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Impact of perioperative blood transfusions on clinical outcomes in patients undergoing surgery for major urologic malignancies

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***Abstract*:** The association between allogeneic perioperative blood transfusion (PBT) and decreased survival among patients undergoing various oncological surgeries has been established in various malignant diseases, including colorectal, thoracic and hepatocellular cancer. However, when focusing on urologic tumors, the significance of PBT and its adverse effect remains debatable, mainly due to inconsistency between studies. Nevertheless, the rate of PBT remains high and may reach up to 62% in patients undergoing major urologic surgeries. Hence, the relatively high rate of PBT among related operations, along with the increasing prevalence of several urologic tumors, give this topic great significance in clinical practice. Indeed, recent retrospective studies, followed by systematic reviews in both prostate and bladder cancer surgery have supported the association that has been demonstrated in several malignancies, while other major urologic malignancies, including renal cell carcinoma and upper tract urothelial carcinoma, have also been addressed retrospectively. It is only a matter of time before the data will be sufficient for qualitative systematic review/qualitative evidence synthesis. In the current study, we performed a literature review to define the association between PBT and the oncological outcomes in patients who undergo surgery for major urologic malignancies. We believe that the current review of the literature will increase awareness of the importance and relevance of this issue, as well as highlight the need for evidence-based standards for blood transfusion as well as more controlled transfusion thresholds.

Keywords: bladder cancer, outcomes, perioperative blood cell transfusion, prostate cancer, renal cell carcinoma, survival, upper tract urothelial carcinoma

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Introduction

Perioperative allogeneic red blood cell transfusion (PBT) is often required in patients undergoing major cancer surgery. Lately, many studies have suggested that allogeneic PBT may increase the risk of infectious complications, reduce long-term survival as well as increase cancer recurrence and decrease long-term survival among patients undergoing oncological surgeries for various malignancies, including colorectal, thoracic and hepatocellular cancer.[1–6]

The current literature regarding urological malignancies is somewhat inconsistent. While numerous recent studies have reported an adverse association between blood transfusions and survival after radical cystectomy (RC) for bladder cancer,[7,8] inconsistent data have been described in patients undergoing radical prostatectomy for prostate cancer (PCa)[9–11] or nephrectomy for renal cell carcinoma (RCC).[12–14] To date, the reported incidence of PBT in patients undergoing major urologic surgical procedures reaches up to 62%.[8,12,15] Therefore, determining the impact of transfusion among patients undergoing surgery for urologic malignancies remains highly clinically relevant.

This review was undertaken to address this critical issue. We performed a literature search to investigate the association between PBT and the clinical and oncological outcomes in patients who undergo surgery for major urologic malignancies. Review of the existing literature revealed an association between PBT and the oncological outcomes in patients who undergo surgery for major urologic malignancies. Hence, carefully restricted indications for PBT, alternative strategies for blood replacement and surgical techniques to minimize blood loss seems necessary.

Methods

Studies were identified by searches of electronic databases (*Medline, Medline In-process, Embase* and *Cochrane Library* databases). References cited in all full-text articles were also assessed for additional relevant articles. Search words included: 'blood transfusion', 'urology', 'bladder cancer', 'prostate cancer', 'renal cell carcinoma' and 'upper tract urothelial carcinoma'.

Bladder cancer

Bladder cancer (BCa) is one of the most prevalent cancers in developed countries.[16,17] A RC with extended pelvic lymph node dissection remains the gold standard for treatment of muscle-invasive BCa and also in cases of high-risk nonmuscle-invasive BCa.[18,19] Despite being the treatment of choice, RC has relatively high complication rates. These include considerable blood loss and a consequent high transfusion rate. In recent years, numerous attempts have been made to reduce blood loss during RC. Several methods including hemostatic agents (topical and systemic),[20] adding epidural anesthesia to general anesthesia[21] or new technical devices such as the bipolar apparatus (LigaSure), harmonic scalpel or a stapling apparatus and laparoscopic surgeries were suggested as useful tools to lessen blood loss and lower the need for transfusions.[22,23] However, although advances in surgical techniques have led to the reduced transfusion rates in some cystectomy series, open RC remains associated with a rather high transfusion rate. Recent reviews reported estimated intraoperative blood loss between 560 ml and 3,000 ml[24,25] and an incidence of at least one intraoperative blood unit transfusion in up to 67% of procedures[26,27] (Table 1). Laparoscopic RC and specifically robot-assisted laparoscopic RC (RARC) have recently become an alternative to open RC and were proven to be well tolerated and feasible with equivalent oncologic efficacy.[28] Cumulative analyses demonstrated that RARC might provide some advantages concerning estimated blood loss (EBL) and transfusion rates. Despite the significant decrease in EBL, transfusion rates are still relatively high and vary between 7% and 44% in most series[29] (Table 1).

