a continually regenerating tumour cell population will not be eradicated. If the latter explanation is correct, pretreatment tumour proliferation rate is providing a guide to the regenerative capacity of the tumour cells. If proliferation does occur between cycles of chemotherapy, this would explain why NSGCTT are more likely to fail treatment if chemotherapy is protracted by delays between cycles.

Volume and extent of disease, and serum concentration of tumour marker are established poor prognostic features in patients with metastatic NSGCTT. MPDT may define individuals within the poor prognostic group who are more likely to fail BEP chemotherapy. Our study suggests that a MPDT of 4 days may be a clinically useful cut off point, but this may not be optimal and a larger investigation to test this hypothesis is needed. Our evaluable group included seven patients who would be considered, by established criteria, to be in a poor risk group. The three patients in this group who died, all had MPDT of $\leq$ 4 days. With such a measure of tumour growth rate, it may be possible to predict those poor risk patients who are most likely to fail conventional chemotherapy. A rational modification might be to deliver chemotherapy more rapidly for these poor risk patients with fast proliferation rates. It is of interest that a more intensive chemotherapy regimen employing weekly bleomycin, vincristine and cisplatin [11] was effective salvage therapy in a patient with a short MPDT who failed conventional BEP chemotherapy.

1. Horwich A. Germ cell tumour chemotherapy. *Br J Cancer* 1989, **59**, 156–159.
2. The Medical Research Council Working Party on Testicular Tumours. Prognostic factors in advanced non-seminomatous germ-cell testicular tumours. Results of a multicentre study. *Lancet* 1985, **i**, 8–11.
3. Steel GG. *Growth Kinetics of Tumours*. Oxford, Clarendon Press, 1977.
4. Roth BJ, Greist A, Kubilis PS, Williams SD, Einhorn LH. Cisplatin-based combination chemotherapy for disseminated germ cell tumours: long-term follow up. *J Clin Oncol* 1988, **6**, 1239–1247.
5. Fossa SD, Pettersen EO, Thoroud E, Melvik J, Ous S. DNA flow cytometry in human testicular cancer. *Cancer Lett* 1985, **28**, 55–60.
6. Peckham MJ, Horwich A, Blackmore C, Hendry WF. Etoposide and *cis*-platinum with or without bleomycin as first line chemotherapy for patients with small volume metastases of testicular non-seminoma. *Cancer Treat Rep* 1985, **69**, 483–488.
7. Crawford SM, Newlands ES, Begent RHJ, Rustin GJS, Bagshawe KD. The effect of intensity of administered treatment on the outcome of germ cell tumours with POMB/ACE chemotherapy. *Br J Cancer* 1989, **59**, 243–246.
8. Sledge GW, Eble JN, Roth BJ, Wuarman BP, Fineberg N, Einhorn LH. Relation of proliferative activity to survival in patients with advanced germ cell cancer. *Cancer Res* 1988, **48**, 3864–3868.
9. Price P, Hogan SJ, Horwich A. The growth rate of metastatic non-seminomatous germ cell testicular tumours measured by marker production doubling time—I. Theoretical basis and practical application. *Eur J Cancer* 1990, **26**, 450–453.
10. Peckham MJ, Horwich A, Easton D, Hendry WF. The management of advanced testicular teratoma. *Br J Urol* **62**, 63–68.
11. Horwich A, Brada M, Nicholls J *et al.* Intensive induction chemotherapy for poor risk non-seminomatous germ cell tumours. *Eur J Cancer Clin Oncol* 1989, **25**, 117–184.
12. Peckham MJ, Barrett A, McElwain TJ, Hendry WF, Raghaven D. Non-seminiferous germ cell tumours (malignant teratoma) of the testis. Results of treatment and an analysis of prognostic factors. *Br J Urol* 1981, **53**, 162–172.

