

Blood Transfusions and Local Tumor Recurrence in Colorectal Cancer

Evidence of a Noncausal Relationship

Olivier R. C. Busch, M.D.,* Wim C. J. Hop., M.Sc.,† Richard L. Marquet, Ph.D.,* and Johannes Jeekel, Ph.D.*

From the Department of Surgery, University Hospital Rotterdam-Dijkzigt, and the Department of Epidemiology and Biostatistics, Erasmus University,† Rotterdam, The Netherlands*

Objective

The authors analyzed the effect of blood transfusions on the pattern of colorectal cancer recurrence.

Background

Retrospective studies suggest that blood transfusions are associated with a poor prognosis in patients who undergo operations for colorectal malignancies. In a previously published, randomized trial, it was investigated whether autologous blood transfusions could overcome this putative detrimental effect. However, this did not appear to be the case.

Methods

In the current study, the authors analyzed the patterns of recurrence in 420 patients who underwent curative operations for colorectal cancer.

Results

Patients who did not require transfusions (N = 143) had significantly better disease-free survival than those who did need transfusions (N = 277); percentages at 4 years were 73% and 59%, respectively ($p = 0.001$). No difference was found between both groups in comparing cumulative percentages of patients having metastases; percentages at 4 years were 25% in the group that did not undergo transfusion and 27% in the transfused group. The percentage of cases having local recurrence, however, was significantly increased ($p = 0.0006$) in the transfused group as compared with the group that did not undergo transfusion; percentages at 4 years were 20% and 3%, respectively. The groups of patients receiving only allogeneic, only autologous, or both types of transfusions all had a significantly higher incidence of local recurrence than the patients who did not receive transfusions, but no differences were found between these three groups.

Conclusions

These findings suggest that the association between blood transfusions and prognosis in colorectal cancer is a result of the circumstances that necessitate transfusions, leading to the development of local recurrences, but not of distant metastases.

It has been suggested that allogeneic blood transfusions are associated with a poor prognosis of patients who undergo operations for colorectal cancer, possibly because of immunologic factors.¹⁻⁴ A recent meta-anal-

ysis, combining the evidence of 20 published retrospective studies, demonstrated that transfused patients with colorectal cancer generally had a worse prognosis when compared with patients who did not undergo transfu-

sion.⁵ However, in a randomized trial of 475 patients, we did not find that patients transfused with autologous blood had a better prognosis than those patients transfused with allogeneic blood, although transfused patients, receiving either type of blood, had a poorer prognosis than patients who did not receive transfusions.⁶ Therefore, the circumstances necessitating transfusions rather than the blood transfusions themselves are the real determinant of prognosis. Naturally, the need for postoperative transfusions was associated with the amount of blood loss. This might be related to technical difficulties to resect the tumor, and to surgical skill.⁷ These factors also may affect the development of local recurrence, because local recurrences originate from remaining viable local tumor residues,⁸ or local spill.⁹ Previous studies reporting on the effects of blood transfusions on prognosis presented data on survival or disease-free survival. However, in only a few studies, the incidence of local recurrence and metastatic disease was evaluated separately, but did not come to conclusions.¹⁰ In the current study, the relationship between blood transfusions and the patterns of recurrent disease in patients participating in the aforementioned trial was investigated.

METHODS

Those evaluated were patients who underwent curative operations and participated in a randomized, multicenter trial to investigate the effect of autologous blood on prognosis of colorectal cancer as compared with standard allogeneic transfusions. The design of this trial has been described in detail elsewhere.⁶ Briefly, patients with a potentially curative resection of a colorectal carcinoma were eligible if they fulfilled the criteria set for autologous blood donation.¹¹ Patients randomized into the autologous group had to donate two units of blood in two sessions before operation. The collected blood was separated into packed red cells and fresh frozen plasma. The transfusion rules were the same for patients in the autologous group as for patients in the allogeneic group. Packed red cells were allowed to be given if blood loss exceeded 500 mL or if the hemoglobin level dropped below 10.5 g/dL.