To date, the 5-year overall survival following surgery for BCa is far from optimal, ranging from 42% to 58% (based on preoperative disease stage). Over recent decades, several clinical and pathological parameters have been described as possible risk factors for disease progression and recurrence. Given the known effect of blood transfusion on survival in other malignancies, PBT has been proposed as a possible risk factor of poor survival following RC, and indeed, several observational studies managed to demonstrate an association between PBT and increased morbidity and mortality after RC.[8] Notably, Linder and colleagues revealed that receipt of PBT was associated with poorer recurrence-free survival (RFS; 58% *versus* 64%; $p=0.01$), cancer-specific survival (CSS; 59% *versus* 72%; $p<0.001$), and overall survival (OS; 45% *versus* 63%; $p<0.001$). In support of these findings, Siemens and colleagues demonstrated worse OS and CSS at 5 years among patients with PBT following RC.[30] However, other studies failed to show this correlation and questioned the validity of this association, suggesting that the clinical or pathological features (such as pathological tumor stage or older age) of patients who received PBT, rather than PBT itself, lead to worse outcomes (acting as confounders;[15] Table 1). Trying to clarify this debate, a few studies have tried to summarize the available data in the form of a systematic review (with meta-analysis). The first to conduct such study was You-Lin Wang and colleagues,[7] who reviewed the outcomes available from six previous studies and concluded that PBT was associated with poorer risks of CSS, OS and RFS. A more recent study by Cata and colleagues[31] included eight studies and supported previous results by suggesting that PBT may be associated with a 27%, 29% and 12% reduction in OS, CSS and RFS, respectively, in patients undergoing RC. Given the study limitations, Cata and colleagues rightfully concluded that a well-designed prospective randomized controlled trial (RCT) is needed.

Kidney cancer

RCC accounts for 2–3% of all malignancies in adults. During recent decades, the incidence of

Table 1. Summary of studies in bladder cancer.

Study	Year	*n*	YOS	% PBT	Median FU (m)	Survival analysis (HR, 95% CI)		
						Disease recurrence	Cancer-specific mortality	All-cause mortality
Abel and colleagues[32]	2014	360	2003–2012	67	18.7	Not significant 1.25 (0.9–1.9)	Not significant 1.45 (0.97–2.2)	Not significant 1.2 (0.9–1.7)
Gierth and colleagues[33]	2014	684	1995–2010	61.8	50	Not significant 1.16 (0.9–1.5)	**Significant** 1.35 (1.0–1.8)	**Significant** 1.8 (1.45–2.3)
Kluth and colleagues[34]	2014	2,895	1998–2010	39	36.1	Not significant 1.13 (0.99–1.3)	Not significant 1.1 (0.96–1.3)	Not significant 1.1 (0.99–1.2)
Linder, and colleagues[8]	2013	2,060	1980–2005	62	10.9 (y)	**Significant** 1.2 (1.01–1.4)	**Significant** 1.3 (1.1–1.57)	**Significant** 1.3 (1.1–1.45)
Morgan and colleagues[15]	2013	777	2000–2008	42	25	N/A	N/A	**Significant** 1.17 (1.01–1.4)
Sadeghi and colleagues[35]	2012	638	1989–2010	32.8	25.5	N/A	Not significant 1.2 (0.85–1.7)	Not significant 1.15 (0.9–1.45)
Soubra and colleagues[13]	2015	5,462	1992–2009	20.4	21	N/A	Not significant 1.05 (0.9–1.2)	Not significant 1.1 (0.99–1.2)
Siemens and colleagues[30]	**2017**	**2,593**	**2000–2008**	**62**	*__60__	N/A	**Significant** 1.39 (1.23–1.56)	**Significant** 1.33 (1.20–1.48)

CI, confidence interval; FU, follow up; HR, hazard ratio; N/A, not available, PBT, perioperative blood transfusion; YOS, year of surgery.
*data reported, 5 year survival.

