

# Inflammatory response, immunosuppression, and cancer recurrence after perioperative blood transfusions

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## Editor's key points

- There is a known association between perioperative blood transfusion and cancer recurrence in colorectal cancer.
- The authors reviewed laboratory and clinical evidence of this association for all types of cancer.
- There is laboratory and animal experiments evidence that stored blood and old erythrocytes may have tumour-promoting effects.
- Awareness of these issues is important in making individualized decisions on blood transfusion in patients undergoing cancer surgery.

**Summary.** Debate on appropriate triggers for transfusion of allogeneic blood products and their effects on short- and long-term survival in surgical and critically ill patients continue with no definitive evidence or decisive resolution. Although transfusion-related immune modulation (TRIM) is well established, its influence on immune competence in the recipient and its effects on cancer recurrence after a curative resection remains controversial. An association between perioperative transfusion of allogeneic blood products and risk for recurrence has been shown in colorectal cancer in randomized trials; whether the same is true for other types of cancer remains to be determined. This article focuses on the laboratory, animal, and clinical evidence to date on the mechanistic understanding of inflammatory and immune-modulatory effects of blood products and their significance for recurrence in the cancer surgical patient.

**Keywords:** cancer; transfusion

In evaluating clinical studies relating blood transfusion to outcomes, it is worth remembering that the circumstances under which patients are given blood products perioperatively are likely to influence cancer recurrence. Recurrence depends on preoperative nutrition and functional status, the presence of preoperative anaemia, tumour type and stage, degree of resectability, duration and type of anaesthesia, amount of blood loss, perioperative stress response, and the presence of postoperative complications.<sup>1–10</sup> The potential impacts of many of these important confounding factors on cancer recurrence are complex and difficult to understand from retrospective studies. There is recent interest in the perioperative management strategies and protocols including regional anaesthesia, avoidance of inhalatory anaesthetics and opioids, and blood transfusion goals that may influence control of minimal residual disease and metastatic spread of tumour.<sup>11–13</sup> First, tumour manipulation during surgical resection increases the load of circulating malignant cells.<sup>14 15</sup> Secondly, volatile anaesthetics and opioids depress the function of host cellular defences, especially NK cells, NKT cells, and cytotoxic lymphocytes. Thirdly, perioperative factors such as inflammatory response to injury, physiological stress response to surgery, hyperglycaemia, and

hypothermia cause a significant imbalance between Th1 and Th2 responses in favour of the latter, which constitutes a pro-tumour environment. The perioperative period, therefore, can foster a potentially pro-tumour environment that may facilitate distal seeding of circulating cells, the growth of micrometastases into established clinical metastases, or both. The combination of surgery-induced and anaesthetic-contributed immunosuppression may be further aggravated by administration of blood products that themselves have inflammatory and immunosuppressive effects. The clinical question, then, is whether transfusion augments the risk of cancer recurrence after potentially curative surgery.<sup>4 16</sup>

While blood transfusion is life saving in many circumstances and is safer than it has ever been, it still poses significant risks, including incompatibility, transmission of infectious agents, coagulopathy, and allergic reactions. It is an accepted fact that the administration of blood products also causes profound negative effects on the human immune system, a condition termed transfusion-related immune modulation (TRIM; Table 1). Mechanisms for TRIM include suppression of cytotoxic cell and monocyte activity, release of immunosuppressive prostaglandins, inhibition of interleukin-2 (IL-2) production, and increase in suppressor T-cell activity.<sup>17–20</sup>

**Table 1** Abbreviations

AP-1	Activator protein 1
BDNF	Brain-derived growth factor
CTL	Cytolytic T lymphocytes
CXCL-7	Chemokine ligand 7
COX	Cyclooxygenase
EGF	Epidermal growth factor
FGF-2	Fibroblast growth factor-2
FFP	Fresh-frozen plasma
HLA	Human leucocyte antigen
IFN	Interferon
IL	Interleukin
LPS	Lipopolysaccharide
Lyso-PC	Lysophosphatidylcholine
MDC	Myeloid dendritic cells
MIP-1 $\alpha$	Macrophage inflammatory protein
NK	Natural killer cell
NF-kB	Nuclear factor-kappa beta
NKT	Natural killer T cell
OR	Odds ratio
PDGF	Platelet-derived growth factor
PG	Prostaglandin
pRBC	Packed red blood cells
RCT	Randomized controlled trial
RBC	Red blood cell
CCL5 (RANTES)	Chemokine ligand 5
STAT-3	Signal transducer and activator of transcription-3
Tc	T cytotoxic
TF	Tissue factor
Th	T helper
TGF- $\beta$ 1	Transforming growth factor-beta 1
Tregs	T regulatory cell
TLR	Toll-like receptor
TXA	Thromboxane
TRIM	Transfusion-related immune suppression
VEGF	Vascular endothelial growth factor

The immunosuppressive effects of allogeneic blood transfusion were even used therapeutically to reduce renal allograft rejection before effective immunosuppressant drugs became available.<sup>21</sup>

In this article, we will discuss the current understanding of the mechanisms by which transfusion of blood components affects the inflammatory response and immune function; the linkage between inflammation, immunity, and cancer progression; and finally, the clinical data on the effects of blood transfusion on recurrence in the cancer patient.

