

Does Intraoperative Cell-Salvaged Autologous Blood Transfusion in Metastatic Spine Tumour Surgery Impact Clinical Outcomes: A Prospective Clinical Study With 4-year Follow-Up

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Naresh Kumar, MBBS, MS, DNB, FRCS, DM¹ , Si Jian Hui, MBBS, MRCS¹ ,
Yiong Huak Chan, PhD², Yong Hao Tan, MBBS, MRCS, MMed¹,
Praveen Jeyachandran, PhD¹, Laranya Kumar, MBBS³, Jiaqian Cui, MBBS⁴,
Rohan Parihar, MBBS, MS¹ ,
James Thomas Patrick Decourcy Hallinan, MBChB, BSc (Hons), FRCR⁵,
Rohit Vijay Agrawal, MBBS, MD, MMed, DNB, FANZCA, EDIC⁴, and
Jiong Hao Tan, MBBS, MRCS, MMed, FRCS¹ 

Abstract

Study design: Prospective Clinical Study.

Objective: Allogeneic blood transfusion (ABT) is the current standard of blood replenishment for metastatic spine tumour surgery (MSTS) despite known complications. Salvaged blood transfusion (SBT) addresses majority of complications related to ABT. We aim to conduct a prospective clinical study to ascertain the long-term clinical outcomes of intraoperative cell salvage (IOCS) in MSTS.

Methods: Patients were divided into three groups based on their BT type: no blood transfusion (NBT), ABT and SBT. Primary outcomes assessed were overall survival (OS) and tumour progression (TP), evaluated using RECIST (v1.1) employing follow-up radiological investigations at 6, 12, 24, 36 and 48 months.

Results: We included 98 patients [53:45 (M/F)] with mean age of 60 years old. 33 (33.7%) patients received SBT, 39 (39.8%) received ABT and 26 (26.5%) had NBT. All BT groups were comparable for demographics and tumour characteristics ($P = 0.215$). Median blood loss was 400 mL and median BT was 620 mL. There were no significant differences between OS of patients who underwent SBT, as compared to ABT or NBT ($P = 0.136$). On multivariate analysis, SBT did not show increase in 4-year tumour progression ($P = 0.423$). Total blood loss was not associated with tumour progression ($P = 0.260$).

¹ University Spine Centre, Department of Orthopaedic Surgery, National University Health System, Singapore

² NUS Medicine Biostatistics Unit (BSU), National University Health System, Singapore

³ Royal College of Surgeons of Ireland, Dublin, Ireland

⁴ Department of Anaesthesia, National University Hospital, Singapore

⁵ Department of Diagnostic Imaging, National University Hospital, Singapore

Corresponding Author:

Naresh Kumar, University Spine Centre, Department of Orthopaedic Surgery, National University Health System, Level 11, 1E, Kent Ridge Road, 119228, Singapore.

Email: dosksn@nus.edu.sg



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Conclusions: MSTs patients who had SBT showed comparable OS and TP to ABT and NBT even on long term follow-up. This is the first long term prospective study to report on the clinical outcomes of SBT in comparison with control groups in MSTs and affirms the clinical role of SBT in MSTs.

Keywords

metastatic spine tumour surgery, salvaged blood, blood transfusion, allogenic blood, intraoperative cell salvage

Introduction

Metastatic Spine Tumour Surgery (MSTS) is an important modality in the treatment of Metastatic Spinal Disease (MSD). With advancement in surgical techniques, it has found its place in the treatment of cord compression, pathological fractures, spinal instability and intractable pain.^{1,2} Improvements in overall oncological treatments have also allowed patients to have overall increased survival and henceforth patients with more extensive disease are being operated on more commonly.³⁻⁵ Recent studies^{4,5} have also shown the increased longevity in patients with MSD. Coupled with the lowering in our surgical threshold, this has allowed patients with poorer comorbidities to also be considered for surgery. Despite these technological advancements, substantial blood loss is still a significant concern in MSTs.^{6,7} Average blood loss in open MSTs is 1418 mL (714mL-3120 mL), while it is 745 mL (184-1320 mL) in minimally invasive surgery (MIS).⁸ In a meta-analysis of MSTs, the pooled mean blood loss in MSTs patients was found to be 2180 mL,⁶ while in a review of cases done in our institution, mean blood loss was 911 mls.⁷

