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Large bowel cancer: the effect of perioperative blood transfusion on outcome

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Perioperative blood transfusion has been reported to adversely affect survival in cancer patients, but the evidence is inconclusive and may be an epiphenomenon. From the Large Bowel Cancer Project, 961 patients who underwent curative resection and left hospital alive have been reviewed to compare the effect of perioperative blood transfusion on outcome; 591 patients (61%) had been given a blood transfusion while 370 (39%) had not been transfused. Some clinical variables were equally distributed between the two groups; ie age, sex, obstruction, perforation, tumour differentiation. Three other variables known to influence patient prognosis were not equally distributed, ie tumour site, Dukes' stage and tumour mobility. Patients with tumours of the rectum and rectosigmoid, with Dukes' stage C lesions and with some degree of tumour fixation were more likely to have received blood transfusions. Using the logrank method of multivariate analysis to allow for differences in distribution of all those variables known to affect prognosis, there was no survival disadvantage for those patients who had received perioperative blood transfusion. Furthermore, there were no overall differences between the two groups of patients in their risk of developing local tumour recurrence or distant metastases. The distribution of metastases differed: in the 'transfused' group only 37% of distant metastases were found in the liver, while 71% were found in this site in the 'not transfused' group ($\chi^2 = 18.46$, d.f. = 1, $P < 0.001$). By contrast, there was a larger proportion of patients with lung metastases in the transfused group (27% *vs* 11%) ($\chi^2 = 5.59$, d.f. = 1, $P < 0.05$).

Therefore, these data do not support the concept of an overall deleterious effect of blood transfusion on patient survival, but suggest that blood given in the perioperative period may change the biology of the metastatic process.

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The improvement in renal allograft survival with pre-transplant blood transfusion is well accepted *(1)*, but the mechanisms by which this effect is produced have not been fully elucidated. Evidence that blood may produce an 'immunosuppression-like' state led to the hypothesis that heterologous blood transfusion may modify host response to other clinical conditions, including enhancement of tumour growth, recurrence and metastasis *(2)* and increased susceptibility to postoperative infection *(3)*. There have been several retrospective studies on the effect of perioperative blood transfusion on tumour recurrence and survival in cancer patients. Some of these studies have shown an association between transfusion and poor outcome *(2,4–11)*. Thus, the evidence to support the concept that perioperative blood transfusion may be deleterious to long-term outcome in cancer patients is inconclusive and the observation may be an epiphenomenon.

To establish the effect of blood transfusion on outcome in a large group of patients we collected blood transfusion

data on patients entered in the Large Bowel Cancer Project.

Patients and methods

The Large Bowel Cancer Project is a collaborative prospective study involving 94 surgeons and 38 pathologists in 23 hospitals in the United Kingdom. All patients presenting for treatment of a primary tumour have had details of their clinical management documented prospectively and recorded by full-time research assistants, who have travelled to the majority of centres to check and collect the data in a well-established and standardised format *(12–14)*. The information has then been transferred to a mainframe computer at the University of London Computer Centre and processed using the Statistical Package for the Social Sciences (SPSS) *(15)*. The project started in 1976, entry ceased in 1980 and follow-up continues.

For this study, all patients who had undergone curative resections for large bowel cancer and left hospital alive (2330) were eligible for inclusion. Eighteen pathology departments were approached and asked to provide information on the transfusion status of patients entered in the Large Bowel Cancer Project. Ten departments complied and transfusion data were obtained on 961 patients. Thus, the clinical and histopathological data were collected prospectively but the information about blood transfusion, although complete from the departments that participated, was obtained retrospectively.

Definitions

Perioperative blood transfusion. Patients who received a blood transfusion in the immediate preoperative, perioperative or postoperative period up to the time of discharge from hospital.

Curative resection. Removal of the primary tumour, with or without an anastomosis, which was histologically complete and had no clinical evidence of intra-abdominal or distant metastases.

In-hospital mortality. Death in hospital on the first or subsequent admission while undergoing treatment for the presenting complaint.

