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Comparing Survival and Recurrence in Curative Stage I to III Colorectal Cancer in Transfused and Nontransfused Patients

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Evidence of the association between blood transfusions and its impact on prognostic outcomes in patients who undergo curative resection of colorectal cancer remains controversial. The aim of this study was to determine whether receiving peri-operative blood transfusions during curative colorectal cancer resection affected overall survival, cancer-related survival, and cancer recurrence. This retrospective study was undertaken at The Royal Brisbane and Women's Hospital, Australia, between 1984 and 2004. The outcomes of 1370 patients undergoing curative colorectal cancer resection for TNM stage I to III were analyzed. Four hundred twenty three patients (30.9%) required transfusion and 947 patients (69.1%) did not. Peri-operative transfusion was associated with higher rates of cancer recurrence on multivariate analysis ($P = 0.024$, RR, 1.257, 95% CI, 1.03–1.53); however, it was not independently associated with poorer overall or cancer-related survival. Where the aim is curative resection, this study contributes to a body of evidence that blood transfusions may be associated with poorer outcomes.

Key words: Colorectal cancer – Overall – Cancer-related – Disease-free survival – Recurrence – Transfusion

Colorectal cancer (CRC) is the third most common cancer and the most frequent cancer presenting in the elderly.[1] Each year there are almost 1 million new cases and 500,000 deaths from colorectal cancer worldwide.[1] Colorectal cancer is a common cause of anemia, contributing to a higher incidence of perioperative blood transfusions in these patients.[2] Peri-operative blood transfusions ranging from 10%–68% have been reported for patients undergoing colorectal cancer resection.[3] Blood transfusions have been associated with tumor recurrence and poorer survival through immunomodulation, with many theories of the mechanisms presented in the current literature.

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Table 1 Studies evaluating the association between survival, recurrence, and receiving blood transfusions during colorectal cancer resection

Authors	Year	Study size	Overall survival: 6 Significant 5 Not significant	Cancer-related survival: 4 Significant 5 Not significant	Recurrence: 5 Significant 4 Not significant
Due	2012	855	Not significant	Significant	Not evaluated
Skanberg	2007	640	Significant	Significant	Not evaluated
Nursal	2006	812	Significant	Not significant	Significant
Miki	2006	117	Significant	Not evaluated	Not evaluated
Jagotidsch	2006	885	Not significant	Not significant	Not significant
Mynster	2001	740	Not significant	Not significant	Not significant
van de Watering	2001	697	Significant	Not evaluated	Not significant
Houbiers	1994	871	Significant	Not significant	Not significant
Heiss	1994	30	Not evaluated	Not evaluated	Significant 2 times greater risk
Busch	1993	423	Not significant	Not significant	Not evaluated
Chung (meta-analysis)	1993	5236	Not significant	Significant	Significant
Tang	1993	725	Significant	Significant	Significant
Tartter	1992	339	Not evaluated	Not evaluated	Significant dose-related effect

A literature review was conducted and 11 relevant studies analyzed (see Table 1).[3–15] Current findings in the literature remain controversial. While most studies agree that nontransfused patients had better outcomes, the magnitude of the association of immunomodulation to blood transfusions, and whether the association is a causal one, remains speculative. Thus there is still impetus to establish whether any concrete causal relationship exists.

This is, to our knowledge, the largest study to date, which aims to determine whether receiving perioperative blood transfusions during curative colorectal cancer resection impacts overall survival, cancer-related survival, and cancer recurrence, as well as the independent outcome predictors.[13]

Materials and Methods

Patients

Data were prospectively collated on a computerized database from the records of 1370 patients undergoing curative colorectal cancer treatment at the Department of Surgery, Royal Brisbane and Women's Hospital, between 1984 and 2004. Informed consent from patients, and approval from the Royal Brisbane and Women's Hospital ethics committee was obtained. The Tumour Node Metastasis (TNM) classification system was used to stage patients. All patients with stage I to III colorectal cancer who underwent curative resection were included in this study.

