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Transfusion Therapy: Is There a Link with Cancer Recurrence?

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Abstract

Purpose of Review To present an updated narrative review of the available clinical evidence regarding the impact of perioperative anemia and blood product administration on cancer recurrence and mortality. To address some of the current strategies to reduce blood transfusions and their safety in oncologic surgery.

Recent Findings Both anemia and packed red blood cells (pRBCs) transfusions have been associated with an increased risk of recurrence and mortality in certain solid malignancies. Anemia directly stimulates protective mechanisms against apoptosis of cancer cells while promoting a favorable micro-environment and reducing the efficacy of anticancer therapies. When transfusion occurs, transfusion-related immunomodulation (TRIM) mediates the immunosuppression and inflammation responsible for the impairment of the host immune system to appropriately eliminate cancer cells. However, pRBCs can also promote tumor growth by non-TRIM mechanisms.

Summary Evidence of the negative impact of perioperative anemia and blood transfusions on cancer recurrence and mortality should raise concern about the appropriate timing of blood transfusions in patients with cancer undergoing surgical procedures. Blood sparing strategies such as acute normovolemic hemodilution, autologous pRBCs transfusions and intraoperative cell savage appear to be safe means to minimize allogeneic pRBCs in the context of cancer surgery, although the safety of these strategies has not been rigorously tested in randomized controlled trials.

Keywords Anemia · Blood transfusion · Cancer · Recurrence · Survival

Introduction

Anemia is a blood disorder that can be present in at least half of the patients with cancer during the course of the disease [1–3]. It can be seen at any time during the disease but its frequency increases in late cancer stages or after the administration of chemotherapy, radiation or immunotherapy [1–3]. Cancer-related anemia is multifactorial and the result of myelosuppression, tumor infiltration, chronic inflammation, hemolysis, nutritional deficiency, or bleeding [3–6].

One of the most commonly indicated therapies to treat anemia is the transfusion of packed red blood cells (pRBCs). The 2015 National Blood Collection and Utilization Survey indicated that more than 11 million pRBCs units were transfused in the United States; 16% of them were given to patients with cancer [7•]. This rate of blood transfusion may vary depending on the type of cancer and the selected trigger to initiate the infusion of pRBCs. However, it has been suggested that a restrictive strategy is most effective to avoid the adverse effects associated with pRBCs transfusions. In particular, transfusion-associated immunosuppression (TRIM) which has been implicated in infections, cancer recurrence and cancer-related mortality [8].

Given that cancer recurrence or progression after surgery is multifactorial, the impact of pRBCs transfusions on tumor progression cannot be isolated from factors such as preoperative nutrition, functional status, preoperative anemia, tumor type and stage and the perioperative stress response [9–14]. Furthermore, data from randomized controlled trials (RCTs) and meta-analyses indicate a negative impact of pRBCs transfusions on some cancers but not in other malignancies which

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depicts the complexity of the association between cancer biology, perioperative anemia and blood transfusions on cancer recurrence or progression [15–18].

The purpose of this work is to present an updated narrative review of the available evidence regarding the impact of perioperative anemia and pRBCs administration in the context of cancer surgery.

Perioperative Anemia and Outcomes in Cancer

Perioperative anemia is a common finding in patients with cancer. Those with gynecological and lung malignancies as well as subjects with advanced cancers or those receiving cancer treatment appear to have the highest incidence of anemia. Moreover, the simultaneous occurrence of two or more of these factors (i.e. occult blood loss and chemotherapy; malnutrition, myelosuppression and blood loss) increases the risk of anemia [2].

Proposed Mechanism of Anemia-Related Cancer Recurrence

The mechanisms behind anemia-driven cancer progression are still poorly understood. However, there are two main proposed hypotheses: 1) tumor hypoxia and 2) pro-inflammatory cytokines [19]. Perhaps, the most relevant of the two is tumor hypoxia.

Reduced oxygen availability in the tumoral microenvironment leads to the activation of hypoxia-inducible factor (HIF), a heterodimer composed of an alpha and a beta subunit that mediates transcriptional adaption to hypoxic stress in cells [20]. HIF regulates the transcription of genes that encode proteins involved in every aspect of cancer biology including: glucose and energy metabolism, formation of reactive oxygen species, promotion of genomic instability, selection of apoptosis-resistant cell clones, formation of vascular endothelial growth factor, facilitation of epithelial-mesenchymal transition, and local infiltration by immunosuppressive cells such as myeloid-derived suppressor cells, tumor-associated macrophages, and T-regulatory cells [21].