Allogeneic blood transfusion (ABT) is the current gold standard of treatment in patients with significant intraoperative blood loss, placing a significant burden on limited blood bank resources.⁹⁻¹¹ ABT is associated with post-operative complications predisposing patients to surgical site infections (SSI), immune-mediated complications commonly affecting the lungs (eg, transfusion-related acute lung injury), wound healing, and survival duration, a poorer prognosis, and promotion of tumour growth.¹²⁻¹⁴ Recent emphasis has also been placed in the development of patient blood management (PBM) measures in MSTs,¹⁵ which is an evidence based and patient tailored approach to reduce the need for ABT and its associated risks. One of the arms of PBM involves the use of intraoperative salvaged blood transfusion (SBT).¹⁶

SBT has an established role in deformity correction and degenerative conditions in the field of spinal surgery.¹⁷ Previous randomized^{18,19} and non-randomized^{20,21} studies on the use of SBT in non-oncological surgical procedures indicate that SBT significantly reduced the need for ABT in elective non-oncological spinal surgeries. There has also been ample evidence for the clinical safety of SBT use in gynaecological, urological, hepatobiliary, gastrointestinal, orthopedic, trauma, and cardiac surgical procedures.²²⁻²⁴ The safety profile of SBT have also been previously established in both basic and clinical

science studies.²⁵⁻²⁷ Previously, our prospective paper²⁸ with 2 year outcomes showed that patients who underwent SBT have lower or similar rates of recurrence compared with the control cohort. The safety profile of SBT has also been shown in a prior retrospective study by Elmsky et al.²⁹

In the present study, we highlight the 4-year long-term outcomes of a prospective clinical study evaluating the clinical use of salvaged blood in MSTs patients. We discuss the long term evaluation of clinical outcomes such as tumour progression, as well as overall survival of patients who received SBT during MSTs, with a view to compare it with similar outcome measures to patients who have had NBT and ABT.

Materials and Methods

This was a single institution prospective study done on patients who underwent MSTs between January 2014 and December 2017. All of the patients' records were retrieved through our hospital's electronic health care records database. Spinal metastases were diagnosed in these patients by one or more of the following investigational modalities: Magnetic Resonance Imaging (MRI), Computed Tomography (CT) and/or nuclear bone scans. Indications for surgery included symptomatic metastatic spinal cord compression and/or instability.

Our study cohort was divided into three categories based on the type of blood transfusion (BT) they received, namely: No blood transfusion (NBT), ABT or SBT (with or without ABT). Primary outcomes were assessed post-operatively through available medical records at 6, 12, 24, 36 and 48 months or death, whichever occurred earlier. These postoperative follow-up time points were commensurate with local standard of care for patients undergoing MSTs.

Data collected included patient demographics, tumour histology and clinical findings related to both the primary tumour and skeletal metastases. Clinical and investigational findings recorded included neurological assessment, Frankel score, ambulatory status (ECOG score),³⁰ number of extra-spinal skeletal, vertebral and visceral metastases and Karnofsky Performance Scale (KPS). These were used to calculate the modified Tokuhashi score.³¹ Operative variables collected included surgical approach and number of spinal levels decompressed and instrumented. Intraoperative blood loss was recorded, together with blood transfusion (BT) details. Post-operative complications, if any, were recorded.

Primary tumour types of MSTS patients were also subgrouped based on their vascularity for analysis.³² Primary patient outcomes measured were OS and disease progression in terms of tumour progression (TP) [increase in size of existing metastatic lesions and/or the appearance of new metastasis]. TP was evaluated based on RECIST criteria (v1.1).³³ TP was defined as loco-regional or distant increase in size of lesions of $\geq 20\%$ increment in the sum of diameters of measurable target lesions (eg, lymph nodes, bone metastases), unequivocal progression of non-target lesions (eg, malignant ascites/pleural effusions) or the appearance of ≥ 1 new metastatic lesions.³³ Follow-up CT chest and thorax–abdomen–pelvis was used to assess lymph node and visceral metastases. MRI spine and bone scans were studied to detect new spinal/skeletal metastases.

