The Use of Intraoperative Cell Salvage in Urologic Oncology

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Intraoperative cell salvage (IOCS) has been used in urologic surgery for over 20 years to manage intraoperative blood loss and effectively minimize the need for allogenic blood transfusion. Concerns about viability of transfused erythrocytes and potential dissemination of malignant cells have been addressed in the urologic literature. We present a comprehensive review of the use of IOCS in urologic oncologic surgery. IOCS has been shown to preserve the integrity of erythrocytes during processing and effectively provides cell filtration to mitigate the risk of tumor dissemination. Its use is associated with reduction in the overall need for allogenic blood transfusion, which clinically reduces the risk of hypersensitivity reactions and disease transmission, and may have important implications on overall oncologic outcomes. In the context of a variety of urologic malignancies, including prostate, urothelial, and renal cancer, the use of IOCS appears to be safe, without risk of tumor spread leading to metastatic disease or differences in cancer-specific and overall survival. IOCS has been shown to be an effective intraoperative blood management strategy that appears safe for use in urologic oncology surgery. The ability to reduce the need for additional allogenic blood transfusion may have significant impact on immune-mediated oncologic outcomes.

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KEY WORDS

Cell salvage • Transfusion • Urologic oncology

Intraoperative cell salvage (IOCS) is an attractive blood management strategy that sustains intraoperative patient blood volume while minimizing the need for additional allogenic blood transfusion.[1] IOCS typically delivers 50% to 60% of the hematocrit level for the volume of blood collected in the operative field.[2] In addition to mitigating the risk of hypersensitivity reactions and infectious disease transmission, limiting allogenic blood transfusion may also have important implications for oncologic outcomes. Since first postulated in 1981,[3] a myriad of data has been published showing an association between the receipt of allogenic blood following oncologic surgery and higher rates of cancer recurrence for a variety of malignancies, theorized to be mediated by acute immune system suppression, provision of growth factors for tumor cells, or both.[4-6]

Multiple studies have demonstrated an association between perioperative allogenic blood transfusion and worse outcomes following surgery for urologic malignancies. One recent study showed significantly worse 5-year recurrence-free survival, cancer-specific survival, and overall survival between patients who did and did not receive perioperative allogenic blood transfusion in a large cohort of patients undergoing radical cystectomy for muscle-invasive bladder cancer.[7] Large epidemiologic studies have specifically identified allogenic blood transfusion as an independent risk factor for decreased survival following partial or radical nephrectomy. Using the Surveillance, Epidemiology, and End Results (SEER) database, Soubra and colleagues[8] found that among 14,379 patients who underwent surgery for renal cell carcinoma (RCC), allogenic blood transfusion was a predictor of increased cancer-specific and overall mortality. Linder and colleagues[9] demonstrated that allogenic blood transfusion was independently associated with decreased 5-year all-cause mortality following partial or radical nephrectomy in a cohort of 2318 patients from their institution, and that this risk increased with each unit of blood transfused. This series underscores the potential harms of allogenic blood transfusion following urologic oncologic surgery, and the utilization of alternate blood management strategies to reduce the need for allogenic transfusion may become paramount as future evidence is amassed.

In addition to the use of IOCS, autologous blood predonation and normovolemic hemodilution are modalities also used to reduce the use of allogenic transfusions. Both autologous predonation and normovolemic hemodilution utilize the same principle of collecting the patient's own blood prior to the start of the surgical procedure; the only difference is the timing of donation. There are several considerations that may prevent the use of these modalities, including baseline patient anemia, high cardiovascular risk, and, in the specific case of hemodilution, the risk of intraoperative hypotension. Several studies have shown the increased cost associated with both of these techniques in comparison with IOCS, which stems mainly from increased cost of blood storage and disposal.[10,11] IOCS, conversely, has been shown to be comparable with allogenic transfusion, if not more cost effective. In a cost analysis review by Waters and colleagues,[12] the overall cost of cell salvage was not only found to be comparable with allogenic transfusion, but resulted in an average savings of $110.54 per unit.

Postoperative anemia may also be managed with a focus on stimulating erythrocyte production by the administration of iron (either intravenous or oral) and/or erythropoiesis-stimulating agents. Although these efforts have shown efficacy in reducing the need for postoperative blood transfusion, they are not well suited as single therapy following procedures with moderate blood loss, as it generally takes 7 days of treatment to produce the equivalent of one unit of transfused erythrocytes.[13-15]

Some urologic oncologists remain hesitant to adopt IOCS for fear of tumor dissemination and subsequent risk of metastatic disease if used during cancer operations. Here we present a comprehensive review of the current urologic literature describing the experience with IOCS as a blood management strategy during surgery for a variety of genitourinary malignancies.

