Review Article

The effect of perioperative blood transfusion on oncological outcomes in radical cystectomy patients: a narrative review

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Abstract: In the last few years, the role of allogeneic blood transfusions (ABTs) on oncological outcomes in patients treated with surgery for various malignancies (i.e., colorectal, kidney and prostate cancer) has been evaluated in several studies. However, only a few data exist regarding the role of transfusions in bladder cancer (BCa) patients treated with radical cystectomy (RC) and results reported in literature are controversial. Therefore, our narrative review aims to summarize the current studies evaluating the complex relationship between perioperative ABT and oncological outcomes in patients who underwent RC for BCa.

Keywords: Bladder cancer (BCa); radical cystectomy (RC); perioperative blood transfusions

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Introduction

Bladder cancer (BCa) is the 6th most common cancer worldwide (1), the second in the genitourinary system with an estimated 80,470 new cases in 2019, and the 9th leading cause of cancer death (2). The majority of BCa is diagnosed after the occurrence of haematuria, with 75% of patients who presents a non-muscle invasive disease (3). However, these patients have a high risk of recurrence (50% of cases) and 20% of risk of progression at 5 years (4). Radical cystectomy (RC) with bilateral pelvic lymph node dissection (PLND) (3) represents the standard of care of very high-risk non-muscle invasive BCa and of muscle-invasive BCa. Nowadays, open radical cystectomy (ORC) is the most commonly performed surgical technique: however, in the last decade, minimally invasive surgical approaches including laparoscopic (LRC) or robotic radical cystectomy (RARC) (5) have spread worldwide. Although the introduction of these procedures, RC remains a complex surgery, burdened by high rates of perioperative morbidity and mortality: about 60% of the cases suffers from at least one complication within 90 days after surgery (6), and 30- and 90-day postoperative mortality rates are around 3% and 7%, respectively (7). Among the most common complications, there is intraoperative bleeding, which can require or not blood transfusions (BTs). This complication could be attributed to two main factors: first of all, to the technical complexity of the procedure and, secondly, to patients' population which usually includes elderly patients with significant comorbidities. Moreover, the neoplasm itself can bleed, causing preoperative anaemia which can increase the risk of postoperative complications

and the need of transfusions. Perioperative transfusion rate in patients undergoing RC is around 60% (8,9). Several studies suggested that perioperative BTs might have an impact on survival outcomes in RC patients but results reported in literature are controversial. For this reason, we sought to review the current available studies to evaluate the association between allogeneic blood transfusions (ABTs) and survival outcomes in patients treated with RC and PLND with curative intent for BCa.

Evidence acquisition

We searched the Medline/PubMed database using individual or/and different combinations of terms including: "bladder cancer", "urothelial carcinoma of the bladder", "radical cystectomy", "perioperative blood transfusion", "cancer recurrence", "survival", "oncological outcomes" and "mortality". Only title and abstract in English language were screened for eligibility: if included, the full text was analyzed. Our research included original article and meta-analyses from 2012 to 2019.

The effect of transfusion in surgical patients

Despite the potential life-saving role, BTs could be related to significant complications including transfusion-associated lung injury (TRALI), transmission of infections, and allergic reactions. For these reasons, over the past 40 years, several studies focused their attention on the effect of ABT in patients treated with surgery, identifying both proinflammatory and immunosuppressive effects. The first observations date back in 1973, when Opelz *et al.* (10) reported improved survival rates in renal-transplanted patients who received ABT compared to those who did not. Other observational studies underlined a role of ABT in decreasing the risk of recurrence in autoimmune disorders (such as Crohn's disease) (11) and in spontaneous abortions in women with a history of recurrent abortions (12). On the other side, this immunosuppressive role can lead to deleterious effects: in 1981 Gantt *et al.* (13) suggested a possible association between ABT and increased risk of cancer recurrence and metastases due to the dysregulated recipient's immune system. Other harmful effects include an increased risk of postoperative bacterial infections (14) and activation of latent CMV and HIV infections (15).

