BLOOD TRANSFUSIONS AND PROGNOSIS IN COLORECTAL CANCER

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Abstract *Background.* Blood transfusions may adversely affect the prognosis of patients treated surgically for cancer, although definite proof of this adverse effect has not been reported.

Methods. We carried out a randomized trial to investigate whether the prognosis in patients with colorectal cancer would be improved by a program of autologous blood transfusion as compared with the current practice of allogeneic transfusion. Patients in the autologous-transfusion group were required to donate two units of blood before surgery.

Results. A total of 475 patients were evaluated. We found no significant difference in prognosis between the allogeneic-transfusion group (236 patients) and the autologous-transfusion group (239 patients); colorectal cancer–specific survival rates at four years were 67 percent and 62 percent, respectively (P = 0.39). Among the 423 patients who underwent curative surgery, 66 percent of those in the allogeneic-transfusion group and 63 percent of those in the autologous-transfusion group had no recurrence of colorectal cancer at four years (P = 0.93). We also found that the risk of recurrence was significantly increased in patients who received blood transfusions, either allogeneic or autologous, as compared with patients who did not require transfusions; the relative rates of recurrence were 2.1 (P = 0.01) and 1.8 (P = 0.04), respectively; these rates did not differ significantly from each other.

Conclusions. The use of autologous blood as compared with allogeneic blood for transfusion does not improve the prognosis in patients with colorectal cancer. Regardless of their type, transfusions are associated with poor prognosis, probably because of the circumstances that necessitate them. (N Engl J Med 1993;328:1372-6.)

PERIOPERATIVE blood transfusions may have a deleterious effect on the survival of patients with a variety of solid tumors,[1,2] possibly because of an immunosuppressive effect.[3,4] This possibility is supported by studies in animals in which tumor growth was enhanced after allogeneic transfusion,[5,6] although conflicting results have also been reported.[7,8] A poor prognosis after blood transfusions has been noted especially in patients with colorectal cancer.

In the studies of the effect of blood transfusions in patients with cancer, the patients were given the transfusions either because of their disease or because transfusion was necessary during surgical treatment. Therefore, the question remains whether the relation between blood transfusion and poor prognosis is causal or coincidental.[9] The need for transfusion could be an indicator of other prognostic factors that are either unknown or difficult to quantify, such as the extent of the tumor and the dissection, the skill of the surgeon, and the nutritional state of the patient.

A randomized trial is the only way in which possible bias in the selection of patients can be avoided. Randomization between transfusion and no transfusion is impossible, however, because giving patients transfusions when there is no medical indication and withholding transfusions that are indicated are ethically unacceptable. Since autologous blood is the safest blood to use in transfusion, comparing the effects of allogeneic and autologous blood transfusions would be a logical option.

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Supported by a grant (KWF 86-13) from the Dutch Cancer Society and a grant (28-1953) from the Dutch Foundation for Preventive Medicine (Preventie Fonds).

We therefore conducted a randomized multicenter trial in patients with colorectal cancer to determine whether autologous blood transfusion would reduce the rate of recurrence of cancer and improve survival as compared with allogeneic transfusion. We previously reported that a notable reduction in the number of allogeneic transfusions can be achieved with a program of autologous blood transfusion.[10]

METHODS

The study was conducted in 14 hospitals in the Netherlands and 1 hospital in England and was approved by the ethics committees of all the participating hospitals. After written informed consent had been obtained, eligible patients were randomly assigned to either the allogeneic-transfusion group or the autologous-transfusion group, with stratification according to the participating hospital. Patients were enrolled from August 1986 to November 1991, when the planned enrollment was reached.

Eligibility of Patients

Patients scheduled for a potentially curative resection of cancer of the colon or rectum were eligible for enrollment if they fulfilled the criteria of the American Association of Blood Banks for autologous blood donation in anticipation of surgery.[11] These criteria required the absence of severe cardiovascular or respiratory disease, no history of epilepsy after infancy, and a hemoglobin concentration above 11.3 g per deciliter (7 mmol per liter). In addition, patients had to have no evidence of metastatic disease, on the basis of chest radiography and ultrasonography of the liver; no other cancer except basal-cell carcinoma of the skin or in situ carcinoma of the cervix; no evidence of ulcerative colitis, familial polyposis, or a fixed rectal carcinoma requiring preoperative radiation therapy; and no history of blood transfusion during the three months before randomization. No adjuvant therapy was allowed except irradiation. If metastatic or recurrent disease developed in a patient during follow-up, all available therapies were allowed.

