcinoma of the bladder. Our results from univariable analysis revealed that PBT as a continuous variable was strongly associated with an increased

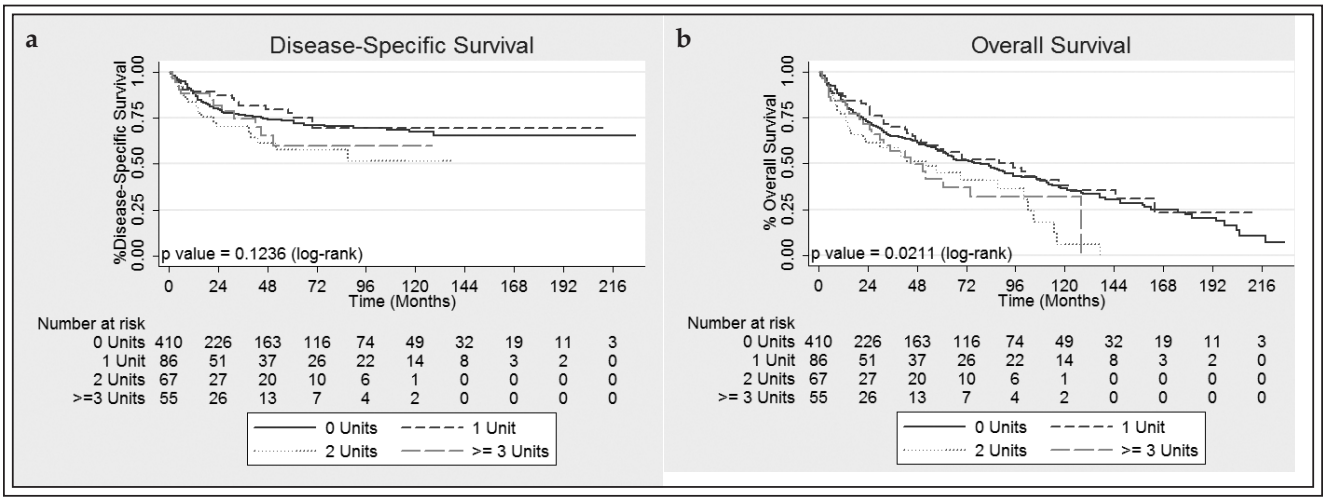

Figure 1. Kaplan-Meier survival analysis of PBT as a continuous variable. **a)** Disease-specific survival (p = 0.124); **b)** Overall survival (p = 0.0211).

risk of cancer-related death (p = 0.049) and overall mortality (p = 0.008). In addition, survival analysis using Kaplan-Meier analysis showed an increased risk of overall death as each additional unit of PRBC was transfused (p = 0.021). However, the administration of additional units of PRBC did not independently modulate this mortality risk after controlling for age, chemotherapy use, pathological stage, and nodal status on multivariable analysis (p > 0.05).

One potential explanation for this study's univariable association between PBT and the increased risk of death involves the selective transfusion of more critically ill patients. The decision to transfuse patients at our institution is based on the discretion of the anesthesiologist and surgeon. Generally, patients with more comorbidities and perioperative complications are given more consideration for PBT than their non-transfused counterparts.[5,10,15] Unfortunately, we were not able to characterize the patient comorbidities in this study.

Currently, there is only one published article in the literature that addresses the survival impact of perioperative PBT during radical cystectomy. In a small study of 130 patients, Jahnson et al did not find a difference in CSS between patients who received 0-6 units of PRBC compared to patients who received 7 or more units.[16] The patient population in their study was unique because 128/130 (98%) of their patients received a PBT with 45% of those patients having 7-27 units transfused; additionally, 100/128 (78%) of the patients who received a blood transfusion were treated with neoadjuvant radiation therapy. Our study, in contrast, had 209/638 patients (32.8%) who underwent PBT with a median of 2 units transfused. Most studies report rates similar to ours, with approximately 30%-83% of all patients undergoing a radical cystectomy receiving a PBT with a median of 2-3 units of blood transfused.[5-7,9] Thus the current study includes a patient population and transfusion rate that is more reflective of clinical practice, and, as such, adds a substantial contribution to the literature on this topic.