Data collection

Data was collected for age ($\geq$70 years, $<$70 years); sex; pre-operative hemoglobin level ($<$12 g/L, $\geq$12 g/L); tumor site (right: cecum to distal transverse colon, left: splenic flexure to distal rectum); tumor size ($>$7 cm, $\leq$7 cm); tumor type (mucinous, non-mucinous); nodal involvement (N_0, $\geq N_1$); tumor grade (poor, well to moderate); TNM stage (0, 1, 2, 3); procedure category (urgent, elective); surgical complications, medical complications, need for reoperation, and when transfusion occurred (intra-operative, postoperative, peri-operative). Blood transfusion data was obtained from patient records. Patients were considered to have had a blood transfusion if they received any blood product during hospitalization before, during, or after surgery. Anemia was defined by a preoperative hemoglobin level of $<$12 g/L. The indication for receiving a transfusion at any time during hospitalization varied and was dependent on individual physiologic reserve. Procedures were considered urgent if undertaken outside of the routine elective colorectal or general surgery operating lists. Surgical complications included wound infections and dehiscence, paralytic ileus, obstruction, anastomotic leakage, and infective diarrhea that occurred within 30 days of surgery. Medical complications included cardiac arrest, arrhythmias, postoperative heart failure, acute coronary syndrome, pneumonia, pleural effusion, acute respiratory distress syndrome, urinary tract infection, urinary retention, and urinary incontinence that occurred within 30 days of surgery.

Survival

Overall survival was defined as the duration of time from curative resection to death from any cause. Cancer-related survival was defined as the duration

of time from curative resection to death from cancer. The patient follow up protocol consisted of 3 monthly reviews for the first 2 years after surgery, then 6 monthly reviews for the next 3 years, and yearly thereafter. Patients were followed up until death or until lost to followup.

Recurrence

Recurrence or disease-free survival was defined as the duration of time that the patient was disease free, from the time of resection to recurrence. Patients were followed up until recurrence, death, or lost to followup. Recurrence was monitored by carcino-embryonic antigen (CEA) levels, radiologic imaging, and colonoscopy or proctosigmoidoscopy as clinically indicated, and at intervals recommended by the National Health and Medical Research Council (NHMRC) and Australia's Cancer Council Clinical Guidelines for each stage of cancer.

Statistical Analysis

Data from 1370 patients who underwent curative colorectal cancer surgery were analyzed using univariate and multivariate analyses to identify factors significantly associated with overall survival, cancer-related survival, and disease-free survival. All data was displayed as categoric variables only. Chi squared (Fisher exact and Pearson's) testing was used to compare transfused and nontransfused groups and predicted prognostic factors. A P value of <0.05 was considered statistically significant. The Kaplan-Meier model and log rank test was used for univariate analysis of the outcome measures. Five year and median survival probabilities were recorded. The Cox regression model was used for multivariate survival analysis. The logistic regression model was used to determine independent predictors of survival and recurrence. Forward and backward regression analysis of variables identified those with a P value <0.05 and these formed the provisional model. Remaining variables were re-entered into the model as potential confounders. A confounding variable was defined as one where the estimate changed by $\geq 10\%$. Factors found to be significant were assessed for 2-way interactions. Independent prognostic significance was presented as a relative risk (RR) with 95% confidence intervals. All statistical evaluations were conducted using the PASW statistics version 19.0 (2010 SPSS Inc; IM, Chicago, IL).

Results

Patients and tumor characteristics

Of the 1370 patients who received curative surgery for stage I to III colorectal cancer, 423 patients (30.9%) required transfusion and 947 patients (69.1%) did not. Characteristics of the transfused and nontransfused groups are listed and compared in Table 2, and shows that the two groups were well matched for demographics and cancer-related characteristics: 44.4% of transfused patients and 27.7% of nontransfused patients had 1 or more surgical complications ($P < 0.001$), and 24.3% of transfused patients and 13.8% of nontransfused patients had 1 or more medical complications ($P < 0.001$). More reoperations were required (13.2%) during the same admission for transfused patients compared to nontransfused patients (4.8%; Table 2).

