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Association of perioperative blood transfusion with oncologic outcomes after radical nephroureterectomy for upper tract urothelial carcinoma

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Abstract

Background: To test the hypothesis that perioperative blood transfusion (PBT)impacts oncologic outcomes of patients treated with radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC).
Methods: Retrospective analysis of 2492 patients with UTUC treated at 23 institutions with RNU between 1987 and 2007.Cox regression models addressed the association of PBT with disease recurrence, cancer-specific mortality and any-cause mortality.
Results: A total of 510 patients (20.5%) patients received PBT. Within a median follow-up of 36 months (Interquartile range: 55 months), 663 (26.6%) patients experienced disease recurrence, 545 patients (21.9%) died of UTUC and 884 (35.5%) patients died from any cause. Patients who received PBT were at significantly higher risk of disease recurrence, cancer-specific mortality and overall mortality than patients not receiving PBT in univariable Cox regression analyses. In multivariable Cox regression analyses that adjusted for the effects of standard clinicopathologic features, PBT did not remain associated with disease recurrence (HR: 1.11; 95% CI 0.92–1.33, $p = 0.25$), cancer-specific mortality (HR: 1.09; 95% CI 0.89–1.33, $p = 0.41$) or overall mortality (HR: 1.09; 95% CI 0.93–1.28, $p = 0.29$).
Conclusions: In patients undergoing RNU for UTUC, PBT is associated with disease recurrence, cancer-specific survival or overall survival in univariable, but not in multivariable Cox regression analyses.

Keywords: Upper tract urothelial carcinoma; Radical nephroureterectomy; Blood transfusion; Surgery outcomes; Disease recurrence

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Introduction

Upper tract urothelial carcinoma (UTUC) is a rare disease resulting in a high rate of morbidity and mortality.[1–4] Radical nephroureterectomy (RNU) with excision of a bladder cuff is the gold standard treatment for patients with normal contralateral kidney and high-grade and/or invasive tumors of the renal pelvicalyceal system and ureter.[1–4] Despite technical advances,[5,6] the rate of perioperative blood transfusion (PBT) in patients undergoing RNU ranges from 10 to 15% in large series.[7]

The impact of PBT on cancer outcomes remains controversial. An immunosuppressive effect of the large amounts of antigens present in transfused blood products has been suggested.[8,9] Various studies have shown an association of PBT with tumor recurrence in patients with colon, ovarian, or hepatic carcinoma.[10–12] A recent study on 2060 patients undergoing radical cystectomy (RC) for urothelial carcinoma of the bladder (UCB) revealed a significant association between PBT and increased risk of cancer recurrence and cancer-specific mortality.[8] However, other retrospective cohort studies did not find an association between PBT and UCB outcomes.[9,13]

To date, the effect of PBT on UTUC remains uninvestigated. The aim of our study was to investigate the potential association of PBT and cancer-specific outcomes in UTUC patients undergoing RNU. We hypothesized that PBT is associated with worse oncologic outcomes of UTUC patients treated with RNU.

Patients and methods

Patient selection and data collection

This was an institutional review board approved study with all participating sites providing the necessary institutional data sharing agreements prior to initiation of the study. A total of 23 international centers provided data, which were submitted to a computerized databank. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication, resolution of all identified anomalies was achieved before analysis. Prior to final analysis, the database was frozen, and the final data set was produced. The study population comprised 2492 patients with UTUC who underwent open (n = 2042, 81.9%) or laparoscopic assisted (n = 450, 18.1%) RNU between 1987 and 2007. Patients with a history of muscle-invasive UCB were excluded. Surgery was performed according to the standard criteria for RNU, that is, extrafascial dissection of the kidney with the entire length of ureter and adjacent segment of the bladder cuff.[14] The hilar and regional lymph nodes were generally resected if palpable intraoperatively or enlarged on preoperative imaging. The extent of lymphadenectomy performed was at the discretion of the individual surgeon. No patient received neoadjuvant chemotherapy or radiotherapy. No patient had distant metastatic disease at the time of RNU. PBT was defined as defined as transfusion of allogenic red blood cells during RNU or postoperative hospitalization. Information on PBT was ascertained by chart review.