Derived RECIST and modified Tokuhashi scores were independently calculated by the first and senior authors, who were blinded to the patients' identity. Any discrepancy was re-evaluated and a consensus score was assigned.

Patient Recruitment and Transfusion Protocol

All patients were given the option of not taking part in the study, taking part either as part of the SBT group, or as controls who would receive ABT if needed. Information about theoretical risk of tumour dissemination and the nonstandard and experimental nature of SBT was disclosed. Recent studies^{26,27,34} disproving this risk were also given to the patients. Patients were given a day to make their decision where clinically possible. Those who agreed to receive SBT, after written informed consent, were transfused with salvaged blood passed through a leukocyte depletion filter (LDF) and when clinically indicated, with additional ABT if the amount of SBT was insufficient. Those who declined to receive SBT but required transfusion were managed with ABT. Patients requiring no transfusion formed the NBT group. Transfusion criteria were standardised at a standard trigger of haemoglobin ≤ 8 g/dL and/or hemodynamic instability. Patients with large amounts of blood loss, who were at risk of developing dilutional coagulopathy, were managed by the anaesthetic team according to rotational thromboelastometry (ROTEM) findings and given fresh frozen plasma and platelets as indicated. Randomisation was not performed as we did not receive ethical board approval for randomisation and due to the difficulty in recruiting sufficient number of patients if randomisation was performed.

The study was performed in accordance with the ethical standards of the institutional research committee. The National Health care Group Domain Specific Review Board (Singapore) has approved the study, with the study reference being 2022/00866.

Statistical Methods

All statistical analyses were generated using STATA/SE 14.0 (StataCorp LP, College Station, TX USA). Statistical tests were assumed to be two-sided with conventional 5%

significance level. Patients' demographic and clinical characteristics were summarised by mean and standard deviation for continuous variables with approximately normal distribution and median (inter-quartile range) for skewed distribution. Categorical variables were summarised using frequency and percentages. Characteristics related to BT type (NBT/ABT/SBT) were analysed by: (i) one-way ANOVA to compare the means of a normally distributed variable across the groups, (ii) Kruskal–Wallis rank test to compare median, and (iii) Fisher's exact test for categorical variables. Pairwise comparison of total blood loss and transfusion between different BT types was performed by Wilcoxon rank-sum test with Bonferroni's correction for multiple testing. For OS, Kaplan–Meier survival curve and log-rank test were adopted for categorical variables. Univariate Cox proportional hazards regression model was used to study individual continuous variables. Multivariable Cox proportional hazards regression was subsequently conducted to adjust for potential confounders for relationship between BT type and OS. Proportional hazards assumption was tested after the final model was obtained. Association between BT type and tumour progression was investigated by competing risks analysis, taking death without tumour progression as the competing event. We plotted cumulative incidence curves of three BT groups nonparametrically. Individual characteristics related to tumour progression were studied by univariate sub-distribution proportional hazards regression. The multivariable sub-distribution proportional hazards regression model was implemented afterwards to adjust for all potential confounders. Finally, Schoenfeld residual of each variable was plotted against survival time and suggested that proportional hazards assumption was adequate.