### Inflammatory burden and immune modulation from administration of blood products

Pre-storage leucoreduction of red cell units is now routine because of the perceived benefits of reducing post-transfusion infections, preventing febrile transfusion reactions, and decreasing the likelihood of HLA alloimmunization

**Table 2** Summary of the biological mediators involved in transfusion immune modulation and tumour growth after blood transfusion

Biological modulator	Activity on tumours	References
<b>Cytokines</b>		
T <sub>H</sub> 1 (IL-2, IFN- $\gamma$ )	Antitumoral	Yu and colleagues, <sup>68</sup> Smyth and colleagues, <sup>78</sup> Swann and Smyth, <sup>79</sup> Palucka and colleagues, <sup>77</sup>
T <sub>H</sub> 2 (IL-4, IL-5, and IL-10)	Pro-tumoral	Cognasse and colleagues, <sup>80</sup> Picker and colleagues, <sup>81</sup> Yu and colleagues, <sup>68</sup> Swann and Smyth, <sup>79</sup> Palucka and colleagues <sup>77</sup>
<b>Eicosanoids</b>		
Thromboxane A <sub>2</sub>	Pro-tumoral	Gately and colleagues <sup>44</sup>
PGE <sub>2</sub> , PGI <sub>2</sub>	Pro-tumoral	Baratelli and colleagues, <sup>42</sup> Soontrapa and colleagues, <sup>41</sup> Mulligan and colleagues, <sup>43</sup> Gately and colleagues <sup>44</sup>
Lysophosphatidylcholines	Pro-tumoral	
<b>Growth factors</b>		
TGF- $\beta$	Pro-tumoral	Apelseth and colleagues, <sup>60</sup>
VEGF	Pro-tumoral	Kanter and colleagues, <sup>59</sup>
PDGF-D	Pro-tumoral	Apelseth and colleagues, <sup>60</sup>
IGF	Pro-tumoral	Hansen-Pupp and colleagues <sup>64</sup>
<b>Other modifiers</b>		
Fas ligand	Pro-tumoral	Ghio and colleagues, <sup>23</sup> Hashimoto and colleagues <sup>82</sup>
HLA class 1 molecules	Pro-tumoral	Ghio and colleagues <sup>23</sup>
Ubiquitin	Pro-tumoral	Patel and colleagues, <sup>29</sup>
Tissue plasminogen activator	Pro-tumoral	Holmes and colleagues <sup>61</sup>

and platelet refractoriness in the recipient. One of the major advantages of leucoreduction is to avoid the accumulation of bioactive substances released from white cells implicated in transfusion-related immune suppression (Table 2).<sup>22 23</sup> Leucocyte numbers are reduced 3 log (99.9) after leucocyte reduction with the use of the most recent third- and fourth-generation screen filters; however, a few leucocytes remain and may still modulate immune responses in the recipient.<sup>22</sup> The concentrations of Th1 and predominantly Th2 cytokines

are increased in non-leucoreduced pRBC units.<sup>24–26</sup> Cytokine concentrations remain non-trivial in aged leucoreduced units.<sup>27</sup> Furthermore, exposure of leucoreduced stored RBC supernatant to whole blood triggers release of IL-6, IL-10, and TNF- $\alpha$ ,<sup>28</sup> reduces lipopolysaccharide-induced release of TNF- $\alpha$ ,<sup>29</sup> and induces regulatory T-cell (Treg) activation.<sup>30</sup> In humans, Treg cells, comprise ~1–2% of circulating CD4<sup>+</sup> T-helper cells that coexpress a very high density of the IL-2 receptor-alpha (CD25<sup>hi</sup>), inhibit IL-2 production and suppress the functions of Th1 responses by CD4<sup>+</sup> and CD8<sup>+</sup> T cells.<sup>31–33</sup> The activation of Treg cells is antigen non-specific as they can be activated by LPS and through the Toll-like receptor-4 pathway to become immune suppressive.<sup>34</sup> These findings may explain why inflammation and immunosuppression may still be encountered after administration of stored RBC products regardless of whether they are leucoreduced.

