The Effect of Packed Cells and Whole Blood Transfusions on Survival After Curative Resection for Colorectal Carcinoma

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The effect of perioperative blood transfusions on survival after curative resection for colorectal carcinoma was studied retrospectively on 270 patients with special emphasis on whole blood transfusion. Eighty-six (32 percent) patients did not receive blood transfusions, whereas the remaining 110 (41 percent) received packed cells and 74 (27 percent) received at least 2 units of whole blood. The recurrence-free and overall 5-year survival rates for the transfused group were 58 and 57 percent, respectively, and for the non-transfused group, 78 and 72 percent, respectively. These differences were highly significant (log rank test, $P < 0.001$). The recurrence-free and overall 5-year survival rates for patients who received only whole blood or a combination of whole blood and packed cells was 51 percent, and of those who received only packed cells was 63 percent. The difference was not statistically significant (log rank test, $P = 0.08$, $P = 0.35$). Administration of more than 6 units of blood is attended with a significantly worse 5-year disease-free survival rate than administration of a smaller volume. The survival was not decreased if 6 or more units of whole blood were given. The authors conclude that perioperative blood transfusions have a significant detrimental effect on survival after curative resection for colorectal carcinoma. This effect is not enhanced by whole blood transfusions.

[Key words: Blood transfusion; Whole blood; Packed cells; Colorectal carcinoma]

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THERE ARE STRONG indications that perioperative blood transfusion may contribute to a higher recurrence rate and lower survival in cancer patients.[1]. This effect is possibly explained by the potentially immunosuppressive effect of blood transfusion, which may also cause the improved survival of kidney grafts after transfusion.[1–3]

Blumberg *et al.*[4] found a distinct relation between the kind and amount of blood components transfused and the incidence of recurrence and death in patients with colorectal carcinoma. Transfusion of whole blood, or more than three units of erythrocytes, was associated with earlier recurrence and death caused by cancer. The explanation for this observation is that plasma factors decrease immune function, thus leading to disease recurrence. We studied recurrence and survival based on a detailed retrospective analysis of patients who did or did not receive perioperative whole blood or erythrocytes, or both transfusions during colorectal surgery for carcinoma.

Patients and Methods

The records of 270 patients who underwent curative resections for colorectal carcinoma in the period from January 1975 through July 1986 were reviewed. There were 137 men and 133 women (mean age, 62 years). In 197 (73 percent) the primary tumor was located in the colon; in 73 (27 percent) it was located in the rectum.

In the period studied, no basic changes in preoperative bowel preparation or surgical procedures were introduced. Before 1979, as a rule, mainly whole blood

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TABLE 1. *Number of Patients and Amount of Blood (Packed Cells, Whole Blood, or Combination) Given*

Units	Total	Packed Cells	Whole Blood	Combination (Whole Blood)
2	24	19	5	0
4	83	62	18	3
6	31	15	11	5
>6	46	14	9	23

was transfused and after that year chiefly packed cells, although some patients received whole blood as well. Information was recorded on tumor location, age, sex, histologic differentiation of the tumor, Dukes' classification, and preoperative anemia. Patients were considered to have had a blood transfusion if they had received whole blood or packed cells before surgery in order to correct anemia, during surgery, or during the hospital stay after surgery.

Patients were divided according to whether they received blood transfusion and whether only packed cells were transfused or at least 2 units of whole blood with or without packed cells (the minimal amount given). No patients were lost to follow-up. Three patients whose cause of death could not be ascertained were considered to have died from noncancer-related disease.

Possible differences in prognostic variables between the groups were analyzed by the chi-square test. The Cox regression analysis was used to compare survival adjusted for multiple factors.[5] Survival curves were computed according to the method of Kaplan and Meier.[6]

Results

Of the 270 patients, 86 (32 percent) did not receive perioperative blood transfusion. Of the other group, 110 (41 percent) received packed cells and 74 (27 percent) received at least 2 units of whole blood (31 patients received both packed cells and whole blood). Table 1 shows the number of blood transfusions given and differentiation according to packed cells and whole blood.