RCC has been increased globally.[36] The increasing trend may be related to a decrease in the average size of tumors at presentation.[37] On the other hand, the rate of RCC-related mortality has increased steadily.[38] To date, the most potentially effective treatment for patients with localized and locally advanced renal masses (cT1–T3) is surgical resection by either partial or radical nephrectomy (PN and RN, respectively). Reported blood transfusion rates after nephrectomy (including PN or RN) show considerable variability ranging from 3.5% to almost 30%.[12,39] These are due to the diversity of procedures, including highly technical operations (laparoscopic or robot-assisted PN) or complex open radical cases in which partial resection is unfeasible due to an unfavorable tumor location or locally advanced tumor growth. Given these factors, as well as the high variability of PBT rate, joined with the increasing data on the adverse effect of PBT in patients undergoing cancer surgery, the risk of bleeding has become one of the most serious complications during and following nephrectomy. Several risk factors for hemorrhage during nephrectomy have been documented, including patient age, high Charlson score, low preoperative hemoglobin level, bigger lesion size, central renal lesions and surgeon/hospital volume quartile.[39,40] Simultaneously, inconsistent results have been reported regarding the association of PBT with RCC recurrence and CSS after nephrectomy (Table 2). While Moffat and colleagues[41] did not detect a significant difference in CSS, Manyonda and colleagues[42] and Mermershtain and colleagues[43] noted that the 5-year CSS was significantly lower in patients who received PBT during PN or RN. Edna and colleagues[44] supported these findings and reported that the number of blood units administrated (>4 units) was also associated with RCC-related mortality. Nevertheless, most early studies examining the effects of PBT on patients undergoing PN or RN were inadequate mainly due to small sample sizes and early patient cohorts. Recently, few large contemporary cohorts, with long-term postoperative follow up began to appear. Linder and colleagues[12] for example, have assessed the relationship between PBT and survival in 2,318 patients with RCC treated with nephrectomy. In this series, the PBT rate was 21% and was associated with poorer OS based on log-rank analyses (56% *versus* 82%; $p < 0.001$) but not CSS.[12] On the other hand, in a larger series by Soubra and colleagues[13] on 14,379 patients with RCC, PBT was associated with better CSS and OS; however, the last was limited given the lack of data regarding additional possible confounders such as tumor size, preoperative hemoglobin, presence of necrosis and capsular invasion, tumor stage and grade.[45,46] A recent study by Abu-Ghanem and colleagues supported these results and indicated an association between PBT administration and adverse RFS (92% *versus* 81%, $p<0.01$), CSS (95% *versus* 85%, $p<0.001$), and OS (81% *versus* 73%, $p<0.001$) in patients undergoing nephrectomy for RCC. Notably, in response to the last issue, Abu-Ghanem and colleagues conducted a multivariate analysis to include the additional clinicopathological variables and discovered that PBT remained significantly associated with increased risks of disease-free survival [hazard ratio (HR) = 2.1, $p=0.02$], metastatic progression (HR = 2.4, $p=0.007$), CSS (HR = 2.5, $p=0.02$) and OS (HR = 2.2, $p=0.001$).[47] Abu-Ghanem and colleagues mentioned that the main effect on prognosis appears only after a follow up of at least 4–5 years.[47]

As opposed to these studies, a multicenter study by Park and colleagues found no association between PBT and prognosis in patients with RCC, following propensity score matching analysis.[14] Recently, Arcaniolo and colleagues[48] addressed this debate by conducting a systematic review and pooled

Table 2. Summary of studies in renal cell carcinoma (RCC).