Procedures for Donation and Transfusion

Patients randomly assigned to the autologous-transfusion group were required to donate blood twice. The minimal interval between the two donations was 72 hours, and the second donation had to occur not later than five days before surgery. At each donation, 450 ml of blood was obtained by standard proce-

dures. The patients were treated with oral iron supplementation immediately after randomization.

The collected blood was separated into packed red cells and fresh-frozen plasma, except at one hospital, where autologous blood was given in transfusion as whole blood. The packed red cells and whole blood were stored at 4°C. Allogeneic blood was always given in transfusion as packed red cells. Standard rules for transfusion were used for both groups. Packed red cells could be given only if the loss of blood exceeded 500 ml or if the hemoglobin concentration dropped below 10.5 g per deciliter (6.5 mmol per liter). If this hemoglobin concentration was not achieved after two autologous transfusions, additional allogeneic transfusions were made. In both groups fresh-frozen plasma was given when indicated.

Surgery and Histopathological Assessment

Standard surgical procedures were used. The operative specimens were classified according to Dukes' classification as modified by Turnbull.[12] A tumor confined to the bowel wall was classified as Dukes' stage A, a tumor extending through the serosa into the pericolic fat as Dukes' stage B, the presence of regional lymph nodes containing metastases as Dukes' stage C, and the presence of distant metastases or unresectable tumor as Dukes' stage D. All patients who had residual tumor evident only on microscopical examination received postoperative radiotherapy. These patients and those who had en bloc resection of adjacent organs were not considered as having Dukes' stage D disease, but rather as having Dukes' stage B or C disease.

Follow-up and Criteria for Recurrent Cancer

The patients were evaluated every three months during the first two years after surgery and every six months thereafter. Each evaluation consisted of a history, a physical examination, and blood tests (to measure the concentrations of hemoglobin and serum carcinoembryonic antigen). Ultrasonography of the liver was performed every six months for three years and each year thereafter. Chest films and colonoscopy were done yearly.

Characteristic abnormalities detected on physical examination or on chest radiography, liver ultrasonography, or abdominal computed tomography were accepted as evidence of metastatic or recurrent disease. If possible, the presence of metastatic or recurrent disease was confirmed by histologic or cytologic examination. Increased serum concentrations of carcinoembryonic antigen without evidence of recurrence at suspected anatomical sites were not considered to indicate metastatic or recurrent disease.

Statistical Analysis

Categorical data were compared by the chi-square test, and continuous data by the Mann–Whitney test. The major end points were disease-free survival and colorectal cancer–specific survival (defined to include all patients who did not die of colorectal cancer, without regard to other causes of death), both as determined from the time of surgery and calculated according to the Kaplan–Meier method. The log-rank test was used to compare these end points. Multivariate analysis was performed by proportional-hazards analysis[13] to obtain a higher level of precision in the comparison of the transfusion groups. Two-sided P values of 0.05 or less were considered statistically significant. P values calculated with adjustment for Dukes' stage are indicated as adjusted P values in the text.

Patients in whom a second primary tumor developed outside the colon were withdrawn from the study with regard to the calculation of disease-free survival. Metachronous tumors in the colon, however, were defined as representing recurrent disease. Postoperative deaths, defined as deaths occurring within 30 days after surgery, and deaths occurring more than 30 days after surgery due to postoperative complications were counted as deaths due to cancer.

Because the analyses of overall survival and colorectal cancer–specific survival gave similar results, only the results for colorectal cancer–specific survival are reported.

Except for the patients who did not have colorectal cancer at the time of surgery, all randomized patients were primarily evaluated according to the intention-to-treat principle. In addition, exploratory analyses were performed according to the number and type of transfusions received.