Analysis of the characteristics of the transfused and nontransfused patients revealed that patients with rectal carcinoma were transfused more often than patients with colonic carcinoma. Also anemic patients were more often transfused (Table 2).

The 5-year disease-free survival of the transfused group was 58 percent (standard error [SE] = 4) and of the nontransfused group 78 percent (SE = 5) (log rank test, $P = 0.009$).

The overall 5-year survival rates were 57 percent (SE = 4) and 72 percent (SE = 6), respectively ($P = 0.006$) (Figs. 1A and B). Considering only noncancer-related causes of death, the 5-year survival rates were 63 percent (SE = 5) and 83 percent (SE = 4), respectively ($P = 0.003$). After adjustment for other covariates, using the Cox regression analysis, blood transfusion remained a significant prognostic variable ($P = 0.008$) next to

TABLE 2. *Comparability of Patients Who Had Blood Transfusions and Those Who Did Not*

	No Transfusion (n = 86)	Transfusion (n = 184)	*P*, chi-square Test
Colon	73 (85%)	124 (67%)	
Rectum	13 (15%)	60 (33%)	0.004
Mean age (SD)	63 (12%)	62 (13%)	0.52*
Sex M	48 (56%)	89 (48%)	
F	38 (44%)	95 (52%)	0.31
Year operation			
75-79	25 (29%)	70 (38%)	
80-86	61 (71%)	114 (62%)	0.19
Histologic differentiation			
Unknown	14 (16%)	16 (9%)	
Poor	7 (8%)	19 (10%)	
Moderate	43 (50%)	101 (55%)	
Well	22 (26%)	48 (26%)	0.31
Dukes' stage			
A	18 (21%)	28 (15%)	
B	45 (52%)	109 (59%)	
C	23 (27%)	47 (26%)	0.44
Anemia			
Yes	18 (21%)	68 (37%)	
No	68 (79%)	116 (63%)	0.013

*T test.

