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# Intraoperative cell salvage in oncological surgery: a narrative review

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**Abstract**: *Background:* Patient Blood Management (PBM) guidelines recommend intra-operative cell salvage (ICS) as a blood conservation strategy. In oncological surgery, however, many anesthesiologists and surgeons remain reluctant to use ICS for fear of causing systemic metastasis of tumor cells.
*Objective:* To review the efficacy and safety of ICS in oncological surgery.
*Methods*: MEDLINE, Embase and the Cochrane Library were searched for relevant articles from January 1st, 1986 until April 1st, 2021 using the keywords: "neoplasm", "cancer", "tumor", "tumour", "allogeneic blood transfusions", "autologous blood transfusions", "cell saver", "intraoperative cell salvage", "leukocyte depletion filter"
*Results:* Allogeneic blood transfusion is associated with several direct and indirect risks. As suggested by PBM-guidelines, it may therefore be prudent to restrict allogeneic blood transfusions. ICS offers an effective alternative to reduce allogeneic blood transfusion. Several systematic reviews and meta-analyses of observational studies suggest that ICS is not associated with metastasis, tumor recurrence or worse outcome after cancer surgery. Randomized controlled trials investigating its safety are however lacking. In light of the risks of allogeneic blood transfusion, the use of ICS should be considered in the setting of oncological surgery. We recommend using leucocyte depletion filters when re-infusing salvaged blood as these are able to remove almost all malignant cells.
*Conclusion:* Although the evidence remains weak, the currently available literature suggests the safety and efficacy of ICS in oncological surgery. Future guidelines should take the risks of anemia, blood loss and allogeneic red blood cell transfusion into account and consider stating a stronger recommendation for the use of cell salvage in oncological surgery when excessive blood loss is anticipated.

**Keywords**: Neoplasms; operative blood salvage; blood transfusion; autologous.

## Introduction

Historically, anesthesiologists and surgeons have been reluctant to use intra-operative cell salvage (ICS) as a blood conservation strategy in oncological surgery for fear of causing systemic metastasis of tumor cells and thereby compromising the patients' survival. Even in recent practice guidelines, only prudent statements are made on the use of ICS in oncological surgery which contributes to confusion and restraint. For example, the "2018 Association of Anaesthetists guidelines on cell salvage for peri-operative blood conservation" state that "there is no absolute contraindication for the use of cell salvage in oncological surgery" (1). Conversely, these same guidelines state that "when the use of cell salvage is proposed in surgery for malignancy or infection, an explanation should be given to the patient of the potential risks and benefits, specific consent should be obtained and leukocyte reduction filters should be used." (1).

Therefore, out of the "first-do-no-harm"-principle, many anesthesiologists and surgeons deny patients undergoing oncological surgery access to autologous blood conservation strategies such as ICS.

Recently however, several retrospective cohort studies in both oncological surgery and non-oncological surgery demonstrated that excessive blood loss and anemia but also allogeneic red blood cell transfusion, are associated with increased risks of postoperative mortality, severe complications and health care resource use (2-7). The concept of Patient Blood Management (PBM), which is endorsed by the European Commission and World Health Organization and defined as "an evidence-based bundle of care to optimize medical and surgical patient outcomes by clinically managing and preserving a patient's blood", addresses these risks (8, 9).

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Recent PBM-related reviews now recommend ICS as a blood conservation strategy to minimize the risks associated with intraoperative blood loss, anemia and allogeneic red blood cell transfusion and have started to advocate its use with increasingly less hesitation also in oncological surgery (10).

This leaves anesthesiologists and surgeons with the following questions: 1) Do PBM-guidelines recommend restrictive allogeneic red blood cell transfusion thresholds also in oncological surgery? 2) Is the use of ICS effective in reducing allogeneic red blood cell transfusion? 3) Is the use of ICS safe in patients presenting for oncological surgery? 4) If ICS would be safe, how can it then best be applied in the setting of oncological surgery?

In this narrative review, we aim to summarize the literature and provide an answer to these questions.