Results

Characteristics of the Patients

A total of 510 patients were enrolled in the study. Thirty-five patients (7 percent) were excluded because they did not have colorectal cancer at the time of surgery. The characteristics of the remaining 475 patients are shown in Table 1. None of the characteristics differed significantly between the two groups. Twenty-six of the 239 patients in the autologous-transfusion group (11 percent) did not donate blood; the majority of these were refused by the blood bank because they did not fulfill the criteria of the American Association of Blood Banks. These patients were included in all the analyses according to the intention-to-treat principle, as were all the patients with metastatic disease or unresectable tumors. The median follow-up period was 2.5 years (range, 1 to 59 months), and no patient was lost to follow-up.

The perioperative hematologic values and use of transfusions are shown in Table 2. The number of patients in the autologous-transfusion group who received allogeneic blood was half the number in the allogeneic-transfusion group (28 percent vs. 56 percent, respectively; $P<0.001$).

Morbidity and Mortality

Five eligible patients (two in the allogeneic-transfusion group and three in the autologous-transfusion

Table 1. Characteristics of the Patients with Colorectal Cancer in the Two Transfusion Groups.

Characteristic	Allogeneic Transfusion (N = 236)	Autologous Transfusion (N = 239)
Median age — yr (range)	68 (33–89)	66 (31–88)
	number (percent)	
Sex		
Male	132 (56)	141 (59)
Female	104 (44)	98 (41)
Tumor location		
Ascending colon	24 (10)	16 (7)
Flexures and transverse colon	12 (5)	16 (7)
Descending colon and sigmoid	62 (26)	65 (27)
Rectosigmoid and rectum	132 (56)	135 (56)
Multiple primary tumors	6 (3)	7 (3)
Dukes' classification*		
A	53 (23)	55 (23)
B	85 (36)	80 (34)
C	78 (33)	72 (31)
D	18 (8)	29 (12)
Histologic differentiation		
Good	35 (15)	33 (14)
Moderate	169 (72)	172 (72)
Poor	29 (12)	29 (12)
Unknown	3 (1)	5 (2)
Adjacent-organ fixation†	15 (7)	17 (8)
Adjuvant irradiation†	15 (7)	16 (8)

*Does not include patients who did not undergo surgery (two in the allogeneic group and three in the autologous group).

†Excludes patients with Dukes' stage D tumors.

group) did not have surgery. Four had more advanced disease than expected, and one patient died before surgery. Eight patients (three in the allogeneic-transfusion group and five in the autologous-transfusion group) died of postoperative complications. Postoperative infectious complications occurred in 26 percent of the patients (25 percent in the allogeneic-transfusion group and 27 percent in the autologous-transfusion group). There were no statistically significant differences between the two groups with respect to postoperative mortality and infectious complications.

Disease-free Survival

Of the 423 patients who underwent curative surgery (216 in the allogeneic-transfusion group and 207 in the autologous-transfusion group), 105 (54 in the allogeneic-transfusion group and 51 in the autologous-transfusion group) had recurrent disease (including three metachronous tumors). The disease-free survival of these 423 patients is shown in Figure 1. The plots for the two groups were almost identical (P = 0.93). Also, there were no differences with regard to disease-free survival in each of the Dukes' stages. After adjustment for various factors, the multivariate analysis also revealed no difference between the groups in disease-free survival (Table 3). Six patients (two in the allogeneic-transfusion group and four in the autologous-transfusion group) had second primary tumors outside the colon during follow-up.

To explore the relation between blood transfusions and disease-free survival, we grouped the patients who underwent curative surgery according to the number and type of transfusions they received. The disease-free survival in the 143 patients who received no transfusions was significantly better (adjusted P = 0.001) than that in the 280 who did receive transfusions; at four years, it was 73 percent and 59 percent, respectively. Among the 280 patients who had transfusions, 136 received only allogeneic transfusions, 102 only autologous transfusions, and 42 transfusions of both types. The disease-free survival at four years in these

Table 2. Hemoglobin Concentrations, Blood Loss, and Transfusions in Patients with Colorectal Cancer, According to Transfusion Group.

