Further Evidence Supporting a Cause and Effect Relationship Between Blood Transfusion and Earlier Cancer Recurrence

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Studies of associations between perioperative blood transfusions and later recurrence of solid tumors have yielded conflicting results. A previous analysis of transfused patients suggested that recurrence was associated with transfusion of whole blood as opposed to red blood cell concentrates. Additional analyses were performed on patients with cancers of the colon, rectum, cervix, and prostate to determine if patients receiving whole blood, red blood cells only, or no transfusions had differing outcomes. Patients receiving 1 unit or more of whole blood had uniformly poor outcomes compared with nontransfused patients ($p < 0.001$). In contrast, patients receiving only red blood cells had progressively worse recurrence and death rates with increasing numbers of transfusions, suggesting the presence of a dose-effect relationship. Employing multivariate techniques, blood transfusions of ≤3 units that included any whole blood were independently and significantly associated with earlier recurrence ($p = 0.003$) and death due to cancer ($p = 0.02$). Transfusions of ≤3 units of blood comprised solely of red blood cell concentrates were associated with no greater risk of recurrence than that seen in patients receiving no transfusions ($p = 0.50$). These results provide a potential explanation for the disparate results reported in studies of blood transfusion and cancer outcome. The marked difference in outcome seen between patients receiving a few units of red blood cells and comparable patients receiving even one unit of whole blood are consistent with the hypothesis that transfusion of stored blood plasma causes earlier tumor recurrence in some instances. Strategies for reducing these risks might include avoidance of whole blood transfusions when only 1–3 units are required, more conservative transfusion practice, use of autologous blood transfusions, and perhaps, use of red blood cells washed free of plasma and white cell debris. Clinical trials to test these hypotheses are urgently needed.

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SINCE THE FIRST REPORT by Burrows and Tartter[1] numerous studies have appeared demonstrating a relationship between perioperative blood transfusions and later recurrence of solid tumors, including cancers of the colon and rectum,[2–6] lung,[7,8] breast,[9,10] kidney,[11,12] vulva,[13] cervix,[14] stomach,[15] and soft-tissue sarcomas.[16] An almost equal number of studies have found smaller or no differences between transfused and nontransfused patients.[17–26]

We recently reported that in patients with colorectal, cervical, or prostate cancers transfused with whole blood there was an independent association between transfusion and poorer clinical outcome.[27] Patients receiving small numbers (≤3) of red blood cell concentrates had fewer and later recurrences than patients receiving equivalent numbers of blood transfusions that included even 1 unit of whole blood. Patients receiving four or more red blood cell transfusions had recurrence and survival experiences similar to those of patients receiving whole blood transfusions. These differences could not be readily explained in terms of other prognostic factors such as age, type of tumor, clinical or histologic stage, preoperative anemia, length of follow-up, or duration of surgery (this last factor being employed as a surrogate measure of surgical difficulty).

These results led us to hypothesize that previous studies failing to find associations between blood transfusions and cancer recurrence might be explained in part by differing patterns of blood component usage. That is, if only red cell concentrates were transfused, and in small numbers, no or smaller differences in recurrence rates between transfused and nontransfused patients might be expected. We report here additional analyses of our previously reported patients intended to test this hypothesis. Comparison is made between the outcome

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in patients receiving no transfusions and that in patients receiving either small numbers of red blood cell concentrates only, or small numbers of transfusions that included at least 1 unit of whole blood. We also present data suggesting a dose-effect relationship between number of red cell transfusions and the likelihood of tumor recurrence.