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Blood Transfusion and Prognosis in Dukes' B and C Colorectal Cancer

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To evaluate the prognostic influence of blood transfusion in cancer patients, transfusion data were reviewed on 468 radically operated patients (260 Dukes' B and 208 Dukes' C) with carcinoma of the rectum and the rectosigmoid. Data on whole blood and packed red blood cell transfusions were recorded together with a number of clinical, pathological and histochemical characteristics. The endpoint used was death with cancer. All patients were followed for 2–7 years or until time of death.

Univariate statistical methods revealed a highly significant trend towards worsened prognosis with increasing volume of transfusion blood. However, this effect was insignificant when multivariate statistical methods were employed: patients receiving whole blood or packed red blood cell transfusions did no worse than expected from their clinico-pathological characteristics.

It is concluded that in this series the observed association between transfusion status and prognosis is adequately explained by a multivariate prognostic model including well-established prognostic factors.
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INTRODUCTION

BLOOD TRANSFUSION has been found by a number of investigators to be associated with a worsening of the prognosis after cancer surgery [1–5]. This association has been interpreted as a causal relationship between blood transfusion and poor survival, a point of view supported with references to the documented immunological effects of massive blood transfusion [1, 2, 6]. However, a number of methodological problems exist in most clinical studies published so far and it is possible that the observed association may be of a more trivial nature: patients who get blood transfusion are likely to be those in a poor general condition, with advanced disease and/or disease requiring complicated surgery.

Although data from several cancer sites have been analyzed, most reports have dealt with colorectal cancer [2, 7–21].

From 1979 to 1985 a total of 494 patients were randomized in a multicenter study [22–25] of the effect of postoperative adjuvant radiotherapy after resection of the Dukes' B and C [26] colorectal cancer. These patients formed the basis for two separate multivariate analyses [24] of prognostic factors in 260 patients with Dukes' B and 208 patients with Dukes' C carcinoma of the rectum and the rectosigmoid who had complete data records. After the completion of these analyses, transfusion data for the same patients were reviewed to test the possible prognostic influence of blood transfusion after correction for known prognostic factors.

MATERIALS AND METHODS

Clinical, pathological and biochemical data on 260 Dukes' B and 209 Dukes' C carcinoma of the rectum and rectosigmoid were evaluated and recorded prospectively in connection with a randomized trial of adjuvant post-operative radiotherapy. The study was open for patient intake from September 1979 to March 1984 (Dukes' B) or March 1985 (Dukes' C). Staging was performed according to Dukes' classification [26], with B tumors defined as having penetrated the bowel wall completely, and C tumors as having regional lymph node metastases regardless of the degree of bowel-wall penetration.

Exclusion criteria were: tumor above the pelvis, patients aged over 80 years, surgery judged to be non-radical, patients bedridden more than 50% of the day 20–25 days after surgery, postoperative complications, previous cancer within 5 years, and previous radiotherapy. Details of the study design and the results of the randomized trial have previously been published [22–25].

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Patients randomized in the trial formed the basis for two separate multivariate regression analyses of prognostic factors in the two Dukes' stages [24] using the Cox Proportional Hazards Model [27]. The endpoint used in the analyses was death with cancer. Table 1 shows the distribution of those patient characteristics that were found to have statistical significance in describing the prognosis in the two Dukes' stages. The randomized trial showed no statistically significant survival benefit from the adjuvant radiotherapy [24]. At the time when the prognostic models were established, the blood-transfusion data had not yet been reviewed.

In this communication, the original database containing patient characteristics and follow-up data was supplemented with data on whole blood and packed red blood cell transfusions administered in the time interval from 1 week before to 4 weeks after surgery. Volume of blood transfusions was recorded according to the type of blood product: whole blood or packed red blood cells. Most patients who received packed red blood cells also received whole blood: only 5% of the Dukes' B patients and 9% of the Dukes' C patients received packed red blood cells without also having whole blood transfusion. As whole blood may be a stronger immunosuppressor than other blood products [28], the data presented in this communication will concentrate on the former. Three analyses were performed. With respect to volume of transfusion blood, two groupings were applied: one, distinguishing between none, moderate ($0 <$ volume < 2000 ml), and massive (volume ≥ 2000 ml) transfusion, the other, dividing the patients into two groups according to whether or not they received any blood transfusion. In a third analysis, whole blood and packed red cell volumes were added and transfusion was scored as none, moderate and massive based on the total volume.