In addition to residual leucocytes and biologically active cytokines, pRBC units also contain non-polar lipids and a mixture of pro-inflammatory lysophosphatidylcholines (lyso-PCs).<sup>35</sup> Lyso-PC modulates the activity of NKT and T cells,<sup>36</sup> acts as an NK cell chemoattractant,<sup>37</sup> induces dendritic cell maturation,<sup>38</sup> and stimulates the production of pro-inflammatory cytokines.<sup>39</sup> Eicosanoids (prostaglandins and thromboxans) can also accumulate in pRBCs.<sup>40</sup> The overall effects of these biological substances are immunosuppression and tumour-promoting action.<sup>41–44</sup>

Atzil and colleagues have demonstrated the role of donor erythrocytes and their storage periods on tumour progression in two non-immunogenic (MADB106 mammary adenocarcinoma and CRNK-16 leukaemia) animal models. Leucocytes were separated before a 14-day storage period and then transfused; their effects on tumour progression were then compared with those for similarly stored packed cells and saline in the two models. Fluorescence-activated cell-sorting analysis indicated that the transfused leucocytes contained all their subpopulations. The results indicated that stored leucocyte transfusion did not cause any increase in tumour retention, whereas packed cells caused an ~3-fold increase in tumour size. These findings raise questions and challenge the role of stored leucocytes (or factors they secrete) in mediating metastasis-promoting effects. In addition, both the leucodepleted erythrocytes and the packed cells resulted in a 3-fold increase in tumour retention compared with that for saline. The investigators also reported that both autologous and allogeneic blood transfusions increased cancer progression when they had been stored for >9 days, whereas fresh blood, whether allogeneic or syngeneic, had no deleterious effects. Proposed hypotheses explaining these observations are immunologic responses (the innate cellular immunity-NK cell activity), the cytokine response to release of degraded lipid membrane-derived factors, and other non-immunogenic mechanisms (hypoxia-induced angiogenic factors). In a hamster model, Tsai and colleagues have shown that exchange transfusion with stored erythrocytes reduced microvascular flow and functional capillary density by >50% of the level achieved with fresh erythrocytes. Moreover, tissue oxygen levels were

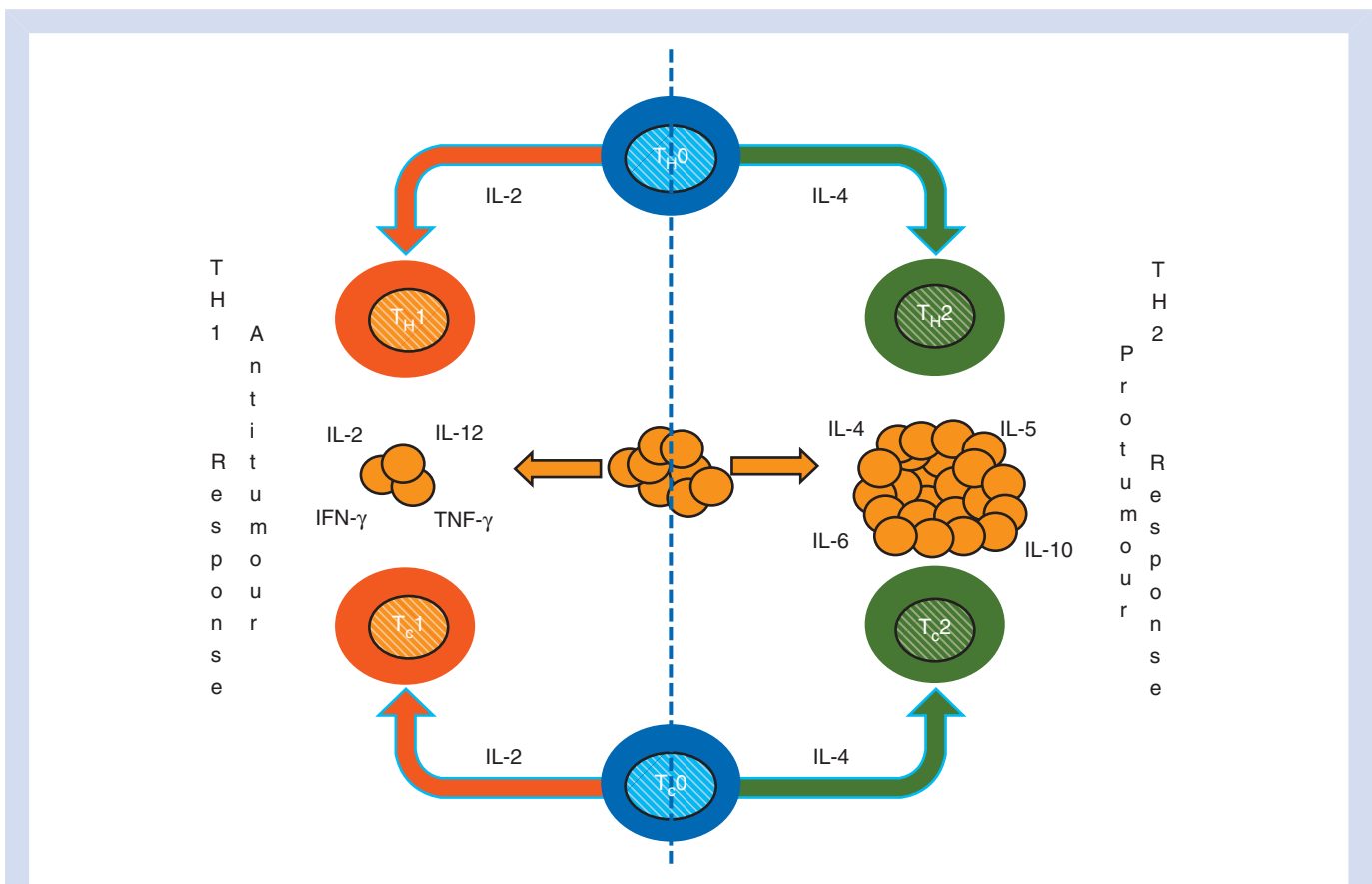
significantly reduced for stored erythrocytes compared with fresh cells. It is, thus, conceivable that the transfusion of stored erythrocytes may induce a favourable environment for tumour progression through both immunologic and non-immune signalling pathways triggered by tissue hypoxia.

