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Effect of Perioperative Blood Loss and Perioperative Blood Transfusions on Colorectal Cancer Survival

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Abstract—*Results of various studies suggest that the perioperative administration of blood transfusions in cancer patients operated upon for cure is associated with a diminished patient survival. Furthermore, recent results from our laboratory indicate that blood loss may also be capable of promoting tumor growth. In order to elucidate these findings a retrospective study was initiated towards the survival of* 164 *patients with colorectal carcinoma, operated upon for cure, at the University Hospital, Rotterdam. In* 117 *patients who perioperatively received blood transfusions the* 5*-year survival was* 68%, *as compared to* 80% *in the non-transfusion group* (P = 0.039; *Wilcoxon*). *The* 5*-year survival in the group of patients with a perioperative blood loss exceeding* 500 ml (n = 88) *was* 70%, *as compared to* 73% *in the group with a blood loss of* 500 ml *or less* (*not significant*). *Multivariate analysis, adjusting for* 11 *relevant parameters, showed that only tumor stage and the administration of blood transfusions were significantly associated with a decrease in survival. It is concluded that perioperative blood transfusions adversely affect colorectal carcinoma survival in this group of patients. Perioperative blood loss was not a significant prognostic factor.*

INTRODUCTION

In 1982, Burrows and Tartter reported, in a retrospective study, that perioperative blood transfusions were significantly associated with a reduction in recurrence-free survival time after operation for colon cancer, which now has been confirmed by many authors [1–4]. In contrast, others did not find such a relation [5–10]. Experimental studies in laboratory animals on this subject are also contradictory in that promotory as well as inhibitory effects of blood transfusions on tumor growth have been demonstrated [11–13]. A variety of reasons have been put forward why blood transfusions may exert a deleterious effect on survival in cancer patients operated upon for cure. Immunosuppression as is seen in organ transplantation has been put forward by most authors as the main cause of tumor progression [2, 3]. However, the question remains whether a difference in recurrence-free survival found in the retrospective studies can indeed be attributed to the administration of allogeneic blood during operation. The group of patients receiving a blood transfusion may be a selected one with an already poor prognosis. In this context, tumor site, tumor stage, packed-cell volume on admission and blood loss during operation should be considered as the possible underlying factors determining patient's disease-free survival, whereas the administration of blood transfusions is merely an expression of these factors.

In this regard we were able to demonstrate a significant effect of blood loss on the number of pulmonary metastases in rats [12]. This finding could imply that the effect found by the above mentioned authors may not be attributable to the administration of allogeneic blood, but instead to the blood loss during the operation preceding these transfusions. Unfortunately, none of the authors who claimed to find a significant effect of blood transfusions on cancer survival reported the amount of blood loss during operation or the possible relation between blood loss and cancer survival.

Only a prospective randomized trial can solve these questions satisfactorily. Therefore, such a prospective trial has been set up in the Rotterdam region. In this randomized trial, colorectal cancer

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survival in patients receiving allogeneic blood transfusions during surgery is compared with colorectal cancer survival in a group of patients who have been enrolled in an autologous predeposit blood transfusion program.

Because of the fact that it will take at least 5 years before this study can provide answers and because of the fact that the experimental findings on blood loss can be of importance in the outcome of the results in the autologous control group, we initiated the present retrospective study, notably focussing on the effects of perioperative blood loss and perioperative blood transfusions.

PATIENTS AND METHODS

The records of patients, operated upon for cancer of the colon or rectum in the University Hospital of Rotterdam from 1977 to 1985, were reviewed. None of these patients had any form of other cancer nor did they receive any kind of treatment for their colorectal carcinoma before admittance to our hospital. Patients who received any adjuvant therapy after surgery, like chemotherapy or radiotherapy, were excluded from this series, as were patients with signs of distant metastatic disease or residual cancer at the time of operation.

Tumor staging was based on the classical Dukes classification. Invasive cancers only partially involving the bowel wall, without any metastasis, were defined as Dukes A. Cancers that penetrated the full thickness of the bowel wall, but still without signs of metastatic disease were classified as Dukes B. Finally, those cancers with nodal involvement but without evidence of distant metastases were defined as Dukes C, regardless of the degree of penetration in the bowel wall.

Information was recorded on age, sex, tumor stage, location of the tumor, type of operation performed, preoperative packed-cell volume, blood loss during operation, the number of blood transfusions, whether whole blood or packed cells were used and the occurrence of postoperative infection. Perioperative blood loss was estimated by weighing surgical gauzes and measurement of sucked up blood volume. Filtrated or irradiated packed cells were never used. No differentiation was made between blood transfusions given preoperatively, during operation or during reconvalescence up to 30 days after operation.