A chi-square test with Yates correction was used to test the statistical significance of differences in the proportions of transfused patients among subgroups with specific clinico-pathological characteristics.

Observed survival in subgroups of patients was estimated by the product-limit method [29]. The Mantel–Cox log-rank test [30] was used as univariate statistical test for difference in prognosis when comparing two groups only. In case of more than two groups a linear test for trend [31] based on the log-rank test was used. Based on the previously published prognostic model and the clinico-pathological characteristics of the individual patients within each transfusion stratum individual prognostic forecasts were estimated as described previously [24]. Subsequently, these prognostic forecasts were summed over all patients in the stratum to provide an estimate of the expected survival in this particular group of patients.

The prognostic significance of blood transfusion was tested in a multivariate setting by inclusion of the covariate describing volume of blood transfusion in the prognostic model. The likelihood ratio test was used to test the significance of adding parameters to the model.

RESULTS

Timing of the blood transfusion relative to the surgery was recorded in four time intervals (Fig. 1): preoperative transfusions (preop.) were defined as transfusions given within 1 week before surgery, perioperative as being given from 12 h before to 12 h after surgery, postoperative as being given within one week after surgery, and 'later' transfusions as being given from 1–4 weeks after surgery. An identical pattern is seen in the two Dukes'

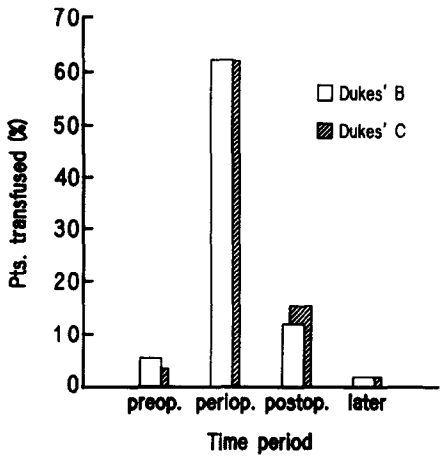

Fig. 1. Timing of whole blood transfusions relative to the operation in patients with Dukes' B and C tumors. The four time periods have been defined in the text.

stages with 62% of the patients receiving perioperative whole blood transfusions. In the time interval from 1 week before to 4 weeks after the operation 66% of the Dukes' B and 67% of the Dukes' C patients received whole blood transfusion, thus the majority of these patients received perioperative blood transfusion also.

Generally, the frequency of transfused patients showed no statistically significant variation between subgroups with different values of the significant prognostic factors (Table 1a, b). One notable exception is tumor localization where patients with low situated tumors had a higher frequency of blood transfusions in both Dukes' stages. This was probably explained by the difference in surgical procedure: 74% of the low situated tumors were operated by abdominoperineal resection in contrast to only 6% of the tumors situated more than 10 cm from the anal verge. The association between blood transfusion and prognostic variables was further investigated in a multivariate linear regression analysis with blood transfusion as the dependent variable and the significant prognostic factors as explanatory variables. In Dukes' B patients there was some association between blood transfusion on one hand and distance from the anal verge ($P < 0.0001$) and preoperative CEA ($P = 0.06$) on the other. A weaker association was found with increasing age ($P = 0.13$) and perineural invasion ($P = 0.16$). In Dukes' C patients blood transfusion was dependent on distance from the anal verge ($P < 0.0001$) and perineural invasion ($P = 0.022$). No other prognostic factors had a significant association with transfusion status.