After standard surgical procedures, the tumors were staged according to the Turnbull¹² modification of the original Dukes' classification. A tumor confined to the

bowel wall was staged as Dukes' A; if the tumor extended through the serosa into the pericolic fat, it was staged as Dukes' B; and if regional lymph nodes contained metastases, it was staged as Dukes' C. En bloc resected tumors with adjacent organ fixation were not staged as Dukes' D. No adjuvant chemotherapy was given, and pelvic radiation was only given in a minority of cases.

A standard follow-up program was used, including history, physical examination, and laboratory tests, every 3 months during the first 2 years and every 6 months thereafter. Chest x-ray and colonoscopy were performed yearly, and ultrasonography of the liver was done twice a year for the first 3 years and once a year thereafter.

If possible, histologic or cytologic evidence was obtained to confirm metastatic or local recurrent disease. Characteristic changes at physical examination, on x-ray, on liver ultrasonography, or on computed tomography scan also were accepted as metastatic disease or as local recurrence.

In this study, the incidence of distant metastases and local recurrence were analyzed as first signs of recurrent disease. Of the 475 randomized patients, 423 patients underwent curative surgery. Three of these patients died from postoperative complications. The remaining 420 patients form the basis of this report.

Incidence implicating cumulative percentages of patients having metastases and cumulative percentages of patients having local recurrences were calculated according to the Kaplan-Meier method.¹³ The log-rank test was used to compare these estimates. Multivariate analyses were performed using Cox regression.¹⁴ Two-sided *p* value ≤ 0.05 was considered the limit of statistical significance.

RESULTS

Patient Characteristics

Of the 420 patients, 214 patients belonged to the allogeneic group and 206 to the autologous group. The median follow-up period of the patients was 2.3 years (range 1 to 59 months). No patient was lost to follow-up.

Of the 420 patients, 277 received transfusions and 143 patients did not. Of these 277 patients, 134 received only allogeneic transfusions, 101 received only autologous transfusions, and 42 patients received both types of transfusions.

Recurrent Disease

For all studied patients—i.e., whether they received transfusions or not—the disease-free survival at 4 years was 66% in the allogeneic group and 63% in the autologous group (*p* = 0.93). In the allogeneic group, 54 of 214 patients developed recurrent disease (39 distant metastata-

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Address reprint requests to Prof. Dr. J. Jeekel, University Hospital Rotterdam-Dijkzigt, Department of Surgery, Dr. Molewaterplein 40, NL-3015 GD Rotterdam, The Netherlands.

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Table 1. FIRST DETECTED SITE OF RECURRENT DISEASE ACCORDING TO RANDOMIZED GROUP

	Allogeneic Group (N = 214)	Autologous Group (N = 206)
Total	54	51
Local recurrence	13	20
Metastatic disease	39	30
Liver	23 (59%)	17 (57%)
Lung	5 (13%)	2 (7%)
Brains	2 (5%)	—
Other	3 (8%)	5 (16%)
Multiple	6 (15%)	6 (20%)
Local and metastatic disease	2	1

ses, 13 local recurrences, and two patients both simultaneously). In the autologous group, 51 of 206 patients developed recurrent disease (30 distant metastases, 20 local recurrences, and one patient both). The distribution of sites of recurrent disease per randomized group is shown in Table 1.

The disease-free survival at 4 years was 59% in the group of 277 patients who received transfusions versus 73% in the group of 143 patients who did not require transfusions ($p = 0.001$). Using multivariate analysis, allowing for various prognostic factors, blood transfusion was a significant determinant of disease-free survival.¹⁵

The characteristics of the patients with metastatic disease and those with local recurrences are shown in Table 2, and the univariate evaluations of different prognostic factors are reported in Table 3. No statistically significant differences were found in the cumulative percentages of distant metastases and of local recurrence in comparing the randomized groups. The Dukes' classification was a significant prognostic factor for both endpoints. The grade of differentiation also was a significant factor for the incidence of metastases, but in Cox regression analysis, allowing for Dukes' stage, this was not the case. Involvement of the rectum, blood loss, and blood transfusions each were related significantly with the incidence of local recurrence, but not with the incidence of metastatic disease (Table 3).