The rectosigmoid. This is a term that has no precise definition but the surgeons participating in this study have found it useful. Removal of a carcinoma at this site followed by restoration of intestinal continuity requires that the anastomosis performed is extraperitoneal.

Local recurrence. Convincing evidence of recurrence of cancer at the anastomosis, in the region of the anastomosis, in the abdominal wound, in the drain site or perineum, but not hepatic or peritoneal secondaries.

Liver metastasis. Convincing evidence of metastasis to the liver but not to other distant sites.

Distant metastasis. Convincing evidence of metastasis to distant sites with or without liver involvement.

Statistical methods

Standard χ^2 analyses and the Wilcoxon rank sum test have been used. Survival curves and their 95% confidence limits have been constructed by the life table method *(16)*. Age adjustment has been performed by comparison with the figures for England and Wales in 1978 *(17)*. The method of Peto and Pike *(18)* employed for the analysis of survival data from the Large Bowel Cancer Project has been previously discussed in detail *(12)*. Results have been quoted as not significant (NS) if the probability of chance occurrence was more than 5%.

Results

Of 961 patients studied, 591 (61%) received a blood transfusion during the perioperative period and 370 (39%) did not. Five of the clinicopathological variables analysed were found to be equally distributed between the two groups of patients (age, sex, presence of bowel obstruction or perforation and tumour differentiation, Table I), while three variables known to affect prognosis *(12–14)* were unequally distibuted (tumour site, Dukes' stage and tumour fixity, Table II).

Table I. Variables not associated with patient transfusion status

Variable	*Not transfused n = 370 (%)*	*Transfused n = 591 (%)*
Age		
<70	201 (54)	319 (54)
>70	169 (46)	272 (46)
Sex		
Male	174 (47)	294 (50)
Female	196 (53)	297 (50)
Obstruction		
Present	64 (17)	85 (14)
Absent	306 (83)	506 (86)
Perforation		
Present	13 (4)	21 (4)
Absent	347 (93)	550 (93)
Suspected	10 (3)	20 (3)
Tumour differentiation (unclassified 22)		
Well	126 (34)	192 (32)
Moderate	192 (52)	330 (56)
Poor	40 (11)	59 (10)

Table II. Statistically significant variables associated with patient transfusion status

Variable	*Not transfused n = 370 (%)*	*Transfused n = 591 (%)*	*Statistical comparison*
Tumour site			
Right colon	101 (28)	161 (27)	
Splenic flexure	19 (5)	18 (3)	$\chi^2 = 31.63$
Left colon	126 (34)	127 (22)	d.f. = 4
Rectum and rectosigmoid	115 (31)	277 (47)	$P<0.001$
Multiple, appendix, anus	9 (2)	8 (1)	
Dukes' stage (unclassified 6)			
A	50 (14)	67 (11)	$\chi^2 = 10.17$
B	225 (61)	316 (53)	d.f. = 2
C	92 (25)	205 (35)	$P<0.01$
Tumour fixity			
Mobile	285 (77)	393 (67)	$\chi^2 = 12.14$
Other	85 (23)	198 (33)	d.f. = 1
			$P<0.001$

Transfused patients were more likely to have rectum and rectosigmoid tumours with some fixity which were of a more advanced stage.

Variables associated with patient transfusion status (Table II)

Tumour site. There was a difference in the distribution of tumours within the large bowel between the 'transfused' and 'not transfused' groups ($\chi^2 = 31.63$, d.f. = 4, $P<0.001$). The commonest tumour site for all patients was the rectum/rectosigmoid, 392 of 961 (41%). Patients given a blood transfusion more often had tumours at this site (277 of 591, 47%) than did patients who were not transfused (115 of 370, 31%) ($\chi^2 = 23.48$, d.f. = 1, $P<0.001$). This difference was mainly accounted for by the number of patients undergoing abdominoperineal excisions who required blood transfusion (142 of 277, 51%) compared to 28 of 115 (24%) who were not transfused ($\chi^2 = 23.90$, d.f. = 1, $P<0.001$).