## Methods

Three biomedical databases (Cochrane Library, Embase, and MEDLINE) were searched for relevant articles with the following search terms: "neoplasms", "cancer", "tumor", "tumour", "allogeneic blood transfusions", "autologous blood transfusions", "cell saver", "intraoperative cell salvage", "leukocyte depletion filter", either as MeSH or Emtree terms, or as part of the title or abstract. We limited our search to articles in English language published between the 1st of January 1986 and the 1st of April 2021. This starting date was chosen because it was in 1986 that the Council on Scientific Affairs of the American Medical Association for the first time stated a strong contraindication for the use of ICS in cancer surgery (11). The screening and selection process was performed by first screening the titles and abstracts, then full texts and finally the references in the full text for relevant papers. Case reports, editorials, letters to the editor, and articles in which ICS was used in patients who underwent surgery for a benign tumor were excluded.

### *The rationale for PBM in oncological surgery*

The concept of PBM, which recommends a restrictive allogeneic blood transfusion strategy, has its origin in the 1980s as a result of two distinct observations (12). First, Denton Cooley, a cardiac surgeon at the Texas Heart Institute, demonstrated that open-heart surgery could be performed successfully in Jehovah's Witness patients without allogeneic blood transfusion (13). His success encouraged other practitioners around the world to perform "bloodless surgery" and to treat Jehovah's Witness patients with major surgery if indicated. Second, the emergence of the acquired immune deficiency syndrome (AIDS) and the realization that the human immunodeficiency virus (HIV) could be transmitted through blood transfusion, created a culture of caution (14).

With regard to this second observation, at present, the risk of contracting HIV or hepatitis C virus (HCV) after allogeneic red blood cell transfusion has fortunately become extremely small. The incidence is estimated to be less than 1 in 1 million transfusions which corresponds to the risk of dying from a bolt of lightning. Other transfusion-related complications, such as acute and delayed hemolytic transfusion reactions (1:10,000 – 1:100,000 transfusions) and transfusion-related acute lung injury (TRALI; 1:10,000 transfusions), also rarely occur with an incidence that is comparable with the risk of a motor vehicle death. Transfusion-related circulatory overload (TACO; 1:100 transfusions) and allergic reactions (1:100 transfusions), however, may occur more frequently after treatment with allogeneic blood. (15)

The aforementioned transfusion-related risks have recently been referred to as direct or deterministic transfusion hazards, as the mechanisms for the post-transfusion damage are clearly traceable to the blood transfused in a cause and effect-manner. They need to be distinguished from indirect or probabilistic transfusion hazards, which are hazards that may be responsible for indirect damage and have been identified as being associated with transfusion through epidemiological studies (Table 1) (16). Concerning the latter, several systematic reviews and meta-analyses indicated a dose-dependent association between perioperative allogeneic red blood cell transfusion and increased risk of mortality and severe morbidity, including multisystem organ failure, stroke, infection, pulmonary complications, renal impairment, immunomodulation, thromboembolism and even cancer recurrence after oncological surgery (17-24). The results of these meta-analyses should however be interpreted with caution, as they mainly included studies with a retrospective study design. This study design can only describe an 'association' between perioperative allogeneic red blood cell transfusion and the risk of decreased survival or tumor recurrence after oncological surgery, but not 'causation'. For example, the risk of postoperative mortality may be attributed to other factors for which a similar association was shown, such as preoperative anemia (25) or intra-operative blood

*Table 1*

The risks of allogeneic blood transfusions

| **Direct or deterministic transfusion reactions** | **Indirect or probabilistic transfusion hazards** |
|---|---|
| Acute or delayed hemolytic reaction | Mortality |
| Transfusion-related acute lung injury (TRALI) | Morbidity |
| Transfusion-related circulatory overload (TACO) | Stroke |
| Febrile non-hemolytic reaction | Immunomodulation |
| Allergic reaction | Multisystem organ failure |
| Anaphylactic shock | Increased ICU admission and increased ICU length of stay |
| Post transfusion purpura | Cancer recurrence |
| Transfusion-associated Graft versus Host disease (TA-GvHD) | Renal impairment |
| Viral Transmissions (HIV or Hep C) | Increased hospital length of stay |
| Hypotension - Hypertension | Thromboembolism |
| Hyperkalemia | Pulmonary complications |
| Transfusion-related immunomodulation (TRIM) | |

loss (2, 6, 7), which both may have necessitated the use of allogeneic red blood cell transfusion.