Five-year survival in groups stratified according to transfusion status are presented in Table 2 and the estimated survivorship functions are plotted in Fig. 2. A subdivision of the patients receiving less than 2000 ml of whole blood into two groups, below and above 1000 ml, gave no significant difference in survival between the two subgroups (data not shown). The test for trend statistics were highly statistically significant: $P = 0.008$ and $P = 0.012$ in Dukes' B and C patients, respectively. Comparing the two extreme groups, i.e. patients receiving more than 2000 ml whole blood against untransfused patients using the log-rank test, gave similar P values: $P = 0.008$ and $P = 0.014$ in Dukes' B and C patients, respectively. Thus univariate methods supported the proposed detrimental effect of blood transfusions.

When the effect of other known prognosticators was taken into consideration, the transfusion effect had no statistical significance. Applying the prognostic model on the various transfusion strata showed differences in expected survival between the various groups that were in good agreement with the observed survival data. The resulting survival curves are presented in Fig. 3 and compared with the product-limit estimates of the observed survival. In other words, the apparent prognostic effect of blood transfusion, statistically significant in univariate analyses, could be explained solely from the differences in the distribution of established prognostic factors in the various transfusion strata.

When blood transfusion was included in the multivariate prognostic model, the model fit to the survival data, evaluated by means of the likelihood ratio test, did not improve significantly either in Dukes' B ($P > 0.25$) or Dukes' C ($P = 0.15$) patients.

Table 1a. Significant prognostic factors and transfusion status in Dukes' B patients*

Covariate	Characteristic	Frequency (%)	Transfused (%)	P value†
Perineural invasion	Yes	24	65	n.s.
	No	76	66	
Distance from anal verge	≤ 10 cm	33	86	< 0.0001
	> 10 cm	67	56	
Venous invasion	Yes	16	69	n.s.
	No	84	65	
Preoperative CEA (ng/ml)	CEA ≥ 7.2	19	76	0.04
	3.2 ≤ CEA < 7.2	25	73	
	CEA < 3.2	56	59	
Age above 60	Yes	35	72	n.s.
	No	65	63	

Table 1b. Significant prognostic factors and transfusion status in Dukes' C patients*

Covariate	Characteristic	Frequency (%)	Transfused (%)	*P* value†
Perineural invasion	Yes	38	73	n.s.
	No	62	64	
Resection of other organs	Yes	11	82	n.s.
	No	89	66	
Venous invasion	Yes	31	66	n.s.
	No	69	67	
Distance from anal verge	≤ 10 cm	48	81	0.0001
	> 10 cm	52	55	
Sex	Male	47	65	n.s.
	Female	53	69	
Preoperative CEA (ng/ml)	CEA ≥ 7.2	35	72	n.s.
	3.2 ≤ CEA < 7.2	23	66	
	CEA < 3.2	43	64	
Maximum tumor diameter (cm)	8+	21	66	n.s.
	5–7	43	70	
	0–4	36	65	

*For each prognostic factor in the table, values associated with a poor prognosis precede values associated with a better prognosis.
†*P* value for testing the hypothesis that the frequencies of transfused patients in the prognostic subgroups are identical.

This conclusion was found to be robust with respect to the exact scoring of the transfusion status. A similar lack of improvement was noted when the three categories no, moderate or massive transfusion were reduced to two: plus or minus transfusion or when whole blood and packed red blood cell volumes were added: $P > 0.25$ in both Dukes' stages in all cases.

Forcing blood transfusion into the model made only minor changes in the regression coefficients for other prognostic variables (Table 3). As expected, the prognostic significance of the tumor distance from the anal verge was slightly reduced as some of the dependency on this variable could be carried by the transfusion variable.

DISCUSSION

An almost uniform tendency was seen towards a more frequent need for blood transfusion in patients having negative prognostic characteristics (Table 1a, b), even though statistical significance was not reached in most cases. This could give the impression of these factors being balanced among patients with differing transfusion status. Small studies, and even the testing of the distribution of relatively infrequent characteristics in large series, are associated with a high risk of type II errors. Of 16 retrospective studies of the transfusion effect in colorectal cancer, only three comprised more than 300 patients [11, 14, 20].