Dukes' stage. Dukes' stage was assessed in 955 of the 961 resected specimens (99%). The distribution of Dukes' stage was different in the two groups ($\chi^2 = 10.17$, d.f. = 2, $P<0.01$). Dukes' C tumours were more common among those who received a transfusion (205 of 591, 35%) than in the 'not transfused' group (92 of 370, 25%) ($\chi^2 = 10.3$, d.f. = 1, $P>0.01$).

Tumour fixity. A greater proportion of transfused patients had some degree of tumour fixation (198 of 591, 33%) than those who were not transfused (85 of 285, 23%) ($\chi^2 = 12.14$, d.f. = 1, $P<0.001$).

Tumour recurrence (Table III)

Local recurrence. Local recurrence developed in 171 patients (18%) of the total group. The risk of developing a local recurrence was 16% (58 of 370 patients) for those not transfused and 19% (113 or 591 patients) if transfused ($\chi^2 = 1.8$, d.f. = 1, P = NS). The modal risk (maximal risk period) for developing a local recurrence was marginally greater in the 'transfused' group, 6% at 6–11 months, than in the 'not transfused' group, 4% at 6–11 months.

Distant metastasis. Distant metastases developed in 98 (17%) of transfused patients, and in a similar proportion,

Table III. Tumour recurrence

	Not transfused n = 370 (%)	*Transfused n = 591 (%)*	*Statistical comparison*
Local recurrence			
Present	58 (16)	113 (19)	$\chi^2 = 1.8$
Absent	312 (84)	478 (81)	d.f. = 1
			P = NS
Distant metastasis			
Present	63 (17)	98 (17)	$\chi^2 = 0.03$
Absent	307 (83)	493 (83)	d.f. = 1
			P = NS

Table IV. Organ distribution of distant metastases

Site	*Not transfused* $n=63$ (%)	*Transfused* $n=98$ (%)	*Statistical comparison*
Liver	45 (71)	36 (37)	
Lung	7 (11)	26 (27)	$\chi^2=21.56$
Bone	5 (8)	10 (10)	d.f. = 5
Brain	0 (0)	4 (4)	$P<0.001$
Multiple	6 (10)	16 (16)	
Other	0 (0)	6 (6)	

63 (17%) of those not transfused ($\chi^2=0.03$, d.f. = 1, P = NS). The modal risk of developing distant metastases was also similar for the two groups, 2.8% and 3.5% at 18–23 months for the 'transfused' and 'not transfused' groups, respectively.

The organ distribution of distant metastases differed between the two groups (Table IV). Forty-five patients (71%) who were not transfused developed liver metastases without evidence of other distant spread, compared to 36 patients (36%) in the 'transfused' group ($\chi^2=18.46$, d.f. = 1, $P<0.001$). The predominance of liver metastases, in the patients who were not transfused, was consistently higher (Fig. 1) during the follow-up period (Wilcoxon rank sum, $P<0.02$).

If the first 12 months are omitted from the analysis, in order to exclude micrometastases undetected at the time of 'curative' resection, then the risk of developing liver metastases ranged from 0 to 1.9% for the 'not transfused' group and 0 to 0.8% for the 'transfused' group (Wilcoxon rank sum, $P<0.003$). The difference in the distribution of liver metastases between the two groups was not accounted for by differences in age, sex, tumour site, Dukes' stage, tumour mobility, or the presence of bowel obstruction or perforation, as significance remained after individual stratification by these variables using logrank χ^2 analysis.