Since 1) randomized controlled trials investigating the plausibility of a causal relationship between perioperative allogeneic red blood cell transfusion and adverse effects after oncological surgery are currently unavailable, 2) the recurrence of cancer after oncological surgery may possibly be explained by transfusion-related immunomodulation (TRIM) (26), and 3) morbidity and mortality after oncological and non-oncological surgery do not appear to be increased with the use of a restrictive transfusion strategy as compared to a liberal strategy (27, 28), it may be prudent to avoid allogeneic red blood cell transfusions when not clearly indicated.

Therefore, PBM-guidelines do not recommend allogeneic red blood cell transfusion to reduce the risks associated with anemia or bleeding unless anemia and/or bleeding is severe – i.e., the patient exhibits symptoms of hemodynamic instability or tissue hypoxia. Instead, PBM-guidelines recommend a wide spectrum of medical and surgical techniques to reduce transfusions, based on three pillars: 1) optimizing erythropoiesis, 2) minimizing blood loss and bleeding, and 3) harnessing and optimizing the patient-specific physiological reserve of anemia while treatment is initiated.

For patients undergoing oncological surgery, strategies belonging to the first pillar of PBM have been well described in the European Society for Medical Oncology (ESMO)-guidelines (29), as well as in the 'International consensus statement on the peri-operative management of anaemia and iron deficiency' (30). These guidelines recommend a timely work-up and cause-specific treatment of anemia and iron deficiency with iron and/or vitamin B12 and/or folate supplements and/or erythropoiesis stimulating agents. The second pillar of PBM which includes several anesthesia- and surgery-related strategies to minimize intraoperative blood loss such as cell salvage, was recently reviewed by Shah et al (10). The third pillar of PBM is well described in the 'International consensus statement on the management of postoperative anaemia after major surgical procedures'(31), which focuses on improving the patient's tolerance for anemia and using restrictive transfusion thresholds while treatment of the underlying cause of anemia is initiated.

To summarize, it may be justified that PBM guidelines recommend restrictive transfusion thresholds in oncological surgery, although the currently available evidence is weak.

To determine if ICS should then be considered as a second pillar PBM-strategy in oncological surgery, it is first imperative to investigate if ICS is effective in reducing allogeneic blood transfusion and the risks associated with transfusion.

*The efficacy of cell salvage*

ICS starts with aspiration of shed blood from the surgical field and mixing it with an anticoagulant, either heparinized saline or acid-citrate dextrose (1, 32). After the collection of this shed blood in a reservoir, it is passed through a filter with a pore

diameter between 120 and 180 µm. Red blood cells are then first separated from whole anticoagulated blood through centrifugation. Next, cell debris, fat globules and bone chips are further removed by washing with intravenous saline 0.9%. This process finally results in transfusion-ready plasma-depleted RBCs suspended in saline, with a hematocrit of 50 – 80%, which can then immediately be re-infused to the patient or within 6 hours of collection. As also the quality of the red blood cells is well preserved, ICS appears to be an attractive alternative to allogeneic red blood cell transfusion (1, 32, 33).

In 2010, the latest Cochrane meta-analysis was published investigating the effect of ICS on the need for allogeneic red blood cell transfusion compared to no ICS. Seventy-five randomized trials were included, encompassing a total of 6025 patients of whom 3048 received ICS in the field of cardiac, vascular and orthopedic surgery. The results indicated that ICS could reduce the rate of exposure to allogeneic red blood cell blood transfusion by a relative 38% (relative risk [RR] = 0.62;95% CI 0.55 - 0.77, P<0.0001) and an absolute 21% (risk difference [RD] = -0.21; 95% CI -0.26 to -0.15, P<0.001) (34). However, not only studies investigating the effects of washed ICS were included, but also studies that investigated unwashed ICS. Filtered, but unwashed ICS blood may lead to adverse effects such as enhanced coagulopathy (and therefore increase allogeneic red blood cell transfusion needs), systemic inflammation and acute respiratory distress syndrome (ARDS) by enrichment of the salvaged blood with inflammatory mediators, fibrin degradation products and interleukins. Therefore, a new meta-analysis was performed in 2016, focusing only on the effects of washed ICS on the need for allogeneic red blood cell transfusion compared to no ICS (35). Forty-seven randomized trials were included, encompassing a total of 3433 patients of whom 1783 received ICS in the field of cardiac, vascular, orthopedic, trauma, oncological and pediatric surgery. ICS once more resulted in a reduced rate of exposure to allogeneic red blood cell transfusion by a relative 39% (RR = 0.61; 95% CI 0.57 – 0.65, P<0.001).

