



Should intraoperative cell-salvaged blood be used in patients with suspected or known malignancy?

Les cellules sanguines épargnées en peropératoire doivent-elles être réutilisées chez des patients ayant des processus malins connus ou suspectés?

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Received: 6 July 2012 / Accepted: 23 August 2012 / Published online: 21 September 2012
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Abstract

Purpose Intraoperative cell salvage (ICS) is used as an alternative to allogeneic blood transfusion in an attempt to avoid or minimize the risks associated with allogeneic blood. Intraoperative cell salvage is generally avoided in surgeries where malignancy is confirmed or suspected due to concern for potential metastasis or cancer recurrence. The application of post-processing methods for ICS is hypothesized to eliminate this potential risk. The purpose of this narrative review is to examine the *in vitro* experimental evidence as it pertains to the removal of tumour cells from ICS blood and to review the clinical studies where ICS blood has been used in patients with malignancy.

Source A search of the English literature for relevant articles published from 1973 to 2012 was undertaken using

MEDLINE and Cochrane databases. Bibliographies were cross-referenced to locate further studies.

Principal findings Leukoreduction filters are an effective method for removal of malignant cells from ICS blood. Small non-randomized clinical studies to date do not show evidence of an increased rate of metastasis or cancer recurrence. Although a theoretical risk of disease recurrence persists, the decision to use autologous ICS blood must be weighed against the known risks of allogeneic blood transfusion.

Conclusion Transfusion of autologous blood harvested via ICS should be considered a viable option for reduction or avoidance of allogeneic product during many oncologic surgeries and may be a lifesaving option for those patients who refuse allogeneic blood products.

Résumé

Objectif L'épargne peropératoire de cellules sanguines (ICS) est utilisée comme méthode de remplacement des transfusions de sang allogène pour éviter ou minimiser les risques qui lui sont associés. L'épargne peropératoire des cellules sanguines est généralement évitée au cours des interventions chirurgicales lorsqu'un processus malin est confirmé ou suspecté en raison de la crainte de métastases potentielles ou de récurrence du cancer. L'hypothèse d'une utilisation des méthodes de traitement post-ICS est formulée pour éliminer ce risque. Cet article a pour objectif d'analyser les données probantes expérimentales *in vitro* concernant la suppression de cellules tumorales de sang d'ICS et de passer en revue les études cliniques au cours desquelles du sang d'ICS a été utilisé chez des patients souffrant de processus malins.

Source Une recherche d'articles pertinents publiés entre 1973 et 2012 a été effectuée dans la documentation en

Author contributions Jacqueline D. Trudeau was the primary author of this review and was responsible for the conception and design of the manuscript. Terrence Waters contributed to manuscript preparation and revision. Kate Chipperfield made substantial contributions to the conception, preparation, and revision of the manuscript.

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langue anglaise des bases de données PubMed et Cochrane. Les références bibliographiques de chaque article ont été également croisées à la recherche de nouvelles références.

Constatations principales *Les filtres de réduction leucocytaire constituent une méthode efficace pour la suppression des cellules malignes dans le sang d'ICS. À ce jour, de petites études cliniques non randomisées n'ont pas fourni de données probantes sur une augmentation du taux de métastases ou de récurrence cancéreuse. Bien qu'un risque théorique de récurrence de la maladie persiste, la décision d'utilisation du sang autologue d'ICS doit être évaluée contre les risques connus d'une transfusion de sang allogène.*

Conclusion *La transfusion de sang autologue récupéré grâce à l'ICS doit être envisagée comme une option viable pour réduire ou éviter le recours à un produit allogène au cours de nombreuses chirurgies oncologiques; cela pourrait être également une option pour sauver la vie des patients qui refusent les produits sanguins allogènes.*

Intraoperative cell salvage (ICS) has traditionally been avoided in patients with known or suspected malignancy due to fear of tumour recurrence or metastasis.¹ Consideration of the risks and benefits of both autologous cell-salvaged blood and allogeneic blood must motivate each intraoperative transfusion. An intimate understanding of the risks and benefits associated with transfusion of ICS blood becomes particularly important in patients who will not accept allogeneic blood products, at which time ICS may be the only acceptable option for replacement of red blood cells. In this review, we examine the literature as it pertains to transfusion of autologous blood from ICS in oncologic surgery. Herein, we discuss this evolving field and its management implications for the perioperative physician in the context of the Canadian blood system.

Methods

The literature search for this narrative review was conducted from April 2011 to March 2012 using the MEDLINE and Cochrane databases and was limited to English language papers published in peer-reviewed journals from 1973 to 2012. The following MeSH terms were searched in PubMed: “operative blood salvage” and “bloodless medical and surgical procedures”. These terms were also searched as keywords. Bibliographies of papers were hand-searched and cross-referenced to locate further studies. We included any *in vitro* study that investigated the efficacy of tumour cell removal following ICS

processing and subsequent filtration or irradiation. In addition, all clinical studies where patients had received ICS blood intraoperatively during malignancy surgery were included (without exclusion). To identify materials in the grey literature, Google Scholar and the Web of Science were consulted for additional references.