Cumulative percentages of metastases comparing the patients who did not undergo transfusion and the transfused patients is shown in Figure 1. The percentage of metastases at 4 years was 25% in the group of patients who did not undergo transfusion and 27% in the transfused group. The percentages of metastases did not differ significantly between the different types of transfusion; at 4 years, the cumulative percentage of metastases in the group of patients receiving only allogeneic transfusions (N = 134), only autologous transfusions (N = 101),

or both types of blood transfusions (N = 42) were 31%, 33%, and 14%, respectively. However, the cumulative percentage of local recurrence was significantly less in the group that did not undergo transfusion as compared with the groups of patients with different types of transfusions (Fig. 2). The percentage of local recurrence was 3% in the group that did not undergo transfusion and 20% in the transfused group ($p = 0.0006$). The cumulative percentages of local recurrence at 4 years in the group of patients receiving only allogeneic transfusions, only autologous transfusions, or both types of blood transfusions were 20%, 18%, and 23%, respectively, and all were significantly higher than the group that did not undergo transfusion ($p = 0.001$, 0.02, and < 0.001 , respectively). The percentages of local recurrence of these three transfused groups of patients did not significantly differ between each other ($p = 0.18$).

Multivariate analyses, not allowing for blood loss, showed that blood transfusion was a significant determinant for local recurrences. This was not the case for metastases (Table 4). When postoperative radiation, given in a minority of cases (Table 2), also was taken into ac-

Table 2. CHARACTERISTICS OF PATIENTS WITH METASTATIC DISEASE AND WITH LOCAL RECURRENCE

	Total	Metastatic Disease	Local Recurrence
Randomization			
Allogeneic group	214	39 (41)	13 (15)
Autologous group	206	30 (31)	20 (21)
Age (yrs)	67	67 (67)	66 (66)
Sex			
Male	242	39 (42)	12 (15)
Female	178	30 (30)	21 (21)
Operation			
Intra-abdominal	171	30 (30)	7 (7)
Rectal involvement	249	39 (42)	26 (29)
Dukes' classification			
A	107	2 (2)	4 (4)
B	165	23 (24)	13 (14)
C	148	44 (46)	16 (18)
Differentiation			
Well	62	6 (7)	2 (3)
Moderate	311	47 (49)	27 (29)
Poor	45	16 (16)	4 (4)
Tumor size (cm)	4	4 (4)	5 (5)
Adjacent organ fixation	32	4 (4)	3 (3)
Adjuvant irradiation	31	11 (12)	5 (6)
Blood loss (mL)	750	900 (900)	1300 (1300)
Blood transfusions			
No	143	21 (21)	3 (3)
Yes	277	48 (51)	30 (33)

Continuous data are presented as medians categorical data as number of patients. Adding those patients with both metastatic disease and local recurrence are shown in parentheses.

Table 3. UNIVARIATE COMPARISONS OF PATIENTS HAVING DISTANT METASTASES AND THOSE HAVING LOCAL RECURRENCE ACCORDING TO VARIOUS FACTORS

	Metastases*	Log Rank p Value	Local Recurrence*	Log Rank p Value
Randomization				
Allogeneic group	27%	NS	11%	NS
Autologous group	25%		17%	
Age (yrs)				
≤65	27%	NS	13%	NS
>65	27%		14%	
Sex				
Male	29%	NS	12%	NS
Female	22%		16%	
Operation				
Intra-abdominal	27%	NS	7%	0.007
Rectal involvement	25%		19%	
Dukes' classification				
A	2%	<0.0001	7%	0.004
B	23%		10%	
C	49%		27%	
Differentiation				
Well	20%	0.0006	7%	NS
Moderate	24%		14%	
Poor	49%		25%	
Tumor size (cm)				
<5	26%	NS	13%	NS
≥5	26%		16%	
Adjacent organ fixation				
No	27%	NS	14%	NS
Yes	13%		8%	
Blood loss (mL)				
≤500	23%	NS	4%	0.001
>500 and ≤1000	28%		14%	
>1000	28%		24%	
Blood transfusions				
No	25%	NS	3%	0.0006
Yes	27%		20%	

