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ORIGINAL ARTICLE

No impact of blood transfusion on oncological outcome after radical prostatectomy in patients with prostate cancer

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Abstract
Purpose To assess the association between blood loss, blood transfusion (BT) and biochemical recurrence (BCR)-free, metastasis-free and overall survival after radical prostatectomy (RP) in a large single-center cohort of patients. Perioperative BT at oncologic surgery has been reported to be a potential risk factor for cancer recurrence and survival in several cancer entities. Current studies addressing the relationship between BT, blood loss and BCR-free survival in prostate cancer patients are controversial and include only series with fairly small patient cohorts.
Materials and methods The data of 11,723 patients who underwent RP between 01/1992 and 08/2011 were analyzed. Cox regression analysis, including preoperative PSA level, pT stage, lymph node status, Gleason score, margin status, blood loss, transfusion rate (allogeneic or autologous), tested the relationship between blood loss, transfusion and BCR-free, metastasis-free and overall survival. Additionally, propensity score-matching analysis was performed to adjust differences in tumor characteristics.
Results There was no statistically significant relationship between blood loss or BT and BCR-free, metastasis-free or overall survival. In multivariate analysis PSA level, pT stage, Gleason score, margin status and lymph node status were independent factors for a BCR ($p < 0.0001$). These results were identical after propensity score matching analysis, comparing patients with and without BT.
Conclusions This large-scale analysis revealed no correlation between blood loss, blood transfusion and oncological outcome in prostate cancer patients treated with RP. Therefore, the association between higher blood loss or transfusion rate and cancer recurrence as described in other surgical treated tumor entities seems to be irrelevant in prostate cancer patients.

Keywords Prostate cancer · Oncological outcome · Blood transfusion · Radical prostatectomy · Blood loss

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Introduction and objectives

Blood loss and blood transfusion (BT) are prevalent complications in radical prostatectomy (RP). Transfusion rate varies from 1.4 to 67.0 % depending on surgical approach [1]. Data suggest an impact of extensive blood loss and BT on oncological outcome [2–4]. In other tumor entities, i.e. colorectal cancer [5–7] or bladder cancer [8], perioperative BT is an independent predictor for the spread of cancer and cancer recurrence [9–11].

In RP, previous studies revealed controversial results for the outcome related to perioperative BT.

Its oncological impact should therefore be clarified, in particular regarding the ongoing discussion on the role of minimal invasive surgical approaches such as robotic-assisted radical prostatectomy (RARP) or conventional laparoscopic RP (LRP). Such approaches result in less blood loss and lower transfusion rates [12]. If BT rate or extensive blood loss during RP was independently associated with cancer recurrence, this would be a strong argument for the larger utilization of such minimal invasive approaches.

The aim of this study was to assess the association between blood loss, BT rate and biochemical recurrence

(BCR)-free, metastases-free and overall survival in a high-volume single-center cohort of 11,723 patients.

Patients and methods

A total of 14,324 prostate cancer patients who underwent RP between 01/1992, and 08/2011, were included in this study. A total of 2,601 patients with unknown margin status ($n = 159$) or missing data concerning blood loss and transfusion status ($n = 1,825$) were excluded. RP was performed using an open retropubic approach ($n = 11,127$) or robotic-assisted laparoscopic approach ($n = 596$), as described previously [13–16]. Lymph node dissection was performed in D'Amico intermediate-risk patients ($n = 3,874/4,989$) and high-risk patients ($n = 1,580/1,719$) according to the German guidelines for prostate cancer. Bilateral and unilateral nerve-sparing prostatectomy was performed in 64 % ($n = 7,478$) and 24 % ($n = 2,838$) patients. Histopathology was performed by an experienced uropathologist in a high-volume center (>2,000 prostatectomy species per year).

Criteria for BT were a hemoglobin concentration (hgb) <8 g/dl (<10 g/dl in patients with preexisting cardiac conditions) or symptomatic hypotension. BCR was defined as PSA level ≥0.2 ng/ml.