First the Kaplan–Meyer product limit survival analysis was performed [14], considering and comparing two groups (yes/no perioperative blood transfusions and yes/no more than 500 ml perioperative blood loss), with the use of the BMDPC-1L program. Because of the non-experimental nature of this study we also performed a multivariate survival analysis in order to investigate whether an effect of perioperative blood transfusion or perioperative blood loss on postoperative survival and disease-free survival would emerge after controlling for the other explanatory variables mentioned above. A piecewise exponential distribution of postoperative survival time or disease-free survival time was assumed, with the mortality rate or recurrence rate considered constant within each half year t ($t = 0,1,2,\ldots$) following the operation. This rate was specified as a log-linear function of the explanatory variables (including the time, t); for the coefficients of this function, which can be interpreted as logarithms of rate ratios, maximum likelihood estimates were computed using a FORTRAN program on a personal computer under MS-DOS.

RESULTS

The above criteria were met by 164 patients, 78 of whom were men and 86 were women. Mean age at the time of operation was 67.2 years (30–91). Of these 164 patients, 117 (71.3%) received blood transfusions. Transfusions consisted either of whole blood (52%), packed cells (22%) or a combination of the two (26%). The mean number of blood transfusions was 3.2 units, ranging from 1 to 9; 43 (37%) patients received more than three units of blood. Mean follow-up time was 3.75 years. Operations were performed in the years 1977–1985, and follow-up was closed on 17-12-86.

From the 164 patients evaluated, 47 died during follow-up: 30 as a result of colorectal cancer recurrence and 17 of causes not related to colorectal malignancy, including two unknown causes.

When all deaths were taken into consideration, Kaplan–Meyer product limit survival analysis showed a significant reduction (Wilcoxon, $\times 2 = 4.27$; DF = 1; $P = 0.039$) in survival time in the group that received blood transfusions (Table 1). In the non-transfusion group survival at 5 years was 80% (90% confidence interval 70–90%), as compared to 68% (90% confidence interval 61–75%) survival at 5 years in the group which received blood transfusions (Fig. 1).

When deaths only due to colorectal carcinoma were considered this statistical significant difference between the two groups disappeared (Table 2). Five year survival in the non-transfusion group was now 86% and in the transfusion group 78%.

The same results were obtained when Kaplan–Meyer curves were computed with regard to recurrence of cancer. Disease-free survival after 5 years in the non-transfusion group was 86% (90% confidence interval 78–94%), and in the transfusion group 78% (90% confidence interval 72–84%). This difference is not significant (Wilcoxon $\times 2 = 1.982$; DF = 1; $P = 0.16$).

Multivariate analysis revealed only tumor stage and blood transfusions as statistically significant factors with respect to colorectal cancer survival.

Table 1. *Mortality (all causes) during postoperative follow-up*

Blood transfusions	Patients	Patient-years	Deaths
No	47	370.0	8
Yes	117	735.3	39
Total	164	1105.3	47

Statistics: Wilcoxon χ^2 (DF = 1) = 4.273; P = 0.0387; Savage χ^2 (DF = 1) = 4.361; P = 0.0368.

Table 2. *Mortality (due to colorectal cancer) during postoperative follow-up*

Blood transfusions	Patients	Patient-years	Deaths
No	47	402.0	5
Yes	117	838.1	25
Total	164	1240.1	30

Statistics: Wilcoxon χ^2 (DF = 1) = 1.982; P = 0.1592; Savage χ^2 (DF = 1) = 3.107; P = 0.0780.

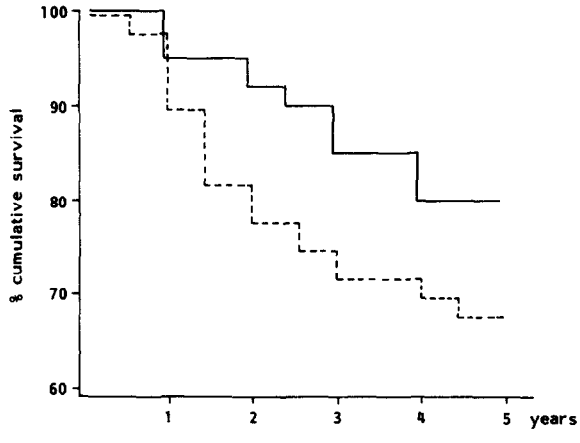

Fig. 1. *Kaplan–Meyer cumulative survival analysis, considering all causes of death, in* 164 *patients with colorectal cancer. Solid line: non-transfused patients* (n = 47); *broken line: transfused patients* (n = 117); P = 0.039.