Hypoxia has also been implicated in treatment resistance to chemotherapy and radiotherapy [22, 23]. The presence of oxygen allows the stabilization of reactive oxygen species (ROS) necessary to produce radiation-induced DNA damage through double-strand breaks. In hypoxic conditions, lack of oxygen enables reduction of ROS by cellular thiol groups and therefore blocks the generation of double-strand breaks [24]. In the case of chemotherapy resistance, HIF-1 expression promotes multidrug resistance genes including multidrug resistance protein (MDR1) and multidrug resistance-associated protein (MRP1). The latter encodes for membrane glycoproteins that facilitate the efflux of antineoplastic drugs out of malignant cells [25•]. An interaction between MDR1 and MRP1 and HIF-1 has been reported in breast, colon, and gastric tumors [26, 27].

An increase in the presence of inflammatory cytokines as a result of anemia also facilitates cancer progression. Humoral mediators generated in tumor microenvironment attracts inflammatory cells such as macrophages, B and T lymphocytes, mast cells, fibroblasts, and myofibroblasts [28]. Then, these cells will secrete interleukin-1 (IL-1), IL-6, transforming growth factor β (TGF-β) and tumor necrosis factor alpha (TNF-α) which results in the promotion of oncogenic transformation of cells, tumor growth, angiogenesis, and metastasis [29].

Clinical Evidence

The studies available in the literature are mostly retrospective in nature, which limits the interpretation of the results because of significant chances of confounding. However, across different studies, anemia has been consistently associated with cancer recurrence and reduced overall survival (OS) in most cancers [10, 30]. For instance, van de Pol et al. analyzed the prognostic significance of hemoglobin (Hb) concentrations during the perioperative period of head and neck cancer surgery. The authors found that preoperative anemia was associated with a reduced OS [31]. Reports from Dietl et al. Reichel et al. and Cordella et al. showed a similar association [32–34]. Anemia has prognostic relevance in lung cancers patients. Two independent investigations concluded that preoperative Hb concentrations <12 g/dl was an independent predictor of OS and cancer recurrence [35, 36].

In gastrointestinal malignancies, there are conflicting findings for gastric cancer. In a study that included 1688 patients who underwent curative resection for stages I and II, anemia was an independent risk factor for reduced OS [37]. However, a more recent study with data obtained from 2163 patients found that preoperative anemia was associated with reduced survival only in those with advanced gastric malignancies [38]. A recent meta-analysis of 12 studies and 3588 patients with rectal cancers found a negative association between preoperative anemia and, OS and DFS for rectal cancer [39•]. Similarly, low preoperative concentrations of hemoglobin were an independent predictor of shorter DFS and OS in subjects with pancreatic cancers [40]. In soft tissue sarcomas, two studies analyzing data from 367 and 376 patients demonstrated anemia was also independently associated with decreased OS and disease-free survival (DFS) [41, 42].

The association between preoperative anemia and reduced survival in urological and gynecological cancers is consistent across most studies. Two meta-analyses by Xia et al. reported earlier recurrences and shorter survival in patients with renal cell and bladder carcinoma [43, 44]. Similarly, Luo et al. demonstrated in a meta-analysis that included 3815 patients, that

low hemoglobin concentrations were an independent risk factor for shorter cancer-specific survival, DFS, and OS in patients with urothelial carcinoma despite the location of the tumors (bladder vs. upper tract) [45]. Collectively, the results from these investigations support that preoperative anemia had a significant adverse impact on DFS and OS in patients with early-stage breast cancers as well as in those with cervical, endometrial and ovarian cancers [46–58].

Based on the presented evidence, it can be theorized that correcting preoperative anemia could have a beneficial impact on survival outcomes. While different strategies such as erythropoiesis-stimulating agents and iron-supplementation have been investigated to reduce perioperative pRBCs transfusion, there is no conclusive evidence to suggest that would prolong long-term survival [59, 60]. Berardi et al. concluded that the correction of perioperative anemia did not reduce the risk of recurrence in non-small-cell lung cancer patients [61].