Baseline characteristics in patients who received BT and patients without blood transfusion (NBT) were compared by the chi-square likelihood test for categorical variables

Table 1 Patients' characteristics, stratified by receipt of blood transfusion

	n	Blood transfusion (BT)	No blood transfusion (NBT)	*p* value
Patients *n* (%)	11,723	1,222 (10.4)	10,501 (89.6)	
Allogenic *n* (%)		684 (56)		
Autologous *n* (%)		538 (44)		
BMI, median (IQR)	26 (24–28)	25.5 (24–28)	26 (24–28)	0.0349
Age, year, median (IQR)	64 (59–67)	64 (60–68)	63 (58–67)	0.0004
Blood loss, ml, median (IQR)	750 (500–1,100)	1,200 (800–1,800)	700 (500–1,000)	<0.0001
Prostate vol., ccm, median (IQR)	40 (30–52)	42 (31–58)	40 (30–51)	<0.0001
PSA presurgery, ng/ml				
<4	1,573	154 (12.7)	1,419 (13.6)	0.5871
4–10	7,224	744 (61.3)	6,480 (62.1)	
10–20	2,171	239 (19.7)	1,932 (18.5)	
>20	684	76 (6.3)	608 (5.8)	
Gleason score *n* (%)				
≤3 + 3	3,421	419 (34.3)	3,002 (28.7)	0.0003
3 + 4	6,303	626 (51.3)	5,677 (54.2)	
4 + 3	1,529	136 (11.1)	1,393 (13.3)	
≥4 + 4	443	39 (3.2)	404 (3.9)	
pT stage *n* (%)				
pT2	8,172	901 (73.7)	7,271 (69.2)	<0.0001
pT3a	2,327	185 (15.1)	2,142 (20.4)	
≥pT3b	1,223	136 (11.1)	1,087 (10.4)	
Lymph node status *n* (%)				
NX	4,884	557 (45.7)	4,327 (41.3)	0.0139
N0	6,270	608 (49.8)	5,662 (54.1)	
N1	540	55 (4.5)	485 (4.6)	
ECE				
No *n* (%)	8,316	909 (74.5)	7,407 (70.6)	0.0041
Unilateral *n* (%)	2,503	217 (17.8)	2,286 (21.8)	
Bilateral *n* (%)	890	94 (7.7)	796 (7.6)	
Positive margin status *n* (%)	2,003 (17.1)	206 (16.9)	1,797 (17.1)	0.8223
Follow-up, month, median (IQR)	48.8 (24.6–84.7)	60.4 (24.9–110.6)	48.7 (24.6–84.4)	<0.0001
BCR (yes), *n* (%)	2,155 (19.8)	231 (20.3)	1,924 (19.7)	0.007
Month, median (IQR)	21.6	25.3 (11.5–55.0)	21.1 (7.6–44.7)	

BMI body mass index, *ECE* extra capsular extension, *BCR* biochemical recurrence rate

and by the Wilcoxon test for continuously variables. In Cox regression analysis (log-rank tests), the impact of perioperative BT in RP patients on (a) BCR-free, (b) metastasis-free and (c) overall survival was assessed on this patient cohort.

A propensity score-matched analysis for receiving a BT was performed in a regression model using preoperative PSA, Gleason score, pT stage, pN-status, surgical margin status and year of surgery as covariates. Propensity score-matched analysis was done as previously described [17]. The probability of BCR-free, metastasis-free and overall survival was compared in both treatment groups using Kaplan–Meier analysis and the log-rank test.

All tests were two-tailed, and p values <0.05 were considered statistically significant. Statistical analyses were performed with JMP software v9.0.2 (SAS Institute, Inc., Cary, NC, USA) and R v2.13.1 (R Project for Statistical Computing, www.R-project.org).

Results

About 1,222 of 11,723 (10.4 %) patients received either allogenic (684) or autologous (538) BT. Transfusion rates decreased over the years to a rate of 7.8 % ($n = 167/2{,}127$ RP) in 2011 ($p < 0.0001$). Median blood loss in the transfusion group was 1,200 ml (IQR 800–1,800 ml), and 700 ml (IQR 500–1,000 ml) in the non transfusion group; $p < 0.0001$. Subdivided in kind of surgical approach median blood loss in patients with RARP was 180 versus 800 ml in open prostatectomy ($p < 0.0001$). Transfusion rate was 1.6 versus 11.4 %, respectively.

Patient's characteristics are described in Table 1. Patients who did not received blood transfusion (NBT) showed significant worse tumor characteristics compared with patients with BT. Median follow-up time was 49 month and differed significantly in both groups (60 vs. 49 month).

In multivariate analysis (Cox regression), neither blood loss nor BT rate had a significant association with BCR-free, metastasis-free or overall survival (Table 2).