Patients and Methods

The 216 transfused patients with cancer of the colon, rectum, cervix, or prostate have been previously reported as part of a comparison of cancer recurrence and death after whole blood or red cell transfusions.[27] Data on the nontransfused patients reported here for the first time were collected simultaneously as part of the same retrospective medical record review. Details of both clinical and statistical methods are identical for both this report and the previous study comparing red cell and whole blood recipients.[27] In brief, the names and identifying numbers of hospital patients seen between 1970 and 1982 with these diagnoses were retrieved from a computerized data base and the medical record reviewed, collecting a variety of demographic, clinical, and treatment data. Transfusion data were also confirmed from blood bank records. Patients were included in the study if they had undergone surgery at our institution, documented follow-up of at least 6 months was available, no evidence existed of metastatic disease at diagnosis, and the transfusion history and diagnosis of cancer were unambiguous. We designated patients as transfused if the transfusions occurred within a 1-month span before or after surgery. The vast majority of transfusions occurred immediately preoperatively, intraoperatively, or within a few days postoperatively. Patients receiving transfusions at other times are not included in this analysis. Individual multivariate analyses for each tumor, including proportional hazards risk models, have been published for the colon and rectal cancer data,[2,3] described in abstract for the cervical cancer data,[14] and are in press for the prostate cancer data. The results for each tumor analyzed separately suggested that transfusion is significantly associated with cancer recurrence and/or death due to the tumor, even after adjustment for clinical stage, anemia at diagnosis, duration of surgery, patient age, *etc.*

All transfused patients received either red blood cells, whole blood, or some combination of these components. A very small number of patients received fresh frozen plasma (13 of 216) or platelet concentrate transfusions (1 of 216). As initial analysis of the data suggested that recurrence was associated with transfusion of whole blood, we grouped the patients into those who had received only red cells and those receiving at least 1 unit of whole blood. Patients who received only red cells and fresh frozen plasma and/or platelets but no whole blood were grouped with the patients receiving whole blood.

A total of 216 transfused patients are analyzed of whom 120 had colon or rectal cancer, 62 had cervical cancer, and 34 had prostate cancer. The 354 nontransfused patients comprised 68 with colon or rectal cancer, 61 with cervical cancer, and 225 with prostate cancer. The numbers of recurrences and cancer related deaths for the colon/rectal, cervical and prostate groups were, respectively, (54; 20), (16; 8), and (19; 6) for the transfused patients and (6; 3), (18; 5), and (69; 21) for the nontransfused patients. The proportion of transfused patients having recurrences or death due to cancer was significantly higher than in the nontransfused patients for the colon/rectal and prostate cancer patients but not for those with cervical cancer. The trends for recurrence and death reported by kind and amount of blood transfused were similar for each tumor. A breakdown of the data by tumor is available from the authors.

Statistical Analysis

The methods detailed in our previous reports were employed.[3,27–31] The prognostic factors in our analyses included age, year of surgery, duration of surgery, admission hematocrit, kind and amount of blood components received, type of cancer, and stage of cancer. In order to analyze this last factor for patients with different types of cancer, an improvised classification was devised for statistical analysis purposes. Early stage included patients with cervical cancers of clinical Stages O and IA, colon and rectal cancers of histologic Stage A, and prostate cancers of clinical Stages A_1 and A_2. Intermediate stage included patients with cervical cancer Stages of IB, IIA, and IIB, colon, rectal, and prostate cancer Stages B_1 and B_2. Advanced stage included patients with cervical cancer Stages IIIA and IIIB, colon and rectal cancer Stages C_1 and C_2, and prostate cancer Stage C. We appreciated that this process would not yield precise data on the effect of Stage upon cancer recurrence, but wished to incorporate broadly representative information on stage in our study of prognostic factors that might be associated with transfusion and cancer recurrence.

When fitting proportional hazards models to time to recurrence and survival time, we first included as predictors all the previously noted prognostic factors, but not the type of blood component transfused.[30] The nonsignificant factors were excluded, and type of blood transfused (none, whole blood, red cells) was then added to the proportional hazards model to see if the change in the log-likelihood after adding transfusion status was

