

The impact of intra-operative cell salvage during open radical prostatectomy

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Background: To examine the effect of intra-operative cell salvage (ICS) in open radical prostatectomy.

Methods: In this retrospective cohort study, all patients undergoing open radical prostatectomy for malignancy at our institution between 10/04/2013 and 10/04/2017 were enrolled. Patients were grouped and compared based on whether they received ICS. Primary outcomes were allogeneic transfusion rates, and disease recurrence. Secondary outcomes were complications and transfusion-related cost.

Results: Fifty-nine men were enrolled; 30 used no blood conservation technique, while 29 employed ICS. There were no significant differences between groups in age, pre- or post-operative haemoglobin, Charlson comorbidity index, operation duration or length of stay. Tumour characteristics were also similar between groups, including pre-operative prostate specific antigen, post-operative Gleason score, T-stage, nodal status and rates of margin positivity. Compared with controls, the ICS group had longer follow up (945 *vs.* 989 days; $P=0.0016$). The control and ICS groups were not significantly different in rates of tumour recurrence (6 *vs.* 3 patients; $P=0.30$) or complications (10 *vs.* 5 patients; $P=0.16$). While the proportion of patients receiving allogeneic transfusion was similar (9 *vs.* 6 patients; $P=0.41$), fewer red blood products transfused (40 *vs.* 12 units) meant transfusion related costs were lower in ICS patients (AUD \$47,666 *vs.* \$37,429).

Conclusions: ICS reduced transfusion related costs, without affecting allogeneic transfusion rates, tumour recurrence or complication rates. These findings extend the literature supporting ICS in oncological surgery. Prospective randomised studies are needed to confirm the existing level III evidence.

Keywords: Prostatectomy; cell salvage; autologous; transfusion; blood; cost

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Introduction

Amongst men, prostate cancer is the most common non-cutaneous cancer and the second leading cause of cancer death (1). Annually in the United States of America (USA), >240,000 men are diagnosed with prostate cancer, with approximately one third undergoing radical prostatectomy (1,2). Operative blood loss has fallen steadily, due to the combined effects of greater understanding of the vasculature, improved technique, more sophisticated

cautery technology and the introduction of minimally invasive approaches (3,4). Despite this, transfusion rates for open radical prostatectomy remain high, at 4–14% (3,5–8). While mature blood banks have made allogeneic transfusion easily accessible and relatively safe, it still carries significant challenges including bacterial and viral transmission, transfusion reactions, tumour recurrence, cost and availability. The overall risk of any adverse event is 77 per 100,000 red blood cell (RBC) transfusions, and death in 1 per 100,000 (9). Studies of >26,000 patients report

allogeneic, but not autologous, transfusion to be associated with worse oncological outcomes, due to transfusion related immunomodulation (10-12). The supply and administration costs of a single RBC unit continues to increase, with current pricing ranging USD \$600–\$1,000 (13,14).

Intra-operative cell salvage (ICS) is a growing blood conservation technique involving the reinfusion of lost blood. Blood spilled in the operative field is collected, anticoagulated, washed, concentrated, filtered and returned to the patient. Reinfusion may occur intra-operatively, or up to four hours post operatively. ICS is safe and effective. Three large audits of 18,000–64,000 units of reinfused salvaged blood report complication rates of <0.027% (15-17). Several studies including a Cochrane review have demonstrated ICS reduces allogeneic transfusion rates (ATR) by over a third (18-22). ICS avoids most of the risks of allogeneic transfusion, and has been demonstrated to be more cost effective (23).

Due to fears of potential reinfusion of tumour cells, ICS was initially thought contra-indicated during cancer surgery. However, a wealth of studies have since found oncological outcomes for ICS patients to be equivalent or even superior to those receiving allogeneic transfusion (20,22,24-34). To date, the literature on ICS in radical prostatectomy consists of eleven cohort studies from the United Kingdom and USA (20-22,26-33,35-37). However, the majority compared ICS to pre-operative autologous donation (PAD) (20,26,30,32,35-37), a technique now seldom used. Additionally, the use ICS in uro-oncology in the Southern hemisphere has not been examined. Therefore, we aim to compare the outcomes of patients who did and did not receive ICS while undergoing open radical prostatectomy.