Perioperative transfusion of allogeneic blood products

Oncologic surgery is associated with a high rate of blood transfusions.² There are many complications associated with the perioperative transfusion of allogeneic blood, including administration of the wrong blood product, acute hemolytic transfusion reaction, transmission of infection, and transfusion-associated acute lung injury (TRALI).² In addition, there are risks associated with transfusion of allogeneic blood specific to the perioperative period. A large number of studies have shown that perioperative transfusion of allogeneic blood is associated with increased morbidity and mortality. Poorer outcomes are ascribed to an increased risk of postoperative infection,^{3–10} pulmonary complications,^{8,11} greater number of ventilator days,^{9,12} renal dysfunction requiring dialysis,⁹ multi-organ dysfunction,¹³ intensive care unit days,¹⁰ increased length of stay,¹⁴ and short-term mortality.^{9,10} Risk-adjusted models have attempted to control for allogeneic transfusion as simply a marker for illness severity or complicated perioperative course.⁹ Although this possibility remains, these analyses have identified allogeneic transfusion as a dose-dependent independent predictor of postoperative morbidity and mortality.⁹

The morbidity and mortality associated with transfusion of allogeneic blood is attributed to a complex, poorly understood interaction between host tissue and transfused allogeneic blood components termed transfusion-related immunomodulation (TRIM).^{15,16} The immunomodulatory properties of allogeneic blood were first recognized following observations of improved renal allograft survival in patients who had received perioperative blood transfusion.^{17,18} Leukocytes and their soluble and cellular breakdown products are thought to contribute significantly to TRIM.¹⁵ Subsequent leukoreduction (LR) of select blood components was initially undertaken to decrease the incidence of adverse events that were known to be related to the leukocyte component of donor products (febrile non-hemolytic transfusion reaction, transmission of cytomegalovirus, and human leukocyte antigen alloimmunization). Universal prestorage LR was implemented to minimize these complications. In prestorage LR, filtration is done by the blood supplier at the time of whole blood separation into components. In 1999, Canada, along with the United Kingdom, France, Portugal, and Ireland instituted universal prestorage LR for all blood products.¹⁹

Complications ascribed to allogeneic blood transfusion derive largely from studies that used non-leukoreduced blood products, either because the study was performed prior to the introduction of prestorage LR, or because the study was performed in a region that does not employ a method of LR. If TRIM is responsible for a measurable component of the morbidity and mortality that is seen as a result of transfusion of allogeneic blood products, a decreased complication rate should be seen following the implementation of a universal prestorage LR program. Randomized controlled trials in cardiac surgery patients have shown that transfusion of leukoreduced allogeneic blood improves short-term^{20,21} and in-hospital²² mortality and infection rates²² when compared with transfusion of a non-leukoreduced product. Similarly, decreased infection rates were seen in colorectal surgery patients²³ and in a meta-analysis of mixed surgical patients²⁴ following transfusion of leukoreduced blood. The effectiveness of universal prestorage LR programs is controversial and continues to be debated.^{15,19,25}

An additional consideration affecting the patient undergoing malignancy resection is whether allogeneic blood transfusion causes immunosuppression that contributes to an increased risk of subsequent cancer recurrence, an observation first described in 1982.²⁶ Impaired function of natural killer cells, decreased T cell production, alteration of T cell ratios, and defective antigen-presenting cell number and function have all been associated with transfusion of allogeneic blood and are thought to be an important contributor to TRIM. Together, these immunological changes may decrease the effectiveness of tumour surveillance in the host.²⁷ Over 100 publications and several meta-analyses²⁸⁻³⁰ have attempted to address this complex issue, with approximately half of these studies suggesting that allogeneic blood transfusion has a detrimental effect on cancer recurrence. In keeping with previous findings, a recent meta-analysis in patients undergoing curative resection for colorectal cancer found a modest dose-dependent effect of perioperative allogeneic blood transfusion on rate of recurrence (overall odds ratio of 1.42 for recurrence rate following transfusion; 95% confidence interval 1.20 to 1.67).³⁰ Data were insufficient to determine whether recurrence rates were altered by institution of prestorage LR.

Ultimately, the risk to benefit profile of allogeneic blood transfusion in the patient undergoing surgery for tumour resection has several considerations. The decision to transfuse is a complex interplay of dynamic factors that include the patient's own wishes, their underlying physiologic status, ongoing blood loss, and coagulation status. Based on our current understanding, it is likely that some impact secondary to TRIM will occur. It is currently difficult to know whether a perioperative allogeneic

transfusion will contribute to a subsequent complication or eventual recurrence of cancer.