Table 2. Corrected 5-year survival vs. blood transfusion

Transfusion, whole blood (ml)	Dukes' B 5-year survival	*n*	Dukes' C 5-year survival	*n*
None	81.0 ± 5.0%	88	39.1 ± 7.2%	68
< 2000	68.5 ± 4.6%	143	31.5 ± 5.7%	111
≥ 2000	49.7 ± 10.4%	28	12.8 ± 6.7%	29
Test for trend *P* value	0.008		0.012	

Five-year survival ± 1 standard error of the estimate.
n: number of patients in group at the time of randomization.

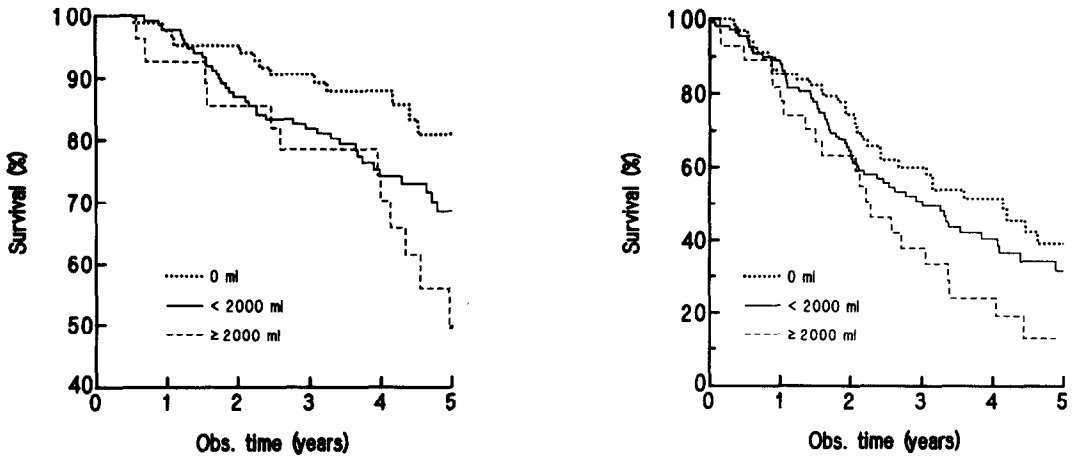

Fig. 2. Product-limit estimates of observed survival versus transfusion status in Dukes' B (a) and Dukes' C (b) patients. Univariate statistical methods showed a highly significant trend towards a worsened prognosis with increasing amount of whole blood transfused: $P = 0.008$ and $P = 0.012$ in Dukes' B and C patients, respectively.

Dukes' stage is by far the strongest prognostic factor in colorectal cancer. Especially the Dukes' A tumors and patients with distant metastasis (Dukes' D) tumors are quite distinct subpopulations both with respect to natural history and therapeutic management, but also between the Dukes' B and C tumors important differences in natural history have been demonstrated [24, 32, 33]. Thus Dukes' stages A–D should, at least in our view, be treated in separate strata when establishing prognostic models in colorectal cancer. Of 16 retrospective studies of the transfusion effect in colorectal cancer, 12 included Dukes' A tumors and one even included Dukes' D tumors in the analysis. Of the remaining four studies, restricting themselves to Dukes' B and C lesions, two showed no significant difference between transfused and non-transfused patients [19, 20], one found a beneficial effect of blood transfusion [10] and the fourth found a detrimental effect of blood transfusion [6].

