Protocol

# Evaluation of the Feasibility of Transfusing Leukocyte Depletion Filter–Processed Intraoperative Cell Salvage Blood in Metastatic Spine Tumor Surgery: Protocol for a Non–Randomized Study

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## Abstract

**Background:** Metastatic spine tumor surgery (MSTS) is often complex and extensive leading to significant blood loss. Allogeneic blood transfusion (ABT) is the mainstay of blood replenishment but with immune-mediated postoperative complications. Alternative blood management techniques (salvaged blood transfusion [SBT]) allow us to overcome such complications. Despite widespread use of intraoperative cell salvage (IOCS) in oncological and nononcological surgical procedures, surgeons remain reluctant to use IOCS in MSTS.

**Objective:** This study aims to analyze safety of IOCS-leukocyte depletion filter (LDF)–processed blood transfusion for patients undergoing MSTS by assessing clinical outcomes—disease progression: tumor progression and overall survival. This study evaluates whether reinfusion of IOCS-LDF–processed blood reduces ABT rates in patients undergoing MSTS by sorting patients undergoing MSTS who require ABT into patients who consent to receive or not receive SBT.

**Methods:** We aim to recruit a minimum of 90 patients—30 patients for SBT, 30 patients for ABT, and 30 patients with no blood transfusion. SBT and ABT form the 2 experimental arms, whereas no blood transfusion forms the control cohort. Available patient data will be reviewed to determine tumor burden secondary to metastasis and postoperative survival and disease progression, improvement in pain, and neurological and ambulatory status. Data collected will be studied postoperatively at 3, 6, 12, 24, 36, and 48 months or until demise, whichever occurs first. Outcomes of the experimental groups will be compared with those of the control group. Outcomes will be analyzed using 1-way ANOVA and Fisher exact test. The Kaplan-Meier curve and a log-rank test will be used to study overall survival. A multivariate and competing risk analysis will be used to study the association between blood transfusion type and tumor progression. All statistical analyses will be done using Stata Special Edition 14.0 (StataCorp LP).

**Results:** This is the largest clinical study on use of IOCS in MSTS from various primary malignancies to date. It will provide significant clinical evidence regarding the safety and applicability of IOCS in MSTS. It will help reduce use of ABT, improving overall blood management of patients undergoing MSTS. A limitation of this study is that not all patients undergoing MSTS will survive for the follow-up period (4 years), theoretically leading to underreporting of disease progression. Study commenced in 2016 and patient recruitment continued till 2019. As of September 2019, we have collected operative data on 140 patients. However, the 2-year outcomes of about 40.0% (56/140) of patients are in the process of collection. The study is aimed to be published in the years 2023-2024.

**Conclusions:** Results will be disseminated via peer-reviewed publications, paving the way for future studies.

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**KEYWORDS**

blood transfusion; autologous blood transfusion; operative blood salvage; leukocyte reduction filtration; intraoperative blood cell salvage; extramedullary spinal cord compression; metastases; tumors; leukocytes

## Introduction

### Background

The skeletal system is the third most common site of metastases, and cadaveric studies show that spinal metastases can be found in 30% to 90% of patients who die of cancer [1,2]. Surgery for metastatic spine disease (MSD) is complex, often requiring wide resection and extensive reconstruction leading to significant blood loss [1,2]. Emergency surgical treatment is often indicated for spinal cord compression with actual or impending paralysis or for spinal instability with severe pain that reduces the quality of life and mobility [3].

Typical blood loss in a patient undergoing tumor decompression and instrumentation in the thoracic and lumbar spine is about 1500 mL, and this requires an average of 3 units of packed red blood cells [4,5]. This blood loss is currently replenished by allogeneic blood transfusion (ABT) across the world, placing a significant burden on the already limited blood bank resources [6,7]. On the contrary, there is increasing evidence of the deleterious effects of ABT. Many studies have shown an increased incidence of postoperative infections [8] and promotion of tumor growth [8,9], which is thought to occur secondary to immunosuppression and other transfusion reactions.

Despite evidence describing multiple postoperative complications related to ABT [10,11], it remains to be the mainstay of blood replenishment in patients with heavy intraoperative blood loss [12]. These are immune-mediated complications and commonly affect the lungs (eg, transfusion-related acute lung injury) [13,14], wound healing [15-17], and survival duration [11,16]. This has prompted efforts to decrease reliance on ABT and to increase the utilization of alternatives, such as autologous predonation or intraoperative cell salvage (IOCS). Autologous predonation may not always be possible in metastatic spine tumor surgery (MSTS) because of suboptimal patient status, medical comorbidities, and in cases where emergency surgery is indicated.