Study	Year	*n*	YOS	OP type	% PBT	Median FU (m)	Survival analysis (HR, 95% CI)		
							Disease recurrence	Cancer-specific mortality	All-cause mortality
Abu-Ghanem and colleagues[49]	2017	1,159	1987–2013	PN, RN	17	63.2	**Significant** 2.1 (1.1–3.9)	**Significant** 2.8 (1.3–5.9)	**Significant** 2.2 (1.4–3.5)
Edna and colleagues[44] *>4 units	1992	201	1974–1987	RN	77	N/A	N/A	**Significant** 2.0 (1.2–3.2)	N/A
Jakobsen and colleagues[50]	1994	208	1982–1994	RN	24	N/A	N/A	N/A	Not significant
Linder and colleagues[12]	2014	2,318	1990–2006	PN, RN	21	9.1 (y)	Not significant 1.04 (N/A)	Not significant 1.15 (0.9–1.5)	**Significant** 1.2 (1.04–1.5)
Manyonda and colleagues[42]	1986	80	1975–1985	RN	69	N/A	N/A	N/A	**Significant** (N/A)
Mermershtain and colleagues[43]	2003	99	1990–1998	RN	14	57	**Significant** (N/A)	N/A	N/A
Moffat and colleagues[41]	1987	126	1973–1985	RN	63	N/A	N/A	N/A	Not significant
Park and colleagues[14]	2016	3,832	N/A	PN, RN	11.7	42	Not significant	Not significant	Not significant
Soubra and colleagues[13]	2015	14,379	1992–2009	PN, RN	10.4	39	N/A	**Significant** 1.36 (1.2–1.6)	**Significant** 1.4 (1.3–1.5)
Soria and colleagues[51]	**2016**	**648**	**2004–2014**	**PN, RN**	**10**	**63**	N/A	**Significant** 2.3 (1.3–4.1)	**Significant** 1.86 (1.2–2.9)

CI, confidence interval; FU, follow up; HR, hazard ratio; N/A, not available; OP, operation; PBT, perioperative blood transfusion; YOS, year of surgery.

analysis of the outcomes of patients undergoing surgery for RCC. By including most of the current evidence, the authors suggest that the use of PBT may be associated with worse oncologic outcomes in patients with RCC undergoing nephrectomy. Notably, the authors concluded that their results should be interpreted with caution, given the intrinsic limitations.[48] Therefore, further validation by a large cohort of patients, preferably a well-designed RCT is still required.

Prostate cancer

Prostate cancer is one of the most prevalent solid tumors in men. With growing awareness of the disease leading to higher uptake of the prostate-specific antigen (PSA) test, more patients are being diagnosed with localized prostate cancer.[52]

At present, radical prostatectomy (RP) is one of the principal management options for localized disease. Historically, RP and particularly open RP (ORP) is associated with substantial operative blood loss and high risk of PBT.[53]

Earlier studies found various preoperative characteristics that predict increased EBL including higher body mass index, prostate volume, operative time, lymph node dissection status and neoadjuvant hormonal therapy. However, parallel to, or maybe due to robust analysis examining all frequently available preoperative factors, the rate of blood loss during open RP has been noticeably reduced in the past decade.[54] Optional explanations include better control of the dorsal venous complex and operative approach. In recent years, the inconsistency in ORP outcomes accelerated the development of less invasive treatment alternatives including laparoscopic RP (LRP) and robotic-assisted LRP (RALP). Despite the relatively low popularity of LRP (mainly due to technical complexity and limited ergonomics), RALP quickly became the standards of care at many centers worldwide.[55] Despite an existing debate regarding the functional and oncological outcomes following RALP in comparison with ORP, there is compelling evidence that RALP is associated with less blood loss and blood transfusion rate. It has been suggested that the positive pressure of the pneumoperitoneum, head-down position as well as meticulous hemostasis, all have a role in reducing intraoperative bleeding.[55,56]

However, despite the significant decrease in PBT rate following RP, the risk of bleeding remains a major concern, mainly since intraoperative bleeding can have an effect on perioperative morbidity, primarily, transfusion requirements.