To summarize, ICS appears to be effective in reducing allogeneic red blood cell transfusion. Finally, to recommend ICS in cell salvage in oncological surgery, we need to determine if ICS is safe and in particular does not increase the apprehended risk of causing systemic metastasis of tumor cells.

*The safety of cell salvage*

Complications associated with ICS include non-immunological hemolysis (due to shear stress injury), air embolism, febrile non-hemolytic transfusion reactions, mis-transfusion, coagulopathy due to platelet and coagulation factor removal, contamination with drugs, bone cement, metal and disinfectants and incomplete washing leading to enrichment with leucocytes, cytokines and other microaggregates. Awareness, as well as appropriate staff training should reduce or even eliminate such complications (1, 32). The two aforementioned meta-analyses that primarily reported on the efficacy of cell salvage could not demonstrate an adverse impact on clinical outcome in patients who had received ICS (34, 35).

Anesthesiologists and surgeons have also feared causing sepsis after reinfusion of blood aspirated from infected surgical fields or contaminated with bacteria. It has been shown that cell salvage significantly, but not completely, reduces bacterial load, especially when leukocyte depletion filters are used (36). Currently, there is no evidence that cell salvage worsens sepsis or prognosis, but it may be prudent to use a waste sucker in fields with high levels of bacterial contamination, e.g. fecal contamination (1, 32).

In a similar way, there has been concern of causing systemic metastasis by re-infusing malignant cells aspirated from tumor-rich surgical fields. The controversy started when in 1975, a case report described how in blood that intra-operatively was aspirated from the pleural cavity in a patient who had undergone a right lung lobectomy for carcinoma, malignant cells were found, even after this blood had gone through a cell-saver (37). In that case, the salvaged blood was not reinfused and therefore the potential impact of re-infusion remained unknown known, neither was the viability of the malignant cells investigated, nor their metastatic potential. Nevertheless, this case report led the Council on Scientific Affairs of the American Medical Association to state an absolute contra-indication for the use of cell salvage in oncological surgery in 1986 (11).

In 2017, Kumar and colleagues reviewed the results of several in vivo studies and found that after passing blood with malignant cells through the combination of a cell-saver and leukocyte depletion filter, either no malignant cells or tumor fragments without metastatic potential or only extremely small numbers of tumor cells were detected (38). Marraccini and colleagues reported that the com-

bination of ICS and leucocyte depletion filtration resulted in a removal of 99.9% of tumor cells (39). Kumar and colleagues therefore concluded that the number of tumor cells in ICS blood would be significantly lower than the number of circulating tumor cells that are always present in oncological patients, even already prior to surgery (33, 38). In addition, any tumor cells that would survive the ICS filtration and washing process, would not retain their replicative potential or metastatic capacity, in contrast to circulating tumor cells in the blood of cancer patients (38, 40). As a consequence, they stated that ICS should be reconsidered as an alternative to conventional allogeneic red blood cell transfusion. Their statement is currently supported by several meta-analyses (41-48) (Table 2) that summarized the results of a large number of observational studies (49-82) (Table 3). Given the risk of bias inherent to the design of these, mainly retrospective, observational studies (e.g., selection bias), the evidence for the safety of ICS currently remains weak. Ideally, randomized controlled trials should investigate the rate of cancer recurrence and other clinical outcome parameters such as mortality in an experimental arm which would receive salvaged blood, compared to a control group which would receive allogeneic red blood cell transfusion. Unfortunately, until today, such randomized controlled trials are not available and therefore definitive statements on the safety of ICS in cancer surgery cannot be made. However, since several meta-analyses of a large number of observational studies suggest the safety of ICS, we may infer that ICS is safe to use in oncological surgery.