Patient blood management is an evidence-based, patient-tailored approach aimed at reducing the need for ABT and its associated risks [18]. Patient blood management has both preoperative and perioperative components. Preoperative techniques include patient optimization via cessation of antiplatelet and anticoagulant medications [19,20] and anemia management [18]. Perioperative management comprises achieving surgical hemostasis, reinfusion of intraoperatively salvaged blood, the use of erythropoietic agents, and hemostatic drugs such as tranexamic acid. Randomized [21,22] and nonrandomized [23] studies on the use of IOCS in nononcological surgical procedures indicate that salvaged blood transfusion (SBT) significantly reduces the need for ABT [21-23]. Despite extensive use of SBT in orthopedic, trauma, and cardiac surgical procedures [24], the concern of reinfusion of tumor cells leading to disease progression persists [25-27]. The initial lack of literary evidence on the safety of SBT in oncological surgical procedures has made oncological surgeons reluctant to use SBT in MSTS [25-27].

This reluctance dates to an American Medical Council report from 1986, which stated that SBT was not suitable for use in tumor surgery [28]. This was in turn based on a case report from 1975 where tumor cells were found in salvaged blood [29]. There were concerns that tumor manipulation and resection would result in the spillage of tumor cells into the surgical field [30], which would lead to further metastasis if reinfused via SBT. Recent evidence indicates that circulating tumor cells (CTCs), which are shed by the primary tumor [31], are the most likely cause of tumor metastasis in oncological patients. CTCs have been shown to be eliminated by the reticular endothelial system [32], once they fail to metastasize (unable to complete the process of metastasis). Other CTCs may undergo cellular apoptosis after being retained in the capillary bed or the bone marrow [32]. These host defense mechanisms can prevent metastasis by reducing the metastatic ability of the vast majority of CTCs [33]. Consequently, one can ask, “Can SBT with a limited load of damaged malignant tumor cells cause tumor metastasis and disease progression?”

Investigation on the use of salvaged blood in MSTS started with a systematic review that we published [34]. It was envisaged that there is a place for salvaged blood in MSTS, provided the safety of IOCS in MSTS is established by the following steps. Our first step was to establish *basic cellular evidence* that there are no viable tumor cells in the salvaged blood. Second, we aimed to *quantify the number of tumor cells in the salvaged blood*, if any, and to demonstrate that the CTCs in the patient’s own blood are far more than those present in the salvaged blood. Our proposed *final phase* of study was to provide *clinical evidence* that SBT is safe for use in oncological surgical procedures, without increasing the risk of disease progression or tumor recurrence or resulting in poorer prognosis [32].

Our working hypothesis for the preclinical phase of this study was that the blood salvaged from patients undergoing MSTS does not contain viable tumor cells, and even if it did, viable tumor cells in the salvaged blood would be significantly lower than the number of CTCs present in the patient’s own blood at any given point in time. Therefore, there should be no increase in the risk of disease progression, in terms of further tumor dissemination, decreased survival, or increased tumor recurrence.

To test this hypothesis, we first conducted a study that analyzed the morphology and structural integrity of the tumor cells present in the patient’s circulation, operative field, and pre- and postfiltration samples of the salvaged blood [24,35]. Using the cell block technique, salvaged blood in the pre- and postfiltration samples was shown to mostly comprise cytoplasmic debris with no viable nuclei [24,25], thereby establishing the safety of IOCS in oncological surgery [36]. This is also supported by evidence from other studies [37] stating that upon passing through the



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IOCS system, 62% of tumor cells were destroyed, whereas the remaining 38% were morphologically altered.

Using flow cytometric studies, we then compared the number of CTCs present in the patient's own blood with that in salvaged blood [38]. We found that salvaged blood contained a significantly lower number of CTCs than those present in the patient's circulation [38]. Furthermore, we provided corroborative evidence that tumor cells passing through IOCS become nonviable and therefore cannot form new metastatic lesions [36]. We were able to demonstrate that CTCs lost the ability to develop into new metastatic lesions after passing through the IOCS apparatus, even without the use of leukocyte depletion filters (LDFs) [36]. LDFs are used to prevent leukocyte-mediated adverse reactions and have applications in both transplant surgery and treatment of hematological conditions [39]. LDFs are used for filtrating blood and have been proven to have the capability to remove tumor cells from the filtrate [38].