Results

A total of 98 patients were included in this study. This included 53 (54.1%) males and 45 (45.9%) females, with a mean age of 60 years old at the time of surgery. Overall median blood loss was 400 mL [IQR 200–900 mL] and overall median BT was 620 mL (IQR: 110 – 1600 mL) for patients receiving BT. The demographics and clinical characteristics of the patients are described [Table 1]. 33 (33.7%) patients received SBT, 39 (39.8%) received ABT and 26 (26.5%) had NBT. The primary tumours were subgrouped into their vascularity levels. The most common were the moderately vascularised tumour subgroup, which included lung, breast, prostate, gastrointestinal and epithelial tumours [Table 2]. Comparison of total blood loss among the three groups revealed no significant difference between ABT and SBT ($P = 0.053$). Pairwise comparison between ABT and SBT also showed no significance difference ($P = 0.412$) in the total amount of blood transfused. This validates the results shown in our previous 2 year study²⁸ that both ABT and SBT can be used for blood replenishment in MSTS patients.

Table 1. Demographic and Clinical Characteristics of 98 Patients.

Characteristic	Overall (n = 98)	Blood Transfusion (BT) Type			P value
		No BT (n = 26)	Allogeneic BT (n = 39)	Salvaged BT ^a (n = 33)	
Age at surgery (year), mean ± SD ^b	59.8±15.8	54.4±21.3	59.3±13.7	64.6±11.6	0.046
Age at surgery, n (%)					0.012
<60 years	43 (43.9)	16 (61.5)	19 (48.7)	8 (24.2)	
≥60 years	55 (56.1)	10 (38.5)	20 (51.3)	25 (75.8)	
Gender, n (%)					0.215
Male	53 (54.1)	15 (57.7)	17 (43.6)	21 (63.6)	
Female	45 (45.9)	11 (42.3)	22 (56.4)	12 (36.4)	
Race, n (%)					0.817
Chinese	63 (64.3)	16 (61.5)	23 (59.0)	24 (72.7)	
Malay	20 (20.4)	6 (23.1)	8 (20.5)	6 (18.2)	
Indian	3 (3.1)	1 (3.8)	2 (5.1)	0 (0.0)	
Others	12 (12.2)	3 (11.5)	6 (15.4)	3 (9.1)	
Total blood loss (mL), median (IQR) ^c	400 (200-900)	200 (50-387.5)	400 (250-925)	700 (390-1450)	0.052
Total blood transfusion ^d (mL), median (IQR)	328.5 (0-1042)	0 (0-0)	500 (0-1081)	705 (1507-2150)	0.412
Surgery type, n (%)					0.333
MIS	36 (36.7)	12 (46.2)	16 (41.0)	8 (24.2)	
Posterior open	52 (53.1)	13 (50.0)	19 (48.7)	20 (60.6)	
Corpectomy	10 (10.2)	1 (3.8)	4 (10.3)	5 (15.2)	
Number of instrumentation, n (%)					0.200
<4	12 (12.2)	5 (19.2)	6 (15.4)	1 (3.0)	
= 4	37 (37.8)	11 (42.3)	15 (38.5)	11 (33.3)	
>4	49 (50.0)	10 (38.5)	18 (46.1)	21 (63.7)	
Number of decompression, n (%)					0.102
0	25 (25.5)	10 (38.5)	11 (28.2)	4 (12.2)	
1	33 (33.7)	10 (38.5)	11 (28.2)	12 (36.4)	
>1	40 (40.8)	6 (23.0)	17 (43.6)	17 (51.4)	
Total tokuhashi score, mean±SD	7.08±2.65	6.92±2.71	7.33±2.72	6.91±2.59	0.751

^aSalvaged with or without Allogeneic BT.

^bSD: standard deviation.

^cIQR: inter-quartile range.

^dOverall median total blood transfusion was 620 mL (IQR: 110-1600 mL) for patients receiving BT.

Table 2. Primary Tumour-type Distribution of 98 Patients.

