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Influence of Blood Transfusions on Tumor Recurrence and Survival Rate in Colorectal Carcinoma

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Abstract—*Determinants for homologous blood transfusion and its influence on postoperative and long-term results were evaluated in 439 curatively resected colorectal cancer patients. The rate of transfusion was significantly higher in rectal cancer, large tumors, advanced pT stage and extended resection but not in tumor stenosis, lower graded tumors, advanced Dukes stage or less experienced surgeons. Transfused patients showed significantly more postoperative complications, higher recurrence rates as well as less favorable long-term survival. Homologous blood transfusions are negatively correlated to survival rates.*

INTRODUCTION

EXPERIMENTAL and clinical studies during the past years showed that homologous blood transfusions may change or weaken immune reactions. In animal experiments as well as in human recipients, lower rejection rates and longer transplant survival were observed after receipt of homologous blood transfusions [1, 2]. In experiments with animals, advancement of tumor growth was found following blood transfusion [3, 4]. It is now a matter of discussion whether blood transfusions given during surgical treatment may result in a less favorable prognosis for patients with malignant tumors. Retrospective studies in colorectal cancer patients with blood transfusions given perioperatively revealed higher tumor recurrence rates as well as shorter survival rates [4–9]. Similar effects were described in carcinoma of the lung [10], in soft-tissue sarcoma [11], and in carcinoma of the breast [12–17]. Other studies demonstrated a significant relationship between blood transfusion and prognosis [7, 8, 18]. Therefore, we examined the influence of homologous blood transfusion on tumor recurrence and survival rate in a large group of our own patients with curatively resected colorectal cancer. Furthermore, we attempted to identify determinants for homologous blood transfusions.

PATIENTS AND METHODS

Only patients with curative resections, i.e. without evidence for a residual tumor or metastases, were evaluated between 1978 and 1985. A total of 439 patients was divided into two groups, one having received blood transfusion and one not. Additionally, subgroups were set up according to variables such as clinical parameters (Table 1), morphologic–histopathological parameters (Table 2), surgical treatment and postoperative course (Table 3), tumor stage and recurrence rate (Tables 4a and b), tumor localization and recurrence rate (Table 5) and tumor stage, recurrence rate and number of blood units received (Table 6). Furthermore, survival rates (according to Kaplan–Meier) of patients with and without transfusion were evaluated for the total collective (Fig. 1a), and for patients differentiated into particular tumor stages (Fig. 1b–d). Patients were defined as having received blood transfusions when homologous stored blood (whole blood or erythrocyte concentrates) was given within 2 weeks pre-, peri- or postoperatively. Patients were examined or followed up during a period varying between 12 and 120 months.

Statistical analysis

Differences of variable distribution between transfused and non-transfused patients were examined in regard to statistical significance with the ax^2 test of Pearson. The analysis of age and duration of patient follow-up was performed using Student's t test. A stepwise, logistic regression analysis was used to detect the determinants guiding the application of homologous blood. The same regression analysis was applied to examine the influence of certain

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independent clinical and pathological variables (age, sex, tumor localization, tumor progression, tumor extent, grade of differentiation, pT stage, lymph node involvement, Dukes stage, postoperative infection) as well as the application of homologous blood or the rate of tumor recurrence (Table 8). The effect of these variables on the survival rate was studied with a proportional hazard regression model by Cox.

RESULTS

Out of 439 patients, 304 (69.2%) received homologous blood transfusions pre-, peri- and postoperatively. One hundred and forty patients received 1–2 units, 100 patients 3–5 units, 50 patients 6–10, and 14 patients more than 10 units. With regard to age, transfused and non-transfused patients were comparable (Table 1). Blood transfusion was significantly more frequent in cases of tumors of the right colon and rectum, in tumors with obstruction, in large tumors, and in those with a higher pT stage, as well as in extended tumor resections with extirpation of adjacent or infiltrated organs. There was no significant relationship found between homologous blood transfusion and extent of tumor stenosis, histology of the tumor, tumor growth, tumor grading, lymph node involvement, Dukes stage, resection with or without artificial anus, or qualification of the surgeon (Tables 1–3). Patients with blood group A received transfusions more often those those with O or AB.