* Cumulative percentages at 4 years, according to Kaplan-Meier estimates.

count in these regression models, the estimates and p values did not change appreciably, and irradiation was not an additional prognostic factor. When blood loss in the multivariate analysis was taken into consideration, the impact of blood transfusions on the local recurrence rate was no longer statistically significant (Table 4).

To explore the effect on prognosis of preoperative autologous donation itself, only the patients who did not undergo transfusion were evaluated. Comparison of those patients in the allogeneic group (N = 94) with those in the autologous group (N = 49) showed no significant differences in disease-free survival (75% vs. 69%), percentage of distant metastases (23% vs. 29%), and percentage of local recurrence (3% vs. 2%).

DISCUSSION

Blood transfusions seem to be associated with poor prognosis of colorectal cancer. This relationship ap-

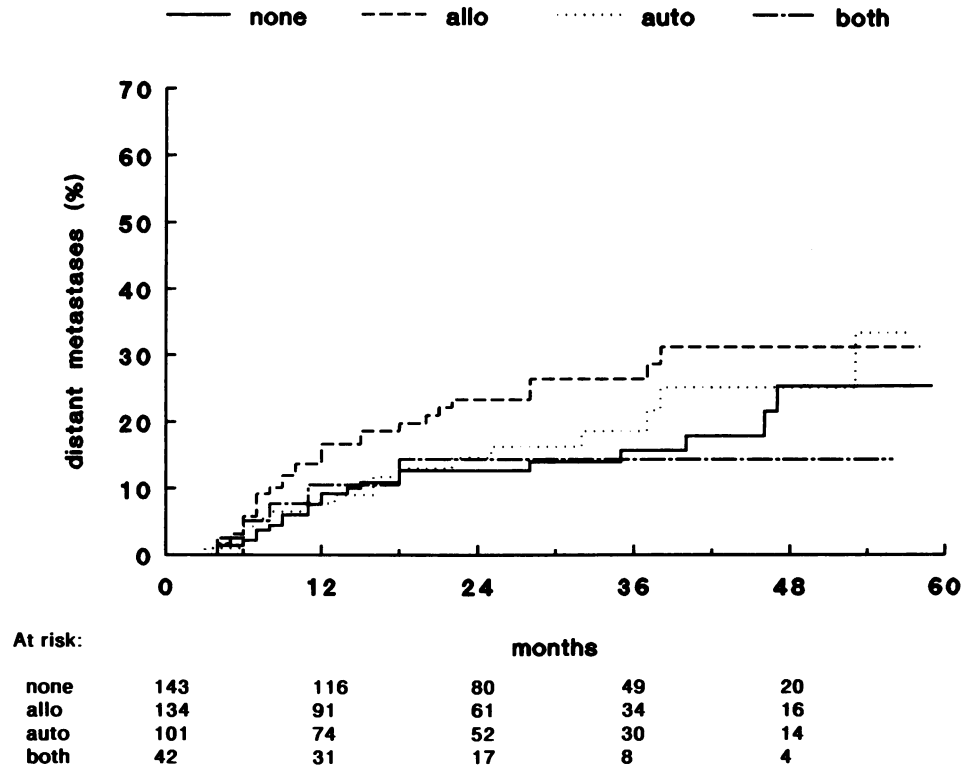
peared not to be causal; rather, the circumstances that necessitate transfusions are of prognostic importance in colorectal cancer patients.⁶ Of all studies reporting on recurrent disease from colorectal cancer and blood transfusions, only a few made a distinction between local recurrence and metastatic disease in the analyses. So far, no additional information has been given about the negative association between blood transfusions and prognosis.