Table 3a. Prognostic models with and without transfusion status in Dukes' B patients

Covariate	Without transfusion*			With transfusion		
	Beta	S.E.	*P* value	Beta	S.E.	*P* value
Perineural invasion	0.769	0.286	0.004	0.787	0.287	0.003
Distance from anal verge ≤ 10 cm	0.647	0.253	0.005	0.558	0.274	0.021
Venous invasion	0.398	0.266	0.068	0.437	0.268	0.051
Preoperative CEA†	0.327	0.148	0.014	0.321	0.150	0.016
Age above 60	0.071	0.021	0.0004	0.068	0.022	0.0008
Transfusion	—	—	—	0.344	0.319	0.14

Beta: regression coefficient in Cox's PHM.
S.E.: standard error of the estimate for beta.
*From Bentzen *et al.* [24].
†Scoring: score 2: CEA ≥ 7.2 ng/ml; score 1: 3.2 ng/ml ≤ CEA < 7.2 ng/ml; score 0: CEA < 3.2 ng/ml.

Table 3b: Prognostic models with and without transfusion status in Dukes' C patients

Covariate	Without transfusion*			With transfusion		
	Beta	S.E.	*P* value	Beta	S.E.	*P* value
Perineural invasion	0.535	0.195	0.003	0.525	0.196	0.004
Resection of other organs	0.444	0.289	0.062	0.432	0.291	0.069
Venous invasion	0.410	0.196	0.018	0.408	0.196	0.019
Distance from anal verge ≤ 10 cm	0.393	0.187	0.018	0.291	0.195	0.068
Sex	0.284	0.194	0.072	0.201	0.108	0.031
Preoperative CEA†	0.207	0.107	0.026	0.368	0.195	0.030
Maximum tumor diameter (cm)	0.039	0.018	0.018	0.038	0.018	0.020
Transfusion	—	—	—	0.092	0.211	0.33

Beta: regression coefficient in Cox's PHM.
S.E.: standard error of the estimate for beta.
*From Bentzen *et al.* [24].
†Scoring: score 2: CEA ≥ 7.2 ng/ml; score 1: 3.2 ng/ml ≤ CEA < 7.2 ng/ml; score 0: CEA < 3.2 ng/ml.

Another concern is the apparent difference in blood transfusion practice in various hospitals. Most studies in colorectal cancer have a transfusion frequency in the range 50–75%. However, frequencies up to 95% [21] have been reported.

Also radicality of the operation is an important factor. To further improve the comparability of patients the present analysis was restricted to patients in which surgery was judged by the surgeon to be radical.

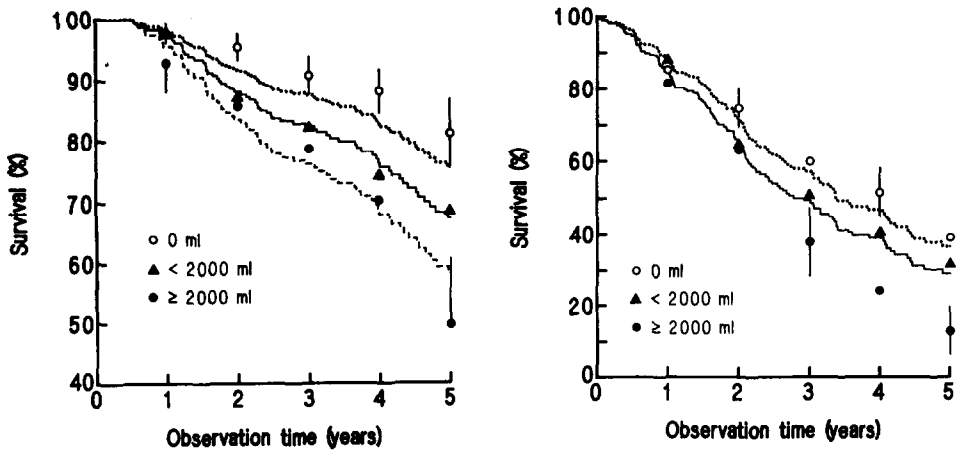

Fig. 3. Observed survival (symbols) at yearly intervals versus transfusion status in Dukes' B (a) and C (b) patients compared with the proportional hazards model predictions (lines). In Dukes' C patients the PHM predicted survival curves for patients receiving less than and more than 2000 ml agreed within ± 2% and only the former is plotted for graphical clarity. Error bars are shown for selected data points, indicating plus or minus one standard error of the estimated survival.