Since Gantt's comment about the potentially negative effect blood transfusion on tumor growth in 1981, numerous studies have investigated the effect of blood transfusion on disease recurrence and mortality from various types of cancers.[3,14,16-29] Shortly thereafter, researchers began exploring the issue of cancer mortality with respect to autologous versus allogenic blood transfusion. Studies found that allogenic blood transfusion had an adverse effect on survival in comparison to autologous blood transfusion, leading researchers to study the potential benefits of leukoreduction of allogenic blood products.[30] Leukoreduction of blood products was reported to decrease the risk of morbidity and mortality by drastically reducing the burden of allogenic donor leukocytes that lead to immunosuppresion.[10-13] Although the pathophysiologic mechanisms of this immunosuppresion are still unclear, the major histocompatibility complex antigens on the donor leukocytes are thought to downregulate the host's cytotoxic T cells and natural killer cells and also to increase the host's number of suppressor T cells.[11-13,22,31,32] In 1998, the FDA approved the universal use of leukoreduced blood products. Currently, most developed countries, with the exception of the United States, use only leukoreduced blood products. The major significance of these cumulative findings is that most of the studies that report a deleterious effect of blood transfusion on survival use patient data gathered during the pre-leukocyte reduced era of blood transfusion. In turn, perioperative blood transfusions may be acting as a surrogate marker for the presence of leukocytes in the transfused blood. It is therefore difficult to draw definitive conclusions about the potentially harmful effects of blood transfusion without accounting for the use of non-leukocyte reduced blood. Our institution began using only leukoreduced blood products in 1999. We were able to account for the use of non-leukocyte reduced blood by comparing the survival outcomes between PRBC received before versus after 1999. In spite of the literature to support the adverse systemic effects of leukocytes from transfused blood, within this study, the use of non-leukocyte reduced blood did not predict overall or disease-specific survival on multivariable analysis (p > 0.05) (not shown).

Perioperative transfusion may also be acting as a surrogate marker for other variables that are not accounted for in most studies that investigate the effect of blood transfusion on mortality. For example, hypovolemia and intraoperative hypotension have been proven to increase the risk of tumor progression and mortality,[33-36] but these variables are usually absent in most studies. Furthermore, many studies do not control for patient comorbidities. It is reasonable to assume that patients who are sicker are more susceptible to adverse events than patients who are healthier. Thus, the poor outcome attributed to blood transfusion may simply be a reflection of the poor overall health of the patient.

Overall, this study showed that PBT is not an independent predictor of survival in patients with bladder cancer undergoing a radical cystectomy. Further work is required to quantify the strength of these associations, including analyzing a larger sample size and including many more variables such

as patient comorbidities, perioperative volumic status, length of operation, and receipt of autologous or non-autologous blood. We were not able to report specific details about the chemotherapy treatments including the type treatment, duration of chemotherapy, and any potential chemotherapy-associated transfusions outside of the surgical hospitalization. In this study, we defined DSS and OS as death within 90 days of radical cystectomy and death > 90 days after surgery, respectively; however, since it is difficult to ascertain the cause of death with any retrospective study, our disease specific mortality may be inaccurate. Because there are numerous confounding variables, it has traditionally been difficult to ascertain a discrete cause and effect relationship between perioperative blood transfusion and mortality. Despite these considerations, however, this study makes valuable contributions to the current literature by looking at this relationship within a large cohort of bladder cancer patients whose transfusion rates are reflective of national trends. This investigation, however, supports prior research showing no independent increased risk of cancer death due to blood transfusion.

Conclusion

In conclusion, during long term follow up, receipt of a PBT during radical cystectomy was not an independent predictor of CSS or OS. The presence of potentially confounding variables makes it difficult to draw definitive conclusions about the effect of blood transfusion on survival. Further investigation is warranted to definitively establish the interplay between PBT during radical cystectomy and survival. Certainly, these findings, if corroborated by subsequent work, have bearings on perioperative management among patients with bladder cancer. □