The current study shows that the relationship between blood transfusions and the increased risk of recurrent disease is a result of an increased risk of local recurrences. No relation was found with the incidence of distant metastases. Similar findings applied to the amount of blood loss, but evaluating blood loss and transfusions simultaneously by multivariate analysis made the significance of either factor disappear. This is a consequence of the strong relationship that existed between blood loss and transfusion because of our transfusion rules (median blood loss in case of no transfusion was 390 mL; in case of transfusion 1050 mL; $p < 0.001$). The only other prognostic factor affecting local recurrence and not metastatic disease was an operation of a rectal tumor, compared with an intra-abdominal tumor. Although resections of rectal tumors are associated with larger amounts of blood loss and therefore, require more transfusions, multivariate analysis showed blood transfusion to be an independent factor of prognosis. In addition, there are studies restricted to colonic cancer that found a detrimental effect of blood transfusions, too.^{16,17} In the current study, we found that the influence of rectal involvement was not additional to the effect of blood transfusions in multivariate analysis. In our patient population, the incidence of rectal involvement was relatively high, which is caused by our inclusion criteria. All patients should be able to donate blood and therefore, must have a hemoglobin level of at least 11.3 g/dL (7 mmol/L). Patients with tumors in the right colon often have had anemia or transfusions preoperatively and are (in both situations) ineligible for our study.

In this study, only three patients had both local recurrence and metastatic disease at the moment recurrent disease was diagnosed. In retrospective studies, this number usually was higher, which probably can be explained by the prospective design of our study and our intensive follow-up program, in which examinations such as liver ultrasonography were performed routinely.

From the moment recurrent disease was detected, the median survival time was similar in patients who had local recurrences and those who had distant metastases. Thus, a detrimental prognostic relationship between transfusions and the development of local recurrence will have a comparable effect on survival. The retrospective studies reporting on the effect of blood transfusions and cancer survival might, therefore, be explained by a

Figure 1. Cumulative percentages of patients having distant metastases according to transfusions received. The group of patients receiving only allogeneic transfusions (allo; N = 134), only autologous transfusions (auto; N = 101), and both types of transfusions (both; N = 42) are all not significantly different from the patients who did not undergo transfusion (none; N = 143).



deleterious relationship of transfusions and local recurrence only.

A recent prospective study by Tartter¹⁸ found a

transfusion effect on the disease-free survival of colorectal cancer patients. The 5-year disease-free survival was 77% for patients who did not undergo transfusion and

Figure 2. Cumulative percentages of patients having local recurrence according to transfusions received. The group of patients receiving only allogeneic transfusions (allo; N = 134), only autologous transfusions (auto; N = 101), and both types of transfusions (both; N = 42) are all significantly different from the patients who did not undergo transfusion (none; N = 143).