Currently, there is ample evidence in the literature for the clinical safety of salvaged blood used in oncological surgical procedures, including gastrointestinal [40], gynecological [41-43], hepatobiliary [40,44-46], and urological [47-54] surgical procedures (Multimedia Appendix 1 [55-64]). Although patients who received SBT required significantly lower amounts of allogeneic blood, their survival rates [44,49,51,52] and disease progression remained comparable with those who did not receive SBT [42,46,54,65]. Patients who received SBT had lower or similar rates of recurrence compared with the control cohort [47,49,51,53].

Despite the validity of the abovementioned literature, there still is hesitation to use IOCS in MSTS [34]. This can be addressed only by using a clinical study. Hence, we have designed this study to analyze the clinical use of IOCS in patients undergoing MSTS.

### Objectives

#### *Primary Objectives*

This study aims to investigate the following clinical outcomes: disease progression, in terms of tumor progression (increase in size of existing metastatic lesions with or without the appearance of new metastasis), and the overall survival (OS) in patients who receive *IOCS in combination with LDF* (IOCS-LDF)–processed blood during MSTS. Therefore, this study aims to refute the prevailing conception that cell salvage should be avoided in MSTS owing to concerns of tumor dissemination.

#### *Secondary Objectives*

The secondary objectives of the study are to investigate whether reinfusion of IOCS-LDF–processed blood can reduce ABT rates in patients undergoing MSTS. We will also compare the length of stay and overall complication rate of patients who receive salvaged blood and those who receive ABT or no blood transfusion (NBT).

### Hypothesis

The working hypotheses of this study are as follows:

1. Reinfusion of IOCS-LDF–processed blood of patients undergoing MSTS does not increase the risk of disease progression, in terms of tumor progression (increase in size of existing metastatic lesions with or without the appearance of new metastasis) and OS.
2. Patients receiving IOCS-LDF blood transfusion require less ABT.
3. Patients receiving IOCS-LDF blood transfusion will experience fewer overall complications and shorter length of stay than patients receiving ABT.

## Methods

### Recruitment

This study aims to recruit a minimum of 90 patients of whom 30 will receive SBT (with or with no allogeneic blood), 30 will undergo ABT, and the remaining 30 will have NBT. From our experience of treating patients with tumor, there are likely to be very few patients who receive only SBT. The majority of patients receiving SBT are likely to receive both SBT and ABT in various proportions. SBT and ABT form the 2 experimental arms, whereas patients with NBT form the control cohort. We will compare the number of patients receiving only SBT with those receiving ABT, if the sample sizes are sufficient.

Patients will be selected from specialist outpatient spine clinics or inpatient wards. These patients may be referred from an inpatient medical oncology team for management, especially in the setting of MSD with cord compression resulting in symptoms such as pain or neurology. A thorough examination of clinical history, physical examination, and review of imaging will be done, and appropriate patient management options will be discussed by the attending orthopedic surgeon. During the enrollment period, whenever a spine surgeon has obtained surgical consent for MSTS in patients with MSD, the principal investigator (NK) will be informed either by a telephone call or by text messaging.

The *research assistant* who is on-site at the National University Hospital during office hours or any member of the research team who is available will interview the patient. During this interview, the interviewer will confirm whether the inclusion criteria are fully met. The study will be explained to suitable subjects, including the advantages as well as possible intra- and postoperative risks of the reinfusion of salvaged blood. A copy of the *patient information sheet and consent form* will be provided to the patient, detailing the recruitment procedures, our objectives, hypotheses, and background information, and any queries will be addressed. Subsequently, written informed consent will be obtained from the patient.

Blood transfusion details will be collected from anesthetists immediately after the operation. Depending on the type of blood transfusion done during the surgery, that is, ABT only or SBT with or with no ABT or NBT, the patient will be categorized into the appropriate study cohort. All patients undergoing MSTS will receive tranexamic acid as an intravenous bolus before induction of anesthesia as per the department protocol, with subsequent top-up dosages every 4 hours during MSTS. If excessive blood loss is expected during surgery, such as in a



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separation surgery, continuous infusion of tranexamic acid is given to the patient.