Several studies tried to clarify the mechanisms of transfusion-related immunomodulation (TRIM) (16). The TRIM effect is mediated by: (I) immunologically active white blood cells (WBC) that downregulate the recipient's immune system by shifting to immunosuppressive Lymphocytes Th2 responses (17); (II) soluble WBC-derived mediators that induce innate immune cell apoptosis and decrease natural killer cell activity (18); (III) platelet (PLT) and PLT-derived factors; (IV) heme and iron derived by aged and damaged red blood cell (RBC) (named as "storage lesions") (19); finally (V) ubiquitin and (VI) extracellular vesicle (EV) counts which increase with storage duration (20). This mechanism is depicted in *Figure 1*.

Moreover, the intra-operative release of circulating tumor cells caused by surgical manipulation (21) and the decrease of host's immune system due to anaesthetics and opioids (22), could have an impact on oncological outcomes in patients treated with perioperative blood transfusions. These association between ABT and worse survival has been investigated in various malignancies, such as colorectal (23), hepatic (24), esophageal (25) and pancreatic cancer (26). In the urological field, contradictory data have been reported among patients with kidney (27,28), prostate (29,30) and BCa and the impact of ABT in these cancers is not yet clarified.

The oncological effect of transfusion in patients who underwent RC

The studies evaluating the effect of perioperative ABT in BCa patients treated with RC are summarized in *Table 1*. Linder *et al.* (8) in 2013 analyzed 2,060 patients treated with RC: of them, 1,279 received ABT (62%). At multivariable analyses ABT was found associated with an increased risk of tumor recurrence [hazard ratio (HR): 1.20, confidence interval 95% (CI): 1.01–1.42; P value =0.04], of cancer-specific mortality (HR: 1.31, 95% CI: 1.10–1.57; P=0.003) and of all-causes mortality (HR: 1.27, 95% CI: 1.12–1.45; P=0.0002). Similar results were reported by Buchner *et al.* (31) who analyzed a cohort of patients treated with RC in a retrospective single-center study. Of the 722 patients included in the analyses, 473 received ABT which was found significantly associated with a decreased cancer-specific survival (HR: 1.11, 95% CI: 1.06–1.16; P<0.001). The authors performed a sub-analysis, dividing BT into two groups: intraoperative blood transfusion (IBT) and postoperative blood transfusion (PBT): both variables remained significantly associated with reduced cancer specific survival with an HR: 1.08, 95% CI: 1.01–1.15; P=0.23 for IBT and an HR: 1.14, 95% CI: 1.07–1.21; P<0.001 for PBT. Similarly, Syan-Bhanvadia *et al.* (32)

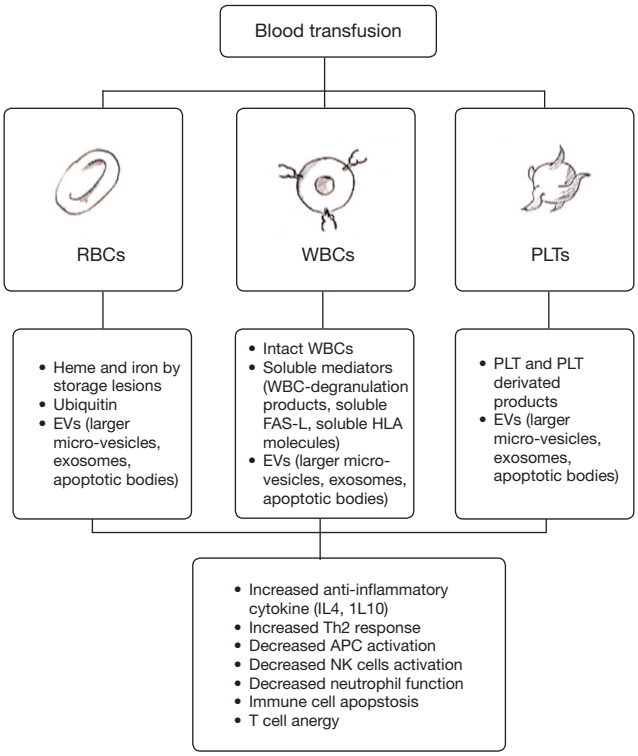

Figure 1 Mechanisms of transfusion-related immunomodulation (TRIM).