Propensity score-matched analysis resulted in a cohort of 1,986 patients (993 patients per group), after adjusting for BMI, age, Gleason score, pretreatment PSA, prostate volume, pT stage, lymph node status, margin status and year of surgery, for controlling the differences in the follow-up time. Neither blood loss nor BT was independent predictors for BCR in this subanalyses ($p = 0.1{,}298$ in pT2; $p = 0.2813$ in pT3 tumors; Table 3). In addition, no influence of BT on metastasis-free survival and overall survival could be shown (Fig. 1).

Discussion

This retrospective analysis including the data of more than 11,000 men is the largest cohort of prostate cancer patients

Table 2 Multivariate Cox regression analysis of factors influencing BCR-free, metastasis-free and overall survival (n=1,0381)

Parameters	BCR-free survival			Metastasis-free survival			Overall survival		
	HR	95 % CI	p value	HR	95 % CI	p value	HR	95 % CI	p value
PSA level									
4–10 versus <4	1.16	0.99–1.37	0.06	0.60	0.42–0.89	<0.05	0.81	0.64–1.05	0.11
10–20 versus <4	1.47	1.24–1.74	<0.05	0.62	0.43–0.93	<0.05	0.90	0.68–1.19	0.46
>20 versus <4	1.89	1.57–2.30	<0.05	0.56	0.37–0.87	<0.05	0.75	0.53–1.07	0.11
pT stage									
pT3a versus pT2	1.93	1.73–2.16	<0.05	1.90	1.28–2.84	0.05	0.89	0.70–1.13	0.36
≥pT3b versus pT2	3.15	2.76–3.60	<0.05	4.65	3.14–6.98	<0.05	1.72	1.32–2.24	<0.05
Gleason score									
3 + 4 versus ≤3 + 3	2.41	2.07–2.81	<0.05	4.66	2.34–10.66	<0.05	1.19	0.95–1.48	0.13
4 + 3 versus ≤3 + 3	5.22	4.39–6.21	<0.05	15.98	7.84–37.16	<0.05	2.02	1.51–2.70	<0.05
≥4 + 4 versus ≤3 + 3	5.57	4.49–6.91	<0.05	23.57	11.1–56.43	<0.05	3.47	2.39–5.00	<0.05
Margin status									
R1 versus R0	1.53	1.38–1.68	<0.05	1.50	1.17–1.94	<0.05	1.48	1.22–1.80	<0.05
Lymph node status									
pNx versus pN0	0.81	0.72–0.9	<0.05	0.62	0.41–0.92	<0.05	0.92	0.74–1.14	0.46
pN+ versus pN0	1.43	1.24–1.64	<0.05	1.82	1.36–2.43	<0.05	1.24	0.91–1.67	0.17
Blood loss (per unit)	1.00	1.00–1.00	0.99	1.00	1.00–1.00	0.60	1.00	1.00–1.00	0.23
Transfusion									
Autologous versus no	1.05	0.87–1.25	0.63	0.95	0.55–1.52	0.84	0.86	0.63–1.14	0.30
Allogenic versus no	0.99	0.80–1.22	0.95	1.32	0.74–2.19	0.33	1.42	0.92–2.11	0.11

Table 3 Propensity score matching, patients' characteristics. Patients were matched for age, BMI, prostate volume, PSA level, Gleason score, pT stage, follow-up time, lymph node- and margin status

	BT	NoBT	*p* value
Patients (%)	993 (50)	993 (50)	
Allogenic transfusion (%)	548 (44.8)		
Autologous transfusion (%)	445 (36.4)		
BMI, median (IQR)	25.4 (23.7–27.9)	25.7 (24.1–28.0)	0.5096
Age, years, median (IQR)	64 (60–68)	64 (59–67)	0.112
Blood loss, ml, median (IQR)	1,200 (800–1,800)	800 (500–1,100)	<0.0001
Prostate volume, ccm median (IQR)	43.3 (33–58)	44 (34–59)	0.5427
PSA level, ng/ml (%)			
<4	127 (12.8)	110 (11.1)	0.4447
4–10	604 (60.8)	631 (63.5)	
10–20	199 (20)	199 (20)	
>20	63 (6.3)	53 (5.3)	
Gleason score (%)			
≤3 + 3	340 (34.2)	354 (35.6)	0.6031
3 + 4	509 (51.3)	515 (51.9)	
4 + 3	113 (11.4)	96 (9.7)	
≥4 + 4	31 (3.1)	28 (2.8)	
pT stage (%)			
pT2	727 (73.2)	743 (74.8)	0.6972
pT3a	157 (15.8)	150 (15.1)	
≥pT3b	109 (11)	100 (10.1)	
Lymph node status (%)			
Nx	447 (45)	443 (44.6)	0.8096
N0	505 (50.9)	514 (51.8)	
N+	41 (4.1)	36 (3.6)	
Margin status, R1 (%)	172 (17.3)	142 (14.3)	
Follow-up, months, median (IQR)	49.6 (24-107.8)	49.1 (24.2–96.5)	0.5231