Platelet concentrates are usually collected by apheresis, leucoreduced, and then stored at 20–24°C for up to 5 days.<sup>45</sup> Stored platelets remain partially activated and, upon transfusion, result in the immediate release of biologically active lipids, growth factors, chemokines, cytokines, and accumulated microparticles, that have significant effects on immune function and tumour growth in the recipients.<sup>46–47</sup> The CD40 ligand is an important multifunctional protein that is released after platelet transfusion. This ligand plays multiple roles in the immune system, including stimulation of proliferation of B-lymphocytes and induction of cytokines with important functions in the inflammatory cascade.<sup>48–50</sup> Microparticles, another component of platelet concentrates, also have significant effects on the immune system through maturation of antigen-presenting cells such as dendritic cells.<sup>51</sup> There are two subsets of dendritic cells, myeloid-derived dendritic cells and plasmacytoid dendritic cells. Plasmacytoid dendritic cells are the most potent producers of IFN- $\alpha$ .<sup>52–53</sup> They greatly influence the differentiation of CD4<sup>+</sup> T cells towards Th1 responses by producing IL-10 and inhibiting the production of IL-12 by myeloid-derived dendritic cells, or enhancing the development of Treg cells, which, in turn, suppresses antigen-specific immune responses.<sup>54–55</sup> On the other hand, IL-12 production by MDC enhances the production of IFN- $\gamma$  by T cells and NK cells and favours a Th1 immune response (Fig. 1).<sup>56</sup>

Growth factors, including VEGF, platelet-derived growth factor, fibroblast growth factor-2, brain-derived neurotrophic factor, epidermal growth factor (EGF), and transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1), are present in leucoreduced platelet concentrates after storage for 6 days,<sup>57–59</sup> washing substantially reduces the concentration of most of these substances.<sup>59</sup> Remarkably, circulating concentrations of TGF- $\beta$ 1 increase within an hour of transfusion.<sup>60</sup> Furthermore, it has been reported that the addition of supernatant from platelet concentrates induces tumour growth and invasion.<sup>61</sup> As with growth factors, cytokine, and chemokine plasma concentrations in the recipient are elevated within an hour after transfusion of platelet concentrates.<sup>60</sup>

Fresh-frozen plasma is a cell-free blood product that is rich in fibrinogen, D-dimer, factor XIII, and von Willebrand factor, along with predominantly Th2 cytokines.<sup>62</sup> Addition of fresh-frozen plasma to peripheral blood obtained from healthy volunteers induces spontaneous and dose-dependent release of TNF- $\alpha$  and IL-10.<sup>63</sup> Growth factors are also present in plasma preparations; for example, insulin-like growth factor is measurable in plasma obtained from healthy donors.<sup>64</sup>

In summary, transfusion of allogeneic blood products (red cells, platelets, and fresh-frozen plasma) is associated with a pro-inflammatory burden (bioactive products) in the recipient. The extent of this pro-inflammatory load in the recipient seems to be proportional to the stored age of the blood



**Fig 1** The figure illustrates the interaction between cellular and humoral responses against cancer cells. The cellular immune response is composed of Th1 and Tc1 (anti-tumour) and Th2 and Tc2 (pro-tumoral) lymphocytes. Similarly, the cytokine immune response is accomplished by Th1 (IL-2, IL-12, IFN- $\gamma$ , and TNF- $\gamma$ ) predominantly antitumour cytokines; in contrast, the Th2 cytokines (IL-4, IL-5, IL-6, and IL-10) have mainly pro-tumour actions.

products. Many of these biological factors have the potential to directly and indirectly affect the innate immune function (NK-cell activity) in the recipient—a key protective mechanism for local tumour control and against metastatic spread in the surgical patient. In addition, other non-immunogenic mechanisms (hypoxia-induced signalling pathways) secondary to pre-existing patient conditions or transfusion of stored cold blood may play an equally important role in promoting a pro-angiogenic environment favouring tumour growth.