Pathological evaluation

All surgical specimens were processed according to standard pathologic procedures at each institution. Tumors were staged according to the 2002 American Joint Committee on Cancer–Union Internationale Contre le Cancer (AJCC/UICC) TNM classification, tumor grade was assessed according to the 1998 WHO/International Society of Urologic Pathology (ISUP) consensus classification.[15] In patients graded according to the 1973 classification, tumor grade was reassigned according to the 1998 WHO/International Society of Urologic Pathology (ISUP) consensus classification. Tumor location was defined as either renal pelvic or ureteral. Tumor architecture was defined as papillary or sessile. In case of mixed pattern the predominant architecture was chosen. Tumor multifocality was defined as the synchronous presence of two or more pathologically confirmed tumors in any location (renal pelvicalyceal system or ureter).[14] Lymphovascular invasion (LVI) was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls.[14]

Follow-up

Patients were followed every 3–4 months for the first year following RNU, every 6 months from the second through the fifth year, and annually thereafter. Follow-up consisted of medical history taking, physical examination, routine blood work, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Elective bone scans, chest computerized tomography, or magnetic resonance imaging was performed when clinically indicated. Disease recurrence was defined as tumor relapse in the operative field, regional lymph nodes, and/or distant metastasis. Occurrences of UCB or contralateral upper tract were not coded as disease recurrence. Cause of death was determined by treating physicians, by chart review corroborated by death certificates, or by death certificates alone.[16] All patients who were coded as dead of cancer had previous disease recurrence. Patients who died in the perioperative period (i.e., within 30 days of surgery) were censored at the time of death for UTUC-specific survival analyses.

Statistical analyses

Associations of PBT with categorical variables were assessed using chi-squared tests. Differences in continuous

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variables were analyzed using the Mann–Whitney *U* test. Disease recurrence-free, cancer-specific, and overall survival curves were generated using the Kaplan–Meier method; log rank test was used to compare survival between patients receiving and not receiving PBT. Univariable and multivariable Cox regression models addressed the association of PBT with disease recurrence, cancer-specific mortality and any-cause mortality after RNU. All parameters significantly associated with outcomes in univariable Cox regression analyses were included in multivariable Cox regression analyses. All *p*-values were two-sided and statistical significance was defined as a $p < 0.05$. Statistical analyses were performed using SPSS Statistics® 20 (SPSS®, IBM Corp, Armonk, NY, USA).

Results

Association PBT with clinicopathologic features

Clinicopathologic characteristics of patients and their association with PBT are shown in Table 1. A total of 510 patients (20.5%) received PBT. There were no differences in clinicopathologic features except tumor stage ($p < 0.001$) and history of previous UCB ($p = 0.04$), which was higher in patients receiving PBT.

Association PBT with disease recurrence

Within a median follow-up of 36 months (interquartile range, IQR: 55 months), 663 patients (26.6%) experienced disease recurrence after RNU. Median time to recurrence was 11 months (IQR: 19 months). Actuarial estimate of 5-year recurrence-free survival was 72% ± 1 (standard error) and 63% ± 1 for patients not receiving and receiving PBT, respectively (Fig. 1, $p = 0.001$). PBT was associated with increased risk of disease recurrence in univariable Cox regression analysis (HR: 1.35; 95% CI 1.13–1.61, $p = 0.001$). However, after controlling for the effect of standard clinicopathologic features, PBT was not associated with disease recurrence (HR: 1.11; 95% CI 0.92–1.33, $p = 0.25$; Table 2).