BT blood transfusion group, *NoBT* group without blood transfusion, *BMI* Body mass index, *ECE* extra capsular extension, *BCR* biochemical recurrence rate

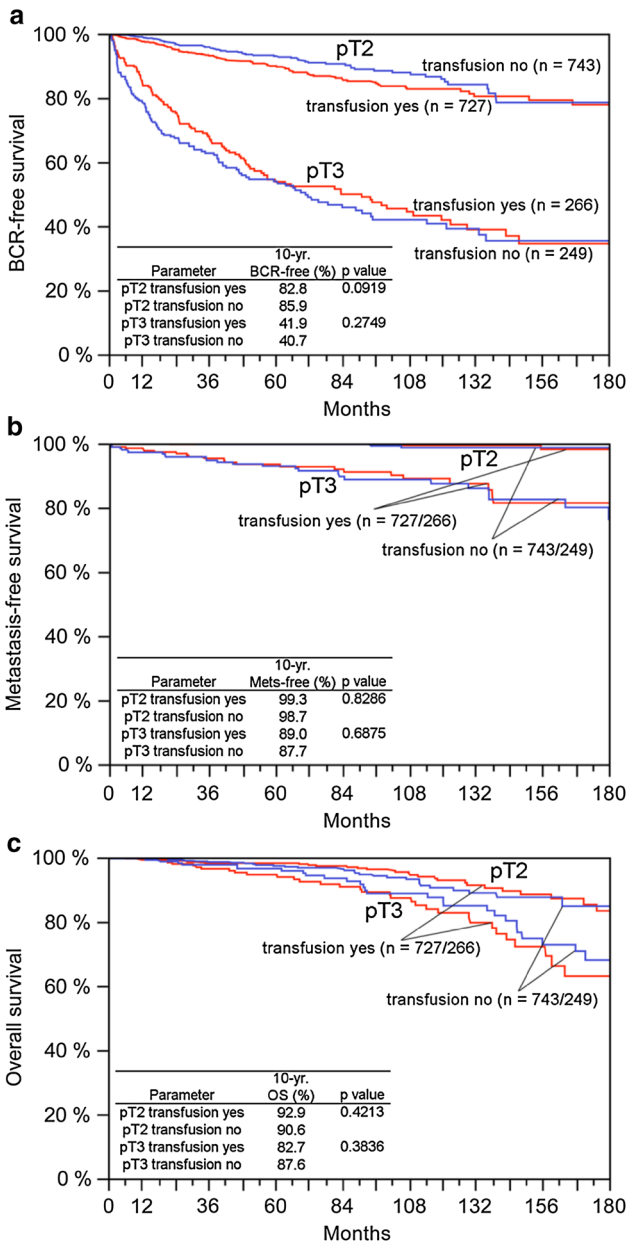

Fig. 1 Kaplan–Meier analysis of 1,968 matched patients, **a** BCR-free survival, **b** metastases-free survival and **c** overall survival in pT2 and pT3 tumors with and without perioperative blood transfusion. *Red curve* = cohort with blood transfusion; *blue curve* = cohort without blood transfusion

analyzing the potential negative effect of BT on oncological outcome. Our results demonstrate that blood loss and/or BT have no negative impact on cancer recurrence rates or development of metastases following RP. Furthermore, BT (allogeneic or autologous) seems not to affect overall survival. These results add important information for the discussion of the role of various existing surgical approaches of RP. The trend to higher blood losses during open RP compared with minimal invasive approaches seems to be irrelevant at least in respect of cancer control. However, there are still possible negative effects of blood loss/blood transfusion such as perioperative infection rates, hemolytic reaction or transfusion-related acute lung injury (TRALI).