### Immunity, inflammation, and cancer

An inflammatory microenvironment is an essential component of most tumours. Inflammatory responses in the body play decisive roles in tumorigenesis and metastasis. Metastatic potential of tumours is dependent on the complex and dynamic interplay between cancer cells, immune and inflammatory cells, and stromal elements in the tissue of origin. The process of metastasis can be divided into four major steps. The first step is epithelial-mesenchymal transition. This is the phase in which cancer cells acquire fibroblastoid characteristics that increase their motility and allow them to

invade epithelial linings/basal membranes and reach efferent blood vessels or lymphatics.<sup>65</sup> In the second step, cancer cells intravasate into blood vessels and lymphatics. Inflammation may promote this process through the production of mediators that increase vascular permeability. This is followed by the third step, in which metastasis-initiating cells survive and travel throughout the circulation. It has been estimated that only ~0.01% of cancer cells that enter the circulation eventually survive and give rise to micrometastases.<sup>66</sup> In the final step, single metastatic progenitors interact with immune, inflammatory, and stromal cells and start to proliferate.<sup>67</sup> Cancer cell invasion requires extensive proteolysis of the extracellular matrix at the invasive front. Inflammatory cells are important sources of proteases that degrade the extracellular matrix. Th2 cytokines promote matrix metalloproteinase expression, invasiveness, and metastasis, while other cytokines, part of the Th1 response, suppress tumour growth.<sup>68</sup>

Once free tumour cells enter the circulation, they must survive in suspension and resist detachment-induced cell death or anoikis. The survival of circulating cancer cells is affected by inflammatory mediators released by immune cells in response to cancer-derived or pathogen-derived stimuli.<sup>69 70</sup> Some of these effects depend on activation of

NF- $\kappa$ B in either inflammatory cells or cancer cells. A variety of cytokines present in the tumour microenvironment, including TNF- $\alpha$ , IL-6, and epiregulin, can promote the survival of circulating metastatic seeds.<sup>71</sup> In addition to activating NF- $\kappa$ B and STAT3, some of these transcription factors can physically link cancer cells to tumour-associated macrophages, allowing them to travel together throughout the circulation.<sup>72</sup> On the other hand, single metastatic cells, which are no longer present within an immunosuppressive environment, may be targeted again by immunosurveillance. It is likely that immunosurveillance and tumour-promoting inflammation can coexist even in the same tumour.<sup>73</sup> NK cells and CTLs engage in tumour killing, whereas Th1 cells boost cytotoxic immunity.<sup>74-76</sup> On the other hand, Tregs suppress anti-tumour immune responses and are therefore pro-tumorigenic.<sup>74</sup> Other critical components of this system are dendritic cells and macrophages, which present antigens and respond to danger and stress signals, and immunoregulatory and cytotoxic cytokines (Th1 cytokines) (Table 2).<sup>77-79</sup>

As is seen from the foregoing discussion, the complex interplay between the inflammatory cells, immune function, and the tumour cells determines tumour progression and establishment of distant metastasis. It is not clear whether acute and chronic inflammatory conditions have similar consequences and whether the same holds true for different types of acute inflammation. Furthermore, is the inflammatory burden from transfusion of stored blood products the same as an inflammatory burden from an acute infectious stimulus? The question still remains whether an acute inflammatory burden (perioperative blood transfusion) in an immunosuppressive environment (perioperative stress) compounds the problem and creates a pro-tumour environment for the establishment of distant metastasis.

## Clinical studies linking perioperative blood transfusions and tumour progression

### Allogeneic or autologous red cell transfusions

In evaluating clinical studies relating blood transfusion to outcomes, it is worth remembering that the circumstances under which patients are given blood products perioperatively are

likely to influence cancer recurrence. Recurrence depends on preoperative nutrition and functional status, the presence of preoperative anaemia, tumour type and stage, degree of resectability, duration and type of anaesthesia, amount of blood loss, perioperative stress response, and the presence of postoperative complications.<sup>1-10</sup> The potential impacts of many of these important confounding factors on cancer recurrence are complex and difficult to understand from retrospective studies. There are relatively few randomized trials related to transfusions and cancer recurrence.