Association PBT with cancer-specific and overall mortality

Within the study period, 545 patients (21.9%) died from UTUC and 884 patients (35.5%) died from any cause, respectively. Actuarial estimate of 5-year cancer-specific and overall survival was 76% ± 1 and 66% ± 1 for patients not receiving PBT and 67% ± 2 and 57% ± 3 for patients receiving PBT, respectively ($p < 0.001$, Fig. 2). In univariable Cox regression analyses, PBT was associated with increased risk of cancer-specific (HR: 1.43; 95% CI 1.18–1.73, $p < 0.001$) and overall mortality (HR: 1.33; 95% CI 1.13–1.55, $p < 0.001$), respectively. In multivariable Cox regression analyses, PBT was not associated with cancer-specific (HR: 1.09; 95% CI 0.89–1.33, $p = 0.41$; Table 2) or overall mortality (HR: 1.09; 95% CI 0.93–1.28, $p = 0.29$; Table 2), respectively.

Subgroup analyses in patients with organ-confined and non organ-confined UTUC

In patients with organ-confined UTUC (tumor stage ≤ pT2, pN0 or pNx) or patients with positive lymph nodes (any tumor stage, pN+), no difference in disease recurrence, cancer-specific mortality and overall mortality could be found in univariable analyses between patients not receiving and receiving PBT. In patients with non organ-confined tumors (tumor stage ≥ pT3, pN0 or pNx), PBT was associated with increased risk of disease recurrence (HR: 1.34; 95% CI 1.06–1.69, $p = 0.02$), cancer-specific mortality (HR: 1.43; 95% CI 1.11–1.84, $p = 0.006$) and overall mortality (HR: 1.36; 95% CI 1.09–1.70, $p = 0.008$) in univariable- but not in multivariable analyses.

Discussion

In the current multi-institutional UTUC study we could not reveal an independent association of PBT with disease-recurrence, cancer-specific mortality or overall mortality. While the association of PBT with cancer-related outcomes in UTUC has not been investigated previously, several studies in other cancer types found comparable results. In a retrospective study on 638 patients undergoing RC for UCB, PBT was associated with cancer-specific and any-cause mortality in univariable, but not in multivariable analyses.[13] Similar results were obtained from another retrospective study on 777 consecutive patients undergoing RC for UCB where PBT was associated with increased risk of overall mortality in univariable analysis.[9] This association retained its significance in a standard multivariable Cox proportional hazards model, in which continuous variables were assumed to have linear relationships with outcomes. However, after adjusting for non-linear relationships between continuous independent variables and outcomes, PBT was not significantly associated with overall mortality.[9] Similarly, a recent retrospective, multicenter analysis of 2895 patients found that PBT at RC was associated with increased risk for disease recurrence, cancer-specific mortality, and any-cause mortality in univariable, but not multivariable analyses.[17] In contrast, a single-center study on 2060 patients undergoing RC for UCB found PBT significantly associated with increased risk of cancer recurrence, cancer-specific and any-cause mortality.[8] Patients receiving PBT were 31% more likely to die from UCB than patients who did not receive PBT. Furthermore, each unit of blood received was associated with a 7% increase in risk of cancer-specific mortality.[8]

The mechanisms underlying the potential cancer-promoting effect of PBT are not completely understood.

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Table 1
Clinicopathologic characteristics of the 2492 patients who underwent radical nephroureterectomy for upper tract urothelial carcinoma.