VARIABLE	ALLOGENEIC TRANSFUSION	AUTOLOGOUS TRANSFUSION	P VALUE*
	median (range)		
Hemoglobin concentration (g/dl)†			
At base line	14.5 (10.5–18.0)	14.4 (10.7–18.5)	NS
Immediately before surgery	14.1 (9.5–18.0)	12.5 (8.4–16.4)	<0.001
At discharge	12.5 (9.2–17.2)	12.2 (9.2–16.2)	NS
Blood loss (ml)	775 (100–11,500)	750 (100–6500)	NS
	no. (%) of patients		
Transfusions			
None	103 (44)	61 (26)	<0.001
Autologous only	— —	112 (47)	—
Allogeneic	133 (56)	66 (28)	<0.001

*NS denotes not significant.

†To convert values for hemoglobin to millimoles per liter, multiply by 0.62.

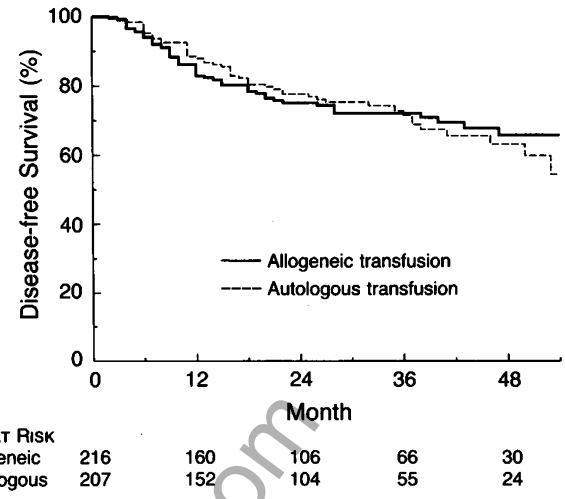

Figure 1. Disease-free Survival of All 423 Patients with Colorectal Cancer Who Underwent Curative Surgery.

The disease-free survival at four years was 66 percent in the allogeneic-transfusion group and 63 percent in the autologous-transfusion group (P = 0.93). The 95 percent confidence interval for the difference between these percentages (autologous minus allogeneic) ranged from −16 percent to +10 percent.

three groups was 56 percent, 62 percent, and 66 percent, respectively (adjusted P = 0.50). No significant difference was found between the 49 patients who received no transfusions in the autologous-transfusion group and the 94 such patients in the allogeneic-transfusion group; the disease-free survival in these patients at four years was 69 percent and 75 percent, respectively.

Because the number of autologous transfusions was limited to two, further comparisons were made between the 75 patients in the allogeneic-transfusion group who received one or two allogeneic transfusions and the 102 patients in the autologous-transfusion group who received one or two autologous transfusions but no allogeneic transfusions. The disease-free survival was significantly worse in the patients in both groups who received transfusions than in the 143 patients who did not, whereas the disease-free survival of the patients who received transfusions in both groups did not differ significantly from each other (Table 4).

Analysis of the results with respect to the use of fresh-frozen plasma revealed no relation between its use and disease-free survival. This was true whether the patients received blood transfusions or not.

Colorectal Cancer–Specific Survival

During the study, 114 patients died of colorectal cancer (53 in the allogeneic-transfusion group and 61 in the autologous-transfusion group). The survival of all 475 eligible patients in the two groups was similar (P = 0.39) (Fig. 2).

In addition to the Dukes' stage, the patient's age was also significantly related to colorectal cancer–specific survival — i.e., older patients generally did worse than younger ones. The ratio of the death rate in the autologous-transfusion group to the death rate

Table 3. Multivariate Analysis of Factors Related to Disease-free Survival in 423 Patients with Colorectal Cancer Who Underwent Curative Surgery.*

Factor	Relative Recurrence Rate	95 Percent Confidence Interval	P Value
Transfusion group			
Allogeneic†	1	—	—
Autologous	1.1	0.7–1.6	0.74
Dukes' classification			
A†	1	—	—
B	4.0	1.7–9.5	0.002
C	10.8	4.7–25.1	<0.001

*Other factors investigated (age and sex of patients, tumor location, adjacent-organ fixation, degree of differentiation, and tumor size) had no significant additional predictive value with respect to disease-free survival, and the effect of randomization was not significantly influenced by any of these factors.