Methods

A retrospective cohort study was performed, enrolling all patients undergoing open radical prostatectomy at our institution between 10/04/2013 and 10/04/2017. Data were collected from hospital electronic and hard copy records. All patients underwent surveillance for tumour recurrence, according to the National Comprehensive Cancer Network (NCCN) post-prostatectomy surveillance guidelines (38). Per NCCN criteria, disease recurrence post prostatectomy was defined as either failure of PSA to fall to undetectable levels, or undetectable PSA followed by PSA detectable and rising on two consecutive measurements (38).

Patients who did (ICS group) and did not (control group) receive ICS were compared. Primary outcomes were ATR and disease recurrence. Secondary outcomes were

complications and transfusion-related cost. Complications were categorised based on the Clavien-Dindo grading system (39). Ethics approval was granted by the Central Adelaide Local Health Network human research ethics committee, reference HREC/17/TQEH/255.

ICS practice

Our institution commenced using ICS for open radical prostatectomy in September 2014. Usage was initially intermittent, reserved for cases deemed high bleeding risk, until following departmental review of evidence in December 2016 it was decided to employ ICS routinely, allowing for surgeon preference. We use the Fresenius Kabi CATSmart Continuous Autotransfusion System™, with a Haemonetics™ RS1VAE leucocyte depletion filter. As recommended by several authors (25,37), we use ICS in a financially tiered system. For all cases utilizing ICS, anticoagulated salvaged blood is collected in a reservoir (basic setup). When desired, this blood is processed and reinfused (reinfusion setup). Thus, the ICS processor set and other items are not wasted when blood is not reinfused.

The transfusion trigger is decided by the anaesthetist, based on patient pre-operative haemoglobin, cardiorespiratory comorbidities, volume of blood collected, ongoing haemorrhage, intra-operative heart rate and blood pressure.

Transfusion related cost calculations

All costs were calculated as of 30/06/17. Transfusion related costs were calculated as allogeneic transfusion cost + ICS setup cost + ICS reinfusion cost. Costs related to length of stay and complications were not included.

Allogeneic transfusion costs include both the product and process. The product cost of one RBC unit at our institution is \$412.66 Australian Dollars (AUD), purchased from the National Blood Authority, Australia (40). Process costs of transfusion, including in-hospital logistics, blood tests, staffing and overhead expenses, are known to be three to five times higher than the product cost (13,14). The first estimate of process costs in Australia by Wood *et al.* in 2006 of AUD \$370 per unit RBC infused (41) were updated in 2010 to AUD \$536 using the Australian Bureau of Statistics consumer price index for hospital and medical services (42). Utilising the same method translated to a subsequent 45.3% increase from end-of-financial-year 2010 to 2017 (43), giving a current process cost of AUD \$779, and a total cost per RBC unit infused of AUD \$1,191.66.

Table 1 The cost of intra-operative cell salvage set up and reinfusion in Australian dollars, as of 30 June 2017

Item	Cost
Sub-total, intra-operative cell salvage (ICS) setup cost	\$586.80
Separate Yanker sucker	\$0.98
Dual lumen sucker line	\$27.50
Anticoagulant; 2 ampoules of 25,000 units/ 5 mL heparin	\$12.64
ICS machine tubing	\$2.13
1×1,000 mL 0.9% normal saline	\$1.10
ICS reservoir	\$72.50
Bacterial filter	\$4.54
Anaesthetic nurse wages per case	\$465.41
Sub-total, ICS reinfusion cost	\$382.00
Leucocyte depletion filter; Haemonectics™ RS1VAE	\$56.00
ICS processor set	\$280.00
Reinfusion bag	\$35.00
10×1,000 mL 0.9% normal saline per 500 mL reinfused at \$1.10/bag	\$11.00