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Cell Salvage Mechanics

The cell salvage apparatus begins with a specialized dual lumen suction device in the surgical field that allows for the mixing of an anticoagulant (generally heparin or citrate) with the suctioned blood. The mixture is then drawn into a reservoir that contains a 40-µm filter that excludes whole cells and larger blood particles. A technician adjusts a series of valves that controls delivery to a large centrifugation bowl, which spins at a speed of 4800 rotations per minute. Due to their greater density, erythrocytes adhere to

the outside of the bowl and plasma and platelets are removed as waste. The erythrocytes are then washed with isotonic saline and then may or may not pass through a specialized leukocyte filter. The final product is a saline suspension of erythrocytes, with a usual hematocrit level between 55% and 65%, which is pumped into a reinfusion bag and available for immediate transfusion through a smaller 20-µm filter. The entire cycle typically takes < 10 minutes.[16]

Viability of Erythrocytes After Processing

Early studies from the 1970s and 1980s evaluated erythrocyte survival after cell salvage processing. Using the radioisotope chromium 51 (^{51}Cr), Buth and associates[17] in 1975 found intact erythrocyte counts after centrifugation to be equivalent to peripheral blood controls. In 1982, Ansell and associates,[18] using a more complex dual-isotope tagging method, concluded that processed erythrocytes have equivalent survival to nonprocessed blood in vivo for up to 10 days. In 1986, Ray and colleagues[19] evaluated the in-vivo survival of ^{51}Cr-tagged erythrocytes after cell salvage processing up to 30 days after transfusion and found no difference in survival (up to 43%) compared with ^{51}Cr-tagged erythrocytes from homologous blood transfusion (40%) and autologous blood transfusion (41%).[19] These studies confirmed the preserved integrity of erythrocytes after cell salvage processing, setting the stage for broader adoption of IOCS across surgical specialties.

Use of Leukocyte Filters

In 1975, a report by Yaw and colleagues[20] identified viable malignant cells in an autotransfused blood sample from a patient undergoing pneumonectomy for lung cancer, leading to widespread concerns about the potential for IOCS to disseminate tumor cells in the bloodstream. Subsequent in vitro studies showed the potential for survival of cancer cells in a variety of cell lines (including pharyngeal, renal cell, prostate, breast, and colon carcinomas) after multiple passes through cell salvage processing.[21,22] In vivo confirmation of metastasis resulting from reintroduction of malignant cells through autotransfusion, however, has never been shown. Prior to surgical intervention, tumors are thought to continuously shed malignant cells into circulation, which does not invariably lead to metastasis. In a 1990 report, Weiss[23] described a patient with RCC found to be shedding an impressive 37 million cancer cells per day into the systemic circulation without any evidence of metastatic disease. Despite this, concern for potential harm from autotransfusion led to the development of leukocyte depletion filters aimed at eliminating nucleated cells by mechanical and affinity binding. Using cell lines from bladder, prostate, and renal cell cancer, Edelman and associates[24] showed that 62%, 40%, and 48% of cells, respectively, were recovered after passage through standard 20-µm blood filters. With the addition of a specialized leukocyte filter, however, the cell recovery rate in all three cell types was 0%. The precise mechanism of action by which leukocyte filters work is proprietary. However, these filters have modernized the cell salvage technique and have helped to alleviate concerns of tumor dissemination leading to systemic circulation and distant metastatic disease.

In vivo confirmation of metastasis resulting from reintroduction of malignant cells through autotransfusion, however, has never been shown.

Complications

Several studies have shown no increase in postoperative complication rates among patients receiving cell salvage transfusions.[25,26] Although rare, the main nononcologic complication associated with cell salvage is the potential for coagulopathy when large volumes are transfused, due to the washing of platelets and coagulation factors during processing of the blood. No specific transfusion volume has been found at which coagulopathies develop; thus, routine intraoperative testing of platelet count, prothrombin time, and fibrinogen should be performed according to local protocols.