Given the previously described association between PBT and cancer prognosis and the risk of bleeding following RP, it is evident that the adverse effect of PBT will be investigated in PCa patients. Like with RCC, most studies presented conflicting results (Table 3). To obtain more conclusive results, Su-Liang Li and colleagues[57] have recently conducted a systematic review and meta-analysis of the literature. In their study, Su-Liang Li and colleagues included 10 published studies and a total of 26,698 patients and concluded that allogeneic PBT was associated with reduced biochemical RFS (HR: 1.09; 95% CI: 1.01–1.16; $p = 0.02$), OS (HR: 1.43; 95% CI: 1.24–1.64; $p < 0.01$) and CSS (HR: 1.74; 95% CI: 1.18–2.56; $p = 0.005$) in patients undergoing RP. These findings provide further support for the role of PBT in cancer outcome and the need for better blood conservation strategies.

Upper tract urothelial carcinoma

Upper tract urothelial carcinoma (UTUC) is uncommon and accounts for only 5–10% of urothelial carcinomas. To date, radical nephroureterectomy (RNU) is the gold-standard treatment in patients with normal contralateral kidney and high-grade/invasive pelvicocaliceal or ureteral tumors.[58] Despite significant progress in surgical and medical management, RNU is still associated with a relatively high rate of PBT, which reaches up to 10–15% in large series.[59] Interestingly, although roughly 20% of patients who undergo RNU for UTUC require PBT, only a few recent studies have investigated the possible association between PBT and CSS in patients with UTUC undergoing RNU (Table 4). Rieken and colleagues[60] were the first to examine this association in a retrospective analysis of 2,492 patients at 23 institutions between 1987 and 2007, all treated with nephroureterectomy for UTUC. In their cohort, the PBT rate was approximately 20.5%; PBT was found associated with worse RFS, CSS and OS in univariable but not in multivariable Cox regression analysis. Following this study, Rink and colleagues[61] conducted similar analysis on 285 patients from three German academic institutions and reported a PBT rate of 28.4%, and demonstrated, on a mean follow up of 52 months, that PBT was a risk factor for worse OS but not CSS or RFS in patients with UTUC

Table 3. Summary of studies in prostate cancer (PCa).

Study	Year	*n*	YOS	% PBT	Median FU (m)	Survival analysis (HR, 95% CI)		
						Disease recurrence	Cancer-specific mortality	All-cause mortality
Boehm and colleagues[62] *Allogeneic	2015	11,723	1992–2011	10.4	49	Not significant 0.99 (0.8–1.2)	Not significant 1.3 (0.7–2.2)	Not significant 1.4 (0.9–2.1)
Chalfin and colleagues[63] *Allogeneic	2014	7,443	1994–2012	3.5	6 (y)	Not significant 1.02 (0.7–1.4)	Not significant 1.5 (0.5–4.6)	Not significant 1.55 (0.9–2.5)
Eickhoff and colleagues[64]	1991	156	1978–1986	38	N/A	N/A	0.6 (0.3–1.2)	N/A
Ford and colleagues[65] *Allogeneic	2008	611	1987–2005	19	44	Not significant 1.05 (0.49– 2.2)	N/A	N/A
Kim and colleagues[11]	2016	2,713	1993–2014	16.5	60.2	**Significant** 1.3 (1.01–1.8)	**Significant** 4.6 (1.6–13.3)	**Significant** 2.3 (1.4–3.8)
McClinton and colleagues[66]	1990	246	1977–1982	29	N/A	N/A	N/A	**Significant**
Oefelein and colleagues[67] *Allogeneic	1995	251	1980–1990	89.2	6.1 (y)	**Significant** 1.08 (1.0–1.16)	**Significant** 1.25 (1.1–7.04)	N/A
Paul and colleagues[10]	2006	1,412	1984–2003	56.7	58.2	Not significant	Not significant	Not significant
Yeoh and colleagues[68]	2014	5,110	1991–2005	16.4	9.4–10.2 (y)	Not significant 0.9 (0.4–2)	Not significant 1.7 (0.4–6.5)	Not significant 1.2 (0.9–1.7)

CI, confidence interval; FU, follow up; HR, hazard ratio; N/A, not available; PBT, perioperative blood transfusion; YOS, year of surgery.

treated with RNU (HR: 1.6; 95% CI, 1.055–2.428; $p = 0.027$).