ICS costs were calculated by pricing every item involved, and also service-specific staffing. Staffing costs represent the majority of the ICS setup cost. The machine is run by one of several dedicated ICS-trained in-house year ≥ 9 anaesthetic nurses. When ICS is requested, our practice is to roster an additional anaesthetic nurse to liberate one whom is ICS trained. Due to a limited in-house staffing pool, it is often necessary to hire an agency nurse for this purpose. Current pricing in our institution for an in-house year ≥ 9 anaesthetic nurse is AUD \$42.28 per hour for a set eight hour shift, and for an equivalent agency nurse AUD \$77 per hour for a flexible duration shift. Of the 29 ICS cases, 16 utilised in-house nurse cover totalling 128 hours, while for 13 an agency nurse was employed for 105 hours in all. This represented an ICS staffing cost of \$13,496.84 total, or \$465.41 per case. Incorporating equipment costs (Table 1), ICS setup cost was AUD \$586.80 per case, with reinfusion an additional AUD \$382.00 per case.

Statistical analysis

Continuous data were summarized as medians with

interquartile range (IQR), and significance assessed using the Wilcoxon (Mann-Whitney) test. Categorical measures were summarized as proportions and assessed with Pearson's chi-square test. All tests were two-tailed and significance was assessed at the 5% alpha level. Data were analysed using SAS v9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Demographics

59 men underwent open radical prostatectomy during the enrolment period. 30 patients did not utilise ICS (control group), while 29 did (ICS group). There was no statistical difference between groups' median age (62.5 *vs.* 65 years; $P=0.28$), Charlson comorbidity index (4 *vs.* 4; $P=0.32$) or serum haemoglobin pre- (148 *vs.* 151 g/L; $P=0.84$) or post-operatively (102 *vs.* 102 g/L; $P=0.72$). Median operation duration (5.8 *vs.* 6.1 h; $P=0.058$) and length of stay was also comparable (5 *vs.* 5 days; $P=0.73$). Follow up was significantly longer for the ICS group (945 *vs.* 989 days; $P=0.0016$) (Table 2).

Oncological characteristics

The two groups had similar pre-operative PSA (6.7 *vs.* 6.8 ng/mL; $P=0.56$). Histopathology of the prostatectomy specimens was also closely matched in the groups, with the most common Gleason score being 7 (3+4), and most common pathological tumour stage being pT2c in both groups. Three controls and one ICS patient had nodal disease ($P=0.32$). No patients had evidence of metastasis at time of procedure. Surgical margins were positive in eight controls and six ICS patients ($P=0.59$) (Table 2).

Primary outcomes

There was no significant difference in tumour recurrence (6 *vs.* 3 cases; $P=0.30$). Nine control patients received a total of 40 units of allogeneic red blood, while six ICS patients were altogether transfused twelve units. There was no significant difference in ATR ($P=0.41$).

Secondary outcomes

Complications were seen in ten control patients and five ICS patients ($P=0.16$) (Table 3). Transfusion related costs were lower in the ICS group, both overall (AUD \$47,666

Table 2 Patient characteristics and outcomes

Parameters	No cell salvage (n=30)	Intra-operative cell salvage (n=29)	P value
Age (years)	62.5 [59–68]	65 [60–69]	0.28
Hb pre-op. (g/L)	148 [143–157]	151 [145–159]	0.84
Hb post-op. (g/L)	102 [96–112]	102 [92–112]	0.72
Charlson comorbidity index	4 [3–5]	4 [4–5]	0.32
Operation duration (hours)	5.8 [5.0–6.1]	6.1 [5.7–6.7]	0.058
Length of stay (days)	5 [4–6]	5 [4–6]	0.73
Follow-up (days)	945 [723–1,282]	989 [834–1,156]	0.0016
Tumour characteristics			
PSA pre-operative (ng/mL)	6.7 [4.7–8.2]	6.8 [4.7–8.2]	0.56
Post-op Gleason score			NA
6 (3+3)	3	4	
7 (3+4)	14	12	
7 (4+3)	8	10	
8–10	5	3	
T stage			NA
T2a	1	1	
T2b	0	3	
T2c	16	17	
T3a	7	3	
T3b	6	5	
Node positive	3	1	0.32
Metastatic pre-op	0	0	1.00
Margins positive	8	6	0.59
Primary outcomes			
Tumour recurrence	6	3	0.30
Allogeneic transfusion (patients)	9	6	0.41
Secondary outcomes			
Complications	10	5	0.16
Transfusion related cost (AUD)	\$47,666	\$37,429	NA

Data given as median [interquartile range]. AUD, Australian dollars; NA, not applicable.

vs. \$37,429) and per patient (AUD \$1,589 vs. \$1,291).

