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Blood transfusion does not have an adverse effect on survival after operation for colorectal cancer

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The effect of perioperative blood transfusion on cancer progression remains controversial because retrospective clinical studies have produced conflicting results. We have collected data prospectively on 379 patients undergoing curative surgery for colorectal adenocarcinoma and assessed the effect of variables, including blood transfusion, on survival. Univariate and multivariate survival analysis has been carried out. When the end-point for analysis used was death due to recurrent colorectal carcinoma and non-cancer deaths were censored, there was no difference in cancer-specific survival between transfused and non-transfused patients. Survival analysis was also carried out without censoring the non-cancer deaths and clearly demonstrated how the statistical analysis and data interpretation could be distorted by age-related non-cancer deaths. The incidence of recurrence of colorectal carcinoma was not greater in the transfused group than in the non-transfused group. We conclude that blood transfusion should not be withheld in colorectal surgery for fear of worsening the prognosis.

Undoubtedly, the availability of blood transfusion has permitted major surgery in malignant disease and has saved countless lives. Morbidity associated with blood transfusion includes incompatibility, transfusion reactions, disease transmission, alloimmunisation and fluid overloading. Such problems may reduce the benefit in some surgical patients. Controversy followed the demonstration of the beneficial effects of blood transfusion on renal allograft survival and the suggestion that transfusion decreases immune responsiveness (*1,2*). Several retrospective studies suggested a detrimental effect of blood transfusion on prognosis after operation for malignant disease (*3–7*). However, it is important to attempt to determine the existence of a causal relationship between blood transfusion and progression of cancer if we are to avoid transfusion for this reason. To conduct prospective randomised studies in this respect obviously introduces considerable ethical problems. We have analysed data collected prospectively on patients undergoing curative resection for colorectal adenocarcinoma in an attempt to assess the effect of blood transfusion on prognosis.

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Materials and methods

From 1981 to 1990, all patients referred to one of the surgical outpatient clinics or, alternatively, present as an emergency case at Trafford General Hospital and subsequently diagnosed as having colorectal cancer were identified. The research nurse interviewed the patient, gathering information on the past medical history, signs and symptoms on an interview sheet. The data from this interview and basic patient details from the case notes were entered on to a specially designed computer document and input to a computer database.

The information collected on each patient were basic demographic details, signs and symptoms, family history and details of any previous treatment and diagnostic tests.

If the patient has an operation, a comprehensive set of operative and postoperative data are also recorded. The patients who have advanced disease at diagnosis and classed as 'inoperable' are followed up only.

The patient is subsequently followed up postoperatively and then at 3-, 6- and 12-monthly intervals in the outpatient clinic or through a letter to the GP. The follow-up form records the date the patient was last seen, the Karnofsky Performance Score at that time and details of any signs of disease recurrence. A patient is only declared 'lost to follow-up' if they actually move out of the area, and in some cases the outcome for these patients was traced using the records kept by the FHSA.

If death occurs, the date and cause of death are recorded on a 'notification of death' form and, from the post-mortem reports, whether death was due to a recurrence of their original disease, new disease in another primary site or due to medical complications. The information collected is therefore a chronological record of what happens to a patient with colorectal cancer from the date of first diagnosis to the last date seen, if death has not already occurred.

Details of blood given during the surgical inpatient stay, either preoperatively, perioperatively, or during the immediate postoperative period were recorded. The site of the tumour as found at operation was recorded and categorised as right (caecum, ascending colon, hepatic flexure to mid-transverse colon), left (mid-transverse colon to splenic flexure, descending colon, sigmoid colon) and rectum (including rectosigmoid, rectum and upper third anal canal). Also recorded was the type of operation, mobility of tumour and whether, in the opinion of the surgeon, the operation was curative (no evidence to the eye of local or distant spread). Based on the depth of penetration and local spread, tumours were given a Dukes' classification as follows: A, not beyond muscularis propria; B, beyond muscularis propria; C, secondary deposits in lymph nodes; D, distant metastasis.

All data recorded on custom-designed forms were input to the University of Manchester mainframe computer for analysis using SPSS (Statistical Package for Social Sciences). Follow-up data of patients' disease status and incidence of recurrence were updated regularly for up-to-date analysis of survival and recurrence times.