Given these inconsistent results, it may appear likely that in patients undergoing RNU for UTUC, the conditions requiring a PBT are predictors of outcome and not PBT itself. Continuing with this line of thought, a recent systematic review, and meta-analysis by Fei Luo and colleagues[69] recently investigated whether preoperative anemia itself (rather than PBT administration) is an independent risk factor for UTUC following RNU. They showed that among patients with UTUC, those with preoperative anemia had significantly poorer CSS, RFS and OS following radical curative therapy. They then concluded that perioperative anemia might be useful as a useful prognostic predictor for patients with UTUC undergoing RNU. Given the paucity of data, future research is warranted for a better assessment of the prognostic implications of PBT in patients with UTUC.

Association of outcomes with the timing of perioperative transfusion

Concurrently, the immunosuppressive effect of blood transfusion is being explored, and additional mechanisms are being suggested to explain this association. Interestingly, some of the proposed mechanisms, including immune function impairment from anesthetic agents,[70] or decreased host immunity caused by tissue injury are likely to have an added effect during surgery.[71] Hence, suggesting that intraoperative transfusion may potentially have a more significant impact on patient outcomes. In support of this idea, a few recent studies by Abel and colleagues[32] and Moschini and colleagues[72–74] have addressed this issue in patients undergoing BCa surgery and

Table 4. Summary of studies in upper tract urothelial carcinoma (UTUC).

Study	Year	*n*	YOS	% PBT	Median FU (m)	Survival analysis (HR, 95% CI)		
						Disease recurrence	Cancer-specific mortality	All-cause mortality
Rieken and colleagues[60]	2014	2,492	1987–2007	20.5	36	Not significant 1.1 (0.9–1.3)	Not significant 1.09 (0.9–1.3)	Not significant 1.09 (0.9–1.3)
Rink and colleagues[61]	2016	285	1992–2012	28.4	30	Not significant 1.16 (0.7–1.8)	Not significant 1.2 (0.7–2.0)	**Significant** 1.5 (1.1–2.2)

CI, confidence interval; FU, follow up; HR, hazard ratio; PBT, perioperative blood transfusion; YOS, year of surgery.

found that patients who received intraoperative, but not postoperative blood transfusion had inferior survival outcomes. Recently, we investigated this association and demonstrated that intraoperative, but not postoperative blood transfusion, was associated with poorer risk of recurrence and cancer-specific mortality in patients undergoing nephrectomy for RCC.[49] On the contrary, a recent study by Bagrodia and colleagues indicated that blood transfusion administration was not associated with clinical or oncological outcomes in patients with UTUC, regardless of timing (either intraoperatively or postoperatively).[75] Nevertheless, there is still a scarcity of data regarding the timing of transfusion and its effect on oncological outcomes in other malignancies, and further studies are required (Table 5).

Discussion

Several retrospective studies have examined the question of whether PBTs are associated with a higher risk of cancer recurrence following surgery. Overall findings suggest that having a PBT during uro-oncology surgery is associated with adverse oncological outcomes (Figure 1). While the association between prognosis and PBT has been established over the years in various malignant diseases, including several Cochrane studies, when focusing on urological tumors, the question regarding the significance of PBT and its adverse effect has hardly been examined. Over the years, only small, retrospective and mostly old studies have been conducted. However, just recently, there has been a renewed rejuvenation and the subject of PBT in urologic tumors has become a relevant research query. One of the expressions of the rising popularity of the matter is reflected in the recent systematic reviews published, whose primary purpose is to try to summarize the small studies that have emerged over the years to form one crucial conclusion. Systematic reviews in both prostate and BCa surgery have supported the association that has been demonstrated in several malignancies, including colon, thoracic and hepatocellular cancer. It seems that although similar analysis is lacking in other major urologic malignancies, it is only a matter of time before further retrospective studies, followed by systematic reviews will address other tumors, mainly UTUC and RCC. These potentially deleterious effects of allogeneic blood transfusion have been explained by several hypothesized mechanisms, primarily *via* the induction of immunosuppression.