Discussion

First impressions can be misleading and lasting, and this has been the case for ICS in oncological surgery.

When introduced, it was feared that re-infusion of blood salvaged during tumour resection could lead to diffuse metastasis. The sole supporting evidence was a 1975 case study in which a patient with lung cancer underwent pneumonectomy utilising ICS, and died four weeks later with diffuse metastasis (44). In 1986 the American Medical

Table 3 Complications

Adverse event	Clavien-Dindo grade
Traditional group	
Ileus	1
Delirium	1
Atrial fibrillation, self-resolving	1
Re-admission 18 days post-operatively with urinary tract infection	2
Re-admitted 19 days post-operatively with symptomatic pelvic collection, managed with analgesia and antibiotics	2
Hospital acquired pneumonia	2
Infected lymphocele, with radiological drainage	3a
Non-infected lymphocele, with radiological drainage	3a
Re-admitted 4 days post-operatively with dislodged indwelling urethral catheter (IUC), requiring reinsertion via flexible cystoscopy	3a
Wound dehiscence, with washout under general anaesthesia	3b
Intra-operative cell salvage group	
Hospital acquired pneumonia	2
Recurrent failed trial of voids, requiring flexible cystoscopy and anastomosis dilatation	3a
Re-admission 18 days post-operatively with acute urinary retention, requiring IUC reinsertion via flexible cystoscopy	3a
Wound collection, requiring incision and drainage under general anaesthesia	3b
Anastomotic leak requiring suprapubic catheter placement under general anaesthesia	3b

Association Council on Scientific Affairs recommended against the use of ICS during tumour resection (45). However, there has since been a steady stream of studies demonstrating oncological safety. Subsequently, ICS use in uro-oncology and other oncological surgery has been supported by many national healthcare bodies, including the United Kingdom's National Institute for Health and Care Excellence (NICE), the Association of Anaesthetists of Great Britain and Ireland, the American Association of Blood Banks (AABB) and the National Blood Authority Australia (46-49).

Despite this broad-based institutional backing, the uptake of ICS has been slow (50) (51), due to persisting perceptions that ICS is expensive, ineffective and risks tumour recurrence. The task, then, is to objectively examine cost, efficacy and safety.

This study found that the use of ICS decreased transfusion related costs. This was despite the conservative practice of employing two anaesthetic nurses for each

case; one to work alongside the anaesthetist and another to run the ICS machine. This study has led to a change in practice at our institution. In the short term, the pool of in-house anaesthetic nurses will be increased to avoid use of the more expensive agency nurses. In the longer term, a single anaesthetic nurse is planned to perform both ICS and anaesthetist-support functions, with rostering of a second nurse to be phased out altogether. Our findings of cost reductions echo recent studies of ICS during prostatectomy and cystectomy (21,22). Additionally, Davies *et al.*'s systematic review of blood conservation economics concluded ICS to be more cost effective than allogeneic transfusion alone (23). However, some authors have found failed to find financial benefit utilising ICS (36,52). Given variation between healthcare sites in models of ICS delivery and allogeneic blood cost, and between procedures in intra-operative blood loss, it is clear ICS will not be cost effective in all circumstances. The AABB recognise this, and recommend ICS use during surgery where anticipated

blood loss is significant, specifically >750 mL, >20% of estimated blood volume, great enough to induce anaemia or leads to transfusion in >10% of patients (49).