†Reference category.

in the allogeneic-transfusion group, after adjustment for Dukes' stage and age, was 1.1 (95 percent confidence interval, 0.8 to 1.7; P = 0.66).

As was the case for disease-free survival, the colorectal cancer–specific survival in the 423 patients who underwent curative surgery was significantly better (adjusted P<0.001) in the patients who did not receive transfusions than in those who did; the survival at four years was 88 percent and 65 percent, respectively. When the patients who received transfusions were subdivided according to the type of transfusions they received (allogeneic, autologous, or both), there were no significant differences (adjusted P = 0.60) between the three subgroups; the survival at four years was 64 percent, 68 percent, and 63 percent, respectively. The survival of patients who did not receive transfusions did not differ significantly (adjusted P = 0.86) between the two randomized groups; the survival of these patients at four years was 87 percent in the allogeneic-transfusion group and 88 percent in the autologous-transfusion group.

When the analysis was restricted to patients who had one or two transfusions of the same type, the patients receiving autologous transfusions and those receiving allogeneic transfusions both had worse survival rates than the patients without transfusions (Table 4).

No relation was found between survival and the transfusion of fresh-frozen plasma.

Discussion

The results of the retrospective studies of the influence of blood transfusions on survival and the recurrence rate in patients with colorectal cancer are conflicting. The studies in which the prognosis in patients receiving transfusions was poorer may have been biased by the selection of patients.[14,15] One way to avoid such confounding by indication[16] is to conduct a randomized trial comparing the effects of autologous and allogeneic blood transfusions.[17,18] The results of this study indicate that as compared with the use of allogeneic blood, the use of autologous blood either to avoid or to reduce exposure to allogeneic blood neither lowered the recurrence rate nor improved survival in patients who had undergone surgery for colorectal cancer. In accordance with some retrospective studies, the recurrence rate was higher in patients who had received transfusions than in those who had not. For patients given transfusions with allogeneic blood, the increase in the recurrence rate was similar to that in the patients who received only autologous blood. The same applied to the survival of the patients.

Recently, Ness et al.[19] reported no difference in survival in a nonrandomized study in which the effects of allogeneic and autologous blood transfusions were compared in patients undergoing radical surgery for prostate cancer. The results of a randomized study comparing both types of transfusion in patients with colorectal cancer were also presented recently.[20] In that study, which included only 120 patients, there were fewer recurrences in the autologous-transfusion group, but on the basis of life-table analysis there were no statistically significant differences between the randomized groups.

An explanation for our findings could be that autologous blood induces the same adverse reactions as allogeneic blood. In animals in which allogeneic transfusions had an adverse effect, no such effect was described for syngeneic blood transfusions.[21,22] Since autologous blood transfusions in humans are comparable to syngeneic transfusions in animals, there is no experimental support for an effect of autologous transfusions on tumor growth. On the other hand, autologous transfusion requires the donation of blood. We have found in rats that the donation of blood can decrease natural-killer-cell activity and stimulate tumor growth.[23-25] Therefore, the patients in the autologous-transfusion group could have had a lower natural-killer-cell activity than the patients in the allogeneic-transfusion group at the time of surgery. However, among the patients who did not receive transfusions, there was no difference in survival between the patients in the autologous-transfusion group, who donated blood, and those in the allogeneic-transfusion group.

Table 4. Disease-free Survival and Colorectal Cancer–Specific Survival, According to Transfusion Status and Dukes' Classification, in Patients with Colorectal Cancer Who Underwent Curative Surgery.

Factor	No. of Patients	Disease-free Survival at 4 yr	Relative Recurrence Rate*	Survival at 4 yr	Relative Death Rate*
		percent		*percent*	
No. of transfusions					
0†	143	73	1	88	1
1 or 2					
Allogeneic	75	59	2.1‡	67	3.6‡
Autologous	102	62	1.8‡§	68	2.8‡§
Dukes' classification					
A†	78	93	1	94	1
B	130	73	4.3‡	85	1.2
C	112	39	15.5‡	50	10.8‡

*Obtained by multivariate analysis.

†Reference category.

‡P<0.05 for the comparison with the reference category.