found an association between ABT and reduced recurrence-free survival (HR: 2.16, 95% CI: 1.13–41.12; P=0.02) and overall survival (HR 2.25, 95% CI: 1.25–4.88; P=0.01). The authors also suggested a restrictive transfusion protocol which could be safer for patients treated with RC. Similar results were reported in Siemens *et al.* study (33), in which 2,593 patients who underwent RC between 2000 and 2008 were analyzed. Of them, 62% received ABT which was found associated with worse overall survival (HR: 1.33, 95% CI: 1.20–1.48; P<0.001) and cancer-specific survival at 5 years (HR: 1.39, 95% CI: 1.23–1.56; P<0.001).

However, Morgan *et al.* (34) reported conflicting results, depending on the statistical method used for the analyses: in a non-transformed model (in which continuous variables were assumed to have linear relationships with the outcomes), the authors found that ABT (n=323, 41.6%) was associated with a significant higher risk of overall mortality (HR: 1.17; P=0.04). On the contrary, in the second model (a restricted cubic splines model for nonlinear relationships) no association was found between them (HR: 1.03; P=0.29). Soubra *et al.* (35) analyzed the relationship between ABT and mortality in patients who underwent surgical treatment for major urologic cancers, such as bladder, prostate and kidney cancer. In the BCa cohort, the authors reported a significant association between ABT and increased all-causes mortality (HR: 1.109, 95% CI: 1.011–1.21; P=0.028), whereas no significant association between ABT and cancer-specific mortality was reported (HR: 1.052, 95% CI: 0.919–1.204; P=0.4648). Kluth *et al.* (36), in a multicenter retrospective study, did not find an association between ABT and worse oncological outcomes in the multivariable analysis (disease recurrence p = 0.06, cancer-specific mortality P=0.17, any-cause mortality P=0.07). Similarly, in a retrospective single-center study, Lee *et al.* (37) compared patients who received ABT (315, 73% of all patients) to those who did not and no significant association was found between ABT and overall survival in the multivariable analysis (HR: 1.56, 95% CI: 0.98–2.48; P=0.058). Similarly, Vetterlein *et al.* (38) recorded data from 611 patients underwent RC in 2011, of whom 315 (52%) received ABT. The authors found that ABT was not an independent predictor of oncological outcomes, including disease recurrence (HR: 0.96, 95% CI: 0.54–1.70; P=0.9), overall survival (HR: 1.34, 95% CI: 0.90–1.99; P=0.2), cancer-specific mortality (sub-hazard ratio (SHR):1.03, 95% CI: 0.57–1.87; P>0.9) and other-

cause mortality (SHR: 2.16, 95% CI: 0.99–4.74; P=0.054).

Finally, there are only two systematic reviews, published by Wang *et al.* (44) in 2015 and by Cata *et al.* (45) in 2016. In the first meta-analysis ABT was an independent factor to predict all-causes mortality, cancer-specific mortality and cancer recurrence. Similarly, Cata *et al.* (45) found a significant association between ABT and cancer-specific survival, overall survival and recurrence-free survival.

Table 1 Summary of studies evaluating the effect of perioperative allogeneic blood transfusion on survival outcomes in patients who underwent radical cystectomy for bladder cancer