Prospective studies are under way trying to identify red cell preparations without a detrimental effect on prognosis. However, as Tartter points out [3], evidence from the laboratory indicates that both red cells and red cell components are associated with immunosuppression. On the more comprehensive problem, whether any kind of blood transfusion reduces survival, randomized studies, despite their statistical attractiveness, are hardly ethically and practically feasible: both to transfuse patients without any indication and/or to withhold necessary transfusions would be unacceptable. As a consequence, analyses of retrospective series are the main source of human data on the prognostic effect of blood transfusion. Such analyses involve potential problems with what Mosteller and Tukey [34] call proxy variables, that is, variables reaching statistical significance in the model, despite the lack of causality between these variables and the response variable, because they act as stand-in for other variables not available in deriving the model. Suggestions are abundant in the literature that blood transfusion could be a proxy variable for a number of other parameters, generally not controlled for in the previously published analyses, all of which would be associated with a poor prognosis: advanced stage of disease, technically difficult surgery, prolonged operations, anemia, and the skill of the surgeon. Except for the last of these, such parameters may be considered as resulting from, rather than causing in themselves, a poor prognosis. Thus multivariate prognostic models may indirectly correct for these aspects provided that the model represents a sufficiently detailed description of prognosis as a function of clinico-pathological characteristics.

CONCLUSION

A detrimental effect of whole blood transfusion after cancer surgery was sought for in two relatively homogeneous groups with radically operated Dukes' B and C tumors, respectively. Although such an effect was evident when univariate statistical methods were used, this effect was explained by the uneven distribution of established prognostic factors among groups receiving none, moderate or massive whole blood transfusions. This study illustrates the importance of correcting for other prognostic factors when searching for an effect of blood transfusions on survival in retrospective series.