Blood conservation and ICS

Concerns regarding complications associated with perioperative allogeneic blood transfusion coupled with resource limitations have refocused attention on strategies to avoid its use, and the concept of "bloodless surgery" has been popularized.³¹ In his recommendations in the wake of Canada's inquiry into the tainted blood scandal, Justice Horace Krever identified alternatives to blood transfusion a priority after thousands of blood transfusion recipients developed HIV and tens of thousands developed hepatitis C.³² Bloodless surgery represents a combination of techniques throughout the perioperative period, with the common goal of minimizing or avoiding allogeneic blood transfusion. Strategies are employed preoperatively (autologous blood donation, iron and erythropoietin supplementation), intraoperatively (ICS, acute normovolemic hemodilution, antifibrinolytic drugs, surgical technique), and postoperatively (minimization of phlebotomy, conservative transfusion trigger, antifibrinolytic drugs, return of shed blood). These strategies are particularly important for those patients that refuse blood products. There are no studies that directly compare the efficacy of various blood conservation techniques for avoidance of allogeneic blood transfusion. In our experience, amongst the most effective of these practices is the use of ICS. The majority of patients that refuse allogeneic blood products are Jehovah's Witnesses (members of the Watchtower Bible and Tract Society). They will not accept transfusion of whole blood or its primary components, namely red blood cells, white blood cells, plasma, or platelets, nor will they accept stored or banked blood.³³ As ICS involves autologous blood, its acceptance is at the discretion of each individual patient.³³

During ICS, blood loss is suctioned and collected, filtered (pore diameter between 120 and 180 μm), and washed for subsequent re-transfusion of autologous red blood cells (RBCs). Contaminants, such as cell debris, fat globules, and bone chips are removed, and a final wash results in transfusion-ready plasma-depleted RBCs suspended in saline (hematocrit 0.6-0.8). By Canadian standards, autologous RBCs processed by ICS can be stored at room temperature and safely transfused within six hours of collection (or stored at 4°C for 24 hr).³⁴ Autologous transfusion of ICS blood has many advantages: the risk of transfusion reaction is reduced; alloimmunization and immunosuppression associated with allogeneic blood are avoided; the quality of the red cell is excellent; and ICS is available regardless of the patient's starting hematocrit.³⁵ When blood loss is > 800 mL, ICS is an effective means of reducing or avoiding allogeneic transfusion.³⁵

The primary objection to the use of ICS in oncologic surgery is the unproven but theoretical possibility that malignant cells from the surgical field will be re-transfused into the patient and result in subsequent tumour recurrence and metastases.¹ This is based on the belief that oncologic surgery often violates the tumour, resulting in “spillage” of the cancer cells into the operative field. This potential controversy was first aired in 1975 when malignant cells were documented in harvested shed blood after processing through the cell saver.³⁶ At that time, it was unknown whether these cells were viable, if they would survive upon transfusion, or if they had proliferative or metastatic potential. More than 35 years later, many of these unknowns remain, and the use of ICS in oncologic surgery remains controversial.

Tumour cells harvested from the operative site—do they pose a risk?

It is reasonable to conclude that the risk associated with autotransfusion of a small number of potentially tumourigenic cells from the operative field is negligible, as many cancer patients already have a significant number of circulating cancer cells prior to surgery.³⁷⁻⁴¹ It is thought that tumour cells are released continuously in a regulated balance between tumour and host. Indeed, the median number of tumour cells released into the renal vein of patients with primary renal cancer has been estimated at 37 million per day.⁴² These cells are felt to be viable and potentially tumourigenic as they are freshly released into a major blood vessel from the tumour site. However, the ability of circulating tumour cells to form metastases is low, a concept that has been termed “*metastatic inefficiency*”.⁴³ Based on animal studies, it has been estimated that as few as 0.01-0.000001% of disseminated cancer cells have the ability to form metastatic lesions.⁴³

Despite acknowledgement of *circulating* tumour cells in most patients, concern persists regarding transfusion of *harvested* tumour cells from the operative site, as many studies have established that tumour cells remain in blood after collection and processing using ICS.^{36,37,44-48} Quantification of remaining tumour cells is variable amongst studies, but the literature is in agreement that ICS alone does not effectively remove or destroy tumour cells that have been collected from the operative field. Advanced stage of disease and intraoperative tumour rupture have been identified as risk factors for gross tumour contamination of blood in the surgical field and the subsequent difficulty in removing these cells with ICS processing alone.⁴⁹ Tumour cells that are harvested at the time of resection are unlikely to be exclusively from the pool of circulating cells (from tumour draining veins for example), and as shown in an elegant study by Hansen *et al.*, they are

more likely a different subset of tumour cells, potentially with different proliferative and metastatic potential.³⁷ In 93% of 61 patients with 15 different tumour types studied, they were able to show the presence of tumour cells in salvaged blood, often in numbers that could not be explained by the percentage of circulating cells.³⁷ Potential sources of these cells include tumour cells that remain at the resection margin or suture line, inadvertent tumour rupture, pressurization of the tumour from handling, presence of peritoneal disease or occult microscopic disease, and lymphatic spillage. In a third of the cases examined, they were able to show that the recovered tumour cells had proliferative capacity by forming cell colonies *in vitro*. One of these cell lines was capable of inducing tumour growth upon injection into nude (athymic) mice.³⁷

Methods for removal of tumour cells from ICS blood

Two methods aimed at eliminating tumour cells from the red cell concentrate of ICS blood have been described and studied: filtration through a LR filter, and gamma irradiation.