Postoperatively, all subjects will be followed up individually by their operating surgeons, as per the standard of care at the National University Hospital. No additional patient follow-up sessions by the research team will be required. Clinical data and patient outcomes will be accessed via the computerized patient support system and EPIC system at monthly intervals. All available radiological data and clinical notes from the patients' follow-up by their treating surgeons or physicians will be reviewed by the research team. This is to determine the postoperative outcomes such as survival and disease progression. The collected data will be analyzed postoperatively at 3, 6, 12, 24, 36, and 48 months. The data collection and follow-up of available records will continue over a period of 4 years postoperatively or until the patient's demise, whichever occurs first. The collected outcomes of the 2 experimental groups (patients who received SBT with or without ABT) will be compared with those of the control group (patients who received NBT) as well as with the available historical data from the literature.

### Statistical Analysis

We have defined *disease progression* as the increase in the size of an existing metastatic lesion or the appearance of a new lesion in the lung, liver, or the spinal column, which can be visualized by using radiological imaging.

Demographic and clinical characteristics of patients will be summarized using mean (SD) values for continuous variables with approximately normal distribution, median (IQR) values for continuous variables with skewed distribution, and frequency (percentage) for categorical variables. A 1-way ANOVA will be used to compare the mean of a normally distributed variable across the 3 blood transfusion groups, whereas a Kruskal-Wallis rank test will be used for the comparison of medians. A Fisher exact test will be implemented for categorical variables accounting for potential small frequencies.

The association between individual characteristics and OS will be studied by using the Kaplan-Meier curve and a log-rank test. The crude hazard ratio and its 95% CI will be used to measure the association between individual characteristics and OS and will be calculated based on their original definitions. Multivariate Cox proportional hazard regression will then be used to adjust for statistically significant confounders for the relationship between the type of blood transfusion and OS. The proportional hazards assumption will be tested after the final model is obtained.

The association between the type of blood transfusion and tumor progression will be investigated by the competing risks analysis, taking death without tumor progression as the competing event. First, cumulative incidence curves of the 3 blood transfusion groups will be plotted nonparametrically, and then we will model the relation via a subdistribution hazard regression model. The measure of association will be quantified by the crude subdistribution hazard ratio; its 95% CI and *P* value will be analyzed in a univariate analysis. Subsequently, a multivariate analysis will be used to adjust for potential confounders. All statistical analyses will be done using Stata Special Edition 14.0 (StataCorp LP). The statistical tests will be assumed to be 2-sided, with the conventional 5% significance level.

#### *Analysis of Primary Outcome Measures*

We intend to compare the proportion of patients with MSTS requiring blood transfusion and the amount of ABT required. The primary analysis will be based on the intention-to-treat principle. A Fisher exact test will be used to compare the 2 arms. The exact 95% CI will also be calculated for the difference in the ABT rate between the 2 arms.

#### *Analysis of Secondary Outcome Measures*

The progression of disease will be assessed using the internationally accepted Response Evaluation Criteria in Solid Tumors (version 1.1) [66,67]. Disease progression is defined as at least a 20% increase in the sum of the diameters of measurable target lesions (eg, lymph nodes and bone metastases with soft tissue components), unequivocal progression of nontarget lesions (eg, malignant ascites or pleural effusions), or the appearance of 1 or more new metastatic lesions.

Computed tomography of chest or abdomen and pelvis will be used to assess metastases in the lymph nodes, lung, liver, or any abdominal organ, all of which can be visualized adequately. Magnetic resonance imaging of whole spine and nuclear medicine bone will also be performed because of their increased sensitivity in detecting early new spinal or skeletal metastases [68]. A lesion identified in a follow-up study in an anatomical location that is not present at baseline is considered a new lesion and will indicate disease progression.

The OS rate will be defined as the proportion of patients who survive until the end of the study period. Median survival times and 95% CI will be estimated using Kaplan-Meier curves for experimental and control groups. The median OS times will be compared using a log-rank test. The survival rate at 6 months after surgery will also be estimated using Kaplan-Meier curves.

### Ethical Considerations

The domain-specific review board of the National Healthcare Group, Singapore (reference numbers: 2014/00065 and 2022/00866), has granted ethical approval for this study. Written informed consent regarding participation in this research study and receiving SBT will be obtained from each patient before the patient is recruited for the study. Data have been anonymized and deidentified. No compensation was provided to patients for this study.