When employed during applicable procedures, ICS is clearly effective in avoiding transfusion. Meta-analyses including a Cochrane review of 75 non-oncological randomised controlled trials (RCTs) found ICS reduced ATR by >38% (18,19). Amongst existing comparative prostatectomy ICS studies, while some have reported significant ATR reductions (20,22), most have not (26,27,30,32,35-37). This lack of effect is likely influenced by the well-documented decreasing blood loss during prostatectomy (3,4) combined with underpowered studies. With reported ICS groups having median ATR of 3.3% (standard deviation 15%) (20,22,26,27,30,32,35-37), to detect ATR one third lower than controls, prostatectomy studies using standard 80% power would need samples of 1,295 patients.

ICS safety includes both complications and tumour recurrence. The scarcity of complications from ICS use has been clearly documented (15-18). Demonstration of oncological safety is both empirical and theoretical. The ten uro-oncological comparative studies to date that report oncological outcomes all report equivalent or reduced disease recurrence (20,22,26-33). Three meta-analyses of ICS in oncological surgery failed to find a single publication demonstrating worse recurrence with ICS (19,34,53).

If empirical data do not demonstrate increased metastatic risk, the alternate test is to construct a realistic theoretical argument for risk. For ICS to cause metastasis, malignant cells must exist in the shed blood, be poorly removed by the ICS machine, have high malignant potential and meaningfully increase numbers of circulating tumour cells. The first of these four premises is undoubtedly true; numerous studies have found tumour cells in ICS blood (24,54,55). Secondly, leucocyte depletion filters are commonly used to remove tumour cells and bacteria. Studies both clinical and *in vitro* have demonstrated the ability of these filters to remove >99.9% of tumour cells (20,24,56,57), with several authors finding tumour cells were completely removed (58-61). Regardless of filter, the sublethal shear stress exerted by the ICS machine on reinfused RBCs (62), at only 8 mm diameter, is likely to be more severe for the larger tumour cells. Filtration may be unnecessary, given most of the uro-oncological ICS studies did not use leucocyte depletion filters, with none reporting worse recurrence rates (26-29,31,35,36). Third is the question of metastatic potential. While

tumour cells dislodged by surgical manipulation are fresh and *in vitro* display metastatic characteristics (54), animal studies indicate great malignant inefficiency, with only 0.000001–0.01% of circulating tumour cells holding metastatic potential (63). Fourthly, is the reinfusion of more tumour cells significant? Several authors have shown that patients with solid organ malignancy often have circulating tumour cells pre-operatively (64,65). Indeed, Glaves *et al.* measured patients with renal cell carcinoma releasing 37,000,000 tumour cells into the renal vein per day (66). Reverse transcriptase serum studies performed pre-, intra- and post-operatively clearly demonstrate that surgical manipulation releases additional tumour cells into the circulation (65,67,68).

In summary, the theoretical model for ICS being a legitimate means of metastasis seems tenuous. While ICS does aspirate tumour cells, nearly all will be removed or destroyed by filters or the ICS machine's shear stress, most of the remainder hold no malignant potential, and those that do will be reinfused into a circulation already containing vastly more pre-existing tumour cells. We must also balance this weak theoretical argument against ICS, unsupported by many studies, with the clear clinical evidence that allogeneic transfusion increases risk of recurrence. In urology, this includes a study of >48,000 patients (11) and two meta-analyses (10,69).

This is the first comparative study of ICS during radical prostatectomy outside the United Kingdom or the USA. It is also only the fourth comparative study of ICS in any specialty in Australia (70-72).

This study is limited by its retrospective nature, small size, non-randomised nature and short follow-up. While there were no significant differences in group demographics, selection bias may nevertheless have impacted our findings.

Conclusions

ICS reduces transfusion related costs, and does not affect tumour recurrence or complication rate. No difference in allogeneic transfusion rate was seen. This study extends the literature in support of ICS in oncological surgery. Prospective randomised studies are needed to confirm these findings.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of retrospective study, formal consent is not required. Nevertheless, ethics approval for this study was granted by the Central Adelaide Local Health Network human research ethics committee, reference HREC/17/TQEH/255.

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