Early studies, mostly retrospective, suggested that allogeneic perioperative blood transfusions increased the risk of cancer recurrence and mortality after oncologic surgery.<sup>83-92</sup> Two initial meta-analyses concluded that perioperative blood transfusions were associated with poor outcomes after surgeries for colorectal cancer and cancer of the ampulla of Vater.<sup>93-94</sup> This finding was corroborated by other retrospective studies that included patients with colorectal, prostate, pancreatic-duodenal, hepatic, and head and neck cancers.<sup>95-99</sup> Specifically, in patients with head and neck cancer and hepatocellular carcinoma, blood transfusion appears to be an independent predictor of both recurrence [odds ratio (OR) 1.6 for both cancer types] and survival (hazard ratios 1.5 and 2.0). These results have been disputed by investigators who did not identify an association between blood transfusion and cancer recurrence.<sup>100-106</sup>

Perhaps the best current evidence comes from a large meta-analysis conducted by the Cochrane group that included randomized control trials (Table 3), along with prospective and retrospective observational studies. Pooled estimates of the effect of perioperative blood transfusions on recurrence in randomized studies yielded an OR of 1.42 (95% confidence interval, 1.20-1.67,  $P < 0.0001$ ) against transfused patients. Although heterogeneity was detected, stratified meta-analyses confirmed these findings by site and stage of disease, timing of administration of blood products, type of products administered, and volume of transfused products. However, given the heterogeneity and the inability to assess the effect of the surgical technique, the authors have not been able to attribute a definite causal relationship.<sup>107</sup>

**Table 3** Summary of randomized controlled trials evaluating cancer recurrence in patients who underwent colon cancer surgery with or without perioperative transfusions. CI, confidence interval

Year	First author	Sample size	Odds ratio	[95% CI]	Outcome
1985	Frankish	174	1.02	[0.5, 2.06]	Recurrence in 24% of both transfused and non-transfused patients
1990	Cheslyn-Curtis	961	1.16	[0.88, 1.52]	Local recurrence or distal metastasis in 33 vs 36% of transfused and non-transfused patients, respectively
1990	Harder	266	1.7	[0.93, 3.10]	Recurrence in 40 vs 28% of transfused and non-transfused patients, respectively
1992	Tartter	339	2.39	[1.46, 3.91]	Recurrence in 40 vs 21% of transfused and non-transfused patients, respectively
1994	Heiss	100	2.1	[0.83, 5.32]	Recurrence in 33 vs 19% of transfused and non-transfused patients, respectively
1994	Houbiers	697	1.23	[0.87, 1.74]	Recurrence in 30 vs 26% of transfused and non-transfused patients, respectively
1995	Busch	420	1.9	[1.22, 2.96]	Recurrence in 41 vs 27% of transfused and non-transfused patients, respectively

Less clear is whether administration of autologous blood modifies the risk of cancer recurrence in comparison with that for allogeneic transfusions.<sup>108 109</sup> An early observational study suggested that, compared with autologous transfusions, allogeneic blood transfusions in patients undergoing head and neck cancer surgery were associated with a 40% increase in cancer recurrence.<sup>110</sup> However, this result contrasts with that of a randomized controlled trial that allocated colorectal cancer patients undergoing surgical tumour resection to allogeneic vs autologous blood transfusion.<sup>111</sup>

Preoperative autologous blood collection and its transfusion intraoperatively appear to be safe in patients with hepatic cellular carcinoma, although the data remain limited.<sup>112 113</sup> In fact, a small retrospective study suggests that the long-term cancer-free survival is longer in patients given autologous blood than in patients given allogeneic blood.<sup>113</sup> Intraoperative cell salvage techniques are sometimes used in major surgeries and patients who refuse allogeneic blood products. A concern for the use of cell salvage techniques during oncologic surgery is the potential for re-infusion of malignant cells collected from the surgical site.<sup>114 115</sup> For instance, malignant cells have been observed in surgically collected and double-filtrated blood samples of patients with hepatocellular carcinoma undergoing liver transplantation.<sup>116</sup> That said, at least one study demonstrated lack of cell staining for markers of malignancy after filtration.<sup>117</sup> More importantly, intraoperative cell salvage techniques and autologous blood transfusion do not seem to have a demonstrable effect on the rate of recurrence in patients undergoing oncologic surgery.<sup>118–120</sup>

In summary, the administration of perioperative blood transfusions in patients with colorectal cancer seems to be associated with increased risk of cancer recurrence.<sup>121–126</sup> This phenomenon is less understood with other cancers. Intraoperative autologous transfusion appears to be safe, but it remains unclear whether it offers any advantages over administration of allogeneic blood transfusions in reference to cancer recurrence or overall mortality.

### Leucocyte-reduced vs non-reduced packed RBCs

The presence of leucocytes and their products in allogeneic blood units may be responsible for some of the immunological derangements observed after red cell transfusions. It has, thus, been supposed that leucodepleted pRBCs would induce less immune suppression and possibly have a beneficial effect by leading to fewer recurrences after oncologic surgery. However, there is still no convincing proof in human trials that an amelioration of the immunomodulatory effect of blood transfusion results from leucoreduction.