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Early History of IOCS in Urologic Surgery

The use of IOCS in urologic surgery was pioneered by Dr. James Baker at the University of Florida (Gainesville, FL) in 1986. His group published a series of 49 patients undergoing urologic surgery incorporating the use of IOCS (24 radical cystectomies,

10 radical prostatectomies, 13 radical nephrectomies, 1 adrenalectomy, and 1 retroperitoneal pelvic lymph node dissection).[27] At a median follow-up ranging from 12 to 13 months, five patients (10.4% of total population) had observed cancer recurrence. They reported, however, that all five had known advanced disease at the time of surgery and that their recurrences were unrelated to the use of IOCS; 2 years later, their group published an additional longitudinal study of 49 patients undergoing radical cystectomy for muscle-invasive bladder cancer.[28] Cell salvage accounted for 40% of total transfusion requirements with a mean volume of 492 mL. At a median follow-up of 26 months, 25 patients (51%) were alive with no evidence of disease. The overall 21% recurrence rate reported was equivalent to the published contemporary rates of recurrence in patients undergoing radical cystectomy without IOCS, leading the authors to conclude that no patient developed diffuse metastatic disease from tumor dissemination resulting from autotransfusion. These studies established a precedent for the use of IOCS in urologic oncology.

Use of IOCS During Radical Prostatectomy

Early use of IOCS during radical prostatectomy was reported by Klimberg and colleagues[27] and Pisters and Wajsman,[29] who initially reported on the safety of the technique. Due to the small numbers of patients undergoing prostatectomy in these series, 10 and 14 patients, respectively, limited conclusions on the potential impact of IOCS on cancer recurrence could be drawn.

Gray and associates[30] were the first to report on the oncologic outcomes of IOCS use during radical prostatectomy. Their retrospective review compared 62 patients in whom IOCS was used as the sole method of transfusion with 101 patients in which autologous predonated blood was used. No difference was found in the preoperative prostate-specific antigen (PSA) level, pathologic stage, or estimated blood loss between the groups. In comparison of postoperative parameters, the cell salvage group was found to have a significantly higher hematocrit level (42.7% vs 39.6%; $P < .001$) and lower allogenic transfusion rate (3% vs 14%; $P = .04$). The incidence of progression-free survival (defined as postprostatectomy PSA level ≥ 0.4 ng/mL) was not different between the two groups ($P = .4$). This study had several limitations, including the lack of standard criteria for transfusion and limited follow-up in the IOCS group, with a mean of only 7 months.

Davis and coworkers[31] in 2003 reported their experience with the use of IOCS in a radical prostatectomy cohort from the University of Miami (Miami, FL). The authors compared 87 patients who received IOCS with 264 patients who received only predonated autologous transfusion and 57 patients who received neither. During the study period, only patients with an estimated blood loss > 700 mL received IOCS or autologous transfusion. At a mean follow-up of 40 months, the recurrence rates (PSA level > 0.2 ng/mL) for each group were 15%, 16%, and 19% for the IOCS, the autologous transfusion, and no transfusion groups, respectively ($P = .784$) indicating no increased oncologic risk for either modality.

In 2005, Nieder and colleagues[32] reported an update on the University of Miami IOCS study. The study compared 265 patients who received cell salvage blood during radical prostatectomy with 773 patients who did not (included patients who received predonated autologous transfusion or no transfusion). At median follow-up of 40 months, the overall risk for developing a recurrence at 5 years (PSA level ≥ 0.4 ng/mL) was 15% for the IOCS group versus 18% for the control group ($P = .76$). Following stratification of patients into low-, intermediate-, and high-risk of recurrence, no difference between the transfusion modalities was seen ($P = .35$). The time to biochemical recurrence (BCR) between the modalities was also analyzed and found to be comparable with a median time to BCR of 27.9 months for patients receiving cell salvage blood and 32.1 months for the control group ($P = .49$). These findings support the use of IOCS for all patients undergoing radical prostatectomy, including those with high-risk disease.

Finally, Raval and coworkers[33] analyzed the effect of cell salvage on metastasis and overall mortality following radical prostatectomy. The study included a total of 74 patients, 42 who received cell salvage blood only versus 32 who underwent predonated autologous transfusion. All patients had at least 5 years postprostatectomy follow-up. The two groups did not differ significantly with respect to demographics, operative time, pathologic cancer stage, grade, or surgical margin status. At minimum follow-up of 5 years, 11 patients (34.4%) developed BCR, 4 patients (12.5%) developed metastatic disease, and 3 patients (9.4%) expired (1 from metastatic prostate cancer and the 2 other from nonprostatic malignancies) in the autologous group. In the IOCS group, only 4 patients (9.5%) developed BCR, and none developed metastatic disease or expired. Although the rates of BCR and metastatic

disease were significantly lower ($P = .02$ and $P = .03$, respectively) in the IOCS patient group, this difference is likely due to selection bias rather than a biologic benefit from cell salvage therapy. The most important finding of this report was the lack of increase in the rate of metastatic disease in the IOCS group with an intermediate length of follow-up, which has been a significant concern in the adoption of cell salvage technology.