Filtration

Leukoreduction filters have been studied extensively for their ability to remove tumour cells from ICS blood. Those currently in use are third and fourth generation filters made of tightly packed small-pore microfibre webs. The mechanism of tumour cell removal by LR filters is not definitely known, but is presumed to be due to interdependent physical and biological processes. As with white blood cell filtration of whole blood, several different mechanisms are likely responsible.⁵⁰ Large tumour cell clusters will be readily trapped (barrier retention), while small clusters or single cells may be removed by barrier retention or via cell adhesion of charged surface molecules (retention by adsorption). Filtration speed has historically limited the applicability of LR filters, but it has improved dramatically with newer generation models that can process a unit of RBC in less than two minutes.⁵¹ The use of a standard blood filter or micro-aggregate filter is unnecessary when a LR filter is used.

Several studies have investigated whether it is possible to eliminate tumour cells from the red cell concentrate of blood collected with ICS using LR filtration (Table 1). These are *ex vivo* studies using oncologic cell lines that are seeded in banked or fresh blood^{45,51-56} or primary tumour cells collected at the time of tumour resection^{48,49,57-59} and then processed via ICS and subsequent LR filtration. Together, these studies show that advanced generation LR filters are very effective in the removal of tumour cells after ICS processing (the results of experiments where tumour cells were *NOT* completely removed are recorded in bold print in

Table 1). Although one could argue the clinical relevance of studies looking at oncologic cell lines rather than primary tumour cells, it does serve proof of principle that the addition of LR filtration is effective for removal of tumour cells. Furthermore, oncologic cell lines are more robust than primary tumour cells and would be expected to “outperform” primary tumour cells through the filtration process, and thus, they are a good test.⁴⁵ Using a sensitive polymerase chain reaction (PCR)-based assay and increasing numbers of cells (hepatocellular carcinoma (HCC) cell line), Gwak *et al.* showed that tumour cell load may affect the performance of LR filtration. Once they reached 1×10^5 cells·mL⁻¹, they were no longer able to filter out tumour cells consistently and effectively,⁵⁶ though other studies have used tumour cell lines in similar numbers and were able to remove tumour cells completely.^{45,51} It is uncertain whether this is a property of the HCC cell line or the exquisite sensitivity of the assay used by Gwak *et al.* One of the criticisms of using a PCR-based assay for this type of study is that a positive result can still be obtained from cell fragments and recovered DNA that have no viability or proliferative potential. Similarly, in the study by Liang *et al.*, tumour cell burden was hypothesized to contribute to ineffective LR filtration.⁴⁹ In patients undergoing resection of HCC, tumour cells were effectively removed with LR filtration unless there was intraoperative tumour rupture (2/15 patients). The authors hypothesized that the tumour burden in these two patients exceeded the filtering capacity of the LR filter, and in one patient, they were able to remove all remaining tumour cells with a second LR filter.

Hansen *et al.* argue that the studies examining LR filter efficacy for removal of tumour cells from ICS blood use methodology that does not possess sufficient sensitivity to detect residual malignant cells and, as a result, show a *reduction* rather than an *elimination* of tumour cells.⁶⁰ In studying nine different LR filters (type and generation *not* specified), they found reduction rates of 4–5 log for tumour cell lines and 3 log for solid tumour cells. With up to 10^7 tumour cells shed during oncologic surgery, they concluded that re-transfusion of ICS blood following LR filtration was not safe practice.⁶⁰ However, in various oncologic surgeries, they have also shown that the number of tumour cells shed was much lower and ranged from 0.2–4,000 cells·mL⁻¹.³⁷ Using similar methodology and assays with comparable and very sensitive limits of detection, multiple studies have now shown efficacy with advanced generation LR filters in cell concentrations up to 1×10^5 cells·mL⁻¹ (Table 1). From all of the available studies, it seems that filtration capacity of the LR filter becomes a realistic concern only at such a tumour cell burden that occurs with either very advanced disease or intraoperative tumour rupture. Within the limits of comparing *in vitro* work with *in vivo* conditions, fears of

undetected potentially malignant cells post-LR processing can be allayed by the inability to propagate these cells further *in vitro*.

Irradiation

Gamma irradiation is known to render sufficiently exposed cells mitotically inactive while preserving the quality of the red blood cell product.⁶¹ It is the basis for prophylactic irradiation of cellular allogeneic blood products in immunocompromised recipients for prevention of transfusion-associated graft *vs* host disease. Although irradiation of a solid tumour *in situ* is often unsuccessful or incomplete, it is thought that the well-oxygenated single-cell suspension that results from ICS processing is optimally suited for tumour cell elimination by irradiation.⁶²

Studies have shown that tumour cells remaining in the red cell concentrate of blood collected and processed with ICS can be effectively eliminated with gamma irradiation (25–50 Gy), as they are rendered mitotically inactive. This was shown both immediately post irradiation^{58,62} and following a period of *in vitro* culture to assess for any occult viable cells⁶² (Table 2). However, a subsequent study comparing the efficacy of irradiation with LR filters found irradiation to be less effective.⁵²

The chief limitation of irradiation of ICS blood is the availability of a gamma irradiator on-site. Relatively few hospital transfusion laboratories house an irradiator because of the high cost, significant maintenance, quality assurance requirements, and limited need outside of specialized transplant and cancer care centres. Further, even if they were available in-house, there is additional risk with moving autologous blood untested for transmissible disease from the operating room area to the transfusion medicine laboratory. This is a risk with respect to wrong blood to wrong patient errors that is borne not only by the surgical patient but also by other patients served by the transfusion service. For this reason, secondary removal of tumour cells by an LR filter prior to re-infusion would likely be the preferred option for most centres.