Together, literature to date suggest that anemia is associated with cancer progression in several malignancies. Anemia directly stimulates protective mechanisms against apoptosis of cancer cells, promotes a favorable micro-environment (inflammation and immunosuppression) for survival of cancerous cells, and it reduces the efficacy of anticancer therapies.

Perioperative Transfusion and Cancer Outcomes

In patients with cancer, perioperative pRBCs transfusions have long been suspected of reducing their long-term survival. For many cancers, the risk for recurrence and death related to pRBCs appears to be caused by mechanisms involving immunosuppression, inflammation and the effects of various molecules and components in the blood able to activate angiogenesis and survival pathways in transformed cells [62]. These mechanisms can be grouped as TRIM and non-TRIM (Fig. 1).

Transfusion-Related Immunomodulation

The interaction between RBCs and the host immune system is one of the most studied phenomena in medicine. Transfusion-related inmmunomodulation or TRIM, refers to the downregulation of the recipient's cellular immunity and immune surveillance system triggered by residual leukocytes, cytokines, degraded products of red blood cell due to storage and other cell-derived micro particles [63••, 64]. Immunosuppression resulting from the exposure to residual leukocytes is thought to be mediated by the release of growth factors such as TGF-β, interleukin (IL)-10, inhibition of IL-2, upregulation of Tregs cells, and suppression of T cell and natural killer cells (NK) activity [65–67].

In addition to residual leucocytes and biologically active cytokines, pRBCs units also contain antigenic membrane lipids such as phosphatidylserine and lysophosphatidylcholine [68]. Phosphatidylserine recognition by phagocytes (granulocytes or dendritic cells) induces secretion of anti-inflammatory cytokines, such as IL-10 or TGF-B, as well as inhibition of the secretion of inflammatory cytokines such as IL-12 or IL-1, IL-6, and TNF-α [68, 69]. Finally, lysophosphatidylcholine downregulates the activity of NK and T cells leading to a state of immunosuppression [70]. As a result, there is a decreased efficacy of antigen presentation, induced tolerance for specific antigens and impairment of the host immune system to appropriately eliminate cancer cells.

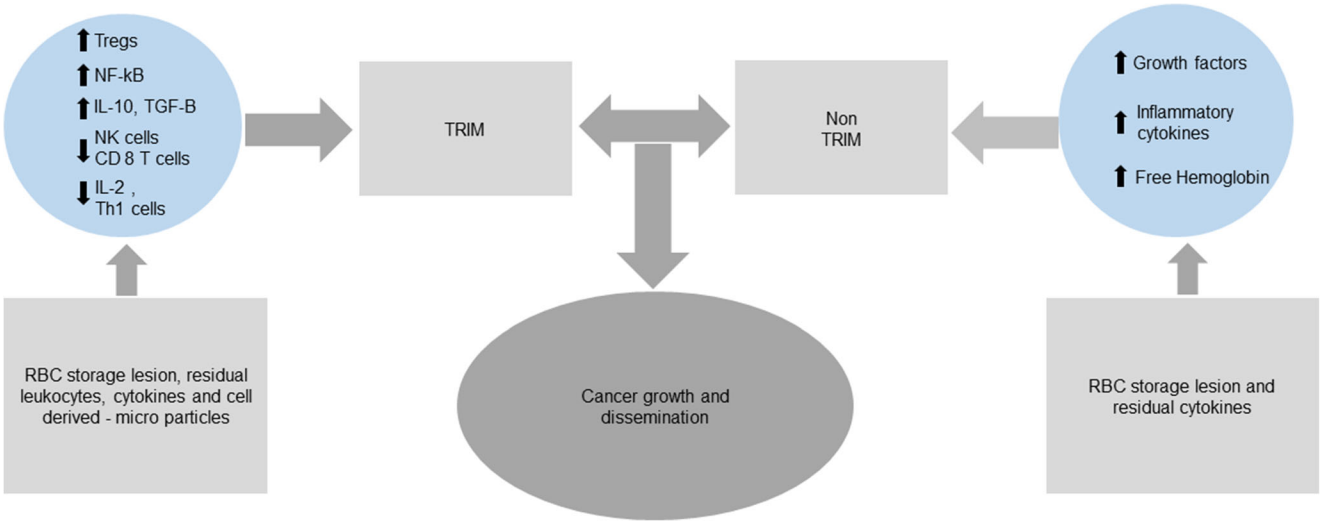

Fig. 1 Mechanisms for cancer progression after pRBCs transfusion. It has been suggested that pRBCs transfusions can promote cancer recurrence or progression via mechanisms involving immunomodulation, inflammation and the effects of growth factors. TRIM: transfusion-related immunomodulation, RBC: red blood cell, IL: interleukin, NK: natural killer, TGF-B: transforming growth factor beta, Tregs: regulatory T cells, NF- KB: nuclear factor kappa B