Use of IOCS During Radical Cystectomy

Although first reported almost 30 years prior in the work of Klimberg and colleagues,[27] contemporary use of IOCS during radical cystectomy was not again described until 2007, when Nieder and coworkers[34] published their experience. They reviewed 378 patients undergoing radical cystectomy, 65 of whom received IOCS blood based on a pre-established threshold to transfuse when intraoperative blood loss exceeded 700 mL. Due to this criterion, patients who received IOCS blood had significantly higher intraoperative blood loss reported than patients who did not (mean 862 mL vs 537 mL). Furthermore, 37% of patients who received IOCS also received additional allogenic transfusion due to their larger overall blood loss. Mean IOCS transfused volume was 362 mL. With similar baseline characteristics and no differences in pathologic stage between the groups, they showed an equivalent 3-year disease-specific survival of 72.2% (IOCS) and 73.0% (non-IOCS) at a median follow-up of 19.1 and 20.7 months, respectively. Overall survival at 3 years between groups was also equivalent, 63.9% (IOCS) and 65.8% (non-IOCS). The authors concluded that IOCS is a safe blood management strategy for patients undergoing cystectomy without increased risk of metastatic disease or death.

Aning and associates reported on a series of 213 patients undergoing radical cystectomy over a 10-year period in the United Kingdom, 91% of whom received IOCS.[35] Over the study period, the authors showed a decline in overall blood loss (2250 mL per patient during the first 2 years compared with 600 mL per patient in the final 2 years of the analysis), likely due to improvement in surgical technique and equipment technology. Although there was no comparison cohort, they demonstrated a minimal need for additional postoperative allogenic blood transfusion in patients who received IOCS blood, which comprised 70% of the overall transfusion requirements by 2010. They reported 3- and 5-year overall survival rates of 58% and 49%, respectively.

Use of IOCS During Nephrectomy

Perioperative blood transfusions during renal surgery have been reported in 3% to 21% of patients,[36-38] making IOCS a potentially attractive option for blood management during these cases. Several contemporary reports have documented the experience with IOCS during surgery for RCC with inferior vena cava (IVC) tumor thrombus. Moskowitz and associates[39] described the return of 3 L of salvaged erythrocytes during a radical nephrectomy with level IV caval thrombectomy without immediate complication, but the patient's long-term outcome was not reported. Casey and coworkers[40] reported outcomes for 10 patients in whom IOCS was used in conjunction with cardiopulmonary bypass during radical nephrectomy with IVC and atrial thrombi. One of these patients died postoperatively from pericardial tamponade after development of heparin-induced thrombocytopenia. At a mean follow-up of 46 months, eight of the patients were deceased, one was alive with metastatic disease, and one was alive with no evidence of disease. Unfortunately, conclusions regarding the safety of IOCS are difficult to ascertain from this report, as IOCS was only used in conjunction with cardiopulmonary bypass in this series, and comparisons of patients treated with and without IOCS are confounded by disease severity and level of caval thrombus.

There are limited data regarding the safety of IOCS during surgery for localized RCC. Klimberg and coworkers[27] reported outcomes of 13 patients in whom IOCS was used during radical nephrectomy. Mean blood loss was 1125 mL and mean volume of IOCS transfused blood was 463 mL. Two of these patients had disease recurrence, both developing pulmonary metastases at 5 and 6 months postoperatively. These authors concluded that their data failed to implicate intraoperative autotransfusion as a cause of disease dissemination, as the incidence and pattern of disease recurrence in this cohort was similar to historic control subjects not treated with IOCS.

Recently, Lyon and colleagues[41] reviewed the outcomes of 69 patients undergoing open partial nephrectomy performed by a single surgeon at their center, comparing 33 procedures during which IOCS was used with 36 in which it was not. At a median follow-up of 23 months, there were no significant differences in complication rate, length of stay, or overall survival between groups. No patients developed metastatic disease, and one patient in the non-IOCS group experienced recurrence. These authors concluded that IOCS during open partial nephrectomy was not associated with inferior outcomes at 2-year follow-up.