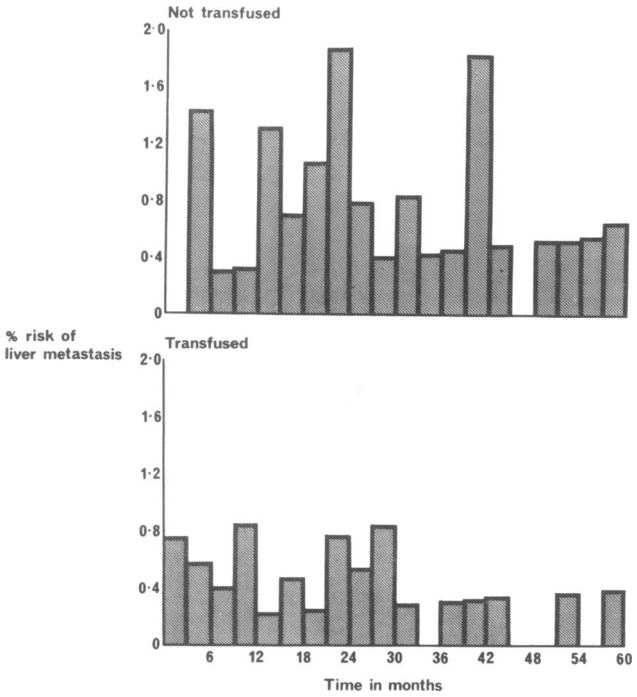
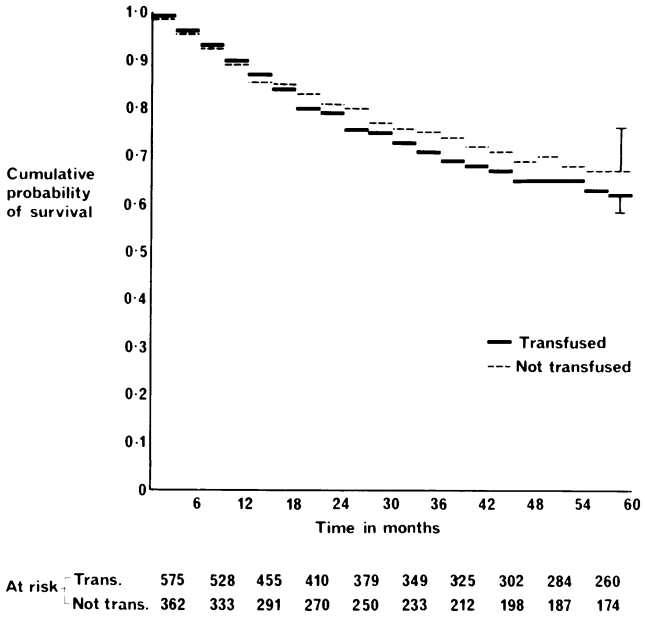


Figure 1. Risk of liver metastasis. The risk of liver metastasis was consistently lower for transfused patients throughout the study (Wilcoxon rank sum $P<0.02$).



At risk											
	Trans.	575	528	455	410	379	349	325	302	284	260
	Not trans.	362	333	291	270	250	233	212	198	187	174

Figure 2. Survival. Error bars represent 95% confidence limits and age adjusted survival is illustrated. There is no difference in survival between the two groups (logrank $\chi^2=0.69$, d.f. = 1, P = NS).

In the 'transfused' group, there were a greater number of metastases to other sites, particularly to the lung 26 (27%) compared to 7 (11%) in the 'not transfused' group, ($\chi^2=5.59$, d.f. = 1, $P<0.05$).

Survival (Fig. 2)

Of 961 patients included in this study six have since emigrated and 31 have been lost to follow-up. This leaves 572 patients who were transfused and 352 who were not. Simple age-adjusted logrank survival analysis showed that the small difference in survival between the two groups was not statistically significant (logrank $\chi^2=0.69$, d.f. = 1, P = NS) (Fig. 2).

Individual stratification by the three variables (tumour site, Dukes' stage and tumour fixity) found to be unevenly distributed between the 'transfused' and 'not transfused' groups was performed to determine if survival was influenced by these variables. The lack of statistical difference in survival between the two groups remained (tumour site: logrank $\chi^2=0.60$, d.f. = 1; Dukes' stage: logrank $\chi^2=0.09$, d.f. = 1; tumour fixity: logrank $\chi^2=0.36$, d.f. = 1). From these results, it seems that the small difference in survival was caused primarily by the excess of Dukes' C tumours in the transfused group. In addition, there was no difference in survival when stratification was performed by other variables including those previously shown to affect prognosis *(12–14)* (age: logrank $\chi^2=1.00$, d.f. = 1; sex: logrank

$\chi^2 = 1.14$, d.f. = 1; obstruction: logrank $\chi^2 = 1.13$, d.f. = 1; perforation: logrank $\chi^2 = 0.93$, d.f. = 1; tumour grade: logrank $\chi^2 = 2.09$, d.f. = 1). Also, simultaneous stratification for more than one of the eight potentially confounding variables did not affect the conclusion that blood transfusion had no significant effect on survival.