Study	Year of publication	Study design	Number of patients	Transfusion group, n (%)	FU (months)	Type of analysis	Outcomes	Results	P value
Linder *et al.* (8)	2013	Retrospective, single-center	2,060	1,279 (62%)	131	MVA cox regression analysis	CSM; OM; recurrence	HR: 1.31, CI: 1.10–1.57	0.003
								HR: 1.27, CI: 1.12–1.45	0.0002
								HR: 1.20, CI: 1.01–1.42	0.04
Gierth *et al.* (9)	2014	Retrospective, single-center	350	Overall 219 (63%): 183 IBT; 99 PBT; 63 IBT + PBT	70	MVA cox regression analysis	RFS for IBT; RFS for PBT; OS for IPB; OS for PBT	HR: 1.50, CI: 1.27–1.77	<0.001
								HR: 1.56, CI: 1.30–1.88	<0.001
								HR: 1.77, CI: 1.47–2.13	<0.001
								HR: 1.76, CI: 1.41–2.21	<0.001
Buchner *et al.* (31)	2017	Retrospective, single-center	722	Overall 473 (66%): 263 IBT; 132 PBT; 78 IBT + PBT	26	MVA cox regression analysis	CSS for IBT; CSS for PBT	HR:1.08, CI: 1.01–1.15	0.23
								HR: 1.14, CI: 1.07–1–21	<0.001
Syan-Bhanvadia *et al.* (32)	2017	Prospective, single-center	173	46 (27%)	37	MVA cox regression analysis	RFS; OS	HR: 2.16, CI: 1.13–41.12	0.02
								HR: 2.25, CI: 1.25–4.88	0.01
Siemens *et al.* (33)	2017	Retrospective, single-center	2,593	1,608 (62%)	–	MVA cox regression analysis	CSS; OS	HR: 1.33, CI: 1.20–1.48	<0.001
								HR: 1.39, CI: 1.23–1.56	<0.001
Morgan *et al.* (34)	2013	Retrospective, single-center	777	323 (42%)	25.0	Non-transformed model; Restricted cubic splines model	OM	HR: 1.17, CI: 1.01–1.36	0.04
								HR: 1.03, CI: 0.77–1.37	0.29
Soubra *et al.* (35)	2015	Retrospective, multicenter	5,462	1,116 (20%)	21	MVA cox regression analysis	CSM; OM	HR: 1.05, CI: 0.91–1.20	0.4
								HR: 1.10, CI: 1.01–1.21	0.02

Table 1 (*continued*)

Table 1 (*continued*)

Study	Year of publication	Study design	Number of patients	Transfusion group, n (%)	FU (months)	Type of analysis	Outcomes	Results	P value
Kluth *et al.* (36)	2014	Retrospective, multicenter	2,895	1,128 (39%)	36.1	MVA cox regression analysis	CSM; OM; recurrence	HR: 1.10, CI: 0.96–1.27	0.17
								HR: 1.10, CI: 0.99–1.22	0.07
								HR: 1.13, CI: 0.99–1.28	0.06
Lee *et al.* (37)	2015	Retrospective, single-center	432	315 (73%)	39.5	MVA cox regression analysis	OS	HR: 1.56, CI: 0.98–2.48	0.058
Vetterlein *et al.* (38)	2018	Prospective, single-center	611	315 (52%)	26	MVA cox regression analysis and MVA competing-risk analysis	CSM; OS; recurrence	SHR: 1.03, CI: 0.57–1.87	>0.9
								HR: 1.34, CI: 0.90–1.99	0.02
								HR: 0.96, CI: 0.54–1.70	0.9
Abel *et al.* (39)	2014	Retrospective, multicenter	360 (UW); 1,770 (Mayo Clinic)	Overall 241 (67%): 66 IBT; 79 PBT; 98 IBT + PBT. Overall 1,100 (62%): 414 IBT; 285 only PBT; 401 IBT + PBT	18.7; 132	MVA cox regression analysis	CSM for IBT; CSM for PBT; OM for IBT; OM for PBT; Recurrence for IBT; Recurrence for PBT.	HR: 1.49, CI: 1.00–2.25	0.056
								HR: 0.91, CI: 0.54–1.53	0.7
							CSM for IBT; CSM for PBT; OM for IBT; OM for PBT; Recurrence for IBT; Recurrence for PBT	HR: 1.40, CI: 1.20–1.62	<0.0001
								HR: 1.06, CI: 0.88–1.27	0.56
								HR: 1.45, CI: 0.84–2.5	0.18
								HR: 1.11, CI: 0.69–1.19	0.76
								HR: 1.55, CI: 1.24–1.94	0.0001
								HR: 0.89, 0.67–1.18	0.41
								HR: 1.40, CI: 1.20–1.62	<0.0001
								HR: 1.06, CI: 0.88–1.27	0.56
								HR:1.4, CI: 1.16–1.81	0.001
								HR: 0.91, CI: 0.68–1.20	0.49