Nevertheless, it has been previously argued, that in the absence of a well-designed RCT, there is no convincing evidence to conclude that red blood cell transfusion to patients undergoing cancer surgery worsens oncological outcomes. Limitations of the retrospective design are mainly attributable to the potential confounding variables or simply incomplete data cohorts. Furthermore, the lack of conclusive guidelines regarding indications for PBT implies some flaws in the previous study design. The decision of whether or not to transfuse is often based on various clinical and laboratory variables, including patient hemodynamic stability, preoperative hemoglobin values and EBL during surgery. However, although many data exist on the best timing of transfusion, substantial variability still exists. One of the potential reasons relates to the fact that the decision to deliver blood transfusion is often derived from clinical judgment and services routines and sometimes exclusively on the primary care physicians' discretionary decision. This practice is mainly problematic in the intraoperative setting, in which different providers (surgeon or anesthetist) may often base their decision to deliver blood only on routines,

Table 5. Summary of studies stratified by timing of perioperative blood transfusion.

Study	Operation	Year	*n*	% PBT		Survival analysis (HR, 95% CI)					
				Intra-OP	Post-OP	Intra-OP			Post-OP		
						Disease recurrence	Cancer-specific mortality	All-cause mortality	Disease recurrence	Cancer-specific mortality	All-cause mortality
Abel and colleagues[32]	RC	2014	360	18	22	NS 1.45 (0.8–2.5)	**Sig 1.8 (1.1–2.9)**	NS 1.5 (1.0–2.2)	NS 1.1 (0.7–1.2)	NS 1.05 (0.6–2)	NS 0.9 (0.5–1.5)
			1,770	23.4	16.1	**Sig 1.45 (1.2–1.8)**	**Sig 1.55 (1.2–1.9)**	**Sig 1.4 (1.2–1.6)**	NS 0.9 (0.7–1.2)	NS 0.9 (0.7–1.2)	NS 1.1 (0.9–1.3)
Moschini and colleagues[72]	RC	2015	1,490	21.6	6.5	**Sig 1.2 (1.03–1.6)**	**Sig 1.6 (1.2–2.3)**	**Sig 1.45 (1.02–2.1)**	NS 1.5 (0.8–2.9)	NS 1.6 (0.8–3.2)	NS 1.4 (0.7–2.6)
Moschini and colleagues[73]	RC	2016	728	N/A	N/A	**Sig 1.4 (1.1–1.97)**	**Sig 1.6 (1.1–2.3)**	**Sig 1.5 (1.1–2.1)**	NS 1.8 (0.9–3)	NS 1.7 (0.96–3)	NS 1.6 (0.95–2.8)
Moschini and colleagues[74]	RC	2017	1,081	11.3	7	[a]NS 1.15 (0.7–1.8)	N/A	N/A	[a]NS 1.3 (0.8–2)	N/A	N/A
			433	28.2	6.5	[a]NS 1.2 (0.6–2.5)	N/A	N/A	[a]NS 1.55 (0.8–2.9)	N/A	N/A
Abu-Ghanem and colleagues[49]	RN, PN	2018	1,168	11.8	6.9	**Sig 2.4 (1.2–4.8)**	**Sig 3.5 (1.6–7.7)**	**Sig 2.1 (1.3–3.5)**	[a]NS 2 (0.8–4.8)	NS 1.4 (0.4–4.9)	**Sig 2.4 (1.3–4.4)**
Bagrodia and colleagues[75]	**RNU**	**2018**	**402**	**6.7**	**10.9**	N/A	N/A	NS **0.95 (0.5–1.78)**	N/A	N/A	N/A

CI, confidence interval; HR, hazard ratio; IntBT, intraoperative blood transfusion; N/A, not available; NS, not statistically significant; OP, operative; PBT, perioperative blood transfusion; PN, partial nephrectomy; PoBT, postoperative blood transfusion; RC, radical cystectomy; RN, radical nephrectomy; RNU, radical nephroureterectomy; Sig, statistically significant.
[a]Distant recurrence.