The death rate for a patient with a Dukes C classified colon or rectal carcinoma was 4.10 ± 1.47 times the death rate for a patient with a Dukes B classified carcinoma ($P < 0.05$).

The death rate for patients who received a blood transfusion perioperatively was 2.47 ± 1.72 times the death rate for patients who did not receive a blood transfusion ($P < 0.05$).

All the aforementioned factors that might influence colorectal carcinoma survival were simultaneously taken into account in this analysis, but none of them was associated with an elevated risk of death due to colorectal carcinoma.

Multivariate analysis with regard to recurrence rate showed only tumor stage to be a significant prognostic factor (rate ratio Dukes C vs. Dukes B = 3.29 ± 1.37, $P < 0.05$), but failed to show a significant effect of transfusion: the rate ratio for patients having received any number of blood transfusions vs. those who did not receive blood transfusions on cancer recurrence was 1.54 ± 1.56.

The transfusion and the non-transfusion group were compared as to age, sex, tumor stage, tumor site, type of operation performed, the existence of a postoperative infection, hematocrit on admission and blood loss during operation (Table 3). The type of operation and blood loss during operation both were significantly associated with the administration of blood transfusions, but had no significant effect on survival or disease-free interval. Preoperative packed-cell volume was only associated significantly with blood transfusions when more than three units of blood were administered (analysis of variance F = 3.36, P = 0.037, DF = 2). All of the other the co-variables mentioned in Table 3 were not associated with elevated death or recurrence rates as a result of colorectal cancer disease.

With regard to the amount of blood loss during operation, the patient material was dichotomized, one group containing all the patients who lost 500 ml of blood or less during operation (n = 76, 46%), the other containing the patients who lost over 500 ml of blood (n = 88, 54%). From both groups Kaplan–Meyer curves were computed and compared. No statistical significant difference was found between the two groups. All deaths considered, 5 year survival in the group of patients that lost 500 ml or less during the operation amounted to 72.5%, as compared to 70% for patients who had a perioperative blood loss exceeding 500 ml (not significant, Wilcoxon, P = 0.51). Cancer survival and disease-free interval were not significantly influenced by the amount of blood loss (cancer survival P = 0.28, Wilcoxon; recurrence P = 0.063, Wilcoxon). Perioperative blood loss was

Table 3. Comparisons of variables

	Blood transfusions	No blood transfusions	Significance
Number of patients	117	47	
Sex			
Male	56	22	NS
Female	61	25	
Age (years)	67.9	65.5	NS
Stage			
Dukes A	7	3	NS
Dukes B	76	31	
Dukes C	13	34	
Site			
Right	27	18	NS
Transversum	11	4	
Left	79	25	
Operation			
Hemicolectomy right	32	15	$\chi^2 = 9.82$
Low anterior	40	5	DF = 3
Sigmoid resection	31	18	$P = 0.02$
Other	14	9	
P.O. infection	31	8	NS
Mortality			
Overall	39	8	$\chi^2 = 4.36$ DF = 1 $P = 0.039$
Cancer	25	5	$\chi^2 = 3.11$ $P = 0.078$
Hematocrit on admission (%)	40.29	41.49	NS
Blood loss in ml	1096	357	$T = -8.87$ DF = 148 $P < 0.001$

Table 4. Amount of blood loss in various sub-groups

	Mean blood loss in ml	Standard deviation	Significance
All patients	884	778	
Stage			
Dukes A	1035	777	$F = 0.1931$
Dukes B	874	801	DF = 2
Dukes C	876	772	$P = 0.825$
Site			
Right	532	474	$F = 6.8310$
Transversum	900	691	DF = 2
Left	1034	863	$P = 0.0014$
Operation			
Low anterior	1327	938	$F = 8.6079$
Sigmoid resection	731	716	DF = 3
Hemicolectomy right	591	483	$P < 0.0001$
Other operation	943	774	
Blood transfusion			
Yes	1096	834	$T = 8.87$
No	357	216	DF = 148 $P < 0.001$

significantly associated with tumor site and type of operation performed (Table 4).

In addition, using a multivariate analysis, no significant effect of perioperative blood loss on survival, cancer survival and recurrence-free survival could be demonstrated (rate ratio for blood loss over 500 ml vs. blood loss less than 500 ml on survival was 0.96 ± 1.24, on cancer survival 0.98 ± 1.29, and on disease-free survival 1.10 ± 1.24).