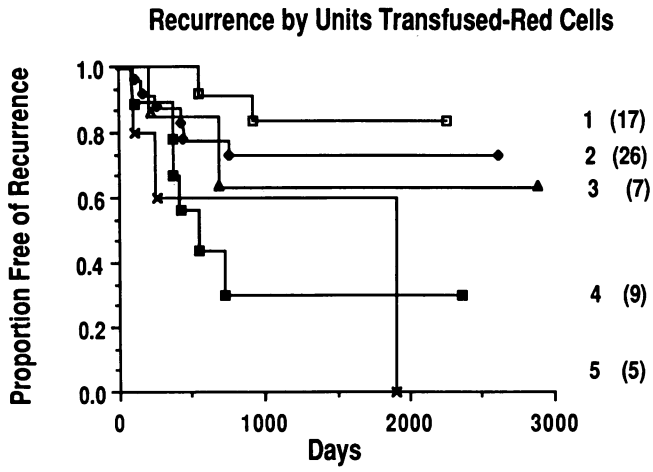

FIG. 1. The Kaplan-Meier plots for the estimated time to recurrence for patients receiving only red blood cell concentrates are shown. The numbers to the right of each line represent the number of units of red blood cells received by the patients in that group. The numbers in parentheses are the number of patients in that group. Six patients received more than five red blood cell units and had similar recurrence-free survivals to those receiving 4 or 5 units of red blood cells. These data are not shown. Because of the small number of patients in each group, data were pooled for statistical analysis. Patients receiving 1 or 2 units of red blood cells had significantly lower recurrence rates than those receiving 3 or 4 units ($p = 0.02$ by Breslow, 0.01 by Mantel-Cox). Patients receiving 2 or 3 units of red blood cells had significantly lower recurrence rates than those receiving 4 or 5 units ($p = 0.06$, 0.03). Patients receiving 3 or 4 units of red blood cells had similar recurrence estimates to those receiving 5 or more units ($p = 0.98$, 0.95).

significant. By entering information on transfusion last we could measure the impact of type of blood component transfused on time to recurrence and survival time

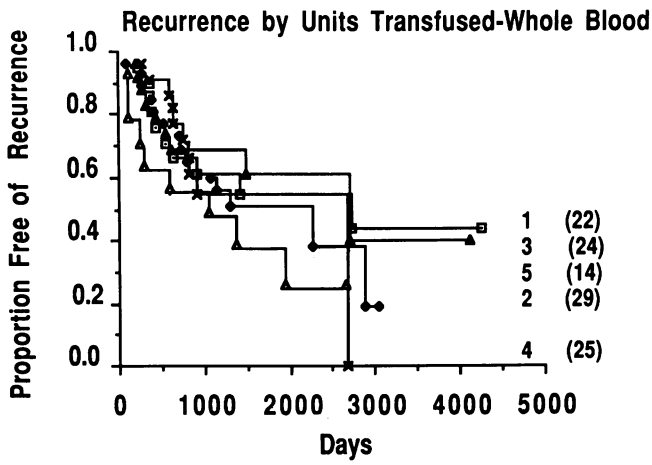

FIG. 2. The Kaplan-Meier plots for the estimated time to recurrence for patients receiving at least 1 unit of whole blood are shown. The numbers to the right of each line represent the total number of units of whole blood and red blood cells received by the patients in that group. The numbers in parentheses are the number of patients in that group. Thirty-two patients received a total of more than 5 whole blood and red blood cell units and had similar recurrence-free survivals to those receiving 1–5 units of whole blood and red cells. These latter data are not shown. None of the differences between these curves achieved statistical significance by the Breslow or Mantel-Cox tests ($p = 0.46$, 0.48 for the comparison of all the plots taken together).

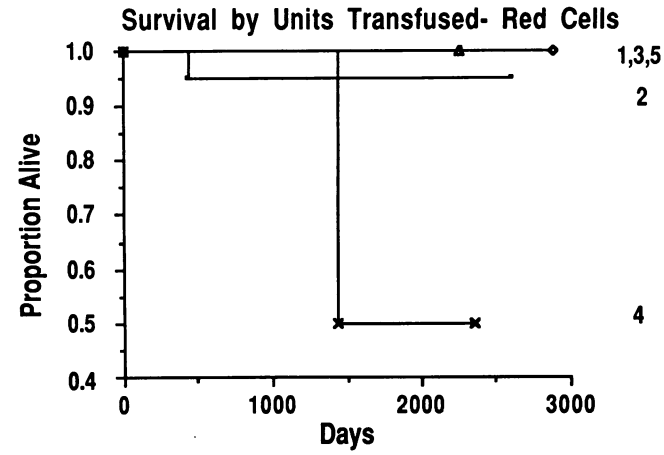

FIG. 3. The Kaplan-Meier plots for the estimated survival time for patients receiving only red blood cell concentrates are shown. The numbers to the right of each line represent the number of units of red blood cells received by the patients in that group. The numbers of patients in each group are identical to those in Figure 1. These curves are not significantly different from each other since there were only four deaths in these groups. However, when the six patients receiving >5 units of red blood cells are included in the analysis and data are pooled, patients receiving 1 or 2 units of red cells had significantly longer estimated survival times than those receiving 5 or more red blood cell transfusions ($p = 0.03$, 0.01).

after adjustment for other factors. We thus obtained an estimate of the effect on recurrence and death attributable to type of blood transfusion.