It is known that the constellation of factors required for a circulating cancer cell to cause metastatic disease in a host is complex and inefficient.^{43,63} Consider the steps required for an intraoperatively shed cancer cell to form metastatic disease upon re-transfusion following ICS and its requisite processing. A cell would have to survive ICS processing, maintain proliferative capacity, and then subsequently find a suitable milieu for formation of disseminated disease. There is evidence that cancer cells lose integrity and proliferative capacity following ICS processing.^{44,46} If a small subset of cells were to survive ICS processing and subsequent LR filtration or irradiation, what is the likelihood that it would engender metastatic

Table 1 Efficacy of LR filters for removal of malignant cells from ICS blood—*in vitro* studies

Study	Model	Filter type	Method used for detection of residual tumour cells	Residual tumour cells detected?*	Comments
Miller <i>et al.</i> ⁴⁵ (1991)	Banked blood (at expiration) seeded with tumour cell lines ($\sim 1 \times 10^5$ mL ⁻¹)	a. ^a SQ40S b. ^b RC-100 c. RC-100 plus subsequent culture for 1 week	Visualization and quantification	a. Yes b. No c. No (vs successful growth in controls and in group a.)	Effective filtration 3 rd generation LR filter (RC-100), but not with microaggregate (SQ40S) filter.
Edelman <i>et al.</i> ⁵¹ (1996)	Bovine whole blood seeded with tumour cell lines ($\sim 1 \times 10^5$ mL ⁻¹)	a. ^a RC-400 b. RC-400 plus subsequent culture.	Visualization and quantification	a. No b. No	Detection limit a. = 1,000 cells/sample b. = 100 cells/culture.
Futamura <i>et al.</i> ⁵² (2005)	Fresh whole blood seeded with tumour cell lines (5×10^4 mL ⁻¹)	^d Immugard III-RC	RT-PCR for CK-19	No	Detection limit = 50 cells·mL ⁻¹ .
Yamada <i>et al.</i> ⁵³ (1997)	Leukodepleted whole blood seeded with tumour cell lines (3.4×10^4 mL ⁻¹)	^e BPF4-BJ	Visualization and quantification, automatic cell counter.	No	Detection limit = 50 cells·mL ⁻¹ .
Fruhauf <i>et al.</i> ⁵⁴ (2001)	a. Fresh whole blood seeded with a tumour cell line (3×10^4 mL ⁻¹) b. Fresh whole blood seeded with primary tumour cells (200–2,000 mL ⁻¹)	^f LeukotrapWB	Immunocytochemistry and visualization and quantification.	a. No b. No—13/14 experiments	Limits of detection not specified.
Kongsgaard <i>et al.</i> ⁵⁵ (1996)	Fresh whole blood seeded with tumour cell lines (1×10^4 mL ⁻¹)	a. RC-400 b. RC-400 plus subsequent culture.	Purification of cells with monoclonal antibody to tumour antigens; visualization and quantification	a. No b. No	Detection limit = $1/1 \times 10^5$ cells
Gwak <i>et al.</i> ⁵⁶ (2005)	Hepatocellular CA cell line in normal saline a. 0.05 mL ⁻¹ b. 0.1 mL ⁻¹ c. 10 mL ⁻¹ d. 1,000 mL ⁻¹ e. 1×10^4 mL ⁻¹ f. 1×10^5 mL ⁻¹	^g RCEZIT	RT-PCR for liver-specific gene (AFP)	a. No—5/5 b. No—7/7 c. Yes—1/11 ^k d. Yes—1/12 ^k e. Yes—1/5 ^k f. Yes—5/5	Detection limit = >2 cells/sample.
Perseghin <i>et al.</i> ⁴⁸ (1997)	ICS blood from patients with lung CA undergoing resection ($n = 16$)	RC-100	Automated and manual counting; Immunocytochemistry (α CK) and light microscopy	No	Detection limit = 1,000 cells·mL ⁻¹ .