Characteristics	Total	No PBT	PBT	*p* Value
Number of patients (n,%)	2492	1982 (79.5)	510 (20.5)	–
Age (years)				
Mean (SD)	68.2 (10.7)	68.1 (10.8)	68.5 (10.6)	0.54
Median (IQR)	69.0 (62–77)	69.0 (62–77)	70.0 (63–77)	
Gender (n, %)				
Male	1681 (67.5)	1341 (67.7)	304 (66.7)	0.67
Female	811 (32.5)	641 (32.3)	170 (33.3)	
Previous UCB (n, %)				
No	1839 (73.8)	1481 (74.7)	358 (70.2)	0.04
Yes	653 (26.2)	501 (25.3)	152 (29.8)	
Pathological tumor stage (n, %)				
pT0	15 (0.6)	13 (0.7)	2 (0.4)	<0.001
pTa	527 (21.1)	429 (21.6)	98 (19.2)	
pTis	48 (1.9)	39 (2.0)	9 (1.8)	
pT1	555 (22.3)	440 (22.2)	115(22.5)	
pT2	473 (19.0)	388 (16.6)	85 (16.7)	
pT3	754 (30.3)	605 (30.5)	149 (29.2)	
pT4	120 (4.8)	68 (3.4)	52 (10.2)	
Lymph node status				
pN0	595 (23.9)	480 (24.2)	115 (22.5)	0.44
pNx	1675 (67.2)	1332 (67.2)	343 (67.3)	
pN+	222 (8.9)	170 (8.6)	52 (10.2)	
Pathologic grade (n, %)				
No tumors	15 (0.6)	13 (0.7)	2 (0.4)	0.32
Low	389 (15.6)	319 (16.1)	70 (13.7)	
High	2088 (83.8)	1650 (83.2)	438 (85.9)	
Tumor necrosis (n, %)				
Absent	1912 (76.7)	1532 (77.3)	380 (74.5)	0.18
Present	580 (23.3)	450 (22.7)	130 (25.5)	
Tumor lo (n, %)				
Pelvicaliceal system	1613 (64.7)	1284 (64.8)	329 (64.5)	0.91
Ureter	879 (35.3)	698 (35.2)	181 (35.5)	
Multifocal tumor (n, %)				
No	1902 (76.3)	1518 (76.6)	384 (75.3)	0.54
Yes	590 (23.7)	464 (23.4)	126 (24.7)	
Lymphovascular invasion (n, %)				
Absent	1905 (76.4)	1526 (77.0)	379 (74.3)	0.20
Present	587 (23.6)	456 (23.0)	131 (25.7)	
Presence of concomitant Cis (n, %)				
Absent	1914 (76.8)	1538 (77.6)	376 (73.7)	0.07
Present	578 (23.2)	444 (22.4)	134 (26.3)	
Tumor architecture (n, %)				
Papillary	1890 (75.8)	1514 (76.4)	376 (73.7)	0.21
Sessile	602 (24.2)	468 (23.6)	134 (26.3)	
Sur Approach (n, %)				
Open	2042 (81.9)	1613 (81.4)	429 (84.1)	0.15
Laparoscopic	450 (18.1)	369 (18.6)	81 (15.9)	
Administration of adjuvant chemot (n, %)				
No	2245 (90.1)	1792 (90.4)	453 (88.8)	0.28
Yes	247 (9.9)	190 (9.6)	57 (11.2)	
Disease recurrence (n, %)				
No	1829 (73.4)	1485 (74.9)	344 (67.5)	0.001
Yes	663 (26.6)	497 (25.1)	166 (32.5)	
Cancer-specific mortality (n, %)				
No	1947 (78.1)	1579 (79.7)	368 (72.2)	<0.001
Yes	545 (21.9)	403 (20.3)	142 (27.8)	
Any-cause mortality (n, %)				
No	1608 (64.5)	1310 (66.1)	298 (58.4)	<0.001
Yes	884 (35.5)	672 (33.9)	212 (41.6)	

CIS: Carcinoma in situ; PBT: perioperative blood transfusion; UCB: Urothelial cancer of the bladder.

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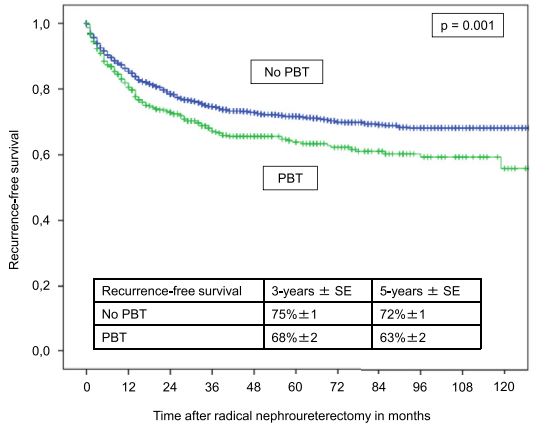

Figure 1. Kaplan–Meier curves depicting recurrence-free survival in 2492 patients who underwent radical nephroureterectomy for upper tract urothelial carcinoma, stratified by administration of perioperative blood transfusion (PBT).