References

1. Opelz G, Sengar DP, Mickey MR, Terasaki PI. Effect of blood transfusions on subsequent kidney transplants. *Transplant Proc* 1973;5(1):253-259.
2. Opelz G, Graver B, Terasaki PI. Induction of high kidney graft survival rate by multiple transfusion. *Lancet* 1981;1(8232): 1223-1225.
3. Gantt CL. Red blood cells for cancer patients. *Lancet* 1981; 2(8242):363.
4. Goodnough LT, Brecher ME, Kanter MH, AuBuchon JP. Transfusion medicine. First of two parts--blood transfusion. *N Engl J Med* 1999;340(6):438-447.
5. Chang SS, Smith JJA, Wells N, Peterson M, Kovach B, Cookson MS. Estimated blood loss and transfusion requirements of radical cystectomy. *J Urol* 2001;166(6):2151-2154.
6. Rosario DJ, Becker M, Anderson JB. The changing pattern of mortality and morbidity from radical cystectomy. *BJU Int* 2000; 85(4):427-430.
7. Lee KL, Freiha F, Presti JC, Gill HS. Gender differences in radical cystectomy: complications and blood loss. *Urology* 2004;63(6): 1095-1099.
8. Parekh DJ, Gilbert WB, Koch MO, Smith JA. Continent urinary reconstruction versus ileal conduit: a contemporary single-institution comparison of perioperative morbidity and mortality. *Urology* 2000;55(6):852-855.
9. Koch MO, Seckin B, Smith JJA. Impact of a collaborative care approach to radical cystectomy and urinary reconstruction. *J Urol* 1995;154(3):996-1001.
10. Hébert PC, Wells G, Blajchman MA et al. A Multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999;340(6):409-417.
11. Bordin JO, Bardossy L, Blajchman MA. Growth enhancement of established tumors by allogeneic blood transfusion in experimental animals and its amelioration by leukodepletion: the importance of the timing of the leukodepletion. *Blood* 1994;84(1):344-348.
12. Blajchman MA, Bordin JO. The tumor growth-promoting effect of allogeneic blood transfusions. *Immunol Invest* 1995;24(1-2): 311-317.
13. Vamvakas EC, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. *Blood* 2009;113(15): 3406-3417.
14. Vamvakas EC. Transfusion-associated cancer recurrence and postoperative infection: meta-analysis of randomized, controlled clinical trials. *Transfusion* 1996;36(2):175-186.
15. Corwin HL, Carson JL. Blood transfusion — when is more really less? *N Engl J Med* 2007;356(16):1667-1669.
16. Jahnson S, Bergstrom R, Pedersen J. Extent of blood transfusion and cancer-related mortality after cystectomy and urinary diversion for bladder cancer. *Br J Urol* 1994;74(6):779-784.
17. Busch O, Hop W, van Papendrecht MH, Marquet RL, Jeekel J. Blood transfusions and prognosis in colorectal cancer. *N Engl J Med* 1993;328(19):1372-1376.
18. Edna TH, Vada K, Hesselberg F, Mjolnerod OK. Blood transfusion and survival following surgery for renal carcinoma. *Br J Urol* 1992;70(2): 135-138.
19. Heal JM, Chuang C, Blumberg N. Perioperative blood transfusions and prostate cancer recurrence and survival. *Am J Surg* 1988;156(5): 374-380.
20. McClinton S, Moffat LE, Scott S, Urbaniak SJ, Kerridge DF. Blood transfusion and survival following surgery for prostatic carcinoma. *Br J Surg* 1990;77(2):140-142.
21. Moir MS, Samy RN, Hanasono MM, Terris DJ. Autologous and heterologous blood transfusion in head and neck cancer surgery. *Arch Otolaryngol Head Neck Surg* 1999;125(8):864-868.
22. Lin HS, Samy RN, Lum J, Dorie MJ, Terris DJ. Effect of blood transfusion in an experimental sarcoma model. *Arch Otolaryngol Head Neck Surg* 2002;128(3):308-312.
23. Shiba H, Ishida Y, Wakiyama S et al. Negative impact of blood transfusion on recurrence and prognosis of hepatocellular carcinoma after hepatic resection. *J Gastrointest Surg* 2009;13(9): 1636-1642.
24. Kooby DA, Stockman J, Ben-Porat L et al. Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. *Ann Surg* 2003;237(6): 860-869; discussion 9-70.
25. Rosen CB, Nagorney DM, Taswell HF et al. Perioperative blood transfusion and determinants of survival after liver resection for metastatic colorectal carcinoma. *Ann Surg* 1992;216(4):493-504; discussion 504-505.

26. Ford BS, Sharma S, Rezaishiraz H, Huben RS, Mohler JL. Effect of perioperative blood transfusion on prostate cancer recurrence. *Urol Oncol* 2008;26(4):364-367.
27. Newman E, Ho M, Heslin MJ, Chapman DS, Brennan MF. The effect of blood transfusion on tumor growth in sarcoma-bearing rats. *Ann Surg Oncol* 1996;3(1):74-79.
28. Chang CM, Quinlan SC, Warren JL, Engels EA. Blood transfusions and the subsequent risk of hematologic malignancies. *Transfusion* 2010;50(10):2249-2257.
29. Eickhoff JH, Gote H, Baeck J. Peri-operative blood transfusion in relation to tumour recurrence and death after surgery for prostatic cancer. *Br J Urol* 1991;68(6):608-611.
30. Blajchman MA, Bordin JO. Mechanisms of transfusion-associated immunosuppression. *Curr Opin Hematol* 1994;1(6):457-461.
31. Opelz G, Vanrenterghem Y, Kirste G et al. Prospective evaluation of pretransplant blood transfusions in cadaver kidney recipients. *Transplantation* 1997;63(7):964-967.
32. Quigley R, Wood K, Morris P. Transfusion induces blood donor-specific suppressor cells. *J Immunol* 1989;142(2):463-470.
33. Younes RN, Rogatko A, Brennan MF. The influence of intraoperative hypotension and perioperative blood transfusion on disease-free survival in patients with complete resection of colorectal liver metastases. *Ann Surg* 1991;214(2):107-113.
34. Younes RN, Rogatko A, Vydelingum NA, Brennan MF. Effects of hypovolemia and transfusion on tumor growth in MCA-tumor-bearing rats. *Surgery* 1991;109(3 Pt1):307-312.
35. Reich DL, Bodian CA, Krol M, Kuroda M, Osinski T, Thys DM. Intraoperative hemodynamic predictors of mortality, stroke, and myocardial infarction after coronary artery bypass surgery. *Anesth Analg* 1999;89(4):814-822.
36. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. *Anesth Analg* 2005; 100(1):4-10.