Primary Tumour type	N (%)	No BT (n = 26)	Allogeneic (n = 39)	Salvaged (n = 33)
Highly vascularised - renal, hepatocellular, thyroid	12 (12.2)	1 (8.3)	6 (50)	5 (41.7)
Moderately vascularised – lung, breast, prostate, gastrointestinal, epithelial	68 (69.4)	21 (30.9)	28 (41.2)	19 (27.9)
Myeloma or lymphoma	9 (9.2)	1 (11.1)	2 (22.2)	6 (66.7)
Others	9 (9.2)	3 (33.3)	3 (33.3)	3 (33.3)

Our cohort showed no significant difference between the OS of patients who underwent ABT or SBT, as compared to NBT ($P = 0.136$) [Table 3]. Every unit increase in the natural log scale of blood loss was associated with a decreased risk of death [Adjusted HR 0.58; 95% CI 0.36-0.96; $P = 0.03$]. Patients with poor general condition had a significant increase in risk of death [Adjusted HR 4.34; 95% CI 1.58-11.95; $P = 0.00$], almost 2 times greater than that of good functional status [Adjusted HR 2.48; 95% CI 1.09-5.686; $P = 0.03$].

Univariate analysis favoured SBT over ABT in having a better survival, but multivariate analysis did not support this association. Overall, OS was better in SBT than in ABT group, represented by our adjusted survival curve [Figure 1]. Sub-group analysis with the vascularity of the primary tumours also showed a significant association with risk of death on the adjusted survival curve [Figure 2].

Association of BT on tumour progression (TP) was also analysed [Table 4]. The type of blood transfusion was not

Table 3. Characteristics Associated With 4-Year Overall Survival (OS).

Characteristic	Number of Deaths (%)	Unadjusted		Adjusted	
		HR ^a (95% CI ^b)	P value	HR ^a (95% CI ^b)	P value
Blood transfusion (BT) type					
No BT	17 (65.4)	1.0	-	1.0	-
Allogenic	27 (69.2)	1.27 (0.69 – 2.33)	0.445	2.67 (0.95 – 7.49)	0.062
Salvaged	17 (51.5)	0.80 (0.41 – 1.57)	0.511	3.17 (1.00 – 10.03)	0.050
Age at surgery					
<60 years	33 (60.0)	1.16 (0.70 – 1.92)	0.568	1.10 (0.55 – 2.19)	0.789
≥60 years	28 (65.1)	1.0	-	1.0	-
Gender					
Male	31 (58.5)	1.0	-	1.0	-
Female	30 (66.7)	1.25 (0.76 – 2.07)	0.381	1.49 (0.69 – 3.23)	0.309
Race					
Chinese	43 (68.3)	1.38 (0.49 – 3.86)	0.539	2.81 (0.60 – 13.13)	0.188
Malay	12 (60.0)	1.36 (0.44 – 4.24)	0.592	2.73 (0.60 – 12.47)	0.195
Indian	2 (66.7)	1.11 (0.20 – 6.06)	0.907	0.36 (0.02 – 5.99)	0.478
Others	4 (33.3)	1.0	-	1.0	-
Surgery type					
MIS	27 (75.0)	1.80 (0.63 – 5.14)	0.275	0.49 (0.12 – 2.02)	0.322
Posterior open	30 (57.5)	1.16 (0.41 – 3.32)	0.775	0.36 (0.11 – 1.23)	0.105
Corpectomy	4 (40.0)	1.0	-	1.0	-
Number of instrumentation					
<4	8 (66.7)	1.0	-	1.0	-
= 4	21 (56.8)	1.07 (0.47 – 2.43)	0.874	0.47 (0.14 – 1.54)	0.212
>4	32 (65.3)	1.06 (0.49 – 2.31)	0.879	0.45 (0.13 – 1.53)	0.203
Number of decompression					
0	20 (80.0)	2.10 (1.14 – 3.87)	0.017	2.46 (0.97 – 6.23)	0.058
1	19 (57.6)	1.17 (0.64 – 2.17)	0.609	1.78 (0.76 – 4.18)	0.186
>1	22 (55.0)	1.0	-	1.0	-
Total tokuhashi score	-	0.82 (0.74 – 0.90)	<0.001	0.82 (0.67 – 1.01)	0.060
Total blood loss ^c (mL)	-	0.77 (0.62 – 0.96)	0.021	0.58 (0.36 – 0.96)	0.033
General condition					
Poor	15 (78.9)	2.71 (1.34 – 5.48)	0.005	4.34 (1.58 – 11.95)	0.004
Moderate	17 (50.0)	1.0	-	1.0	-
Good	29 (64.4)	1.29 (0.71 – 2.35)	0.404	2.48 (1.09 – 5.68)	0.031
No. Of extra spinal met					
=>3 lesions	25 (59.5)	1.20 (0.67 – 2.17)	0.539	0.99 (0.37 – 2.64)	0.981
1-2 lesions	16 (72.7)	1.23 (0.64 – 2.38)	0.537	1.11 (0.41 – 2.99)	0.844
0 lesions	20 (58.8)	1.0	-	1.0	-
No. Of vertebral body mets					
=>3 lesions	49 (67.1)	2.54 (0.99 – 6.46)	0.052	2.96 (0.68 – 12.87)	0.149
2 lesions	7 (50.0)	1.01 (0.32 – 3.18)	0.987	1.43 (0.32 – 6.71)	0.649
1 lesion	5 (45.5)	1.0	-	1.0	-
Mets to major internal organs					
Non-removable	32 (69.6)	1.81 (1.06 – 3.10)	0.031	1.07 (0.42 – 2.74)	0.885
Removable	6 (66.7)	1.07 (0.43 – 2.63)	0.886	0.61 (0.17 – 2.21)	0.449
None	23 (53.5)	1.0	-	1.0	-