§Not significantly different (P>0.60) from the allogeneic-transfusion group.

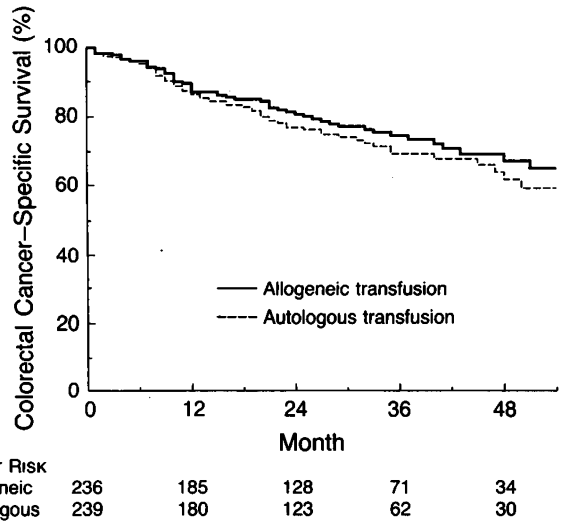

Figure 2. Colorectal Cancer–Specific Survival in All 475 Patients with Colorectal Cancer.

The colorectal cancer–specific survival at four years was 67 percent in the allogeneic-transfusion group and 62 percent in the autologous-transfusion group (P = 0.39). The 95 percent confidence interval for the difference between these percentages (autologous minus allogeneic) ranged from −18 percent to +7 percent.

The most likely explanation for our findings is that there is no causal relation between blood transfusions and prognosis in patients with colorectal cancer. Thus, the findings in the retrospective studies in which blood transfusion was a determinant of prognosis were probably due to patient selection. We think it is not the blood transfusions themselves, but rather the circumstances necessitating the transfusions, that are the real determinant of prognosis. The need to give patients transfusions during the perioperative period is obviously determined by a number of factors, such as blood loss, the extent of the tumor and the dissection, and the skill of the surgeon, although we found tumor size not to be a determinant of prognosis in the multivariate analysis. In some retrospective studies the groups receiving transfusions contained more patients with rectal tumors — who have a poorer prognosis than patients with colon cancer — than did the groups not receiving transfusions.[26,27] We found that the higher recurrence rates in both groups receiving transfusions, as compared with the rate in the group receiving no transfusions, were not affected by the location of the tumor. Because of our rules regarding transfusion, there was such a strong relation between blood loss and transfusion that it was impossible to separate these two factors. Other possible reasons for transfusion, such as the extent of the dissection and the skill of the surgeon, are difficult to assess. Although it seems beneficial to operate on patients with colorectal cancer in such a way that blood transfusions are either avoided or minimized, there is no reason, with respect to either cancer recurrence or survival, to use a program of transfusion with autologous blood in patients undergoing surgery for colorectal cancer.

We are indebted to the principal investigators at the participating centers, as follows: R.U. Boelhouwer, Ikazia Ziekenhuis, Rotterdam; E.D.M. Bruggink, Canisius-Wilhelmina Ziekenhuis, Nijmegen; C.J. van Duin, De Wever Ziekenhuis, Heerlen; J.J. Jakimowicz, Catharina Ziekenhuis, Eindhoven; C.K. Jongsma, Havenziekenhuis, Rotterdam; B.L.A.M. Langenhorst, Academisch Ziekenhuis Dijkzigt, Rotterdam; F.T.T. Liem, Carolus Ziekenhuis, Den Bosch; W.S. Meijer, St. Clara Ziekenhuis, Rotterdam; J.J. Petit, Zeeweg Ziekenhuis, IJmuiden; K.M. Rigg, University of Newcastle-upon-Tyne, Newcastle-upon-Tyne, United Kingdom; M.K.M. Salu, Zuiderziekenhuis, Rotterdam; Th.J. van Straaten, St. Joseph Ziekenhuis, Veldhoven; B.C. de Vries, Westeinde Ziekenhuis, Den Haag; W.F. Weidema, Reinier de Graaf Gasthuis, Delft; and J.C.J. Wereldsma, St. Franciscus Ziekenhuis, Rotterdam.

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