Discussion

The evidence that blood transfusion alters immune function is convincing. The beneficial effect of pretransplant blood transfusion on renal allograft survival is well accepted and believed to have an immunological basis *(1)*. Humoral factors including anti-idiotypic antibodies, Fc-receptor-blocking antibodies and lymphocytotoxins have been detected in recipients' blood after transfusion. Blood transfusion also stimulates a cellular response by inducing suppressor cell activity, by reducing natural killer cell and T-helper cell activity and through impairment of macrophage function. However, more recently it has been suggested that the beneficial effects of blood transfusion on the survival of renal allografts may be attributed to clonal deletion and not to immunosuppression *(19)*.

Concern has been expressed that, by altering immune function, blood transfusion may encourage the growth and spread of tumours in cancer patients. Impairment of immune function has been demonstrated in patients who have later developed recurrence of their tumour *(20)*. An increased incidence of cancer is well recognised in patients with chronic renal failure and as a complication of renal and other organ transplantation due to long-term immunodeficiency produced by uraemia and/or immunosuppressive therapy *(21,22)*. However, there have been variable reports of the effect of blood transfusion on tumour occurrence after transplantation *(22,23)*. Anaesthesia and operation also transiently affect immune function and, in an animal model of operative trauma, reticuloendothelial system clearance of intravenously administered tumour cells was impaired *(24)*. By delaying the clearance of tumour cells from the circulation and altering their organ distribution, the development of metastases may be enhanced, thereby impairing survival. However, White and Griffiths *(25)* reported longer survival in patients in whom circulating tumour cells were found at the time of curative resection for colorectal cancer. They concluded that cells remaining in the circulation die before they can implant to produce metastases and that fibrinolytic therapy may prevent implantation. This is supported by the recent study by Janvrin and Blair *(26)* which demonstrated a better survival for colorectal cancer patients who received a perioperative blood transfusion and showed that this might be due to an anticoagulant effect.

The first report of an adverse effect of perioperative blood transfusion on outcome in cancer patients was a retrospective study of 122 patients who had curative resections for colorectal cancer *(2)*. Several other retrospective studies have confirmed these findings for colorectal cancer *(5,6,10,11)* and for other tumours including breast *(7)*, lung *(4,9)*, and soft tissue sarcomas *(8)*. All authors conclude that the association of blood transfusion with tumour recurrence and shorter survival is causal, but they also consider that this effect may be an epiphenomenon. As our study and others have shown, blood transfusion is more likely to be given for tumours which are more difficult to remove and include those of a more advanced stage, many of which will have some degree of fixation. These factors may account for the poorer outcome of transfused patients. This theory is supported by the findings of Francis and Judson *(27)* who showed that tumour recurrence was higher in patients transfused during operation.

Other studies have reported a trend towards a worse prognosis but that statistical significance was lost when analysis was controlled for such variables as age, site, stage and fixity *(28)*. Therefore, although blood transfusion appears to be adversely associated with tumour recurrence, other variables may be producing this effect. All, except one *(10)*, of these retrospective studies contain less than 200 patients. Nevertheless, the size of the difference in prognosis in some of these studies *(5,6,10)* and the statistical methods used (logrank and Cox proportional hazard regression analyses) support the conclusion that perioperative blood transfusion may have an independent influence on survival.