^aHR hazard ratio.^bCI confidence interval.^cThe unadjusted/adjusted HR (95% CI) and P value were computed based on the ln transformation of total blood loss.

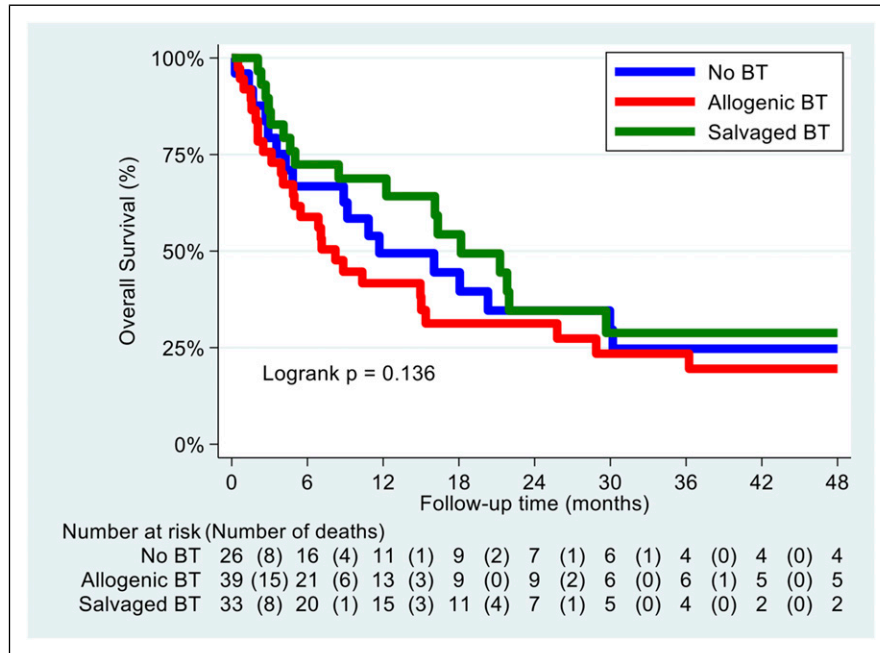


Figure 1. Adjusted survival graph based on blood transfusion (BT) types.