Table 1 (*continued*)

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Study	Year of publication	Study design	Number of patients	Transfusion group, n (%)	FU (months)	Type of analysis	Outcomes	Results	P value
Moschini *et al.* (40)	2015	Retrospective, single-center	1,490	Overall 580 (39%): 322 IBT 97 PBT 161 IBT + PBT	125	MVA cox regression analysis	Recurrence for IBT; Recurrence for PBT; CSM for IBT; CSM for PBT; OM for IBT; OM for PBT	HR: 1.24, CI: 1.03–1.65	0.04
								HR: 1.50, CI: 0.78–2.89	0.5
								HR: 1.60, CI: 1.20–2.26	0.02
								HR: 1.60, CI: 0.81–3.17	0.2
								HR: 1.45, CI: 1.02–2.08	0.03
								HR: 1.36, CI: 0.72–2.60	0.4
Moschini *et al.* (41)	2016	Retrospective, single-center	728	–	97	MVA cox regression analysis	Recurrence for IBT; Recurrence for PBT	HR: 1.43, CI: 1.15–1.97	0.03
								HR: 1.83, CI: 0.92–3.01	0.1
Moschini *et al.* (42)	2017	Retrospective, single-center	1,081 (testing cohort); 433 (validation cohort)	Overall 445 (42%): 274 IBT; 76 PBT; 122 IBT + PBT. Overall 183 (42%): 122 IBT; 28 PBT; 28 IBT + PBT.	52; 83	MVA cox regression analysis	Distant recurrence for IBT; Distant recurrence for PBT; Distant recurrence for IBT; Distant recurrence for PBT	HR: 1.15, CI: 0.74–1.78	0.5
								HR: 1.32, CI: 0.84–2.05	0.2
								HR: 1.22, CI: 0.6–2.46	0.6
								HR: 1.55, CI: 0.84–2–87	0.4
Sadeghi *et al.* (43)	2012	Retrospective, single-center	638	209 (33%)	25.5	MVA cox regression analysis	CSS OS	HR: 1.2, CI: 0.85–1.69	0.3
								HR: 1.15, CI: 0.91–1.45	0.246

FU, follow up; MVA, multivariable; CSM, cancer-specific mortality; HR, hazard ratio; CI, confidence interval; OM, overall mortality; IBT, intraoperative blood transfusion; PBT, postoperative blood transfusion; RFS, recurrence-free survival; OS, overall survival; CSS, cancer-specific survival; SBH, sub-hazard ratio.

Effect of timing of blood transfusion on survival

Few data exist regarding the role of the timing of ABT, considered as IBT or PBT.

Gierth *et al.* (9) collected data from 350 patients treated with RC. Overall, 219 patients were treated with ABT and 183 (52%) received IBT, whereas 99 (28%) PBT. The authors showed that both IBT and PBT are significant independent predictor of progression-free survival (HR: 1.50, 95% CI: 1.27–1.77; P<0.001 and HR: 1.56, 95% CI: 1.30–1.88; P<0.001 for IBT and PBT, respectively) and overall survival (HR: 1.77, 95% CI: 1.47–2.13; P<0.001 and HR: 1.76, 95% CI: 1.41–2.21; P<0.001 for IBT and PBT, respectively). On the contrary, Buchner *et al.* (31) reported that PBT was associated with a decrease in cancer-specific survival (HR: 1.14, 95% CI: 1.07–1.21; P<0.001), whereas IBT was not significant (HR: 1.08, 95% CI: 1.01–1.15; P=0.23). Abel *et al.* analyzed two different cohorts of patients treated with RC: a primary cohort of 360 patients from University of Wisconsin (UW) and a validation cohort of 1,770 patients from Mayo Clinic and