The rate of postoperative complications was significantly diminished in patients without transfusions (16.3% to 33.9%). Among the typical complications occurring more frequently in patients with blood transfusion were anastomosis insufficiency, peritonitis, sepsis, ileus or postoperative bleeding. Hospital mortality was also increased (transfused: 3.9%, non-transfused: 0.7%). Wound infection occurred more often (11.2% compared to 4.4%) (Table 3). In the transfused group the locoregional tumor recurrence rate of 11.3% was

Table 1. Blood transfusions and clinical parameters in patients with curatively resected colorectal carcinomas (T = transfused, NT = not transfused)

	T		NT		
Variable	(*n*)	(%)	(*n*)	(%)	*P* value*
Patients	(304)	69.2	(135)	30.8	
Age (mean)		63.7 y		61.2 y	0.897
Sex	(304)		(135)		0.005
male		44.7		59.3	
female		55.3		40.7	
Age groups	(304)		(135)		0.218
≤40 years		2.3		3.0	
≤50 years		10.6		12.6	
≤60 years		22.1		24.4	
≤70 years		28.3		63.3	
≤80 years		32.0		20.0	
≤90 years		4.0		3.7	
>90 years		0.7		—	
Blood group	(304)		(135)		0.024
A		46.7		35.6	
B		11.2		12.5	
O		40.1		45.2	
AB		2.0		5.7	
Rhesus factor	(304)		(135)		0.104
Rh+		84.2		77.8	
Rh−		15.8		22.2	
Symptoms	(295)		(130)		
hemorrhagic stool		59.0		62.8	0.461
loss of weight		29.3		17.2	0.009
asymptomatic		8.1		13.1	0.109
ileus (obstruction)		9.1		5.4	0.092

*χ^2 test according to Pearson.

Table 2. Blood transfusion and morphologic-histological parameters of resected carcinomas (T = transfused, NT = not transfused)

	T		NT		
Variable	(*n*)	(%)	(*n*)	(%)	*P* value*
Tumor stenosis	(301)		(131)		0.298
slight		34.5		35.9	
visible		50.3		45.8	
subtotal		11.6		16.8	
total		3.6		1.5	
Tumor growth	(294)		(128)		0.478
polypous		33.0		39.1	
ulcerous		62.2		56.2	
diffuse-infiltrating		4.8		4.7	
Tumor extension	(294)		(131)		0.059
local wall section		20.9		39.1	
hemi-circular		38.0		35.8	
circular		40.1		31.6	
Tumor size	(281)		(121)		0.006
2 cm		5.7		12.4	
2–5 cm		60.5		66.9	
5 cm		33.8		20.7	
Tumor stage	(301)		(135)		0.021
pT1		6.6		14.8	
pT2		30.6		25.9	
pT3		61.1		59.3	
pT4		1.7		—	
Stage of lymph node involvement	(287)		(120)		0.792
pN0		72.1		70.8	
pN1		27.9		29.2	
Dukes stage	(301)		(134)		0.778
A		29.6		32.8	
B		43.9		41.0	
C		26.5		26.2	
Differentiation grade	(295)		(131)		0.069
G1, G1–2		10.2		17.6	
G2		68.5		66.4	
G2–3, G3		21.3		16.0	
Tumor localization	(304)		(135)		0.0001
right colon		18.8		9.6	
left colon		13.5		14.1	
sigma		14.1		39.3	
rectum		51.6		34.8	
multiple		2.0		2.2	

*χ^2 test according to Pearson.

higher than that in the non-transfused group (6.7%). Distant metastases and total tumor recurrence were also higher (Table 4a). Statistical significance between transfused and non-transfused patients was found concerning locoregional recurrence but not in connection with distant metastases. Both collectives were comparable with regard to the mean follow-up period.

When differentiating according to tumor stages pT1–4, or Dukes stage A–C respectively, the transfused group again showed a higher tumor recurrence rate.

Table 3. Blood transfusion, surgical treatment and postoperative course (T = transfused, NT = not transfused)

	T		NT		
Variable	(*n*)	(%)	(*n*)	(%)	*P* value*
Year of operation	(304)		(135)		0.182
1987–1981		42.8		49.6	
1982–1985		57.2		50.4	
Operating surgeon	(301)		(133)		0.232
chief		21.9		23.3	
senior surgeon		39.5		30.1	
junior surgeon		16.9		18.0	
assistant		21.7		28.6	
Number of stored blood units given	(304)		(135)		
1–2		46.1			
3–5		33.9			
6–10		16.4			
10		4.6			
Extended resection	(303)	9.2	(134)	3.7	0.044
Resection with artificial anus	(206)	9.3	(127)	8.7	0.853
Postoperative course	(304)		(135)		0.002
with complications		66.1		83.7	
without complications		33.9		16.3	
Postoperative bleeding	(303)	2.3	(135)	0	0.075
ileus	(303)	4.0	(135)	0.7	0.067
wound infection	(302)	12.2	(135)	4.4	0.039
insufficiency of anastomosis	(135)	5.2	(86)	1.2	0.119
Diffuse peritonitis	(303)	2.3	(133)	0	0.075
Sepsis	(303)	3.3	(135)	0.7	0.114
Hospital mortality	(304)	3.9	(135)	0.7	0.067

χ^2 test according to Pearson.