Non-TRIM Mechanisms

The non-immune mechanisms promoting tumor growth comprise the effects of growth factors, cytokines, chemokines and free hemoglobin released from stored RBCs. Once pRBCs are transfused, free hemoglobin enters into the circulation and reacts with the vasodilator nitric oxide (NO) resulting in increased NO consumption, vasoconstriction, vascular injury and angiogenesis [64]. There is also a release of other active substances that directly promote tumor growth and cancer progression, such as eicosanoids, C-C chemokine ligand 5 (CCL5), epidermal growth factor (EGF), fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), angiogenin and platelet-derived growth factor (PDGF) [71–75]. Examples of upregulation of CCL5 and angiogenin have been seen in aggressive breast, cervical and pancreatic cancers [76–78].

In summary, a complex network of interacting cytokines, chemokines, growth factors, soluble mediators and cellular elements are behind TRIM and non-TRIM mechanisms.

Prioperative Red Blood Cells Transfusions

The rate of perioperative pRBCs transfusions in patients with cancer remains high. Among the most prevalent malignancies, pRBCs transfusion rates range from 9.4 to 55.4% for lung cancers, 14 to 83% for breast cancers, 7 to 40% for prostate cancers and 60 to 90% for colon cancers [79, 80, 81, 82•, 83]. These numbers reflect a lack of consensus on triggers of pRBCs transfusion in patients with cancer.

The appropriate triggers to initiate a blood transfusion in the surgical patient with malignancies are controversial. Although hemoglobin cutoff values do not reflect absolute oxygenation state or patient comorbidities, they are still the main accepted parameters to guide perioperative transfusions [84••]. The literature indicates that there are two hemoglobin cutoff strategies to guide perioperative transfusion: a restrictive (7–8 g/dL Hb) and a liberal (9–10 g/dL Hb). Both strategies have been evaluated in different clinical scenarios, with most of the available data coming from studies in patients undergoing cardiac surgery or those critically ill. In the context of cancer surgery, a recent RCT by de Almeida et al. found a negative impact of a restrictive postoperative blood transfusion strategy on short-term outcomes compared to a liberal transfusion strategy in cancer patients [84••, 85••].

Gastrointestinal Cancers

Evidence from two meta-analyses by Amato et al. strongly indicates that the administration of pRBCs in the context of colorectal cancers has a negative impact on survival regardless of timing (pre-, intra-, or postoperative), type, and number pRBCs units [15, 86] This is supported by data from recent meta-analysis and observational studies (Table 1) [83, 87•, 88, 89, 90].

There is also evidence suggesting that pRBCs transfusions are an independent risk factor for esophageal and gastric cancers recurrence regardless of the number of transfused pRBCs units [91–95]. Interestingly, patients with esophageal cancers who received autologous pRBCs transfusion and a lower volume transfusion (<3 pRBCs units) had better survival rates than those treated with allogeneic transfusion and > 3 pRBCs units transfused [93].

Eight different studies have reported on the impact of perioperative pRBCs transfusions in patients with hepatobiliary cancers. Overall, the results from these investigations are conflicting [96–100]. While a meta-analysis by Wang et al. found perioperative pRBCs transfusion to affect OS after curative resection for cholangiocarcinoma negatively, recent retrospective studies using a propensity score matching method, could not replicate the results [96–98]. In a meta-analysis by Liu et al. the administration of pRBCs demonstrated a negative impact on clinical outcomes in hepatocellular carcinoma, including increased risk of death, recurrence, and perioperative complications [101]. Similarly, pRBCs transfusions were an independent risk factor associated with shorter DFS and OS in subjects with pancreatic cancers [102–104].

Lung and Head and Neck Cancers

Luan et al. conducted a meta-analysis of retrospective studies investigating the impact of perioperative blood transfusion on the survival of patients with lung cancers. The study included 5,915 patients and found a negative association with DFS and OS [79]. In concordance with this evidence, pRBCs transfusions were also linked to reduced OS and increased tumor recurrence in patients with head and neck cancers [16, 105].