Recurrence

Peri-operative blood transfusions were independently associated with earlier cancer recurrence. This result remained significant even when subclassifying patients according to whether they had a transfusion pre-operatively, intra-operatively or postoperatively. Overall peri-operatively, 63.8% of patients in the transfused group and 68.6% in the non-transfused group developed recurrence at 5 years ($P = 0.024$) [see Table 3]. Preoperative hemoglobin was not associated with poorer disease free survival. Multivariate analysis found that sex, stage, lymph node involvement, grade, urgency of procedure, reoperation, perioperative transfusion including postoperative and intraoperative transfusions, were also independently related to recurrence.

Overall survival

On univariate analysis the overall survival was 35.2% in the transfused patients, and 43.8% in the nontransfused patients ($P = 0.001$; Table 4). Multivariate analysis found that age, sex, stage, lymph node involvement, grade, urgency of procedure, medical complications, reoperation, and intra-operative transfusion were all independently related to overall survival. Intraoperative transfusion recipients had a median survival time of 50 months while those who were not transfused or transfused at a different time had a median survival time of 78 and 77 months respectively. This was found to be statistically significant on multivariate analysis (RR

Table 2 Characteristics of 947 nontransfused and 423 transfused patients—Chi squared test

Variable	Nontransfused %	Transfused %	*P* value
Age			
>70 (1)	43.9	48.0	0.177
<70 (0)	56.1	52.0	
Sex			
Male (1)	52.8	47.2	0.218
Female (0)	43.5	56.5	
Pre-operative hemoglobin			
>12 (0)	66.3	56.9	0.001
<12 (1)	33.7	43.1	
Tumor site			
Right (0)	40.7	35.7	0.093
Left (1)	59.3	64.3	
Tumor size			
>7 cm (1)	49.7	44.8	0.126
</=7 cm (0)	50.3	55.2	
Tumour Type			
Mucinous	84.2	15.8	0.808
Nonmucinous	84.8	15.2	
Lymph node			
N_0 (0)	67.1	64.3	0.323
N_1, N_2 (1)	32.9	35.7	
Grade			
Poor (1)	12.2	16.1	0.059
Well/moderate (0)	87.8	83.9	
Stage			
0	1.2	1.2	0.772 (Pearson)
1	18.7	18.6	
2	47.7	45.1	
3	32.4	35.2	
Urgency			
Elective	82.4	85.3	0.183
Emergency	17.6	14.7	
Surgical complications			
Yes	27.7	44.4	<0.001
No	72.3	55.6	
Medical complications			
Yes	13.8	24.3	<0.001
No	86.2	75.7	
Re-operation			
Yes	4.8	13.2	<0.001
No	95.2	86.8	

= 1.31, $P = 0.004$). Pre-operative hemoglobin, peri-operative transfusion, postoperative transfusion, and number of units transfused were not found to be significantly associated with overall survival on multivariate analysis.

Cancer-related survival

On univariate analysis the cancer-related survival in transfused and nontransfused patients was 69.7% and 73% respectively ($P = 0.051$; Table 5). Multivariate analysis found that sex, stage, lymph node involvement, grade, urgency of procedure, medical complications, and intra-operative transfusion were independently associated with cancer-related survival. Pre-operative hemoglobin, peri-operative transfusion, postoperative transfusion, age, and re-operation, were not found to be significantly associated with cancer-related survival on multivariate analysis.

Discussion

Transfusing patients peri-operatively for curative colorectal cancer resection is often done based on immediate clinical and biochemical indicators, with the aim of resuscitation and decreasing peri-operative mortality and morbidity. The indications for blood transfusions have been well established in the literature and include acute or subacute hemorrhage, severe anemia, hemolytic crisis, as well as applying good clinical judgment.[2,7,16] However, the impact of the transfusion on the patient's cancer-related prognosis might not be considered or discussed with the patient.