Cost Considerations

Many studies have validated the cost effectiveness of IOCS, most notably Ubee and colleagues,[42] specific to open radical prostatectomy. The authors calculated a per-unit cost of transfused homologous blood of £135 in patients whose surgeries took place prior to the availability of cell salvage as compared with £77 per case cost of IOCS, including machine consumables, leukocyte filters, irrigation fluid, and anticoagulants, independent of the amount of blood collected and reinfused. They concluded that the £4200 fixed purchase of the cell salvage machine would be recovered after just 20 cases based on the fourfold reduction in the rate of more costly homologous blood transfusion. Other studies have corroborated the cost effectiveness of contemporary IOCS across a variety of surgical specialties.[43-45]

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Conclusions

Appropriate blood management strategies during urologic surgery serve a twofold purpose: to minimize the need for allogenic blood transfusion, potentially conferring an immune-mediated oncologic benefit, and to maximize postoperative hematocrit levels, which has been associated with enhanced patient recovery.[46,47] Several retrospective series have demonstrated both the operative and oncologic safety of IOCS as a blood management strategy during radical prostatectomy, radical cystectomy, and partial or radical nephrectomy, and have failed to provide evidence that the incidence of recurrence or metastasis is increased. Table 1 lists all known reports of cell salvage use during urologic oncologic surgery. Unfortunately, no prospective evidence is available. The methodologic quality of available studies is low, and these should be interpreted with an

TABLE 1

Summary of Studies Using Intraoperative Blood Salvage During Urologic Oncologic Surgery

Study	Design	Cancer Type	Number of Patients (IOCS/No IOCS)	Follow-up	Outcome
Klimberg I et al[27]	Retrospective cohort	RCC, urothelial, prostate	13/0 24/0 10/0	12-23 mo	2/13 developed pulmonary mets 2/24 had pelvic recurrence 1/10 had pelvic recurrence
Hart OJ 3rd et al[28]	Retrospective cohort	Urothelial	49/0	26 mo	21% overall recurrence
Gray CL et al[30]	Retrospective cohort	Prostate	62/101	7 mo	Equivalent progression-free survival
Davis M et al[31]	Retrospective cohort	Prostate	87/321	40 mo	Equivalent rates of biochemical recurrence
Nieder AM et al[32]	Retrospective cohort	Prostate	265/773	40 mo	Equivalent rate of biochemical recurrence; same for low-, intermediate-, and high-risk disease
Raval JS et al[33]	Retrospective cohort	Prostate	42/32	Minimum 5 years	Lower rates of biochemical recurrence and metastatic disease in IOCS group
Nieder AM et al[34]	Retrospective cohort	Urothelial	65/313	19 mo	Equivalent disease-specific survival
Aning J et al[35]	Retrospective cohort	Urothelial	194/19	24 mo	3- and 5-y survival 58% and 49%; no comparison between groups
Lyon TD et al[41]	Retrospective cohort	RCC	33/36	23 mo	No cases of metastasis, 1 recurrence in non-IOCS group

IOCS, intraoperative cell salvage; RCC, renal cell carcinoma.

awareness of their limitations, including the potential for selection bias, the small number of patients studied, and their relatively short follow-up. Furthermore, there are no available data on IOCS use for patients with testicular or penile cancers; thus, conclusions as to its safety cannot be drawn in these populations.

Despite these limitations, the potential for harm from allogenic blood transfusion following oncologic surgery has been demonstrated, and surgeons must weigh these risks against the potential risks of IOCS.[3-8] Multiple retrospective series have failed to demonstrate an association between IOCS and the rapid development of widespread metastasis following surgery for urologic cancers; therefore, these risks remain theoretic. Until further data are available, IOCS can be considered a viable perioperative blood management strategy for patients undergoing surgery for prostate, bladder, or renal malignancies. ■

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MAIN POINTS

- Intraoperative cell salvage (IOCS) is an attractive blood management strategy that sustains intraoperative patient blood volume while minimizing the need for additional allogenic blood transfusion.
- Myriad data have been published showing an association between the receipt of allogenic blood transfusion following oncologic surgery and higher rates of cancer recurrence for a variety of malignancies. In addition to mitigating the risk of hypersensitivity reactions and infectious disease transmission, limiting allogenic blood transfusion may also have important implications for oncologic outcomes.
- Numerous studies have confirmed the preserved integrity of erythrocytes after cell salvage processing, setting the stage for broader adoption of IOCS across surgical specialties.
- Several retrospective series have demonstrated both the operative and oncologic safety of IOCS as a blood management strategy during radical prostatectomy, radical cystectomy, and partial or radical nephrectomy, and have failed to provide evidence that the incidence of recurrence or metastasis is increased. IOCS can be considered a viable perioperative blood management strategy for patients undergoing surgery for prostate, bladder, or renal malignancies.

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