Urological and Gynecological Malignancies

In patients with urological cancers, the results of multiple investigations are conflicting. Two meta-analyses demonstrated that blood transfusions were associated with poor oncological outcomes in patients who underwent radical cystectomy whereas more recent studies were not able to confirm the same negative impact [106•, 107, 108, 109, 110, 111, 112, 113]. Similarly, the findings in patients with renal cancers are mixed [114–118]. On another hand, pRBCs had a negative impact in prostate cancer patients and those with adrenocortical carcinomas [82•, 119].

There is no evidence of a negative impact of blood transfusions in cancer recurrence or survival in patients undergoing radical hysterectomy for cervix cancer [18, 120, 121]. In regard to ovarian cancer, data on the effect of perioperative pRBCs transfusions on disease progression is conflicting.

Table 1 Impact of perioperative pRBCs transfusions on overall survival and disease free survival in cancer patients

Author Ref #	Study design	Primary tumor	Sample size	Recurrence risk Recurrence free survival (95% CI)	Mortality risk Overall survival (95% CI)
Lyu [87•]	Meta-analysis	Colon cancer	10,621	RR: 1.38 (1.23–1.56)	RR: 1.24 (1.11–1.38)
Luan [79]	Meta-analysis	NSCLC	5,915	RR: 1.42 (1.20–1.67)	RR: 1.25 (1.13–1.38)
Woolley [16]	Meta-analysis	Head and neck cancer	143	OR: 2.6 (1.9–3.7)	NA
Agnes [92]	Meta-analysis	Gastric cancer	21,485	HR: 1.48 (1.18–1.86)	HR: 1.49 (1.32–1.69)
Boshier [93]	Meta-analysis	Esophageal cáncer	4,190	NA	HR: 1.49 (1.26–1.76) ≥3 pRBCs units were associated with lower long-term survival compared to patients who received <3 units HR: 1.59 (1.31–1.93) Increased 3-year OS in autologous transfusion compared to allogenic transfusion
Wang [96]	Meta-analysis	Cholangiocarcinoma	1,719	NA	HR: 1.45 (1.14–1.83)
Zhou [97]	Retrospective	Cholangiocarcinoma	605	HR: 0.94 (0.6–1.46)	HR: 1.17 (0.75–1.81)
Liu [101]	Meta-analysis	Hepatocellular carcinoma	5,635	1 year OR:1.70 (1.38–2.10) 3 year OR: 1.22 (1.08–1.38) 5 year OR: 1.16 (1.08–1.24)	3 years OR:1.92 (1.61–2.29) 5 years OR: 1.60 (1.47–1.73)
Mavros [102]	Meta-analysis	Pancreatic cancer	4,339	NA	OR: 2.43 (1.90–3.10)
Cata [107]	Meta-analysis	Bladder cancer	15,655	OR: 1.12 (1.12–1.31)	OR: 1.27 (1.15–1.40)
Vetterlein [113]	Retrospective	Bladder cancer	611	HR: 0.92 (0.53–1.58)	HR: 1.06 (0.55–2.05)
Linder [114]	Retrospective	Renal carcinoma	2,318	HR: 1.04 CI not reported	HR: 1.23 (1.04–1.46)
Park [115]	Retrospective	Renal carcinoma	3,832	HR: 1.28 (0.90–1.81)	HR: 1.34 (0.91–1.98)
Li [82•]	Meta-analysis	Prostate cancer	26,698	HR: 1.09 (1.01–1.16)	OR: 1.43 (1.24–1.64)
Poorman [119]	Retrospective	Adrenocortical Carcinoma	149	HR: 1.7 (1.0–2.9)	HR: 2.0 (1.1–3.8)
Bogani [121]	Retrospective	Cervix carcinoma	275	HR: 2.71 (0.91–8.03)	HR: 1.71 (0.73–4.01)
De Oliveira [122]	Retrospective	Ovarian cancer	136	HR: 1.06 (1.005–1.12) for each transfused unit	NA
Warner [124]	Retrospective	Ovarian cancer	587	HR: 0.88 (0.59–1.3)	HR: 1.12 (0.65–1.92)
Nadeem [125•]	Meta-analysis	Breast cancer	7,384	NA	OR: 0.79 (0.72–0.86)
Paulino Pereira [126]	Retrospective	Spine metastatic disease	649	NA	HR: 1.03 (0.8–1.31)
Janssen [127]	Retrospective	Long-bone metastatic disease	789	NA	HR: 1.06 (0.87–1.3)