In order to determine the effects of transfusion and other variables on the course of the disease, analysis was restricted to patients undergoing curative resections for colorectal adenocarcinoma between 1981 and 1990. Life table analysis was performed using program PL1 (BMDP) and significant differences demonstrated by the log rank test. The trial time for each patient was from operation up to June 1991 or to death. The combined effects of variables on survival were analysed using Cox's regression analysis. In this analysis, any non-significant variables were deleted in a backward-stepwise manner, using the likelihood ratio test and a 5% level of significance. Analysis was carried out for the whole group and also according to tumour site, since it is well-recognised that rectal tumours have a poorer prognosis than colonic tumours (*8*). Initially, in the univariate and multivariate analysis we used death from any cause as the end-point. We then used death from colorectal cancer as the end-point (censoring all non-cancer deaths). This was to assess the confounding effect of not censoring the non-cancer deaths on our statistical analysis and on the interpretation of such data. Finally, we recorded the incidence of recurrence of colorectal carcinoma in both transfused and non-transfused groups.

Results

Between 1981 and 1990, 379 patients out of a total of 743 underwent curative resection for colorectal adenocarcinoma. In all, 221 (58%) received a perioperative blood transfusion and 158 (42%) did not. The median age of the transfused group was 74 years and of the non-transfused group 68 years. Table I illustrates the clinicopathological variables equally distributed between the two groups of patients; these are sex, performance status, admission status, mobility of tumour, Dukes' staging and tumour differentiation. Table II illustrates the variables unequally distributed; these are age, haemoglobin at presentation and tumour site. Those over 70 years of age were more likely to have received a transfusion. Patients anaemic at presentation were more likely to have been transfused. Patients with right-sided or rectal tumours were more likely to have received a transfusion than patients with left-sided tumours. Median haemoglobins at presentation were 10.1 g/dl (right-sided tumours), 13.1 g/dl (left-sided tumours) and 13.1 g/dl (rectal tumours). This explains the higher transfusion rates in patients with right-sided tumours. Table III illustrates the transfusion status according to the type of operation carried out. Patients with rectal tumours were more likely to have been transfused if they underwent abdominoperineal resection rather than anterior resection.

Survival

Of 379 patients included in this study, at the end of the analysis 94 (25%) had died of recurrent disease, 44 (12%) had died of unrelated causes, and 230 (61%) were still alive. Eleven were lost to follow-up and were censored in the survival analysis. Median follow-up for the survivors was 5 years (range 6 months–10 years).

Figure 1 shows the survival curves for 379 patients divided into the transfused and non-transfused groups. Non-cancer deaths are not censored. There was no statistical difference in survival (log rank $\chi^2 = 2.86$, $df = 1$, $P = 0.09$). Individual stratification by tumour site (right, left and rectal) was performed. There was no difference in survival between the transfused and non-

Table I. Variables not associated with patient transfusion status in 379 patients undergoing curative surgery for colorectal adenocarcinoma

Variable	*Transfused*	*Not transfused*	*P value*
Sex			
Male	101 (53%)	89 (47%)	$\chi^2 = 3.75$, df = 1,
Female	120 (63.5%)	69 (36.5%)	$P = 0.0501$
Performance status			
0	79 (56%)	61 (44%)	$\chi^2 = 0.92$, df = 3,
1	79 (58%)	58 (42%)	$P = 0.8235$
2	46 (60.5%)	30 (39.5%)	
3 and 4	17 (65%)	9 (35%)	
Admission status:			
Emergency	55 (60%)	36 (40%)	$\chi^2 = 0.008$, df = 1,
Elective	166 (58%)	122 (42%)	$P = 0.9272$
Tumour mobility*			
Mobile	158 (56%)	122 (44%)	$\chi^2 = 1.82$, df = 1,
Partly fixed	63 (65%)	34 (35%)	$P = 0.1742$
Tumour grade†			
Well differentiated	151 (60%)	99 (40%)	$\chi^2 = 4.26$, df = 2,
Mod/well differentiated	58 (52%)	54 (48%)	$P = 0.1169$
Poorly differentiated	10 (77%)	3 (23%)	
Dukes' staging‡			
A	24 (48%)	26 (52%)	$\chi^2 = 2.74$, df = 2,
B	142 (61%)	92 (39%)	$P = 0.2526$
C	55 (59%)	38 (41%)	

* Two tumours unknown
† Four tumours were not graded
‡ Two tumours were not staged

Table II. Variables associated with transfusion status in 379 patients undergoing curative surgery for colorectal adenocarcinoma