Table 1 continued

Study	Model	Filter type	Method used for detection of residual cells	Residual tumour cells detected?*	Comments
Liang <i>et al.</i> ⁴⁹ (2008)	Hepatocellular CA (<i>n</i> = 32) (intraoperative sampling): a. surgical field b. post ICS processing c. post ICS and LR filter processing d. post an additional LR filter	^b FTS-R202	RT-PCR for liver-specific gene (AFP) ⁵¹	a. Yes—20/32 b. Yes—15/32 c. Yes—2/32 ¹ d. Yes—1/32	Detection limit = 1–10 cells/sample.
Catling <i>et al.</i> ⁵⁷ (2008)	Gyne-oncology patients (<i>n</i> = 50) (intraoperative sampling): a. effluent tumour vein b. central venous c. operative field d. post ICS processing e. post ICS and LR filter processing	ⁱ LeukoguardRS	Immunocytochemistry (αCK) and light microscopy	a. No b. Yes—2/50 c. Yes—34/50 d. Yes—31/50 e. No	Detection limit for CK + cells = ~1/1 × 10 ⁶ ⁸⁶
Poli <i>et al.</i> ⁵⁸ (2008)	Prostate CA (<i>n</i> = 15) (intraoperative sampling): a. peripheral b. post ICS processing c. post ICS and LR filter processing d. post ICS and LR filter processing + 25 Gy gamma irradiation	^j LeukotrapRC	RT-PCR for prostate CA specific gene GSTP-1	a. No b. Yes—3/15 c. Yes—2/15 ^m d. No	Detection limit = > 1 cell/sample.
Martin <i>et al.</i> ⁵⁹ (2005)	a. ICS blood from pts with metastatic colon CA undergoing hepatectomy (<i>n</i> = 10) b. ICS blood from patients with pancreatic CA undergoing resection (<i>n</i> = 10)	Not specified	Immunocytochemistry (αCK) and light microscopy, and flow cytometry with αCK antibodies.	a. No b. No	Detection limit for CK + stained cells = ~1/1 × 10 ⁶ ⁸⁶ flow cytometry = < 100 CK + cells in 1 unit of ICS blood.

LR = leukoreduction; ICS = intraoperative cell salvage; CA = carcinoma; CK = cytokeratin; αCK = anti-cytokeratin antibodies; AFP = alpha fetal protein; GSTP-1 = glutathione-S-transferase gene; ICS = intraoperative cell salvage; LR = leukoreduction; pts = patients; RT-PCR = reverse transcriptase-polymerase chain reaction

*Experiments where tumour cells were *NOT* completely removed are resulted in bold print

^a SQ40S (Pall Corporation; 40 μm microaggregate blood filter), ^bRC-100 (Pall Corporation; 3rd generation filter), ^cRC-400 (Pall Corporation; 3rd generation filter), ^dImmugard III-RC (Terumo; 4th generation filter), ^eBPF4-BI (Nihon Pall; 4th generation filter), ^fLeukotrapWB (Pall Corporation; 4th generation filter), ^gRCEZIT (Pall Corporation; 4th generation filter), ^hFTS-RC202 (Shuangweibio Corp., Nanjing, China; 4th generation filter), ⁱLeukoguardRS (Pall Corporation; 4th generation filter), ^jLeukotrapRC (Pall Corporation; 4th generation filter), ^kRequired reamplification, ^lIntraoperative tumour rupture, ^mA different filter (type and generation not specified) was used in these 2/15 samples

Table 2 Efficacy of gamma irradiation for removal of malignant cells from ICS blood—*in vitro* studies

Study	Model	Gamma irradiation dose	Method used for detection of residual cells	Residual cells detected?*	Conclusions/comments
Poli <i>et al.</i> ⁵⁸ (2008, from Table 1)	Prostate CA (<i>n</i> = 15) (intraoperative sampling): c. post ICS and LR filter processing d. post ICS and LR filter processing + 25 Gy gamma irradiation	LeukotrapRC followed by 25 Gy	RT-PCR for prostate CA specific gene GSTP-1	c. Yes —2/15 ^a d. No	Detection limit = > 1 cell/sample.
Hansen <i>et al.</i> ⁶² (1999)	Fresh whole blood seeded with tumour cell lines and cells from solid tumours (>1 × 10 ⁶ mL ⁻¹)	50 Gy	a. Immunocyto-chemistry (αCK and nucleolar organizer regions) and light microscopy b. cell culture for 14 days	a. No b. No	Limits of detection not specified.
Futamura <i>et al.</i> ⁵² (2005)	Fresh whole blood seeded with tumour cell lines (5 × 10 ⁴ mL ⁻¹)	a. 25 Gy b. 100 Gy	RT-PCR for CK-19 (immediately post and 1 day post irradiation)	a. Yes b. Yes	Detection limit = 5,000 cells·mL ⁻¹

CA = carcinoma; CK = cytokeratin; αCK = anti-cytokeratin antibodies; GSTP-1 = glutathione-S-transferase gene; ICS = intraoperative cell salvage; LR = leukoreduction; RT-PCR = reverse transcriptase-polymerase chain reaction

*Experiments where tumour cells were *NOT* completely removed are resulted in bold print

^a A different filter (not specified) was used in these two samples

disease upon re-transfusion to the patient? Ultimately, the answer to this question is unknown, but the previously described *in vitro* experiments herein provide good evidence that tumour cells are effectively removed prior to autotransfusion. The *in vivo* component of this question, i.e., *whether patients who receive autotransfused blood are at higher risk of hematogenous metastases*, can be answered only through clinical studies.