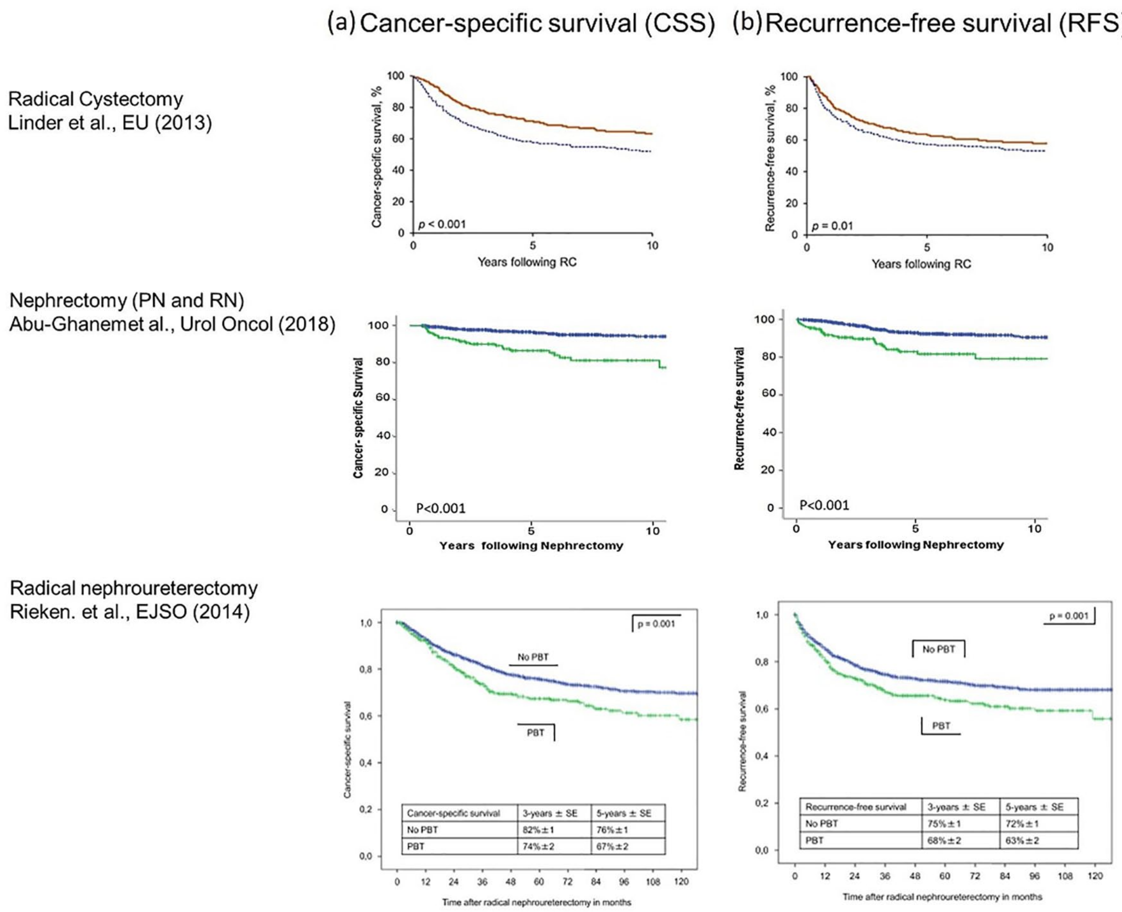

Figure 1. Kaplan–Meier survival analysis assessing distant recurrence in the testing (a) and in validation (b) cohorts of patients treated with radical cystectomy, nephrectomy and radical nephroureterectomy owing to bladder cancer, renal cancer and upper tract urothelial carcinoma (respectively).
CSS, cancer-specific survival; PN, partial nephrectomy; RFS, recurrence-free survival; RN, radical nephrectomy; SE, standard error.

experience, or simply 'intuition'; however, in the presence of existing data, even if it is difficult to ascertain this association at the highest level of evidence, one can still draw a few conclusions:

- Clear transfusion thresholds should be applied.
- Evidence-based guidelines regarding the indications and timing of PBT are needed.
- Alternatives to allogeneic blood transfusions should be explored to minimize the rate of PBT during cancer surgeries.

To date, there are no specific transfusion thresholds nor clear indications for blood administration. We believe that the current review of the literature, emphasizes the need for better blood delivery standards to minimize perioperative blood administration and to avoid the possible 'abuse' of blood products.

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