1. Gantt CL. Red cells for cancer patients. *Lancet* 1981, **2**, 363.
2. Francis DMA, Shenton BK. Blood transfusion and tumour growth. Evidence from laboratory animals. *Lancet* 1981, **2**, 871.
3. Tartter PI. Does blood transfusion predispose to cancer recurrence? *Am J Clin Oncol* 1989, **12**, 169–172.
4. Schriemer PA, Longnecker DE, Mintz PD. The possible immunosuppressive effects of perioperative blood transfusion in cancer patients. *Anesthesiology* 1988, **68**, 422–428.
5. Collins JA. Recent developments in the area of massive transfusion. *World J Surg* 1987, **11**, 75–81.
6. Burrows L, Tartter P. Effect of blood transfusion on colonic malignancy recurrence rate. *Lancet* 1982, **2**, 662.
7. Ota D, Alvarez L, Lichtiger B *et al.* Perioperative blood transfusions in patients with colon carcinoma. *Transfusion* 1985, **25**, 392–394.
8. Foster RS Jr, Costanza MC, Foster JC *et al.* Adverse relationship between blood transfusions and survival after colectomy for colon cancer. *Cancer* 1985, **55**, 1195–1201.
9. Blumberg N, Agarwal M, Chuang C. Relation between recurrence of cancer of the colon and blood transfusion. *Br Med J* 1985, **290**, 1037–1039.
10. Blair SD, Janvrin SB. Relation between cancer of the colon and blood transfusion. *Br Med J* 1985, **290**, 1516–1517.
11. Nathanson SD, Tilley BC, Schultz L, Smith RF. Perioperative allogeneic blood transfusions—survival in patients with resected carcinomas of the colon and rectum. *Arch Surg* 1985, **120**, 734–738.
12. Frankish PD, McNee RK, Alley PG, Woodfield DG. Relation between cancer of the colon and blood transfusion. *Br Med J* 1985, **290**, 1827.
13. Corman J, Arnoux R, Peloquin A *et al.* Blood transfusions and survival after colectomy for colorectal cancer. *Can J Surg* 1986, **29**, 325–329.
14. Parrott NR, Lennard TWJ, Taylor RMR *et al.* Effect of perioperative blood transfusion on recurrence of colorectal cancer. *Br J Surg* 1986, **73**, 970–973.
15. Francis DMA, Judson RT. Blood transfusion and recurrence of cancer of the colon and rectum. *Br J Surg* 1987, **74**, 26–30.
16. Voogt PJ, van de Velde CJH, Brand A *et al.* Perioperative blood transfusion and cancer prognosis. Different effects of blood transfusion on prognosis of colon and breast cancer patients. *Cancer* 1987, **59**, 836–843.
17. Weiden PL, Bean MA, Schultz P. Perioperative blood transfusion does not increase the risk of colorectal cancer recurrence. *Cancer* 1987, **60**, 870–874.
18. Creasy T, Veitch P, Beau PRF. A relationship between perioperative blood transfusion and recurrence of carcinoma of the sigmoid colon following potentially curative surgery. *Ann R Coll Surg Engl* 1987, **69**, 100–103.
19. Ross W. Blood transfusion and colorectal cancer. *J R Coll Surg Edinburgh* 1987, **32**, 197–201.
20. Kiff RS. Perioperative blood transfusion and recurrence of colorectal carcinomas. Presented to the British Association of Surgical Oncology, 26 April 1987, London.
21. Arnoux R, Corman J, Péloquin A *et al.* Adverse effect of blood transfusions on patient survival after resection of rectal cancer. *Can J Surg* 1988, **31**, 121–126.
22. Balslev I, Pedersen M, Teglbjaerg PS *et al.* Postoperative radiotherapy in rectosigmoid cancer Dukes' B and C. Interim report from a randomized multicentre study. *Br J Cancer* 1982, **46**, 551–556.
23. Balslev I, Pedersen M, Teglbjaerg PS *et al.* Postoperative radiotherapy in Dukes' B and C carcinoma of the rectum and rectosigmoid. A randomized multicenter study. *Cancer* 1986, **58**, 22–28.
24. Bentzen SM, Balslev I, Pedersen M *et al.* A regression analysis of prognostic factors after resection of Dukes' B and C carcinoma of the rectum and rectosigmoid. Does postoperative radiotherapy change the prognosis? *Br J Cancer* 1988, **58**, 195–201.
25. Kronborg O, Fenger C, Bertelsen K *et al.* Escape clauses in a multicentre trial. Unforeseen problems and their potential influence on the general validity of the conclusions. *Theoret Surg* 1988, **2**, 157–164.
26. Dukes CE, Bussey HJR. The spread of rectal cancer and its effect on prognosis. *Br J Surg* 1958, **12**, 309–320.
27. Cox DR. Regression models and life tables. *J R Stat Soc B* 1972, **34**, 187–220.
28. Blumberg N, Heal J, Chuang C, Murphy P, Agarwal M. Further evidence supporting a cause and effect relationship between blood transfusion and earlier cancer recurrence. *Ann Surg* 1988, **207**, 410–415.
29. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
30. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966, **50**, 163–170.
31. Tarone RE. Tests for trend in life table analysis. *Biometrika* 1975, **62**, 679–682.
32. Chapuis PH, Dent OE, Fischer *et al.* A multivariate analysis of clinical and pathological variables in prognosis after resection of large bowel cancer. *Br J Surg* 1985, **72**, 698–702.
33. Sugarbaker PH, Gunderson LL, Wittes RE. Colorectal cancer. In: DeVita S *et al.*, eds. *Cancer. Principles and Practice of Oncology*. Philadelphia, JB Lippincott, 1985, Vol. 1, 795–884.
34. Mosteller F, Tukey JW. *Data Analysis and Regression. A Second Course in Statistics*. Reading, Addison-Wesley, 1977, 317–331.

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