## Results

This study has been funded by the National Medical Research Council of Singapore in November 2016 and approved by domain-specific review board of the National Health Group in April 2016.

Data were collected from November 2016 to present (as of submission date of manuscript). Numbers recruited into study, as of submission of the manuscript, were 140. The status of data analysis and expected results are expected to be published in the years 2023-2024, when the information is available.



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## Discussion

### Study Findings

This is the largest prospective clinical study on the use of IOCS in MSTS from a variety of primary malignancies. It will provide significant clinical evidence regarding the safety and applicability of IOCS in MSTS. The clinical safety of the use of IOCS has been established in oncological surgical procedures involving gastrointestinal [40], gynecological [41-43], hepatobiliary [40,44-46,55-57], and urological [47-54,58-62] specialties (Multimedia Appendix 1). However, the use of IOCS has neither been studied nor practiced regularly in metastatic musculoskeletal tumor surgeries (MMTSs). This may be because of the skepticism among surgeons about the safety of SBT in MMTSs, despite the presence of substantial supporting evidence in other surgical specialties in the field of oncology [40-54,63,64]. Amidst all the apprehension regarding IOCS, a retrospective comparative review has shown that SBT indeed reduces the need for postoperative ABT [69]. More recently, the use of SBT has been studied prospectively, demonstrating its safety for IOCS in MSTS [70]. Nonetheless, these studies did not have a comparative arm and had a small sample size.

This prospective clinical study is founded on substantiating evidence that salvaged blood is free from viable tumor cells, proven in our earlier methodical basic sciences approach [32,38]. We aim to study the OS, as well as tumor progression in MSTS patients through analysis of their various outcome measures. The results from this approach will help debunk the prevailing myth that IOCS contributes to disease progression either in the form of new metastasis or in the form of an increase in the size of the index lesion.

### Limitations

The limitation of this study is that not all patients undergoing MSTS will survive for the total follow-up period of 4 years, thereby theoretically leading to potential underreporting of disease progression. The sheer number of possible primary tumors in MSD also inevitably leads to heterogeneity, which can be overcome through propensity score–matching analysis.

### Broader Implications

Through the reporting of our analysis, this study will help reduce the use of ABT, reduce the burden on blood banks, and improve the overall blood management of patients with MSTS. This improvement in blood management will prevail even with the improvement of surgical techniques in the management of MSTS, that is, introduction of minimally invasive surgery techniques and the regular use of navigation. This is because the 2 techniques mentioned earlier will reduce blood loss during the steps of spinal instrumentation but are unlikely to have any effect on blood loss while performing decompression. Decompression and separation surgery presently still form a major component of MSTS and will continue to do so, resulting in significant bleeding that requires replenishment potentially in the form of SBT.

In this protocol, we have proposed a prospective observational nonrandomized study design as the ethical appropriateness of blinding or randomizing these patients is a key concern in our region and country. Blinding or randomization of patients with MSD could be deemed unethical, especially among patients who may not agree to receive SBT or ABT as this will limit the blood transfusion type applicable for them. This could be attributed to the current lack of clinical evidence that SBT does not lead to disease progression or shortened survival among patients undergoing MSTS who receive SBT. With this research proposal, we aim to highlight the safety profile of SBT, together with a design protocol applicable for use in patients with MSD. Future research, such as propensity-matched studies, can be done to further validate the outcomes from our current protocol.

### Conclusions

We surmise that the results of our proposed study design will pave the way for future randomized studies on the use of IOCS in MSTS and MMTSs, given that the granting bodies and their reviewers would be more open to considering funding for such studies.

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### Data Availability

All data generated or analyzed during this study will be included in published manuscripts and their supplementary information files.

### Conflicts of Interest

None declared.

### Multimedia Appendix 1

Key papers evaluating the use of intraoperative cell salvage in various cancer surgeries.
[DOCX File , 39 KB-Multimedia Appendix 1]

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## Abbreviations

**ABT:** allogeneic blood transfusion
**CTC:** circulating tumor cell
**IOCS:** intraoperative cell salvage
**LDF:** leukocyte depletion filter
**MMTS:** metastatic musculoskeletal tumor surgery
**MSD:** metastatic spine disease
**MSTS:** metastatic spine tumor surgery
**NBT:** no blood transfusion
**OS:** overall survival
**SBT:** salvaged blood transfusion

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