Several studies *(26,29–32)*, like ours, have failed to show an adverse effect of blood transfusion on cancer patients and include a preliminary report from another prospective trial *(32)*. One study has even demonstrated an improved survival after blood transfusion *(26)*. Our data have shown that there is no survival advantage for patients who have not been transfused. The most significant finding was the difference in the distribution of distant metastases. Liver metastases developed more frequently in the group of patients who were not transfused and this trend continued throughout the follow-up period. This unexpected finding may have been due to the intrinsic nature of the tumour. Alternatively, if blood transfusion produces a transient effect on immune function, it may be sufficient to cause a delay in the hepatic clearance of tumour cells from the circulation and increase the chance of their dissemination and seeding to other sites, either at the time of or shortly after operation. We were unable to collect sufficient data on the timing of transfusion or the type of blood used, but as other studies have reported *(27)*, we would expect most blood to have been given peroperatively or in the immediate postoperative period. Also, whole blood has been shown to have a greater effect than red blood cells on prognosis in large bowel cancer *(33)*.

Although the data in this study suggest no overall effect of blood transfusion on cancer patient survival, it strongly indicates that heterologous blood given in the perioperative period changes the site of metastasis formation. Further prospective randomised trials are needed but may be difficult to formulate *(34)*. Meanwhile, we feel that (i) greater efforts need to be directed to the technical aspects of surgery to limit blood loss during

operations so that blood transfusion may be avoided, and (ii) autologous blood collection should be considered for patients with bulky tumours and in whom abdominoperineal excision is planned.

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Ashford General Hospital, Middlesex	N Baker R J Burkitt OD Morris	WC Richards JM Webster*
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Newcastle General Hospital, Newcastle upon Tyne	J Chamberlain AH Petty CW Venables RG Wilson	P Saunders* Professor BE Tomlinson AG Watson
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Royal Berkshire Hospital and Battle Hospital, Reading	GL Bohn RG Faber D Goodwin CS Kirkham C Latto M Ross NG Rothnie	C Barton* F Hampson Mrs Quelch
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Notes on books

Computed Tomography of the Abdomen in Adults by A Wackenheim and A Badoz. 159 pages, illustrated, paperback. Springer-Verlag, Berlin. DM35.

Eighty-five CT scans of the abdomen occupy the first half of this small pocket book. The second half comprises a detailed analysis of each scan together with a line drawing showing the essential features. Strongly recommended for prospective surgeons who are studying for the basic science component of the FRCS examination.

Diagnostic Surgical Pathology edited by Stephen S Sternberg. 2 volumes. 1992 pages, illustrated. Raven Press, New York. $312.50.

There can be no doubt that these two volumes comprise an important publication. Detailed, authoritative, well-referenced and with an abundance of high quality black and white and colour photographs, surgical pathologists everywhere will find the work a boon companion. The authors have been specially selected not only for their knowledge but also for their skill in written communication. They were asked by the editor to provide the reader with their reasoning when approaching a differential evaluation of a surgical biopsy specimen, thereby giving the flavour of a personal consultation. Although expensive, the size of the volumes together with the very large number of illustrations and the wealth of text should ensure a sale to all surgical pathology departments as well as many libraries.

Prospects of Heart Surgery: Psychological Adjustment to Coronary Bypass Grafting by Alan Radley. 246 pages illustrated. Springer-Verlag, New York. DM98.

Written by a social scientist from Loughborough, this monograph reports a study of how patients and their spouses adjusted to the prospect and then to the outcome of coronary graft surgery. It focuses upon patients' social relationships rather than upon the individuals themselves and shows that people bear their illness as part of a wider adjustment involving both spouse and other individuals. In part it is a social–psychological study of illness in general.

High Altitude Medicine and Physiology by Michael P Ward, James S Milledge and John B West. 515 pages, illustrated. Chapman and Hall, London. £50.00.

The first author of this important textbook will be well known to many readers of this journal as being a highly distinguished mountaineer when not engaged in surgery. His two fellow authors are both physicians, one in England and the other in the USA. Between them they have produced the most comprehensive textbook available on the medicine and physiology of high altitude. The book covers all aspects of the subject including mountain sickness, cold injury and the physical and mental performance of man at altitude. There is a fascinating chapter giving the history of mountain ascents and each chapter is fully referenced for further reading. An important publication.