Variable	*Transfused*	*Not transfused*	*P value*
Age groups			
< 70 years	101 (53%)	89 (47%)	$\chi^2 = 3.75$, df = 1,
> 70 years	120 (63.5%)	69 (36.5%)	$P = 0.0069$
Haemoglobin at presentation	*	†	
Males < 12 g/dl	52 (78%)	15 (22%)	$\chi^2 = 26.4$, df = 1,
Males > 12 g/dl	39 (36%)	68 (64%)	$P = 0.00001$
Females < 10 g/dl	39 (85%)	7 (15%)	$\chi^2 = 10.5$, df = 1,
Females > 10 g/dl	76 (57%)	58 (43%)	$P = 0.002$
Tumour site			
Right	79 (69%)	36 (31%)	$\chi^2 = 11.80$, df = 2,
Left	44 (45%)	53 (55%)	$P = 0.0034$
Anorectal	98 (59%)	69 (41%)	

* Fifteen results missing
† Ten results missing

Table III. Type of operation and transfusion status in 379 patients undergoing curative surgery for colorectal adenocarcinoma

	Transfused	*Not transfused*
Right hemicolectomy	65 (68%)	31 (32%)
Left hemi-, transverse or sigmoid colectomy	60 (51%)	48 (49%)
Anterior resection	52 (48.5%)	55 (51.5%)
Abdominoperineal resections	48 (74%)	17 (26%)
Other colectomies	6	7

transfused groups with right-sided or with rectal tumours. There was a significant difference in survival with left-sided tumours, the non-transfused groups faring better than the transfused group (Fig. 2, log rank $\chi^2 = 5.32$, df = 1, $P = 0.02$). The results of the multivariate analysis using the Cox Proportional Hazards regression model are shown in Table IV. The variables significantly associated with worse survival were performance status, positive transfusion status, increasing Dukes' stage and male sex in that order. Multivariate analysis confined to the patients with left-sided tumours also confirmed that positive transfusion status was associated with worse survival (data not shown).

The results of survival analysis, this time by censoring the non-cancer deaths showed marked differences. Figure 3 shows the survival curves for 379 patients divided into the transfused and non-transfused groups. There was no difference in survival (log rank $\chi^2 = 0.53$, df = 1, $P = 0.47$). Individual stratification by tumour site (right-sided, left-sided and rectal) demonstrated no difference in survival between the transfused and non-transfused groups for any of the three tumour sites (Fig. 4). The results of the multivariate analysis using the Cox Proportional Hazards regression model are shown in Table V and can be compared with Table IV.

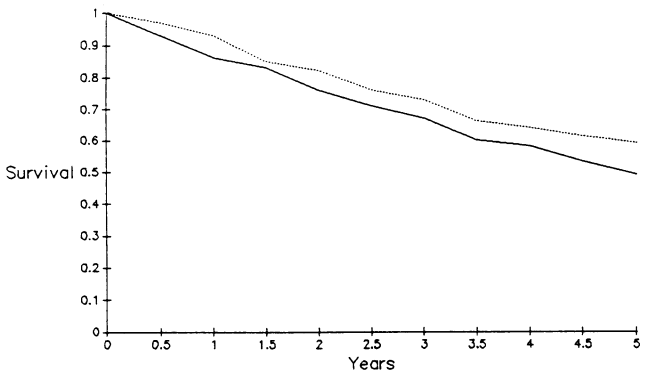

Figure 1. Crude survival curves for 379 patients undergoing curative surgery for colorectal adenocarcinoma (non-cancer deaths not censored). ..... Not transfused, ——— Transfused.

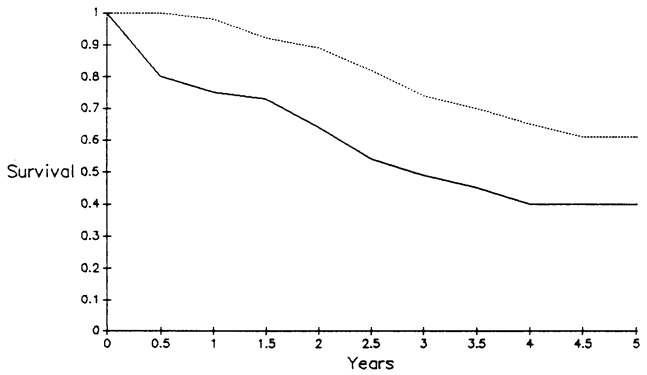

Figure 2. Crude survival curves for 97 patients undergoing curative surgery for left-sided colonic adenocarcinoma (non-cancer deaths not censored). ..... Not transfused, ——— Transfused.