This is one of the largest studies to date and supports a growing body of evidence suggesting that peri-operative transfusions potentially have a negative impact on cancer related outcomes, particularly cancer recurrence. This finding is important, as alternative resuscitation methods and earlier preoperative optimization may need to be considered more carefully in patients with colorectal cancer.[16] Closer followup protocols may need to be considered in transfused patients.

Blood transfusions have been associated with tumor recurrence and poorer survival possibly due to immunologic factors and have been termed transfusion-related immunomodulation.[17,18] The current literature offers numerous theories as to the exact mechanism of this immunomodulatory effect. Figure 1 summarizes the cell-mediated processes and humoral components involved. Most studies conclude that host down-regulation of immune function by blood transfusion allows cancer cells to escape the immune surveillance system causing micrometastases and recurrence, which then impacts the clinical course of the disease.[19]

Table 3 Factors related to recurrence in patients with stage I to III colorectal cancer

	Patients (died)	Univariate analysis			Multivariate analysis		
Parameter	(tf) n	5 yr[a]	Median[b]	*P* value	RR	95% CI	*P* value
Age							
>70 (1)	66.4	63.1	120				
<70 (0)	68.4	65.4	133	0.331			NS
Sex							
Male	65.3	60.8	101				
Female	69.7	67.9	200	0.006	1.253	1.037–1.514	0.019
Preoperative Hemoglobin							
>12	66.8	63.5	120				
<12	68.9	66.2		0.348			NS
Stage							
Stage 3	48.6	44.6	46				
Stage 1–2	76.7	74.6		0.000	1.707	1.210–2.407	0.002
Lymph node							
N_1, N_2 (1)	48.6	44.6	46				
N_0 (0)	76.7	74.6		0.000	2.182	1.791–2.659	0.000
Grade							
Poor (1)	57.4	56.2	89				
Well/Mod (0)	68.8	65.5	200	0.000	1.378	1.077–1.763	0.011
Urgent							
Yes (Emergency)	57.1	49.0	57				
No (Elective)	69.3	67.1	161	0.000	1.428	1.135–1.797	0.002
Medical complications							
Yes	64.9	52.7	88				
No	67.8	66.2	141	0.002			NS
Re-operation							
Yes	54.9	44.5	49				
No	68.3	65.6	133	0.000	1.632	1.195–2.229	0.002
Intra-op transfusion							
Yes	60.2	55.8	103				
No	68.2	65.8	133	0.017	1.372	1.068–1.763	0.013
Peri-op transfusion							
Yes	63.8	58.9	103				
No	68.6	66.8	133	0.012	1.257	1.030–1.533	0.024
Postop transfusion							
Yes	63.9	57.1	88				
No	68.0	66.2	133	0.017	1.272	1.014–1.594	0.037

NS, not significant.

[a]5-year Kaplan-Meier survival probability.

[b]median survival time.

The studies listed in Table 1 have evaluated the effects of perioperative blood transfusions on patients with colorectal cancer,[3–15] 9 studies[5,7–11,13–15] assessed the effect of blood transfusions on cancer recurrence and 5 studies[5,11,13–15] found that it was significant. However, only 7 of these studies[5,7–10,14,15] used multivariate analysis and of these studies, 3 found an independent association[5,14,15] (Table 6). Eleven studies[3–10,12–14] tested the impact of blood transfusions on overall survival. Of these, 6 studies[4–6,9,10,14] found an independent association (Table 1).

We found that peri-operative blood transfusions were significantly associated with poorer overall survival on univariate alone. Its loss of significance on multivariate analysis suggests that the impact on survival is likely a result of confounding factors.