*Table 2*

Systematic reviews and meta-analyses concerning ICS in oncological surgery

| Author | Publication year | Included studies | Conclusion |
|---|---|---|---|
| Waters et al. (41) | 2012 | 11 cohort studies | ICS is not inferior to allogeneic blood transfusion regarding tumor recurrence or metastasis |
| Zaw et al. (42) | 2016 | 24 cohort studies | ICS does not increase risk of distant metastasis |
| Li et al. (43) | 2017 | 10 cohort studies | ICS has a higher survival rate and higher disease free survival rate compared to allogeneic blood transfusion |
| Guo et al. (44) | 2018 | 8 cohort studies | ICS does not increase risk of cancer recurrence and mortality in patients with hepatocellular carcinoma |
| Kumar et al. (45) | 2018 | 22 cohort studies | Sufficient evidence for the safety of ICS in oncological surgery |
| Kinnear et al. (46) | 2019 | 14 cohort studies | ICS does not result in higher tumor recurrence. ICS reduces need for allogeneic blood transfusion and results in a lower cost |
| Wu et al. (47) | 2019 | 9 cohort studies | ICS does not increase tumor recurrence rates. ICS has no impact on 5 year survival rate |
| Frietsch et al. (48) | 2020 | 27 cohort studies | ICS reduces risk of cancer recurrence<br>ICS does not impact mortality compared to allogeneic blood transfusion<br>LDF removes up to 99,9% of malignant cells |

*Table 3*

Tumor recurrence in patients who received ICS auto transfusion during oncological surgery: clinical studies

| Authors | Type of tumour/ surgery | Study design | LDF use | Study group | Follow up (Months) | Outcome |
|---|---|---|---|---|---|---|
| Klimberg et al (49) (1986) | Urogenital cancer | Prospective cohort study | No | ICS 49 / No control group | 12 | Pattern of recurrence and low incidence of isolated metastases, not consistent with ICS causing tumor dissemination. |
| Hart et al (50) (1989) | Bladder cancer | Case series | No | ICS 49 / No control group | 24 | No evidence for dissemination of tumor caused by ICS. |
| Fujimoto et al (51) (1993) | HCC | Prospective cohort study | No | ICS 54 / No-ICS 50 | 36 | No significant difference in recurrence (62,8 vs 67,3%) or Survival (61,9 vs 52,8%) in ICS vs No-ICS. |