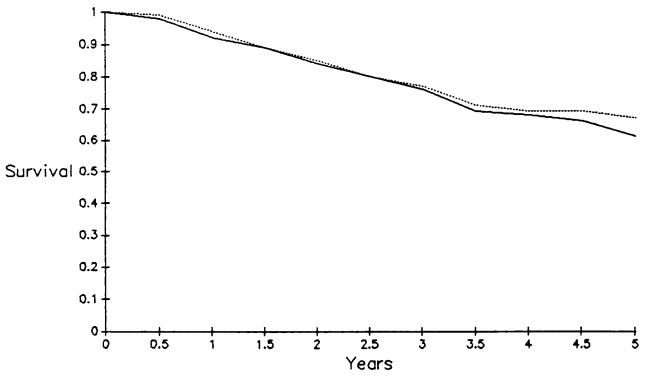

Figure 3. Survival curves for 379 patients undergoing curative surgery for colorectal adenocarcinoma (non-cancer deaths censored). ..... Not transfused, ——— Transfused.

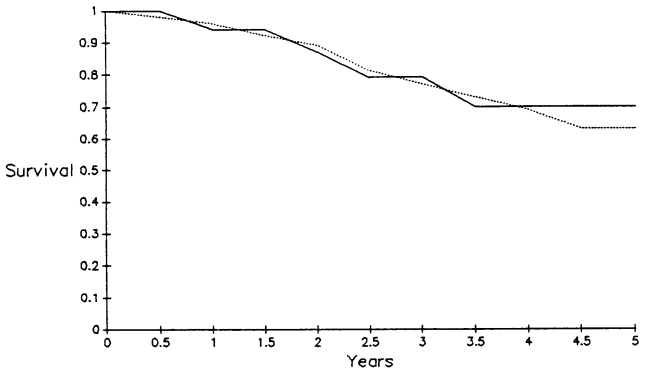

Figure 4. Survival curves for 97 patients undergoing curative surgery for left-sided colonic adenocarcinoma (non-cancer deaths censored). ..... Not transfused, ——— Transfused.

Table IV. Cox proportional hazards regression model (non-cancer deaths uncensored)

Covariate	*Coefficient*	*(SE)*	*Significance*
Performance status	0.4078	(0.0984)	$P = 0{\cdot}0001$
Transfusion status	0.4467	(0.2039)	$P = 0.0251$
Dukes' stage	0.3629	(0.1725)	$P = 0.0357$
Sex	−0.3822	(0.1901)	$P = 0.044$

Table V. Cox proportional hazards regression model (non-cancer deaths censored)

Covariate	*Coefficient*	*(SE)*	*Significance*
Dukes' stage	0.7033	(0.1928)	$P<0.0001$
Sex	−0.5827	(0.2134)	$P=0.007$
Tumour mobility	0.4263	(0.1475)	$P=0.01$

Variables significantly associated with worse survival were Dukes' staging, male sex and partial tumour fixation in that order. Positive transfusion status was not associated with worse survival.

Finally, in the transfused group 51 patients (23.1%) developed recurrent disease and in the non-transfused group 34 patients (21.5%) developed recurrent disease, there being no significant difference. In the transfused group 32 (14.5%) developed local recurrence and in the non-transfused group 20 (12.7%) developed local recurrence; again there was no significant difference between the two groups.

Discussion

Interest in the possible immunomodulating effects of blood transfusion arose following reports that blood transfusion given preoperatively to prospective renal transplant recipients can improve graft survival *(1,2,9)*. Using animal tumour models, some studies *(10)* have shown tumour progression associated with blood transfusion but other studies *(11)* have not. Controversy followed in the literature regarding the possible detrimental effect of blood transfusion on prognosis after curative surgery for colorectal carcinoma.