Table 4 Factors related to overall survival in patients with stage I to III CRC

	Patients (died)	Univariate analysis			Multivariate analysis		
Parameter	(tf) n	5 yr[a]	Median[b]	*P* value	RR	95% CI	*P* value
Age							
>70 (1)	35.3	48.0	55	<0.001	1.82	1.57–2.10	<0.001
<70 (0)	25.7	63.7	93				
Sex							
Male	33.6	51.5	62	0.004	1.31	1.13–1.51	<0.001
Female	27.4	61.6	80				
Pre-op Hb							
>12 (normal)	36.1	58.7	77	0.008			NS
<12	24.5	52.6	64				
Stage							
Stage 3	31.6	42.3	47	<0.001	1.45	1.25–1.67	<0.001
Stage 1–2	46.3	63.6	85				
Lymph node							
N_1, N_2 (1)	24.1	42.6	47	<0.001	1.44	1.25–1.67	<0.001
N_0 (0)	37.0	63.7	85				
Grade							
Poor (1)	9.6	45.4	48	<0.001	1.34	1.11–1.63	0.003
Well/moderate (0)	51.2	58.0	76				
Urgent							
Yes (Emer)	11.2	45.7	50	<0.001	1.30	1.08–1.56	0.006
No (Elec)	49.9	58.3	77				
Medical complications							
Yes	27.4	35.4	39	<0.001	1.63	1.37–1.95	<0.001
No	44.3	60.8	80				
Re-operation							
Yes	5.5	37.1	39	<0.001	1.37	1.07–1.75	0.014
No	55.5	57.8	74				
Peri-op transfusion							
<4 units (0)	38.8	60.0	78	0.001			NS
>4 units (1)	20.0	48.6	57				
Intra-op transfusion							
Yes	30.1	48.4	50	0.012	1.31	1.09–1.59	0.004
no	42.9	57.7	74				
Postop transfusion							
Yes	37.9	45.4	53	0.004			NS
No	42.0	59.3	77				
Peri-op transfusion							
Yes	35.2	48.6	57	0.001			NS
No	43.8	60.0	78				

NS, not significant.

[a]5-year Kaplan-Meier survival probability.

[b]median survival time.

This suggests that the phenomenon could be due to the circumstances that necessitate transfusion rather than the transfusion itself. Tatter *et al* (1992) found a more significant association as the number of units transfused increased; however, this study did not find any significant "dose-related association."[15] Nine studies evaluated the effect of blood transfusion on cancer-related survival and 4 of these found an association; however, only 2 of these were multivariate analysis.[3–5,7,8,10,12–14]

Table 5 Factors related to cancer related survival in patients with stage I to III colorectal cancer

	Patients (died)	Univariate analysis			Multivariate analysis		
Parameter	(tf) n	5 yr[a]	Median[b]	*P* value	RR	95% CI	*P* value
Age							
>70 (1)	71.7	68.5	202				
<70 (0)	72.3	71.2	163	0.565			NS
Sex							
Male	69.4	66.6	111				
Female	75.2	73.8	200	0.001	1.338	1.089−1.644	0.006
Pre-operative hemoglobin							
>12	72.2	70.5	163				
<12	72.6	69.9		0.848			NS
Stage							
Stage 3	53.4	49.7	58				
Stage 1−2	81.4	81.1	240	<0.001	1.783	1.204−2.640	0.004
Lymph node							
N_1, N_2 (1)	53.4	49.7	58				
N_0 (0)	81.4	81.1	240	<0.0001	2.458	1.982−3.047	0.000
Grade							
Poor (1)	60.0	57.9	89				
Well/mod (0)	73.8	71.9	200	0.000	1.568	1.211−2.030	0.001
Urgent							
Yes (Emergency)	62.9	57.6	86				
No (Elective)	73.8	72.4	200	0.000	1.425	1.110−1.829	0.005
Medical complications							
Yes	68.5	57.3	99				
No	72.8	72.3	199	0.000	1.570	1.218−2.025	.001
Re-operation							
Yes	62.4	57.2	96				
No	72.8	71.0	199	0.003			NS
Intra-op transfusion							
Yes	65.9	60.9	133				
No	73.0	71.7	199	0.030	1.338	1.019−1.756	0.036
Peri-op transfusion							
Yes	69.7	63.7	200				
No	73.0	73.1	163	0.051			NS
Postop transfusion							
Yes	70.2	62.1	200				
No	72.5	72.3	199	0.084			NS

NS, not significant.