A recent animal study found that erythrocytes rather than leucocytes are implicated in cancer-promoting effects of both autologous and allogeneic blood transfusions.<sup>127</sup> van de Watering and colleagues<sup>128</sup> found no effect of leucocyte depletion status of RBCs on overall 5-year survival or cancer recurrence in colorectal cancer. Finally, two other randomized controlled trials did not support improvement

in disease-free survival after leucoreduced vs non-leucoreduced pRBC transfusions in patients with gastrointestinal cancer.<sup>129 130</sup>

Thus, the literature suggests that the leucoreduced status of RBC units transfused during the perioperative period may not decrease cancer recurrence after oncologic surgery (Table 4).

### Transfusion volume, blood product storage duration, and timing of transfusions

Several observational reports (Table 4) indicate that large-volume perioperative transfusions (generally >3 units) are associated with a greater chance of recurrence.<sup>94 131</sup> In fact, intraoperative administration of  $\geq 3$  units has been associated with a relative risk of 2.1 [1.048, 4.135;  $P=0.036$ ] of having shorter survival after surgery for ampulla of Vater cancer, and administration of  $\geq 2$  units has been associated with a hazard ratio of 1.6 [1.1, 2.3;  $P=0.015$ ] after surgery for oesophageal cancer.<sup>94 132</sup> The strongest evidence comes from Amato and Pescatori's meta-analysis, which reports that the risk of cancer recurrence increases by 40, 69, and 102% after 1–2 [OR, 1.40 (1.18, 1.67;  $P<0.0001$ )], 3–4 [OR, 1.69 (1.4, 2.03;  $P<0.00001$ )], and >5 [OR, 2.02 (1.65, 2.48,  $P<0.00001$ )] units of packed RBC transfusion, respectively.<sup>107</sup> In contrast, the amount of blood transfused ( $\geq 8$  units) in the perioperative period is associated with shorter overall survival after oesophageal cancer surgery [OR: 2.14 (1.14, 4.01,  $P=0.01$ )], but not with higher risk of local or distant recurrence.<sup>6 133</sup> It is plausible to speculate that the number of units transfused may depend on the complexity of surgery and tumour size or invasiveness to adjacent structures, thus reflecting only disease stage which would make patients with higher tumour stages more likely to have a poor prognosis regardless the number of units transfused. Interestingly, Swisher and colleagues<sup>133</sup> found that those patients receiving 8 units or more still had a poorer survival after adjusting for tumour grade, lymph nodes, metastasis, and infectious complications.

One of the consequences of multiple blood transfusions is the risk of coagulopathy. This *per se* is associated to poor prognosis in non-operable cancer patients and the tissue factor (TF) pathway has been the focus of attention of several investigators.<sup>134 135</sup> Thus, it is plausible to speculate that perioperative coagulation disorders associated with blood transfusion, mainly after massive blood transfusion, may also have a negative impact on cancer recurrence. Unfortunately, there are no clinical studies to support this hypothesis.

Storage duration of the transfused blood units has also been considered as a potential deleterious factor in the context of cancer recurrence.<sup>136</sup> In an animal model, for instance, prolonged storage of transfused RBCs has been shown to enhance tumour progression.<sup>127</sup> In contrast, in a *post hoc* analysis of a randomized controlled trial, Mynster and Nielsen<sup>137</sup> did not find increased cancer recurrence

**Table 4** The table summarizes according to the type of study the effect of different blood product transfusions on cancer recurrence and overall survival after oncological surgery. BT, blood transfusion; LD, leucodepleted; 84, overall effect no association between BT and cancer recurrence, however, there was an association in patients with intrahepatic metastasis; 92, BT had effect only in local recurrence, not in metastasis; 120, no difference in RFS; however, the number of distant metastasis was statistically significant larger in the transfused group of patients; 123, patients who received autologous BT had better RFS for local recurrence but not distant metastasis; 128, an association for poor RFS and OS was found for transfusions of >3 units; 135, an association for poor OS was found for transfusions of >2 units. OS, overall survival; RFS, recurrence-free survival; DFS, disease-free survival

	Impact on RFS or DFS		Impact on OS	
	No	Yes	No	Yes
RBCs				
BT vs no BT				
Meta-analysis	118, 128	104	7	91
RCT	119, 120	92, 108, 127	1, 3, 80, 86, 99, 100, 101, 135	108, 118, 125, 127
Observational	4, 9, 84, 86, 97, 98, 99, 100, 101, 117	7		10, 120
Retrospective		1, 2, 81, 85, 87, 89, 93, 94, 95, 96, 102, 122, 128		2, 4, 81, 82, 83, 85, 91, 93, 94, 95, 96, 128, 129, 130, 135, 136
Autolog vs Allog				
RCT	92, 108, 123			
Retrospective	97, 101, 105	107		
LD vs non-LD				
RCT	125, 127	118		
Retrospective	129			
Duration of storage				
Retrospective	16, 108, 123			
Fresh-frozen plasma				
Retrospective	3			3
Platelets				
Retrospective		138		

after transfusion of older vs younger blood in patients who had colorectal surgery—a finding consistent with those of two other retrospective studies (Table 4).<sup>16 138</sup>