The main difficulty comparing the results from the different retrospective studies seems to be that the statistical methods used and the particular detrimental effects or end-points examined vary from study to study. The timing of recurrence of colorectal carcinoma is used often as the end-point in analyses. Recurrence after curative resection invariably occurs as a result of micrometastases which may be present at the time of operation or may develop later as a result of implantation. It may be argued that one can use the time at which there is clinically overwhelming evidence of recurrence as the end-point in analysis, but again this depends on the intervals at which patients are examined by the clinicians. Recurrence of disease will have been present and clinically silent beforehand. For these reasons in our particular study we chose not to use the time of clinically evident recurrence as end-point. We have preferred to perform life table analysis on patient survival using as the end-point initially death from any cause and subsequently death from recurrent colorectal carcinoma. The results of our multivariate analysis using uncensored data initially appeared to suggest that transfusion was associated with worse survival, especially with left-sided tumours. Censoring the non-cancer deaths and using death from colorectal cancer as the end-point will have provided more accurate estimates of the chance of dying of recurrent colorectal carcinoma. It is therefore likely that a better assessment of the possible effect of transfusion status on disease progression, if any, will have been obtained. The results of our multivariate analysis suggest that there is no effect of transfusion status on the estimates of the chance of dying of recurrent colorectal carcinoma after potentially 'curative' surgery.

A number of good quality retrospective studies suggest a detrimental effect of transfusion on prognosis after operation, but the methods of analysis differ. Blumberg *et al. (4)* suggested perioperative transfusion may be a significant risk factor in the prognosis of cancer of the colon. They reported a 5-year recurrence-free survival of 40% and 90% in the transfused and non-transfused patients respectively. Creasy *et al. (5)* examined recurrence of disease after resections of sigmoid carcinomas and came to a similar conclusion. These studies, however, did not examine patient survival. Parrott *et al. (6)* came to the conclusion that blood transfusion may be associated with increased mortality and recurrence in patients undergoing curative surgery for colorectal cancer. They do not perform life table analysis related to cancer-specific deaths. Foster *et al. (7)* reported better overall cancer-specific survival in a non-transfused group of patients with colonic cancer compared with a transfused group. However, they do not demonstrate a similar effect with rectal carcinomas.

Other retrospective studies failed to reveal any association of blood transfusion with a worsened prognosis. Nathanson *et al. (12)* showed no difference in recurrence rates between a large transfused group and a non-transfused group. More recently, data from the UK Large Bowel Cancer (LBC) study have been examined *(13)*. The conclusion was that blood transfusion was not associated with an altered prognosis after operation in 591 patients studied. They construct survival curves and then perform age adjustment by comparison with the figures for England and Wales in 1978. A further study by Crowson *et al. (14)* examines recurrence and overall survival in relationship to transfusion status and comes to a similar conclusion.

It is difficult to come to a convincing conclusion because the data analysis of these studies has been variable. Our study of data collected prospectively on patients operated on between 1981 and 1990 would reflect closely present surgical and anaesthetic practice. The results from the multivariate analysis suggest it is important that when analysing the effects of variables on cancer progression, non-cancer deaths should be censored. When we censored non-cancer deaths, Dukes' staging was the most important factor in determining cancer-specific survival and this is what one would be expecting. In the past, male sex has been shown to be associated with poorer survival *(15)* and our results seem to agree with this. Transfusion status is not associated with worse cancer-specific survival. The results of our

initial analysis when the non-cancer deaths were not censored show how the statistics and the data interpretation can be distorted by age-related deaths. In this situation performance status and transfusion status were more important variables in determining survival than Dukes' staging.

It is clear that the use of blood transfusions should be minimised in order to avoid the accompanying risks and that greater efforts need to be made to avoid blood loss during operation. We must conclude, however, that one should not be reluctant to use blood transfusions for fear of worsening the prognosis in colorectal carcinoma and, probably, that factors leading to the need for transfusion during operation have a greater influence on prognosis than the transfusion itself.

We thank Mr P A Sykes and Mr E M Hoare for allowing us to include their patients in this study.

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Invited comment

This is a very fair and easy to read prospective study of 379 colorectal cancer patients who underwent curative surgery between 1981 and 1990. Data, including transfusion status, have been collected and have been analysed using powerful modern statistical methods. The overall message is that older patients tend to get transfused, and it is older patients who tend to die. If this is not taken into account, then a spurious transfusion effect may be seen, but when it is taken into account there seems to be no disadvantage to blood transfusion (other caveats such as transfusion reactions, viral transmission, etc, being accepted).

There are two points that should be borne in mind about this paper. The first is that these are very powerful statistical methods, and they work by having large numbers to play with. They reduce the original sample into multiple smaller fractions for subgroup testing and then they build them all up again. This means that, unless the original sample size is very large indeed, there is a tendency for comparisons in these subgroups to be