Clinical experience

Reports of autotransfusion of ICS blood collected during surgery for resection of malignancy date back to 1986.⁶⁴ Malignancy recurrence or metastases secondary to perioperative transfusion practices is a difficult field of study given the heterogeneity of the clinical circumstance, the type and stage of cancer, and the long follow-up times required. Nonetheless, 15 clinical studies have been published reporting outcomes on patients who received transfusion of ICS blood intraoperatively during malignancy surgery⁶⁴⁻⁷⁸ (Table 3). The majority of these studies were single-centre non-randomized small studies where the outcome of patients who received intraoperative ICS blood was compared with historic or case controls. Four of these were controlled studies comparing intraoperative transfusion of ICS blood with transfusion of preoperatively donated autologous blood^{70,71} or transfusion of allogeneic blood or no blood.^{73,78} It is critical to point out that the majority of studies (13/15) involved ICS blood that was transfused *without* the benefit of subsequent LR filtration or irradiation. The notion that autotransfusion of ICS blood

increases a patient's risk of disease recurrence through hematogenous dissemination is not supported by any of these studies. A very recent meta-analysis supported this conclusion.⁷⁹ A ten-year follow-up study of patients who underwent resection of HCC showed that avoiding allogeneic blood with the use of ICS improved outcomes⁷² (Table 3). Critics will rightfully argue that these studies lack the power and the follow-up time to discern a meaningful difference⁶²; however, an analysis of these data collectively is the best evidence to date.

Evolution of practice

In 1986, at a time when autologous transfusion programs in the United States were becoming increasingly available, the Council on Scientific Affairs published a report endorsing autologous blood transfusions in the form of cell salvage or preoperative autologous donation.⁸⁰ It cited patient safety via avoidance of infection and alloimmunization and the sparing of blood bank resources as the primary advantages. Without any supporting *in vivo* evidence (at the time or in the intervening years), the presence or suspicion of malignant cells within the surgical field was introduced as a contraindication to the use of ICS.

This view has influenced the practice of autologous transfusion since, and the intervening years have been dominated largely by guidelines citing malignancy as a contraindication to ICS. During this time, however, a large research effort has been invested to prove or disprove this theory. Multiple surgical programs have continued to recognize both the potential benefit of autologous transfusion

Table 3 Tumour recurrence in patients who received intraoperative autotransfusion of ICS blood during malignancy surgery—clinical studies

Study	Design	Type of cancer surgery	Study groups: ICS [n/(# also receiving allogeneic RBC)] No-ICS [n/(# receiving allogeneic RBC)]	Filter/irradiation?	Follow-up time (months)	Outcome
Klimberg <i>et al.</i> ⁶⁴ (1986)	Prospective, non-randomized cohort	Urogenital (prostate, bladder, kidney)	ICS [49/(36)] No control group	None	>12	43/49 pts disease free, 5 documented recurrences. Pattern of recurrence and low incidence of isolated metastases, not consistent with ICS causing tumour dissemination.
Hart <i>et al.</i> ⁶⁵ (1989)	Case series	Bladder CA	ICS [49/(41)] No control group	None	12-38 (mean 24)	Overall and disease-free survival rates of 88% (43/49), and 80% (39/49), respectively.
Fujimoto <i>et al.</i> ⁶⁶ (1993)	Prospective, non-randomized cohort; historic case controls	Hepatocellular carcinoma (HCC)	ICS (and PAD) [54/(39)] No-ICS [50/(49)]	None	36	No significant difference in recurrence (62.8 vs 67.3%) or survival (61.9 vs 52.8%) in ICS vs No-ICS.
Zulim <i>et al.</i> ⁶⁷ (1993)	Retrospective cohort	Primary or metastatic hepatic malignancy	ICS [39/(28)]; PAD in 11 No control group	None	1.4-39 (mean 11.5)	Overall predicted 2 yr survival—75%; predicted 2 yr disease-free survival—28%. Consistent with published data.
Connor <i>et al.</i> ⁶⁸ (1995)	Prospective, non-randomized cohort; historic case controls	Cervical cancer	ICS [31/(4)] No-ICS [40/(1)]	None	1-43 (mean 24)	ICS: one pelvic recurrence No-ICS: two pelvic recurrences. No disseminated disease.
Mirhashemi <i>et al.</i> ⁶⁹ (1999)	Retrospective cohort	Cervical cancer (IA, IB, IIA)	ICS [50/(6)] No-ICS [106/(32)]	None	0-90 (mean 22)	ICS: 86% survival (all pelvic recurrences). No-ICS: not specified. (consistent with in-hospital and literature rates).
Gray <i>et al.</i> ⁷⁰ (2001)	Retrospective cohort	Prostate CA	ICS [62/(2)] PAD [101/(14)]	RC-400 LR filter	7 (ICS) 43 (PAD)	Biochemical recurrence- ICS: 5% PAD: 24% Progression-free survival not significantly different.
Davis <i>et al.</i> ⁷¹ (2003)	Retrospective cohort	Prostate CA	ICS [87/(0)] No-ICS [57/(0)] PAD [264/(0)]	None	12-104 (mean 40)	Biochemical recurrence: ICS: 15% No-ICS: 19% PAD: 16% No significant difference.
Hirano <i>et al.</i> ⁷² (2005)	Prospective, non-randomized cohort; historic case controls	Hepatocellular carcinoma (HCC)	ICS (and PAD) [54/(39)] No-ICS [50/(49)]	None	120 *10 yr follow-up study of ref ⁶⁶	10 yr cumulative survival rates: ICS: 20% No-ICS: 8% (Significant difference) All deaths secondary to recurrence of original cancer.