Kaplan-Meier's product-limit method was used to estimate the unadjusted distributions of time to recurrence and survival time.[31]

Results

In our initial study of the transfused patients, earlier recurrence and death due to cancer was associated most strongly with any transfusion that included at least 1 unit of whole blood, and with transfusion of ≥4 units of red blood cells.[27] Therefore, we initially analyzed the unadjusted time to recurrence and survival time according to number of units of blood transfused by the Kaplan-Meier method. Estimates of the recurrence-free interval and survival time for patients receiving different amounts of whole blood or red blood cells are shown in Figures 1–4. The plots for the whole blood recipients are not statistically significantly different from each other (Figs. 2 and 4). The recurrence plots for the patients receiving only red blood cell transfusions are significantly different and suggest a dose-effect relationship (Fig. 1). That is, increasing numbers of transfusions appear to be associated with proportionally greater numbers of earlier recurrences. Because of the small number of deaths in the patients receiving only red blood cells, no assessment of a dose-effect relationship between number of transfusions and earlier death can be made in this group (Fig. 3).

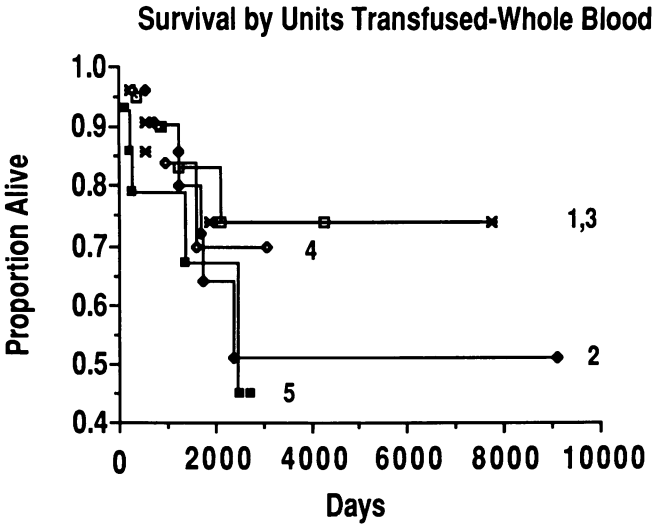

FIG. 4. The Kaplan-Meier plots for the estimated survival time for patients receiving at least 1 unit of whole blood are shown. The numbers to the right of each line represent the total number of units of whole blood and red blood cells received by each of the patients in that group. The numbers of patients in each group are identical to those in Figure 2. These plots are not statistically significantly different from each other (p = 0.52, 0.63). Addition of the patients receiving more than five transfusions and pooling of data do not alter the results of the analysis.

To assess the differences in recurrence and survival between patients transfused with comparable, small numbers of whole bloods or red blood cells, and those who were not transfused at all, we performed further Kaplan-Meier analyses on patients receiving no blood or no more than 3 units of blood. We limited this particular analysis to patients with mild to moderate blood loss in order to avoid including patients with particularly difficult resections or massive hemorrhages.

We further performed on this subset of our patients a multivariate proportional hazards risk analysis (Cox regression) of the factors predicting recurrence and death due to cancer, including patient age, year of surgery, duration of surgery, hematocrit on admission, type of cancer, histologic or clinical stage of cancer, and kind of blood component received. Because such a small proportion of the prostate cancer patients were transfused (13%) as compared with patients with colorectal (64%) or cervical (50%) cancer, the comparisons of pooled data between transfused and nontransfused patients were restricted to patients with colon, rectal, and cervical cancers. Only five patients with prostate cancer received red cells exclusively, an inadequate number for comparing the patients in this group with the 225 nontransfused patients. The 29 patients with prostate cancer who received whole blood transfusions or ≥4 units of red blood cells had significantly shorter recurrence-free intervals and survival times than the 225 nontransfused patients (data not shown).