HR hazard ratio, *OR* odds ratio, *RR* relative risk, *CI* confidence interval, *NA* not applicable

Although De Oliveira et al. found an increased risk of recurrence in patients with advanced ovarian cancer, subsequent articles by Altman et al. and Warner et al. show no association [122–124]. Lastly, blood transfusion were linked to decreased OS in breast cancer patients [125•].

Other Cancers

In patients with metastatic fractures and spinal metastasis, pRBCs transfusions did not impact their survival [126, 127].

Red Blood Cell Storage Duration and Cancer Outcomes

As previously discussed, during the course of pRBCs storage, numerous well-characterized structural, biochemical, metabolic and inflammatory changes termed "storage lesion" contribute to the adverse effects seen in TRIM. Although the time dependent effect of the storage lesion has been demonstrated in vitro, [64] the clinical significance of these changes on cancer outcomes remains uncertain. Only one study investigated the impact of blood storage duration on the survival of patients with non-metastatic prostate cancer. Neither the use of

"old" allogeneic nor autologous pRBCs was associated with a significant effect on RFS and OS [128].

In summary, evidence of a deleterious effect of perioperative blood transfusion has been reported in the context of colon, head and neck, lung, esophagus, stomach, pancreas, adrenals, prostate and breast cancers. Deleterious effects have not been reported for cervix cancers, long-bone metastatic fractures, and spinal metastasis. In other cancers, there is still a lack of consensus based on the available evidence (Table 2).

Perioperative Platelet and Fresh Frozen Plasma Transfusions in Patients with Cancer Progression: Clinical Evidence

Thrombocytopenia is also a frequent hematological disorder of patients with cancer. Thrombocytopenia can occur as by disease itself or secondary to anticancer therapies. Preoperative thrombocytopenia is associated with significantly higher risk of blood transfusion and life threatening hemorrhage, therefore when clinically indicated prophylactic or therapeutic platelet transfusion should be granted [129]. Nonetheless, evidence from in vitro and animal models indicate that the transfusion of platelets can contribute to tumor cell proliferation and metastasis through immunomodulatory functions and secretion of growth factors, chemokines, proangiogenic factors and proteolytic enzymes within the tumor micro-environment [130]. In the clinical setting, the relationship between perioperative platelet transfusion and cancer progression is not well established. In a small retrospective study ($n = 153$), Kaido et al. found that RFS was reduced in patients with hepatocellular carcinoma who received platelets concentrates during liver transplantation [131].

The current clinical evidence addressing the effect of fresh frozen plasma transfusion on cancer progression is conflicting. Although experimental studies have shown promotion of tumor growth following the infusion of the plasma fraction recovered from pRBCs [132], the use of fresh frozen plasma in patients with cancer has shown mixed results. For instance, Kaibori et al. [133] and Tomimaru et al. [134] have reported that in patients undergoing resection of hepatocellular carcinoma, the administration of fresh-frozen plasma was not associated with a negative impact on disease-free survival or OS. On the other hand, recent studies by Nakaseko et al. [135] and Shiba et al. [136] demonstrated an increased risk for cancer recurrence and decreased OS in patients undergoing metastatic liver resections and pancreatic cancer surgery, respectively.

In summary, the available evidence regarding the effect of perioperative platelet transfusion or fresh-frozen plasma transfusion on cancer progression is inconclusive.

Strategies to Reduce Blood Transfusion

In view of the association of perioperative anemia and perioperative pRBCs with cancer progression, strategies to reduce the need for allogeneic blood transfusion during anemia treatment should be a priority. This approach should begin since the preoperative evaluation of the cancer patient [84••, 137]. During preoperative evaluation, the presence of anemia should be investigated in all elective oncologic surgical procedures. Laboratory tests such as complete blood count, reticulocytes, peripheral blood smear, assessment of serum ferritin, transferrin saturation, vitamin B_{12} and folic acid are indicated to identifiy the different types of anemia [3, 137]. When possible, reversible causes of anemia such as hematinic deficiencies should be corrected.