patients were divided into a group which received IBT and a group which received PBT. In the primary cohort, the authors found that IBT was an independent risk factor for cancer-specific mortality (HR: 1.77, 95% CI: 1.06–2.94; P=0.03), while PBT was not associated with worse survival outcomes. No significant relationship was found for intra and PBT regarding tumor recurrence and all-causes mortality in the same cohort. Moreover, in the validation cohort from Mayo Clinic, IBT was found associated with a significant higher risk of tumor recurrence (HR: 1.45, 95% CI: 1.16–1.81; P=0.001), cancer-specific mortality (HR: 1.55, 95% CI 1.24–1.94; P=0.0001) and all-causes mortality (HR: 1.40, 95% CI: 1.20–1.62; P<0.0001), while PBT was not associated with worsening prognosis. Similarly, Moschini *et al.* (40) recorded data from 1,490 patients who underwent RC between 1990 and 2013. Of them, 322 patients received IBT, 97 received PBT and 161 received both IBT and PBT. In the multivariable analysis patients who received IBT and both IBT and PBT were combined in a single group. The authors found that IBT was an independent risk factor for cancer-specific mortality (HR: 1.6, 95% CI: 1.20–2.26; P=0.02), all-causes mortality (HR: 1.45, 95% CI: 1.02–2.08; P=0.03) and tumor recurrence (HR: 1.24, 95% CI: 1.03–1.65; P=0.04). On the contrary, the administration of PBT was not associated with worse oncological outcomes. The same result was found in another study (41), in which IBT was found significantly associated with cancer-specific mortality and overall mortality, whereas no association was found for PBT (P>0.05). Moreover, Moschini *et al.* (42) in another study, evaluated the risk of distant recurrence after RC in two independent cohorts of patients (testing and validation cohort), considering patients according timing of administration of ABT (IBT *vs.* PBT). In both cohorts, timing of BT was not significantly related to an increased risk of distant recurrence (all P≥0.2).

Number of units transfused

Only a few studies investigated the relationship between number of units transfused and survival outcomes of patients treated with RC.

Linder *et al.* (8) found a positive association between number of units transfused and increased risk of cancer-specific mortality (HR: 1.07; P<0.0001) and all-causes mortality (HR 1.05; P<0.0001): each blood's unit received was associated with a 7% increased risk of cancer-specific mortality. Likewise, Lee *et al.* (37) recorded that an increased number of units transfused (i.e., >4 units) was a significant independent predictor of overall survival (HR: 1.69, 95% CI: 1.15–2.49; P=0.007). Abel *et al.* (39) reported that among patients who received an IBT in the primary cohort from University of Wisconsis, each unit transfused conferred a 17% increased risk of cancer-specific mortality (HR: 1.17, 95% CI: 1.03–1.32; P=0.01), whereas no association was found among patients who received PBT in the same cohort (HR: 1.05, 95% CI: 0.72–1.54; P=0.8). Similar results were reported for the validation cohort from Mayo Clinic (HR: 1.07, 95% CI: 1.03–1.11; P=0.0001 for IBT and HR: 0.92, 95% CI: 0.79–1.06; P=0.26 for PBT). Similarly, Gierth *et al.* (9) found a worse prognosis in terms of progression-free survival and overall survival the more blood units were transfused (P<0.001 for IBT and PBT).

On the contrary, Sadeghi *et al.* (43) analyzed data from 638 patients: of them 209 (33%) received ABT. On multivariable analysis the number of units transfused was not an independent factor to predict cancer-specific survival (P=0.3) and overall survival (P=0.246). In Moschini *et al.* (42) study, the number of unit transfused was not found associated with an increased risk of distant recurrence.

Conclusions

RC represents a complex surgery, which often requires BTs. Several studies have investigated the effects of perioperative blood transfusions in patients with BCa treated with RC, especially in terms of oncological outcomes, investigating also the correct timing of perioperative blood transfusions. Unfortunately, the relationship between ABT and survival outcomes is still unclear, with contrasting results reported in literature: further studies are needed to explain this complex relationship in order to address the medical practice to an individualized treatment and to improve prognosis of these fragile patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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