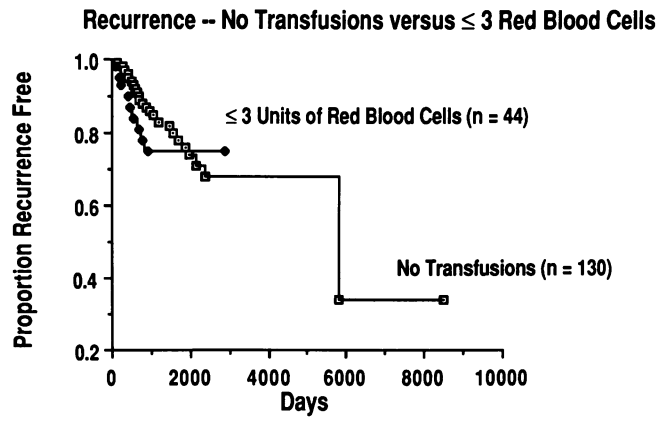

FIG. 5. The Kaplan-Meier plots for the estimated time to recurrence are compared for patients with cervical and colorectal cancers receiving ≤3 units of red blood cells and for patients receiving no transfusions (the prostate cancer patients are not included in these data as only five patients received ≤3 units of red blood cells). These curves are not significantly different from each other (p = 0.15, 0.31). The plots for estimated survival time are similar to these shown for recurrence and not significantly different (data not shown) (p = 0.97, 0.83).

Figure 5 displays a comparison of the unadjusted estimated time to recurrence in colorectal and cervical cancer patients who received ≤3 units of red blood cells and those patients with these cancers who received no blood transfusions. The differences are not significant (p = 0.15; 0.31). The results for comparisons of the estimated time to death due to cancer were similarly not significantly different (data not shown, p = 0.97; 0.83). Figure 6 shows a similar comparison for patients receiving ≤3 units of blood including at least 1 unit of whole blood and for the same group of patients shown in Figure 5 who were not transfused. The results in these two groups are significantly different (p = 0.0009; 0.002).

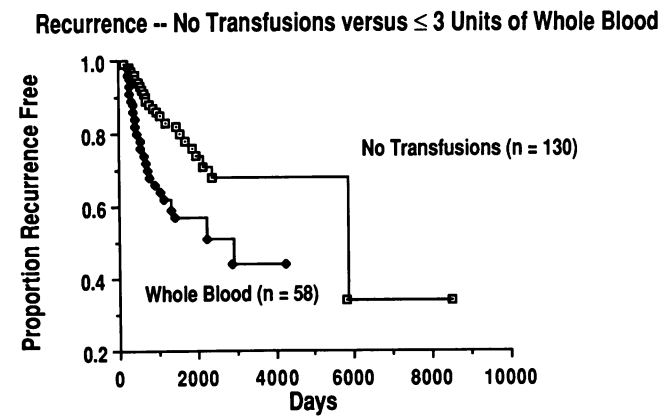

FIG. 6. The Kaplan-Meier plots for the estimated time to recurrence are compared for patients with cervical and colorectal cancers receiving a total of ≤3 units of blood including at least 1 unit of whole blood, and for patients receiving no transfusions (the prostate cancer patients are not included in these data). These curves are significantly different from each other (p = 0.0009, 0.002). The plots for estimated survival time are similar to these shown for recurrence and are significantly different (data not shown) (p = 0.0004, 0.0002).

Virtually identical results were obtained when survival times were estimated ($p < 0.001$; data not shown).

The factors that were significantly associated at the $p < 0.05$ level with earlier recurrence in the initial Cox regression analysis of patients receiving ≤3 units of red blood cells or no transfusions were older age, cervical cancer, and surgical duration of 2–3 hours. When transfusion type (*i.e.*, no transfusions vs. ≤3 units of red blood cells) was added back to this model, no statistically significant increase in the log-likelihood of recurrence or death was found after adjustment for the aforementioned prognostic variables ($p = 0.50$). Thus, transfusion status was not a significant independent predictor of time to recurrence in patients receiving only red blood cells in amounts ≤3 units or no transfusions. A Cox regression to determine which of the prognostic factors were significantly associated with shorter survival times demonstrated that only year of initial diagnosis was a significant predictor of survival time. Diagnosis prior to 1975 was significantly associated with death due to cancer. When transfusion status was added back to the model the contribution of this variable to prediction of cancer-related death was not significant ($p = 0.65$).