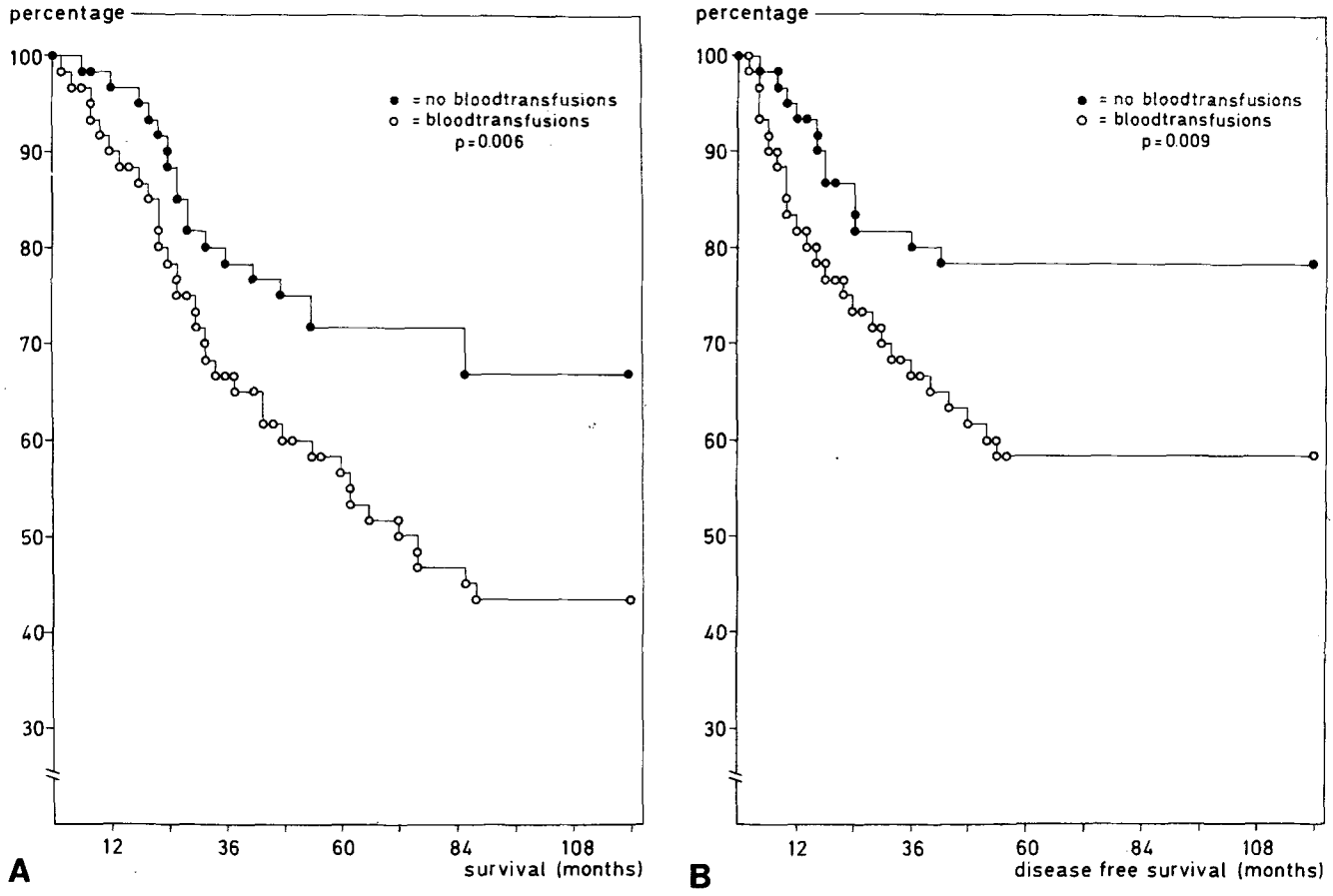

FIG. 1A, B. Significant difference in survival and disease-free survival between patients who received perioperative blood transfusions and those who did not.

Dukes' stage and histologic differentiation. Age was significantly related to overall survival ($P = 0.002$) but not to disease-free or cancer-specific survival (Table 3).

Comparison of the characteristics of patients who received at least 2 units of whole blood to those who received only packed cells revealed that the majority of women were transfused with packed cells whereas the majority of men received whole blood ($P = 0.001$). Before 1980, more whole blood was administered, whereas packed cells were used more often in subsequent years (Table 4). In Table 5 the survival of packed cells and whole blood recipients is analyzed by the log rank test. The differences in disease-free survival, overall survival, and survival corrected for other causes of death were not significant.

Analysis of the volume of transfused blood showed that the disease-free survival and the survival corrected for other causes of death was significantly better for patients who received less than six units of blood (packed cells with or without whole blood) compared with patients who received more than six units. This significant difference was not found for the overall survival.

Combining these two factors in a Cox regression analysis revealed the amount of blood as a factor significantly related to the disease-free period (Table 6, Fig. 2).

Discussion

A profound discussion persists regarding the detrimental effect of perioperative blood transfusions on patients with malignant tumors.

It has not been proven, however, that blood transfusions are the cause of this effect.[7] Until now there has been no prospective clinical study to confirm the relationship between blood transfusion and survival, and earlier recurrence, although some experimental animal studies support the retrospectively found data. Moreover, it is known that blood transfusions may influence the immunologic status of the patient.

TABLE 3. *Cox Regression Analysis of Influence of Blood Transfusion*

	Recurrence-free Survival		Overall Survival	
	β	P	β	P
Blood transfusion	0.82	0.008	0.74	0.008
Rectum	0.29	0.30	0.19	0.45
Age	0.007	0.42	0.027	0.002
Sex (male)	0.18	0.46	0.88	0.33
>1980	−0.11	0.66	−0.07	0.77
Histologic differentiation				
Unknown	−0.11	0.80	−0.23	0.53
Poor	−0.26	0.50	−0.49	0.18
Moderate	−0.63	0.02	−0.85	<0.001
Dukes' stage				
B	1.92	0.009	0.84	0.04
C	3.21	<0.001	2.05	<0.001
Anemia	−0.55	0.07	−0.29	0.27

Retrospective studies fail to demonstrate other possibly important prognostic variables, although Francis and Judson,[8] for example, found that the extent of the tumor and the difficulty of resection are more important factors than receipt of blood transfusion *per se*; however, these factors are difficult to define retrospectively.