Table 3 continued

Study	Design	Type of cancer surgery	Study groups: ICS [n/(# also receiving allogeneic RBC)] No-ICS [n/(# receiving allogeneic RBC)]	Filter/ irradiation?	Follow-up time (months)	Outcome
Muscari <i>et al.</i> ⁷³ (2005)	Prospective cohort	Liver transplant for hepatocellular carcinoma (HCC)	ICS [31(28)] No-ICS [116(7)]	None	12-169 (median 34)	Recurrence: ICS: 6.4% No-ICS: 6.3% No significant difference.
Nieder <i>et al.</i> ⁷⁴ (2005)	Retrospective cohort	Prostate CA	ICS [265(4)] No-ICS [773(5)]	None	0.1-142 (median 40)	Biochemical recurrence: ICS: 15% No-ICS: 18% No significant difference.
Stoffel <i>et al.</i> ⁷⁵ (2005)	Prospective cohort	Prostate CA	ICS [48(ns)] No-ICS [64(ns)]	None	ICS: mean 43 No-ICS: mean 46	Biochemical recurrence: ICS: 19% No-ICS: 32% ICS not an independent predictor of recurrence.
Nieder <i>et al.</i> ⁷⁶ (2007)	Retrospective cohort	Bladder CA	ICS [65(24)] No-ICS [313(51)]	None	0-170 (median 20)	3-year disease-specific survival rate: ICS: 72.2% No-ICS: 73.0%
Maclvor <i>et al.</i> ⁷⁷ (2009)	Retrospective cohort	Prostate CA	ICS: [63(2)] PAD: [40(0)]	Pall RS-1 LR filter	ICS: mean 24.8 PAD: mean 35.6	Overall 3 year survival: ICS: 63.9% No-ICS: 65.8% No significant difference.
Bower <i>et al.</i> ⁷⁸ (2011)	Prospective cohort	Various gastrointestinal CAs	ICS: [32(ns)] No-ICS: [60(ns)]	None	median 18	Rate of recurrence: ICS: 1.6% PAD: 9.4% Rate of recurrence: ICS: 39% PAD: 38% No significant difference.

CA = cancer; ns = not specified; LR = leukoreduction; ICS = intraoperative cell salvage; PAD = preoperative autologous blood donation; pts = patients; RBC = red blood cells

and the potential harm of allogeneic transfusion, and they have persisted in offering ICS (\pm perioperative autologous donation) to their patients undergoing resection of malignancy.^{66,69,70,72,74,76} This practice has afforded more than 20 years of experience from some of these teams who clearly have experienced benefit rather than detriment to their patients. The current body of *in vitro* evidence together with a growing clinical experience suggest that ICS should not be withheld from patients with malignancy. In contrast, there is a substantial body of literature showing increased morbidity and complication in patients who receive allogeneic blood transfusion in this setting. Recent practice guidelines, including those from the National Institute for Health and Clinical Excellence (NICE) and from the Society of Thoracic Surgeons and Cardiovascular Anesthesiologists are now recommending the use of ICS with subsequent LR filtration for some malignancy surgeries, suggesting that in many circumstances the known risks of ICS blood are less than those of allogeneic blood.⁸¹⁻⁸³

Conclusion

Although transfusion of allogeneic blood is considerably safer than it was several decades ago, it still poses significant risk to the patient. The impact of TRIM, particularly in the patient with cancer, has yet to be completely understood. Pertinent to Canadian practice, the effect of prestorage LR on reducing TRIM-related adverse events has not been completely elucidated. Nevertheless, there is some evidence to support the observation that patients who receive allogeneic blood suffer more infections, a higher incidence of tumour recurrence, and increased morbidity as compared with patients who receive only autologous blood. Universal prestorage LR, as is practised in Canada, likely has some benefit with respect to the reduction in immunomodulation associated with allogeneic transfusion in the cancer patient, but this has yet to be fully understood.

When ICS is used for oncologic surgery, harvested red blood cell concentrates do contain a significant number of malignant cells. Despite this, the evidence to date does not show an increased risk of tumour recurrence or metastasis as a result of using ICS during oncologic surgery. A large body of evidence suggests that the safety of ICS blood can be improved further when used for cancer surgery with the subsequent use of an LR filter or irradiation. The majority of evidence, together with ease of use, has resulted in a recommendation for LR filters (over irradiation) in new practice guidelines.

A high-quality randomized controlled trial would be a difficult undertaking due to the heterogeneity of patients and their oncologic disease, the complexity of the decision

to transfuse blood (autologous, allogeneic, or both), the number of patients required to detect a clinically meaningful difference, and the follow-up time necessary. In the current climate of increasing acceptance of ICS use in oncologic surgery, it is conceivable that such a trial may be realized.⁸⁴ Given the difficulty of these studies, the suggestion of establishing local, national, or international registries to monitor tumour recurrence and patient survival deserves attention and has been suggested previously in the literature.⁸⁵

Avoidance of allogeneic blood products is not possible for all patients undergoing resection of malignancy. Nevertheless, transfusion of autologous blood harvested via ICS should be considered a viable option for reduction or avoidance of allogeneic product and may be a lifesaving option for those patients who refuse allogeneic blood products.

Acknowledgements The authors sincerely thank Dr. Don Griesdale for critical appraisal of the manuscript.

Disclosures None.

Funding sources/affiliations None.

Competing interests None declared.

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