A similar Cox regression analysis was performed including patients receiving ≤3 units of whole blood and the aforementioned group of nontransfused patients. The significant predictors of earlier recurrence included low admission hematocrit (<38), more advanced clinical or histologic stage (intermediate and advanced stages), and surgery duration of 2–3 hours. After transfusion type was added back to this model, whole blood transfusion was an independent and significant predictor of earlier recurrence ($p = 0.003$). Low admission hematocrit, more advanced stage, and surgery duration of 2–3 hours were also associated with earlier death due to cancer in this group of patients (those receiving no transfusions or ≤3 units of whole blood). When the variable representing transfusion type (whole blood *vs.* no transfusions) was added to the regression model for survival time, whole blood transfusion was significantly and independently associated with shorter survival times ($p = 0.02$).

Discussion

These data further characterize the previously reported relationship between the kind and amount of blood transfused perioperatively, and the likelihood of later recurrence of, or death due to cancer. Our retrospective methodology and pooling of data from patients with widely differing tumors creates a risk of confounding factors distorting the analysis. Therefore, it is striking that a clear-cut pattern is evident. Patients with cervical or colorectal cancers receiving even 1 whole blood transfusion appear at markedly higher risk of tumor recurrence than patients receiving either ≤3 units of red blood cells or no transfusions at all. This risk is independent of other prognostic factors such as clinical or histologic stage, patient age, anemia, duration of surgery, and year of surgery. In contrast, patients receiving small numbers of transfusions limited to red blood cells did not have significantly worse recurrence or survival experiences than those receiving no transfusions, even when adjusted for other prognostic variables.

These results provide a likely explanation for the conflicting results seen in other retrospective studies of cancer recurrence and blood transfusion.[1-26] Transfusion practices vary greatly among medical centers. Our findings suggest that such variation could dramatically affect the results of analyses that do not take into account the kind of blood component transfused, as well as the number of units of blood transfused.

Employing surrogate markers for surgical complexity (duration of surgery) and tumor invasiveness (clinical and histologic staging), we find no evidence to support the hypothesis that transfusion status is acting as a marker for the tumor's aggressiveness or the clinical state of the patient. In fact, transfused patients with cervical or prostate cancer had somewhat more favorable clinical stage disease, on average, than patients who were not transfused. The best predictors of transfusion are preoperative anemia and lengthier surgeries. Even when these two factors predicting transfusion are adjusted for, transfusion of whole blood is a significant independent predictor of tumor recurrence and death due to cancer. If transfusion status were indeed only a surrogate indicator of tumor invasiveness or a patient's overall clinical condition, it is extremely improbable that this property would be evidenced to such different degrees in recipients of whole blood as opposed to those receiving red cell concentrate transfusions. The most likely explanation for the dramatic differences in outcome between those receiving no transfusions or ≤3 units of red cells and those receiving whole blood is that something present in whole blood modifies the mechanisms that prevent tumor recurrence.

Blood transfusion with plasma-rich components such as whole blood appears to increase the risk of solid tumor recurrence. An immunologic mechanism is most probably at work.[32] As such, transfusions of whole blood, plasma or its components, or large numbers of red cell concentrates should be avoided except when absolutely essential for patient well-being. These points previously have been made by others.[33,34] Obviously, these findings do not in any way argue against the appropriate treatment of significant hemorrhage with the indicated blood components. Severe hemorrhage presents an immediate and clear-cut threat to the patient whereas the risks we have described are long-term and still hypothetical.

Autologous predeposit transfusions also have much to recommend them in the clinical settings we describe. These include a decreased risk of post-transfusion viral infection.[35] There is no evidence that autologous transfusions would ameliorate the deleterious effects of blood transfusion we have proposed. However, if the effect of blood transfusion on outcome after cancer surgery is mediated by exposure to allogeneic antigens in transfused blood, it is reasonable to hope that such effects might be reduced or abrogated by the use of autologous blood transfusions. Given the other compelling reasons for use of autologous blood, its use in perioperative elective transfusions of cancer patients would seem a reasonable strategy, when feasible.

It also appears likely that use of red blood cells washed free of plasma, anticoagulant-preservative solutions, white cell, and platelet debris would mitigate to some degree the postulated effects of transfusion on tumor recurrence, but this remains to be proven in prospective, controlled interventional investigations.

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