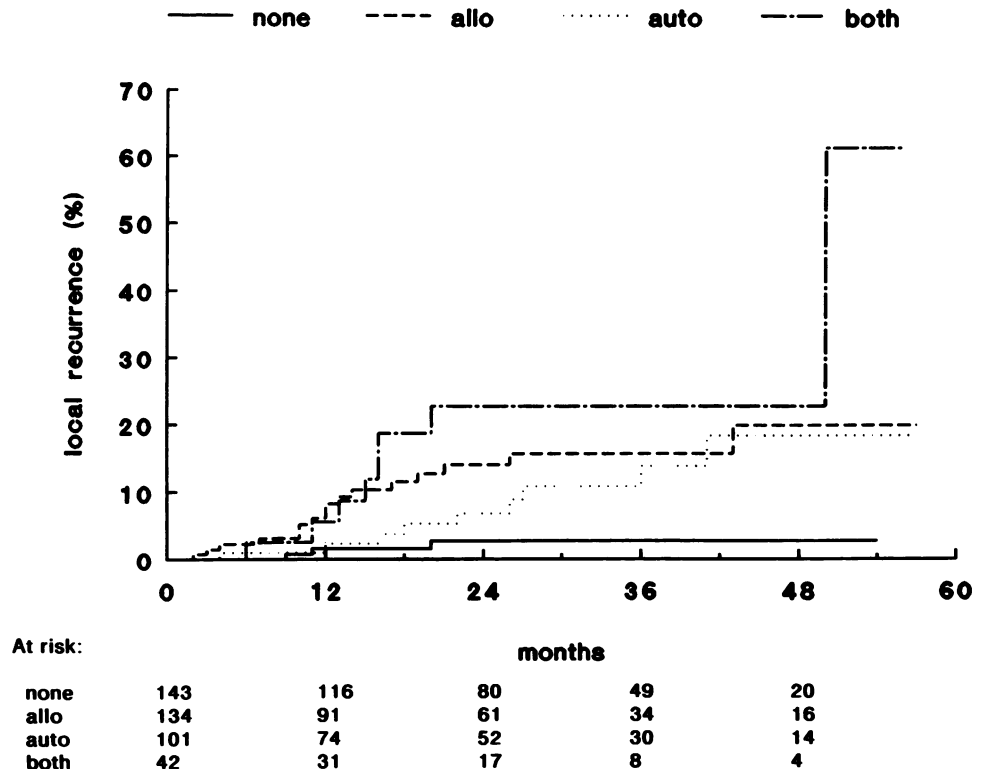


Table 4. MULTIVARIATE ANALYSIS OF THE INCIDENCE OF METASTASES AND LOCAL RECURRENCE

Factor	Relative Metastases Rate	p Value	Relative Local Recurrence Rate	p Value
Blood transfusions				
No	1		1	
Yes	1.6	NS	5.2*	0.008
Dukes' stage				
A	1		1	
B	7.6	0.006	2.2	NS
C	23.8	<0.001	5.1	0.004
Operation				
Intra-abdominal	1		1	
Rectal involvement	1.0	NS	2.0	NS

* This estimate is 3.5 (p = 0.06) when in the analysis also blood loss was taken into account (relative local recurrence rate = 1.3 as compared with 50% lower amount of blood loss; p = 0.14). The addition of blood loss did not appreciably change the other estimates or their p values.

57% for transfused patients. In a recent meta-analysis⁵ representing over 5000 patients, a relationship between blood transfusions and poor prognosis was reported of the same magnitude as found in our study. Unfortunately, in those studies, there were no data available on the incidence of local recurrence and the incidence of metastatic disease separately.

The fact that local recurrence represents failure of the surgical technique is demonstrated by McArdle and Hole,¹⁹ who reported on the variability among surgeons on postoperative complications and ultimate survival. It has been suggested that a more meticulous and careful dissection of the pararectal tissues reduces the incidence of local recurrence for rectal tumors.²⁰ Recently, the results of total mesorectal excision for rectal cancer were reported and showed that such surgery gave better disease-free survival than other studies had demonstrated using adjuvant radiation or chemotherapy.^{21,22}

Another explanation of the current findings might be the presence of growth factors released from platelets after blood loss in the peritoneal cavity. An enhanced peritoneal tumor load was found in rats receiving serum intraperitoneally as compared with those that did not receive it.²³ However, the rate of liver metastases also was increased in this animal model.

The current study shows that the prognostic association between blood transfusions and colorectal cancer is mainly a result of an increased risk of local recurrences and not an increased risk of metastatic disease. Assuming that local recurrence and the need for blood transfusions are related to surgical difficulties and skill, operations on patients with colorectal cancer should be performed in a meticulous way, with precise tumor excision and as few transfusions as necessary.

Therefore, patients who are scheduled for potentially curative resections of colorectal malignancies may have better prognoses if their surgeries are performed by surgeons who are experienced in colorectal cancer surgery.

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