[a]5-year Kaplan-Meier survival probability.

[b]median survival time.

Complications were higher in the transfused group, and this is consistent with most other studies.[3,5,7–9] The fact that some studies have found postoperative infections to increase with postoperative transfusions only, has led to suggestions that the effect of transfusions is short term as well as long term with recurrence.[4,5,7,8,12] One study found that preoperative transfusion did not increase wound infections after elective colorectal resection; however, this may not apply to this study's sample as preoperative transfusion was associated with lower preoperative hemoglobin and overall poorer physiologic reserve.[5] Mystner *et al* (2000) found that transfusions were not significantly associated with

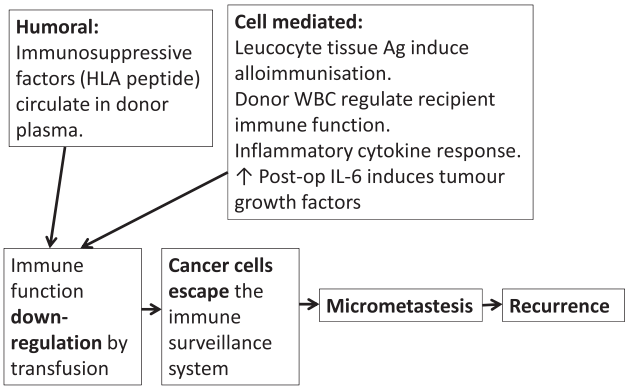

Fig. 1 How blood transfusion affects survival and recurrence in transfusion-related immunomodulation.

reduced survival, but were significantly associated with recurrence, and attributed this mainly to the association between transfusions and postoperative infections.[8] A fatal infectious complication is anastomotic failure, which can also lead to poorer survival and recurrence and has been included in this study as an unmeasured outcome as part of the surgical complications.

Limitations of this study include retrospective data and inclusion of patients between a 20-year period during which time blood product processing has markedly changed. Blood products are now mostly separated rather than pooled, have better infection screening, and superior cross-matching technology. Changing surgical technique and standards of practice over time must also be considered. Randomization is not possible between transfused and nontransfused patients and therefore selection bias will always exist. Survival outcomes based on the type of blood product given were not analyzed as some patients would have received whole blood during the earlier years of this study.

Conclusion

In conclusion, peri-operative blood transfusion in this study was found to increase the likelihood of colorectal cancer recurrence but was not found to be associated with overall survival or cancer-related survival. This study contributes to a body of evidence that blood transfusions may be associated with poorer outcomes and recurrence, and is significant enough to indicate caution. Where the aim is curative resection of colorectal cancer, this study emphasizes the importance of administering blood products with discretion and after considering the short and long-term risks and benefits.

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Table 6 Studies relating to transfusion and recurrence

Author	Year	Study size	Design	Analysis	Recurrence
Nursal	2006	812	Randomized. Single center	Multivariate	Significant
Jagotidsch	2006	885	Single center	Multivariate	Not significant
Mynster	2001	740	Multicenter	Multivariate	Not significant
van de Watering	2001	697	Prospective. Randomized multicenter	Multivariate	Not significant
Houbiers	1994	871	Prospective. Randomized multicenter	Multivariate	Not significant
Heiss	1994	30	Randomized	Univariate	Significant
Chung	1993	5236	20 Study meta-analysis	Odds ratio	Significant
Tang	1993	725	Randomized. Single center	Multivariate	Significant
Tartter	1992	339	Prospective	Multivariate	Significant dose-related effect
Total: 9					5 Significant 4 Not significant

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