| | | | | | | |
|---|---|---|---|---|---|---|
| Zulim et al (52) (1993) | HCC | Retrospective cohort study | No | ICS 39 / No control group | Mean 11,5 | Overall predicted 2y survival 75%, predicted 2y disease free survival 28%. Consistent with published data. |
| Connor et al (53) (1995) | Cervical cancer | Prospective cohort study | No | ICS 31 / No-ICS 40 | Mean 24 | ICS: 1 Pelvic recurrences No-ICS: 2 Pelvic recurrences. No disseminated disease. |
| Park et al (54) (1997) | Bladder cancer | Prospective cohort study | No | ICS 6 / ICS + PAD 4 | Mean 47 | ICS seems feasible in reducing or avoiding allogeneic blood transfusions in radical cystectomy |
| Vagner et al (55) (1998) | Kidney cancer | Prospective cohort study | No | ICS 20 / No-ICS 19 | 60 | No difference in recurrence rate, mortality ICS 40,9% vs No-ICS 42,1% |
| Mirhashemi et al (56) (1999) | Cervical cancer | Retrospective cohort study | No | ICS 50 / No-ICS 106 | Mean 22 | ICS: 86% survival (all pelvic recurrences) No-ICS: not specified (consistent with literature rates) |
| Gray et al (57) (2001) | Prostate cancer | Retrospective cohort study | Yes | ICS 62 / PAD 101 | ICS 7 vs PAD 43 | ICS recurrence 5%, PAD recurrence 24%. No significant difference in progression-free survival. |
| Davis et al (58) (2003) | Prostate cancer | Retrospective cohort study | No | ICS 87 / No-ICS 57 / PAD 264 | Mean 40 | Recurrence ICS 15%, No-ICS 19%, PAD 16%. No significant differences. |
| Hirano et al (59) (2005) | HCC | Prospective cohort study | No | ICS + PAD 54 / No-ICS 50 | 120 | Survival rate ICS 20% vs No-ICS 8% (significant difference). All deaths were secondary to recurrence of original cancer. |
| Muscari et al (60) (2005) | HCC | Prospective cohort study | No | ICS 31 / No-ICS 16 | median 34 | Recurrence ICS 6,4% vs No-ICS 6,3%. No signifcant difference. |
| Nieder et al (61) (2005) | Prostate cancer | Retrospective cohort study | No | ICS 265 / No-ICS 773 | Mean 40 | Recurrence ICS 15% vs No-ICS 18%. No significant difference. |
| Stoffel et al (62) (2005) | Prostate cancer | Prospective cohort study | No | ICS 48 / No-ICS 64 | ICS: mean 43 No-ICS: mean 46 | Recurrence ICS 19% vs No-ICS 32%. ICS is not an independent predictor of recurrence. |
| Nieder et al (63) (2007) | Bladder cancer | Retrospective cohort study | No | ICS 65 / No-ICS 313 | median 20 | 3y disease specific survival ICS 72,2 vs No-ICS 73%. No significant difference. |
| Catling et al (64) (2008) | Endometrial , cervical and ovarian cancer | Prospective cohort study | Yes | ICS 50 / no control group | / | No malignant cells were detectable in any of the final filtered samples. |
| Ford et al (65) (2008) | Prostate cancer | Prospective cohort study | Not specified | ICS 252 / No-ICS 117 | Mean 44 | No significant difference in recurrence between no transfusion (14%), ICS (10%) and Allogeneic blood transfusion (16%) |
| MacIvor et al (66) (2009) | Prostate cancer | Retrospective cohort study | Yes | ICS 63 / PAD 40 | ICS: mean 24,8 vs PAD: mean 35,6 | Recurrence rate ICS 1,6% vs PAD 9,4% |
| Foltys et al (67) (2011) | HCC | Retrospective cohort study | No | ICS 40 / No-ICS 96 | Median 33 | No significant difference in tumor recurrence between ICS (12,5%) vs No-ICS 18,8% |
| Ubee et al (68) (2011) | Radical Cystectomy | Prospective cohort study | Yes | ICS 25 / No-ICS 25 | 60 | Reccurence of 4% in ICS vs 16% in No-ICS. No evidence that ICS increases risk of tumor recurrence. |
| Engle et al (69) (2011) | Cervical cancer | Prospective cohort study | No | ICS 31 / No-ICS 40 | Mean 144 | No significant difference in recurrence between ICS (3%) vs No-ICS 7,5%) |
| Bower et al (70) (2011) | Gastro-intestinal cancers | Prospective cohort study | No | ICS 32 / No-ICS 60 | Median 18 | No significant difference in recurrence between ICS (28%) vs No-ICS (43%) |
| Gorin et al (71) (2012) | Prostate cancer | Retrospective cohort study | No | ICS 395 / No-ICS 1467 | Median 48 | 5year survival of 82,4% ICS vs 83,7% No-ICS. 8year survival of 73,4% ICS vs 76,6% No-ICS. No significant differences. |

| | | | | | | |
|---|---|---|---|---|---|---|
| Raval et al (72) (2012) | Prostate cancer | Retrospective cohort study | Yes | ICS 42 / PAD 32 | Mean 60 | Significantly fewer recurrence in ICS (9,5%) vs PAD (34,4%). |
| Kim JM et al (73) (2013) | HCC | Retrospective cohort study | Yes | ICS 121 / No-ICS 109 | Mean 53 | Recurrence-free survival rates for 1, 3, and 5 years were 91.3%, 83.3%, and 83.3%, respectively, in ICS, and 84.6%, 79.0%, and 77.4%, respectively, in No-ICS. No significant increase in tumor recurrence when using ICS. |
| Chalfin et al (74) (2014) | Prostate cancer | Retrospective cohort study | No | ICS 5124 / No transfusion 2061/ ICS + allogeneic blood 258 | Median 72 | Neither autologous nor allogeneic blood transfusion was independently associated with tumor recurrence or mortality. |
| Lyon et al (75) (2015) | Kidney cancer | Retrospective cohort study | No | ICS 33 / No-ICS 34 | Median 23 | No metastatic progression or cancer-specific mortality in either group. |
| Akbulut et al (76) (2016) | HCC | Retrospective cohort study | No | ICS 24 / No-ICS 52 | Mean 17,9 | No significant difference in recurrence rate between ICS (29%) and No-ICS (25%) |
| Araujo et al (77) (2016) | HCC | Retrospective cohort study | Yes | ICS 122 / No-ICS 36 | Median 27 | No significant difference in recurrence between ICS (8,2%) vs No-ICS (11,2%). No significant differences in overall survival. |
| Han et al (78) (2016) | HCC | Retrospective cohort study | Yes | ICS 222 / No-ICS 97 | 60 | No significant difference in recurrence between ICS (20,3%) vs No-ICS (24,1%) |
| Elmalky et al (79) (2017) | Metastatic spine tumors | Retrospective cohort study | Yes | ICS 63 / No-ICS 113 | Unclear | No significant difference in overall survival between ICS (58,7%) vs No-ICS (54,9%) |
| Kinnear et a (80) (2018) | Prostate cancer | Retrospective cohort study | No | ICS 29 / No-ICS 30 | Mean 30 | No significant difference in recurrence between ICS (10%) vs No-ICS (20%) |
| Kinnear et al (81) (2018) | Kidney cancer | Retrospective cohort study | Yes | ICS 16 / No-ICS 24 | ICS: median 9,3 vs No-ICS: median 27 | No significant difference in recurrence between ICS (18%) vs No-ICS (7%) |
| Myrga et al (82) (2019) | Radical cystectomy | Retrospective cohort study | Yes | ICS 87 / No-ICS 70 | Mean 18 | No significant difference in recurrence between ICS (23%) vs No-ICS (24%). No difference in mortality (ICS 12% vs No-ICS 17%) |