Table 4a. Blood transfusion and tumor recurrence (locoregional tumor recurrence and/or distant metastases) (T = transfused, NT = not transfused)

	T		NT		
Variable	(*n*)	(%)	(*n*)	(%)	*P* value*
Locoregional tumor recurrence (LR)	(304)	11.3	(135)	6.7	0.1417
Distant metastases (DM)		13.2		14.1	0.795
Tumor recurrence total (LR and/or DM)		18.4		14.8	0.357
Follow-up period (mean) (months)		38.1		39.4	0.835

Table 4b. Blood transfusion, tumor stage and tumor recurrence rate (T = transfused, NT = not transfused)

Stage	T	(%)	NT	(%)	*P* value
Locoregional tumor recurrence					
pT1	1/20*	(5.0)	0/20	(0.0)	0.311
pT2	7/92	(7.6)	2/35	(5.7)	0.731
pT3	24/184	(13.8)	7/80	(8.8)	0.090
pT4	2/5	(40.0)	—	—	
Dukes A	6/89	(6.7)	2/44	(4.5)	0.616
Dukes B	15/132	(14.4)	2/55	(3.6)	0.041
Dukes C	13/80	(16.3)	5/35	(14.3)	0.789
Total tumor recurrence rate (LR and/or FM)					
Dukes A	8/89	(9.0)	2/44	(4.5)	0.048
Dukes B	22/132	(16.7)	8/55	(14.5)	0.718
Dukes C	25/80	(31.3)	10/35	(28.6)	0.773

*Patients with tumor recurrence/total number of patients.

Local tumor recurrence in primary Dukes B tumors and total tumor recurrence in Dukes A tumors were significantly higher. Tumor recurrence rate also depended on the localization of the tumor. In both groups recurrence rates of tumors of the right colon were very low. A significant relationship between tumor recurrence rate and number of blood units received could not be demonstrated (Table 6). Under the conditions of our study it was not possible to determine whether the likelihood or recurrence in transfused patients having received whole blood differed from those having received packed red cells.

With regard to the survival rates (Fig. 1a–d) for the total number of patients and for the stages A and B, patients belonging to the transfused group had a significantly less favorable prognosis. The application of blood transfusions was generally associated with parameters such as tumor localization, pT stages or sex, less often with grading or Dukes stage (Table 7).

This multivariate logistic regression analysis showed that the probability of tumor recurrence depends mainly on parameters such as pT stage, lymph node involvement, and less on Dukes stage or homologous blood transfusion (Table 8). Survival rates depended mostly on lymph node involvement, age and pT stage, but also on homologous blood transfusions (Table 9).

DISCUSSION

The discussion concerning the possible negative influence of blood transfusion on tumor recurrence and survival rates has continued for almost 10 years [4]. Heterogeneity in tumor stage, degree of tumor stenosis, tumor grading and especially varying surgical technique of tumor resection as well as the individual qualification of the surgeon have been brought up as arguments against the feasibility of comparing transfused and non-transfused patient

Table 5. Tumor recurrence rates (locoregional tumor recurrence and/or distant metastases) depending on tumor localization and transfusion (T = transfused, NT = not transfused)

	Localization				
	Right colon	Left colon	Sigma	Rectum	Total
T	8/57*	8/41	7/43	32/157	55/298
	(14.0)	(19.5)	(16.3)	(20.4)	(18.4)
NT	0/13	4/19	9/53	7/47	20/132
	(0.0)	(21.0)	(16.9)	(14.9)	(15.2)
Total	8/70	12/60	16/96	39/204	74/430
	(11.4)	(20.0)	(16.7)	(19.1)	(17.4)

*Patients with tumor recurrence/total number of patients (%).

Table 6. Tumor recurrence rate depending on tumor stage (Dukes A–C) and number of given blood cells

Tumor stage	Number of blood units					Total
	0	2	5	10	More than 10	
Dukes A	2/44*	1/38	3/33	1/13	3/5	10/133
%	(4.5)	(2.6)	(9.1)	(7.7)	(60.0)	(7.5)
Dukes B	8/55	11/58	7/43	3/24	1/7	30/187
	(14.5)	(19.0)	(16.3)	(12.5)	(14.3)	(16.00)
Dukes C	10.35	12/38	10/25	2/3	1/4	35/115
	(28.6)	(31.6)	(40.0)	(15.4)	(25.0)	(30.4)
All	18/134	24/134	20/101	6/50	5/16	74/435
stages	(13.4)	(17.9)	(19.8)	(12.0)	(31.2)	(17.2)

*Patients with tumor recurrence/total number of patients (%).