While transfusion-related immune modulation is well established, its influence on the immune competence of the recipient and its effect on cancer progression remain unclear.[18] Transfusion-related immune modulation includes suppression of activity of cytotoxic cells and monocytes, increase of suppressor T-cell activity, and release of various cytokines and growth factors.[18] In patients with hepatocellular carcinoma, postoperative levels of CD8 T-lymphocytes in transfused patients were elevated as compared with a non-transfused group of patients.[19] In addition, the transfusion of red blood cells has been shown to induce a shift of the type1/type-2 CD4 T-helper cell balance toward TH2 dominance in patients undergoing cardiac surgery.[20] However, a dose-effect relationship between number of units transfused and immunologic response could not be established yet. In a syngenic tumor model in rats, blood transfusion was found to be an independent and significant risk factor for cancer progression, causing a doubling in mortality rates.[21] Interestingly, blood storage time (≥9 days) was the critical determinant of these deleterious effects.[21] One potential explanation for this observation may be the detection of various cancer promoting cytokines and growth factors like epidermal growth factor (EGF), platelet-derived growth factor BB (PDGF-BB), and regulated upon activation, normal T cell expressed and secreted (RANTES) in the plasma fraction of stored human packed red blood cells used for blood transfusion.[22] However, these proposed mechanisms warrant further investigation in prospective studies to analyze their impact on cancer outcomes.

When evaluating the impact of PBT on cancer outcomes, it is also crucial to identify the circumstances under which patients were given PBT. In our study, patients receiving PBT had a higher rate of pT4 tumors than patients not receiving PBT. As tumor stage is one of the strongest prognostic factors in UTUC,[23] the detrimental outcomes in patients receiving PBT in our cohort are likely to be driven by the higher rate of patients with advanced tumor stage.

Table 2
Multivariable Cox regression analyses predicting disease recurrence, cancer-specific mortality and any-cause mortality in 2492 patients treated with radical nephroureterectomy for upper urinary tract urothelial cancer.

Characteristics	Disease recurrence			Cancer-specific mortality			Any-cause mortality		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Age (continuous)	1.01	1.00–1.02	0.006	1.02	1.01–1.03	<0.001	1.04	1.03–1.05	<0.001
Previous UCB	–	–	–	–	–	–	1.41	1.22–1.63	<0.001
Pathological tumor stage									
pT0-pTa-pTis-pT1	–	Referent	<0.001	–	Referent	<0.001	–	Referent	<0.001
pT2	2.31	1.74–3.06	<0.001	2.61	1.89–3.60	<0.001	1.52	1.23–1.89	<0.001
pT3	3.86	2.97–5.02	<0.001	4.79	3.55–6.47	<0.001	2.53	2.07–3.09	<0.001
pT4	10.01	7.05–4.22	<0.001	12.28	8.27–18.26	<0.001	6.51	4.74–8.94	<0.001
High grade vs. low grade tumor	1.82	1.16–2.84	0.009	2.03	1.18–3.51	0.01	1.29	1.00–1.67	0.06
Nodal status									
pN0	–	Referent	<0.001	–	Referent	<0.001	–	Referent	0.003
pNx	1.11	0.94–1.39	0.19	1.31	1.04–1.64	0.02	1.12	0.95–1.33	0.18
pN+	1.83	1.42–2.36	<0.001	1.96	1.47–2.61	<0.001	1.53	1.20–1.96	0.001
Tumor multifocality	0.89	0.73–1.05	0.16	0.96	0.79–1.17	0.66	1.00	0.86–1.18	0.93
Laparoscopic surgical approach	–	–	–	0.70	0.53–0.94	0.02	–	–	–
Presence of LVI	1.28	1.07–1.54	0.01	1.31	1.12–1.66	0.002	1.30	1.10–1.53	0.002
Presence of concomitant Cis	1.23	0.95–1.36	0.16	1.03	0.84–1.26	0.77	1.04	0.88–1.22	0.64
Sessile vs. papillary architecture	1.48	1.24–1.77	<0.001	1.40	1.15–1.70	0.001	1.28	1.09–1.51	0.003
Presence of Necrosis	0.96	0.81–1.15	0.67	0.93	0.77–1.13	0.48	1.06	0.91–1.24	0.45
Administration of adjuvant chemotherapy	1.61	1.31–1.98	<0.001	1.47	1.16–1.85	0.001	1.20	0.97–1.47	0.09
Administration of perioperative blood transfusion	1.11	0.92–1.33	0.25	1.09	0.89–1.33	0.41	1.09	0.93–1.28	0.29