Clinical studies on tumor recurrence and/or survival with year of publication and study design. Comparison of intraoperative cell salvage (ICS) autotransfusion versus control group (No-ICS) or preoperative autologous blood donation (PAD).

*Practical application of cell salvage in oncological surgery*

Since the World Health Organization (83) and more recently the European Commission (84) have endorsed Patient Blood Management, Belgian clinicians willing to implement this concept in daily practice may have questioned the safety of ICS as a second pillar PBM-strategy in oncological surgery. Our findings suggest that ICS is safe to use in this context and may even be considered over allogeneic blood transfusion, although high quality evidence from randomized controlled trials is currently lacking.

For practical use of ICS in oncological surgery, we find guidance in the recommendations by the Association of Anaesthetists (1) and the National Institute for Health and Clinical Excellence (NICE), although in the latter only for radical prostatectomy or radical cystectomy. Both guidelines recommend obtaining specific informed consent for the theoretical risk of re-infusing cancer cells. We can only agree that specific informed consent is obtained for any procedure that may potentially result in harm for the patient. However, we believe that the information brochure provided by NICE is actually outdated. In light of our findings, in addition to the low-quality evidence from meta-analyses of a large

number of observational studies suggesting the safety of ICS, patients should also be informed of the potential risks of tumor recurrence associated with allogeneic blood transfusion and the high-quality evidence suggesting the efficacy of ICS to reduce the risks associated with allogeneic blood transfusion.

In agreement with the Association of Anaesthetists guidelines, we would suggest the collection of blood for potential cell salvage ('collect only' mode) in any oncological surgical procedure with an expected blood loss exceeding 500 ml (or > 10% of calculated total blood volume) in adult patients, or > 8 $ml.kg^{-1}$ (> 10% of calculated total blood volume) in children weighing > 10 kg. Also in agreement with these guidelines, we would then suggest to start the blood processing system if more than 500 ml of blood would be collected. For re-infusion, we would suggest to use a leucocyte depletion filter, as this (as mentioned earlier) has been demonstrated to almost completely remove all malignant cells. Several leucocyte depletion filters with variable pore sizes are commercially available . We suggest using filters with a high leucocyte reduction filtration rate (e.g., 90% leukocyte reduction Haemonetics RS Filter® versus 71% Haemonetics LipiGuard® SB Filter). Gamma-irradiation of salvaged blood as an alternative to leucocyte reduction filters has been shown to be less effective. In addition, the limited on-site availability of gamma irradiators makes this alternative impractical (33).

## Conclusion

In summary, allogeneic blood transfusion is associated with poor clinical outcome and even tumor recurrence. ICS is an effective second pillar PBM-strategy to reduce allogeneic red blood cell transfusion and its associated risks. In addition, ICS does not appear to increase the risk of tumor recurrence, although definitive statements cannot be made due to the lack of randomized controlled trials. In light of the risks of allogeneic blood transfusion however, we suggest future guidelines should formulate a stronger recommendation for the use of ICS in oncological surgery when excessive blood loss is anticipated. In addition, we recommend future randomized controlled trials to establish definitive evidence concerning the safety of ICS in oncological surgery.

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