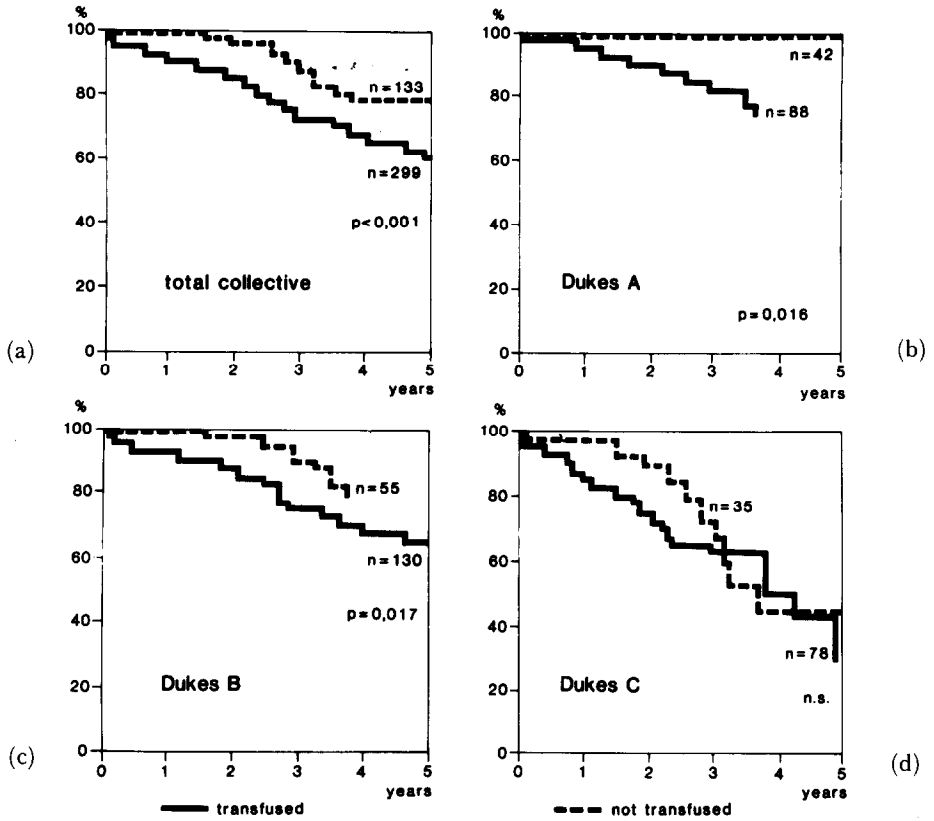

Fig. 1a–d. Blood transfusion and cumulative survival rates (Kaplan–Meier) after curative resection of colorectal carcinoma (—— = transfused, ------ = not transfused). a. Total number of patients (n = 432), b. Dukes A, c. Dukes B, d. Dukes C.

groups in regard to differences in survival rates and local tumor recurrence.

In our extensive study, no statistical relationship was found between homologous blood transfusion and preoperative extent of tumor stenosis, histology of the tumor, tumor growth, tumor grading, lymph node involvement, Dukes stage, resection with and without artificial anus or individual qualification of the surgeon (Tables 1–3). Both collectives were thereby comparable according to statistical standards.

The rate of postoperative complications was significantly less in patients without transfusions (Table 3). The same effect was described by Tartter *et al.* [19]. However, the question whether blood transfusion directly leads to a higher complication rate by means of immunodepression, or whether blood transfusions are more frequent due to previous complications, cannot be answered by a retrospective study.

Our own study revealed a relationship between homologous blood transfusion and prognosis of

Table 7. Blood transfusion and clinical/histopathologic parameters. Stepwise logistic regression analysis with blood transfusion as a constant variable

Variable	*P* value
Sex	0.0044
Age	0.0095
Tumor localization	0.0000
Type of tumor growth	0.6548
Tumor extension	0.0334
Histologic differentiation grade	0.4132
Tumor stage pT	0.0000
Tumor stage pN	0.8723
Dukes stage	0.8500
Postoperative infection	0.1375

Table 8. Tumor recurrence rate and clinical/histopathological parameters. Stepwise logistic regression analysis with blood transfusion as a constant variable