The timing of transfusions has also been considered. Briefly, pre-, intra-, and postoperative administration of blood increases the likelihood of cancer recurrence by 50, 74, and 36%, respectively.<sup>107</sup> However, in a retrospective analysis of patients who underwent pancreatic surgery for exocrine tumours, postoperative blood transfusion was associated with higher mortality.<sup>139</sup>

In summary, perioperative administration of blood is associated with greater risk of cancer recurrence in colorectal cancers, and this association is stronger when larger volumes of blood are administered. However, clinical studies thus far have suggested that duration of storage contributes little, if any, additional risk of cancer recurrence.

### Platelet concentrates and fresh-frozen plasma

As we have seen, administration of whole blood or pRBCs containing platelets and plasma may substantially impair anti-cancer immunity. But whether platelet concentrates and fresh-frozen plasma administration increases the risk of cancer recurrence after potentially curative cancer surgery remains unclear (Table 4). Experimental studies have indicated that the plasma fraction recovered from

packed erythrocyte units stimulate tumour growth. Furthermore, enhancement of tumour growth was greatest with plasma from units that were stored longer suggesting storage-dependent growth promotion.<sup>140</sup> In contrast, Tomimaru and colleagues<sup>3</sup> have reported that administration of fresh-frozen plasma to patients undergoing resection of hepatocellular cancers did not worsen disease-free survival duration, although it did worsen overall survival duration.

Limited information exists regarding the administration of platelet concentrates and cancer recurrence after oncologic surgery. The only data available are those from a small retrospective study in which patients given platelet concentrates during surgery for hepatic adenocarcinoma had a higher risk of recurrence.<sup>141</sup>

Currently, there is no conclusive evidence that transfusion of fresh-frozen plasma or platelet concentrates to patients undergoing cancer surgery accelerates cancer recurrence.

### Conclusion

Perioperative blood product transfusions cause substantial alterations to the anti-inflammatory/pro-inflammatory milieu in the recipient. Administration of stored blood products may be more deleterious than fresh products from the inflammatory-immunomodulatory perspective. Recent data

in animal models suggest that old red cells, rather than leucocytes or soluble fractions, may be responsible for tumour-promoting effects. The net result of the transfusion of blood products in the recipient is immunodepression, although the extent and clinical significance of this phenomenon are not yet certain. Because of the growing evidence indicating that the presence of circulating tumour cells are linked to prognosis, studies showing no association between cell saver utilization and cancer recurrence should be accepted with caution.<sup>142</sup>

The best clinical evidence to date associating perioperative blood transfusions with cancer recurrence is in colorectal cancer. Whether blood transfusion also increases recurrence risk for other cancers is unclear because of the paucity of well-conducted randomized controlled trials that have addressed this question.

### Future directions

Blood transfusion is an inherently hazardous and costly therapy that should be prescribed only when definite evidence for patient benefit outweighs the potential for harm. Accumulating evidence for potentially deleterious effects of blood transfusions in the cancer patient (i.e. recurrence) demands a more deliberate and cautionary approach in deciding the need for perioperative blood transfusions.

It is desirable that we institute a multidisciplinary team to develop patient-specific blood management protocols for the perioperative period. The aim of this approach should be to manage patients safely and effectively through their perioperative care continuum by utilizing all available measures to optimize patient erythrocyte mass and function and limit the need for transfusion of blood products. Patient blood management protocols should comprise three main components: (i) evaluating high-risk patients and optimizing erythrocyte mass and function for such patients, (ii) minimizing perioperative erythrocyte loss through blood-sparing surgical techniques, maintenance of normothermia, intraoperative cell salvage techniques when appropriate, use of antifibrinolytics when indicated, and optimized fluid therapy and haemodynamic control, and (iii) using patient-specific transfusion triggers to decide when administration of blood products is warranted.

It is necessary to highlight the fact that cancer progression and postoperative recurrence is affected by factors other than blood transfusions including stage of disease at the time of surgery, age, preoperative Karnofsky status, the presence of residual disease on postoperative margins, regional lymph nodes, or perioperative adjuvant therapy.<sup>143–145</sup> Thus, we need to study whether comprehensive perioperative regimens aimed at preserving the immune function have a long-term effect on recurrence-free and overall survival in the cancer patient. There is an immediate need for well-designed clinical trials to study the effects of allogeneic blood transfusion on recurrence-free and overall survival in the cancer patient population.

### Declaration of interest

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