Iron deficiency (serum ferritin <100 ng/ml and/or transferrin saturation < 20%) is the most common hematinic deficiency in patients with cancer. A recent study in patients with solid tumors found that 42.6% of them had iron deficiency. That rate was highest in pancreatic (63%), colorectal (52%), and lung (51%) cancer patients [138]. The etiology behind ferropenic anemia in cancer patients is multifactory and due to the impaired availability to handle the iron required for effective erythropoiesis which can be attributed to chronic inflammation, chronic blood loss, nutritional deficiency or a combination of all [139].

The treatment for hematinic deficiency in the context of cancer surgery requires the oral or intravenous iron administration

Table 2 Summary of available evidence on perioperative blood transfusion impact in cancer

No association	Conflicting/Controversial evidence	Negative impact
• Cervix cancer	• Hepatobiliary carcinomas	• Gastric cancer
• Long-bone metastatic fractures	• Bladder cancer	• Esophageal cancer
• Spinal metastasis	• Renal cell carcinoma	• Colon cancer
	• Ovary	• NSCLC
		• Pancreatic cancer
		• Adrenocortical carcinoma
		• Prostate cancer
		• Breast cancer
		• Head and neck cancers

[140–142]. In a retrospective study of 116 anemic patients who underwent colorectal cancer surgery, the use of oral iron preoperatively for at least 2 weeks was associated with a significant lower rate of pRBCs administration than the control group (9.4 vs 27.4% respectively; $P < 0.05$) [140]. Intravenously administered iron is prefered to correct perioperative ferropenic anemia. Borstslap et al. demonstrated that intravenous iron administration corrected anemia and restore iron levels faster than oral iron therapy [143]. In relation to the safety of iron use in cancer patients, there are no clinical studies addressing long-term effects of iron therapy in cancer progression [144].

Significant intraoperative blood loss is one of the major complications derived from cancer surgery, most of the times leading to blood transfusion and its subsequent deleterious effects [145]. Among the most recognized strategies to minimize the need for blood transfusion derived from expected blood loss is perioperative autologous blood donation, which includes preoperative autologous donation, intraoperative blood salvage and acute normovolemic hemodilution (ANH).

In preoperative autologous donation, the patient donates his/her own (autologous) blood during the weeks preceding the elective procedure. This strategy is sufficient to reduce perioperative pRBCs allogeneic transfusions. However, concerns such as red blood cell storage lesions, recovery of unnecessary blood units and anemia has been a concern [146, 147]. Intraoperative blood salvage involves the collection of whole blood from the operative field that then it is filtrated, washed, and re-administered to the patient. This strategy also reduces pRBCs allogeneic transfusion [148]. This blood conservation strategy is still rarely used in cancer surgery because of the theoretical concern of reinfusing tumor cells from the salvaged blood, thereby promoting tumor dissemination. However, two meta-analyses have indicated that there is no associated increased risk in cancer recurrence [149, 150••].

During acute normovolemic hemodilution, blood is collected from the patient at the time of surgery and the volume removed is replaced with either a crystalloid or a colloid solution. The collected blood is then transfused back during or after surgery. Acute normovolemic hemodilution has been proven to be a simple, safe and cost-effective method to reduce allogeneic transfusion in high blood loss procedures such as cardiac, orthopedic, thoracic, or liver surgery [84••]. In the case of cancer surgery, acute normovolemic hemodilution has proven to be a safe technique that effectively reduces the need for allogeneic pRBCs transfusions in colorectal surgery, radical prostatectomy, head and neck tumor resection surgery and liver resections [151–154].

Conclusion

Anemia is associated with cancer progression in several malignancies, even when adjusting for other risk factors. Similarly, there is reasonable evidence to raise concern against the routine use of pRBCs in anemic patients with cancer undergoing surgical procedures. Iron supplementation, acute normovolemic hemodilution, autologous pRBCs transfusions and intraoperative cell savage appear to be effective means to minimize allogeneic pRBCs in the context of oncological surgery. Although the safety of these strategies has not been rigorously tested in RCTs, observational studies indicate that their use is not associated with an increased risk of cancer recurrence or progression.

Compliance with Ethical Standards

Conflict of Interest Ruben D. Agudelo-Jimenez, Juliana A. Heatter, and Juan P. Cata declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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