Few data exist comparing the perioperative administration of whole blood with recurrence and survival of cancer. In most series mentioned in the literature, whole blood and packed cells are taken together. Blumberg *et al.*[4] were the first to point out that the administration of any amount of whole blood was associated with earlier recurrence and death from cancer than the administration of erythrocytes. This suggests that plasma factors may be responsible for this effect. Support for this finding is given by Horimi *et al.*[9] who found an accelerated tumor growth in mice after plasma transfusion.

However, Singh *et al.*[10] found no promotion of artificial lung metastases in the rat by plasma transfusions, whereas erythrocytes, leukocytes, and whole blood had a stimulative effect. Voogt and coworkers[11] and Persijn *et al.*[12] consider leukocytes to be an immunosuppressive factor, analogous to findings

TABLE 4. *Comparability of Patients Who Received at Least 2 Units of Whole Blood and Those Who Did Not*

	Packed Cells (n = 110)	Whole Blood (n = 74)	P, chi-square Test
Colon	80 (73%)	44 (59%)	
Rectum	30 (27%)	30 (41%)	0.085
Mean age (SD)	63 (12%)	60 (14%)	0.062*
Sex M	42 (38%)	47 (64%)	
F	68 (62%)	27 (36%)	0.001
Year operation			
75-79	28 (26%)	42 (57%)	
80-86	82 (74%)	32 (43%)	<0.001
Histologic differentiation			
Unknown	13 (12%)	3 (4%)	
Poor	10 (9%)	9 (12%)	
Moderate	59 (54%)	42 (57%)	
Well	28 (25%)	20 (27%)	0.31
Dukes' stage			
A	18 (16%)	10 (14%)	
B	64 (58%)	45 (69%)	
C	28 (26%)	19 (26%)	0.87
Anemia			
Yes	42 (38%)	26 (35%)	
No	68 (62%)	48 (65%)	0.79

*T test.

TABLE 5. *Five-year Survival Analyzed by Log Rank Test and Cox Regression Analysis*

Survival	Packed Cells	Whole Blood	Log Rank *P*-value	Cox regression Beta	Cox regression *P*-value
Recurrence free	63% (6)*	51% (6)	0.075	0.32	0.24
Overall	63% (6)	51% (6)	0.35	0.18	0.47
Corrected	69% (6)	57% (6)	0.13	0.28	0.33

*Standard error.

in renal transplanation. Therefore, this group proposes a trial with leukocyte-free blood. So, for now, there are contradictory findings that cannot be explained. The results of our study about the effect of perioperative blood transfusions generally compare well with those of others.[11,13,14] Besides histologic differentiation, Dukes' stage, and anemia, we found perioperative administration of blood to be a significant factor in negatively influencing recurrence rate and survival. Because significantly more patients with rectal carcinoma received blood, and the prognosis of this tumor is worse than for colon carcinoma, the detrimental effect is seemingly attributed to this. In the Cox regression analysis, however, this factor proved to be of no importance.

The data concerning whole blood transfusions may give the impression that the detrimental effect is more enhanced than with packed cells transfusions alone; however, the differences in the disease-free and overall survival of 12 percent were not significant. Our series of patients is too small to prove that a difference in survival of 12 percent is significant. Only a significant difference of about 20 percent could be detected in our group.[15]

The fact that most of the recipients of whole blood were treated before 1980 may be of some consequence. A possible other cause for the difference in survival may be that the prognosis of patients with colorectal carcinoma has been improved during the period studied, although for patients treated in the Netherlands, no