DISCUSSION

Since Burrows and Tartter in 1982 stated that blood transfusions might have a deleterious effect on colorectal cancer survival many publications have followed, in which this relation was confirmed [1–4] or rejected [6–10]. Also the literature concerning a blood transfusion effect on other types of cancer is not unanimous [15–21]. Several reasons have been proposed why such an ambiguity of results exists. The discussion focuses on whether the blood transfusion effect found by some authors is a separate entity or a reflection of an already poor prognosis. It has been stated that the effect, found by Burrows and Tartter in 1982, might be due to the inclusion of rectal carcinomas. Rectal tumors are technically more difficult to remove, and therefore their removal tends to require more blood transfusions. Furthermore, rectal tumors are known to have a higher local recurrence rate than colon carcinomas [22]. Nevertheless other studies that did include rectal carcinomas failed to show a blood transfusion effect [5, 8, 23]. In the present study rectal carcinomas were also included, and although there is a significant relation between the administration of blood transfusions and low anterior resection for rectal carcinoma, this does not account for the transfusion effect found, as demonstrated by the multivariate analysis.

The type of transfusion administered, i.e. whether whole blood or packed cells are given, could account for the difference in the outcome of the various studies. This might be an important topic, since in some studies which deal with the effects of transfusions in organ transplantation, the immunomodulating effects of blood transfusions were found to be most prominent when whole blood was being administered [24]. In our series, 78% of the transfused patients received whole blood, either alone, or in a combination with packed cells. The type of transfusion given in the present studies did not have any effect on cancer survival.

In seven studies concerning other types of cancer than colorectal cancer a relation between the number of transfusions and survival could only be demonstrated in two [18, 21]. In organ transplantation there seems to be a 'dose-dependent' effect of blood transfusions: the more transfusions administered preoperatively, the better the graft survival [25]. We could not find an effect of the number of blood transfusions in this study. Preoperative hemoglobin, or packed cell volume on admission, are also factors that might influence the effect of blood transfusions on cancer survival, because these factors both can provoke the administration of blood transfusions, and at the same time might be a determinant of advanced cancer. Blumberg *et al.* [26], found a significant association between packed cell volume on admission of less than 38%, and a shorter survival time. Unfortunately, different types of cancer were included in these series. Despite the fact that we were not able to demonstrate a relation between packed cell volume on admission and death due to colonic cancer, we found a correlation between the number of transfusions (0,1–3, > 3) and the hematocrit ($P < 0.05$). Most investigators did not mention this parameter. From the six reports that claimed an adverse effect of transfusions, four [2, 16, 19, 27] showed a correlation between a low hemoglobin level on admission, and the administration of blood transfusions.

In the present material a significant relationship could be demonstrated between the administration of blood products and the amount of blood lost during surgery. Although this relationship may seem rather obvious, it is not mentioned in the literature concerning the blood transfusion effect. If the amount of blood lost reflects the difficulties in removing the tumor, either because of unfavorable tumor stage or poor surgical techniques, the transfusion effect could be attributed to this bias. In this context some investigators have recorded the operation time, but this parameter did not show a relationship with cancer survival.

In an experimental setting, we studied the effect of blood loss on metastatic growth in rats, and found that blood loss alone was capable of promoting metastatic growth [12]. No other reports concerning the effects of blood loss on cancer growth, either experimental or clinical, have appeared in literature yet. Focussing on the impact of blood loss on cancer survival in our material, we were unable to demonstrate a significant relation between the amount of perioperative blood loss and survival prognosis, although blood loss during operation was associated with the administration of blood transfusions.

All the above mentioned studies except one [8] have been performed in a retrospective way, and many investigators have confined their studies only to recurrence rates. Others have already stated that mortality rates are superior to recurrence rates, when a rigid follow-up scheme is lacking [28]. We fully subscribe to this view, and think that this is the reason that we found no statistical significant difference between the transfusion and non-transfusion groups when recurrence was being investi-

gated, whereas we did find a significant difference as to cancer survival.

This study shows a negative effect of perioperative blood transfusions on colorectal cancer survival. The only other factor significantly related to colorectal cancer survival, namely tumor stage, did not correlate with blood transfusions. The three variables which are associated with blood transfusions, namely perioperative blood loss, type of operation performed and packed-cell volume on admission, bear no relation to cancer survival. Therefore it can be concluded that the administration of perioperative blood transfusions may be a reflection of the difficulties in removing the tumor or of an already advanced cancer, but that the effect of blood transfusions found in this study is independent of these factors.

It is our belief that only a sufficiently large, prospective randomized study, including proper immunologic screening, can give an answer to the question whether or not blood transfusions may compromise cancer survival. Hence in August 1986, a prospective trial has been started in the Rotterdam region, which will elucidate this important topic.

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