Increased blood loss and BT are still one of the most common side effects of RP [18, 19]. Modifications of surgery in open RP over the years and introduction of LRP and RARP combined with an increasing number of operations are being performed in high-volume centers, resulted in a decreased blood loss [19]. Besides this and the decreased transfusion rates, the benefits of minimal invasive techniques

Table 4 Patients characteristics and impact of blood transfusion on BCR rate in four retrospective analyses

	Current study	Gallina et al. [3]	Ford et al. [2]	Lloyd et al. [3]
Patients, *n*	1,1723	1,291	611	1,077
Blood loss, ml, median (IQR)	750 (500–1,100)	1,000 (100–3,000)		900 (600–1,400)
No BT	700 (500–1,000)	1,000 (100–2,400)	929	n.i.
BT allogenic/autologous	1,200 (800 –1,800)	1,000 (300–3,000)	2,818/1,573	n.i.
Transfusion rate	10.4 %	15.9 %	60 %	n.i.
BCR rate overall	16.2 %	26.9 %		32 %
NoBT	16.1 %		14 %	
Allogenic	12.6 %		16 %	
Autologous	23.1 %	20.8 %	10 %	
Impact of BT on BCR	$p = 0.88$	$p = 0.2$	$p = 0.42$	n.i.
Impact of BL on BCR	$p = 0.99$			$p = 0.02$
Impact of BT on metastasis-free survival	$p = 0.60$	n.i.	n.i.	n.i.
Impact of BT on overall survival	$p = 0.13$	n.i.	n.i.	n.i.

NoBT no blood transfusion, *BT* blood transfusion, *BCR* biochemical recurrence rate, *n.i.* not investigated

are still under debate [12]. A meta-analysis of 400 studies showed a median blood loss of 745 ml in RRP, 377 ml in LRP and 188 ml in RARP. The mean BT rate was 16.5 % (RRP), 4.7 % (LRP) and 1.8 % RARP [20]. These results are comparable with our study. Blood loss and transfusion rate in RRP (800 ml; 11.4 %; 95 % CI: 400–1,600 ml) were significantly higher than in RARP (180 ml; 1.6 %; 95 % CI: 50–400 ml). Our analysis revealed a significant higher blood loss in patients with a lower Gleason score and an organ-confined tumor. The rate of metastases was also lower. In these patients, a nerve-sparing procedure might have been performed more often and resulted in a higher blood loss for an improved functional outcome.

The impact of blood loss and transfusion rate on BCR following RP is discussed controversially. Lloyd et al. showed that blood loss/bleeding might have a negative effect on BCR [4], whereas the studies by Gallina et al. [3] and Ford et al. [2] showed no difference in BCR rates comparing patients with BT versus no BT in the perioperative setting. These studies were based on smaller patient cohorts with only $n = 611$ and $n = 1{,}291$ men included (Table 4). The endpoint for these studies was BCR, which is clinical less substantial than metastases-free survival and overall survival.

In colorectal cancer patients, the influence of BT on oncological outcome is an often described phenomenon, as well as in bladder cancer [8]. BT seems to be an independent predictor for the spread of cancer [5] and for cancer recurrence [6]. This could be due to transfusion-related immunosuppression [9], down-regulation of cellular immunity and changes in inflammatory innate immunity [10, 11].

Changes in transfusion standard (storage period, white blood cell reduction, less blood product pooling) in the last decade could be the reason for a reduced immunological reaction related to BT [21]. In Linder's cystectomy- [8] or Lloyd's prostatectomy cohorts [4], patients had a former date of surgery. In our study, the most of the analyzed patients underwent surgery between 2002 and 2011 (9,390 out of 11,723). This might explain the decrease in immunologic response and therefore does not increase BCR rates in our cohort. For this reason, we analyzed a subgroup of patients with RP earlier than 2003 (2,333 patients). BT, given perioperative between 1992 and 2003 had no impact on BCR rate neither in pT2 ($p = 0.3975$) nor in pT3 tumors ($p = 0.7081$, data not shown).

In spite of their strengths, our study is not without limitations: First is its retrospective design, even though the data acquisition was prospective. Secondary, BT may be a minor candidate among various pretreatment and posttreatment clinical and pathological prognostic factors. Therefore, we tried to appease a potential bias by performing propensity score matching. Nonetheless, it is not out of the question that possible confounders were not included in the propensity score matching.

One drawback of this study is that perioperative transfusion was not standardized and the willingness for BT may have changed over the years. As another limitation, our database did not provide information about patients with preoperative anemia who could have received BT even with a lower blood loss. Anyhow, number of patients should be negligible. In other tumor entities, preoperative anemia might influence the oncological outcome as well as the overall survival.

Conclusion

This study with the highest number of patients so far should finally answer the persisting discussion and should ease the

fear that BT has a negative effect on oncological outcome as being described for other tumor entities.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard All patients gave their informed consent prior to data collection. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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