Variable	*P* value
Sex	0.1675
Age	0.4313
Tumor localization	0.1168
Type of tumor growth	0.2589
Tumor extension	0.9823
Histologic differentiation grade	0.2099
Tumor stage pT	0.0031
Tumor stage pN	0.0024
Dukes stage	0.7572
Postoperative infection	0.2626
Blood transfusion	0.7816

Table 9. Survival rates and clinical/histopathologic parameters. 'Proportional Hazard' model according to Cox

Variable	*P* value
Sex	0.0435
Age	0.0026
Tumor localization	0.5914
Type of tumor growth	0.4490
Tumor extension	0.2726
Histologic differentiation grade	0.5635
Tumor stage pT	0.0282
Tumor stage pN	0.0001
Dukes stage	0.6990
Postoperative infection	0.0163
Blood transfusion	0.0217

colorectal carcinoma following surgical treatment [4–9]. In patients with blood transfusion, higher rates of tumor recurrence (Table 4a and b) as well as lower survival rates following curative resections (Fig. 1a–c) were found. Since tumor stages A–C were equally distributed in both patient groups, the unfavorable prognosis of the group having undergone transfusion cannot be explained by a higher number of patients with advanced tumor stage. Transfusion frequency was also comparable for the different periods of measurement (1978–1985 and 1982–1985, respectively). In the regression analysis, the variable homologous blood transfusion was revealed to be an independent, unfavorable parameter in prognosis, with influence on survival rate (Table 9). This influence was even higher than variables such as Dukes stage or grading system. The discussion concerning the influence of blood transfusion on the prognosis remains controversial [5, 7, 18, 20]. However, regression analysis has not been used in all previous studies. The number of blood units given seems to be of minor importance for the prognosis [8]. In contrast to pre- or postoperative transfusions, those given perioperatively seem to have either no or even a negative influence on tumor recurrence rate [8]. Are blood transfusions a reason for higher recurrence rates or less favorable prognosis? Or are they merely indicators for other, still unknown or yet not clearly defined causes? The immunosuppressive effect of homologous blood transfusions in kidney transplantation, improving transplant survival time is a well-known and documented fact [2, 21]. Such effects can be transferred to other clinical situations and are explained by an immunomodulation, causing lower resistance against circulating tumor cells [4, 7, 21]. Conflictual processes between host organism and tumor, resulting in increased tumor growth could also be altered by blood transfusions [18]. From experiments with animals such immunosuppressive transfusion effects with increased tumor growth by blood transfusions are known [4]. One still has to find out, if the status of defense or immunity during operation is of importance for the long-term prognosis [9].

Which alternatives to the immunomodulatory effect of homologous blood transfusion could be mentioned? Transfusion could be an indication for further, not yet clearly defined factors, unfavorable for prognosis. The use of stored blood might not have any causal relationship to tumor recurrence rate [5, 8]. In patients with a preoperative anemia or a low hematocrit respectively, the hematopoietic system may already be suppressed. Thus, a direct comparison of transfused and non-transfused patient groups might not be possible any more [8]. It could not be proved yet that a perioperatively low hematocrit has an effect on further prognosis [18]. However, the perioperative transfusion frequency was directly correlated to the preoperative hematocrit. Local technical difficulties in tumor resection, excessive manipulation of the tumor and inadequate operative technique are other parameters which might be important for the prognosis. The significance of such parameters is very difficult to prove retrospectively [18]. Exact data concerning the pati-

ent's general state of health, ability to compensate blood loss, and the necessity for application of stored blood are only seldom found in patient files [8]. Transfusions are often given perioperatively, without clear indication [5]. Exact analysis revealed that in 25% of all colorectal carcinoma resection the homologous blood transfusions given were not necessary or were given without clear indication [22]. This fact was also confirmed in our study. 46.1% of all patients with blood transfusions received merely one or two blood units pre-, peri- or postoperatively. It would seem to be possible to operate on a substantial number of patients without any homologous blood transfusions.

A retrospective analysis with its difficulties of standardization and obtaining patient groups is one of the main disadvantages of all studies. Further clarification can only be reached by prospective studies considering in particular intraoperative technical as well as immunological status which have not been taken into acount as of now. If the thesis of a less favorable prognosis can be confirmed, homologous blood transfusions should be avoided. However, the results gained at the present time should already lead to stricter indication for the application of blood transfusions. Increasing problems with AIDS is another reason for avoiding such transfusions.

Further studies have to prove whether autologous blood or preparations without leucocytes or frozen erythrocytes, which are claimed to have a less immunodepressive effect [2, 6, 18, 21], should be given in patients with a clear indication.

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