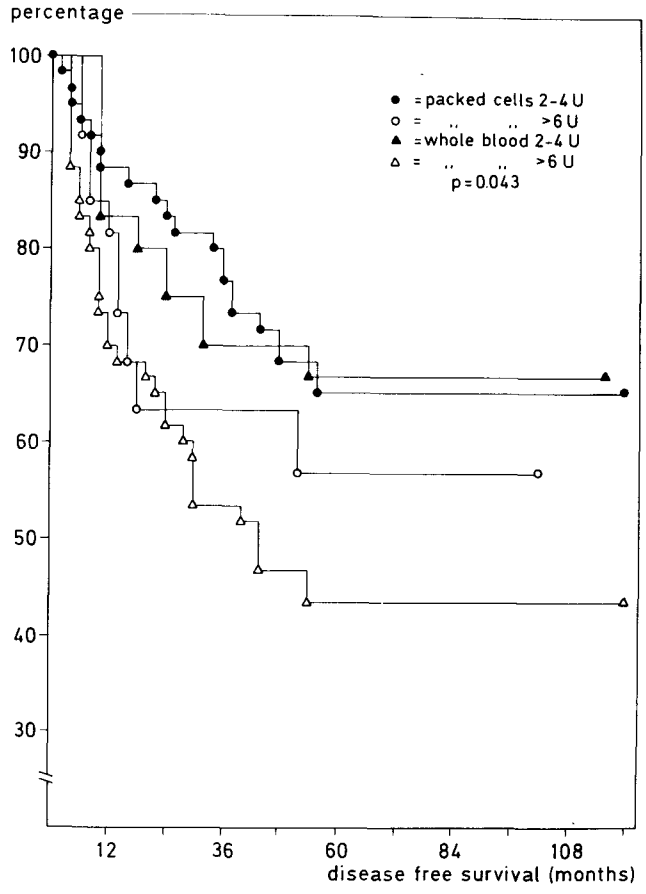

FIG. 2. Disease-free survival in relation to amount of blood given.

TABLE 6. *Cox Regression Analysis of Type and Volume of Transfused Blood*

	Recurrence-free Survival		Overall Survival	
	β	*P*	*β*	*P*
Type of blood	0.19	0.50	0.12	0.65
> 6 units	0.62	0.043	0.25	0.34
Age	−0.003	0.73	0.02	0.027
Sex (male)	0.19	0.50	0.30	0.24
Dukes' stage				
B	1.85	0.013	1.00	0.039
C	2.95	<0.001	2.06	<0.001
Rectal carcinoma	0.05	0.87	0.11	0.70
Anemia	−0.76	0.025	−0.39	0.18
Histologic differentiation				
Unknown	0.005	0.92	0.093	0.83
Poor	−0.28	0.49	−0.33	0.39
Moderate	−0.96	0.002	−0.91	<0.001
>1980	0.19	0.52	0.06	0.83

data are available at this point. However, there was no clear change in preoperative bowel preparation, antibiotic regimen, and surgical procedures during the time studied. In fact, all operations were performed by residents under the direct supervision of a staff member. Stapler techniques were used sparingly, but imperceptible changes, introduced in the course of the years, may be of influence.

On the basis of our study, we have too few arguments to share the opinion of Blumberg in an enhanced detrimental effect of whole blood, although the minimal amount given in our patients was two units, one unit more than in Blumberg's series.[4]

In our series, there was a relationship between survival and the volume of blood given. Significant differences were found in the disease-free survival if more than six units of blood were given. This difference was also found if there was a combination of whole blood. Cox regression analysis of the factors that might be responsible for this difference in survival revealed that the administration of more than six units of blood was not a significant factor, but it seems to be more important than the type of blood.

What do our findings and those of others mean to the surgeon? As long as the effect of blood transfusions on cancer patients is unclear, the administration of blood must be considered seriously each time. As Spratt[16] commented: "The cancer surgeon may need to become a bloodless surgeon."

Although our study does not support the findings of Blumberg at a significant level, we believe the surgeon and the anesthesiologist must refrain from administering any whole blood to the cancer patient. More data are needed about the effect of whole blood. Prospective studies should give more light on the real effect of perioperative blood transfusion.

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