CIS: Carcinoma in situ; cont.: continuous, LVI: Lymphovascular invasion; UCB: Urothelial cancer of the bladder.
Blank values indicate non-significance in univariable analyses.

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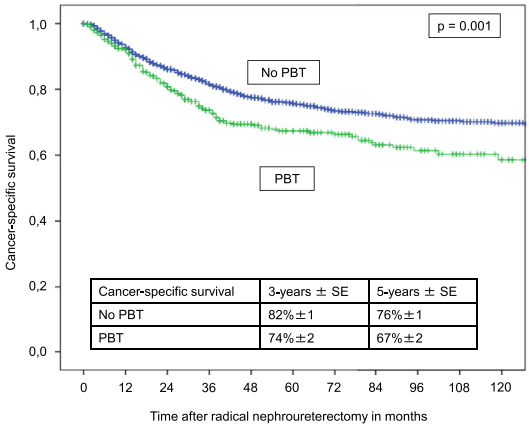

Patient numbers at risk for cancer-specific mortality											
Months	0	12	24	36	48	60	72	84	96	108	120
No PBT	1982	1639	1286	1027	816	652	503	397	332	262	193
PBT	510	420	333	235	185	147	119	90	66	47	34

Figure 2. Kaplan–Meier curves depicting cancer-specific survival in 2492 patients who underwent radical nephroureterectomy for upper tract urothelial carcinoma, stratified by administration of perioperative blood transfusion (PBT).

Comparable results were reported from studies, which found an independent association of PBT with cancer-specific outcomes in UCB patients undergoing RC. Patients who received PBT were significantly older, had a lower ECOG performance status, a higher ASA class, more advanced pathologic tumor stage, a higher rate of lymph node invasion and a higher rate of positive surgical margins.[8,9] Thus, it may be possible that PBT is rather a surrogate for a combination of several unfavorable prognostic factors than the cause of detrimental cancer outcomes.

Our study has several limitations. First and foremost the limitations due its retrospective design which warrant further confirmation in a prospective study. As a multi-center study, the cohort of patients underwent RNU by several surgeons and several pathologists analyzed the pathological specimens. However, all physicians were dedicated to uro-oncology. In addition, administration of PBT was at the discretion of each physician/surgeon and we were not able to ascertain for the indications of PBT. Furthermore, we did not have any information on number of transfused units, so that we were not able to reveal a dose-effect relationship. We also did not have any information on estimated blood loss and were not able to differentiate between intra- and postoperative transfusions, which may have an effect on outcomes. In addition, we did not have information on ASA score or ECOG performance status of the patients, which have been shown to be associated with outcomes in UTUC. Moreover, we were not able to control for several other factors like preoperative hemoglobin, BMI, fresh frozen plasma as well as preoperative blood transfusions which have been shown to reduce the need for PBT.[24] Despite its limitations, this study is the first to assess the impact of PBT on oncologic outcomes of patients with UTUC undergoing RNU.

To conclude, in patients undergoing RNU for UTUC, PBT is associated with disease recurrence, cancer-specific survival or any-cause survival in univariable but not in multivariable Cox regression analysis. It appears likely that not PBT itself, but the conditions necessitating a PBT are prognosticators of outcome of UCB.

Conflict of interest statement

A. Bachmann: Company consult for American Medical Systems, Orion Pharma, Schering, Olympus, Caris Life Sciences.

S.F. Shariat: Advisory board for Ferring Pharmaceutics.

All other authors have nothing to disclose.

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