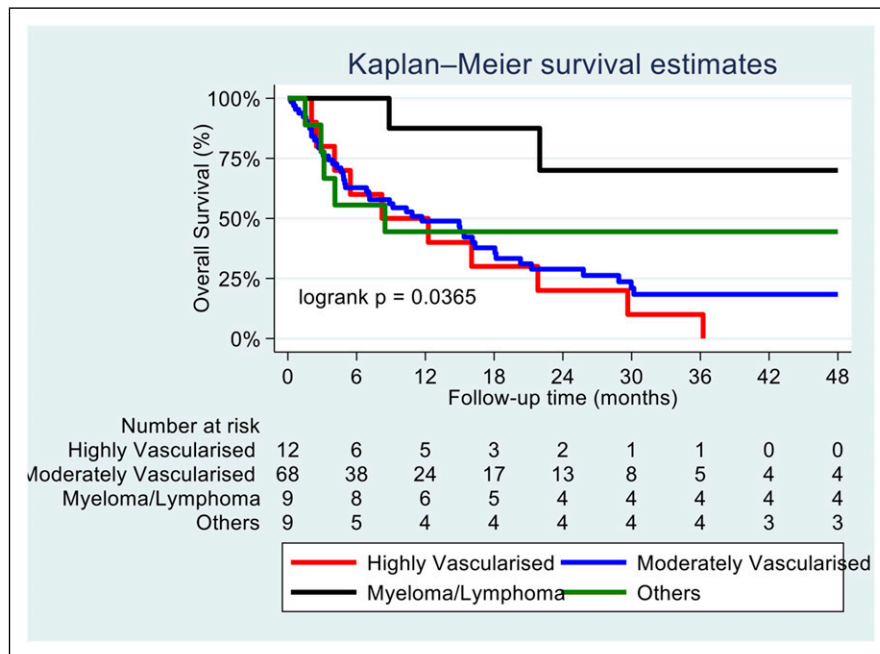


Figure 2. Adjusted survival graph based on vascularity of primary tumour.

associated with 4-year tumour progression. Specifically, SBT did not show any increase in 4-year tumour progression [Adjusted HR 0.57; 95% CI 0.14-2.22; $P = 0.42$]. Total blood loss was also not associated with tumour progression [Adjusted HR 0.51; 95% CI 0.15-1.65; $P = 0.26$]. Adjusted cumulative incidence plot [Figure 3] of TP demonstrated that

SBT also had comparable rates of TP when compared to ABT and NBT ($P = 0.375$).

The rate of surgical and medical complications were comparable throughout all three groups with no significant difference between the groups. Days of SHD/ICU stay as well as total length of hospital stay were similar [Table 5].

Table 4. Characteristics Associated With 4-Year Tumour Progression (TP).

Characteristic	Number of patients with TP ^a (%)	Unadjusted		Adjusted	
		sHR ^a (95% CI ^b)	P value	sHR ^a (95% CI ^b)	P value
Blood transfusion (BT) type					
No BT	7 (26.9)	1.0	-	1.0	-
Allogenic	5 (12.8)	0.52 (0.18 – 1.50)	0.230	0.18 (0.01 – 2.17)	0.175
Salvaged	7 (21.2)	1.07 (0.42 – 2.76)	0.881	0.57 (0.14 – 2.22)	0.417
Age at surgery					
<60 years	7 (16.3)	1.0	-	1.0	-
≥60 years	12 (11.8)	1.37 (0.57 – 3.28)	0.476	1.96 (0.62 – 6.19)	0.254
Gender					
Male	8 (15.1)	1.0	-	1.0	-
Female	11 (24.4)	1.62 (0.71 – 3.71)	0.255	2.08 (0.50 – 8.78)	0.315
Race					
Chinese	12 (19.1)	1.48 (0.27 – 8.10)	0.649	0.87 (0.05 – 14.0)	0.920
Malay	5 (25.0)	2.21 (0.37 – 13.3)	0.385	1.18 (0.08 – 17.1)	0.903
Indian	1 (33.3)	3.23 (0.34 – 31.0)	0.310	0.62 (0.01 – 45.2)	0.826
Others	1 (8.3)	1.0	-	1.0	-
Surgery type					
MIS	9 (25.0)	1.93 (0.31 – 11.9)	0.480	3.63 (0.52 – 26.2)	0.200
Posterior open	9 (17.3)	1.34 (0.22 – 8.20)	0.749	2.22 (0.31 – 15.9)	0.426
Corpectomy	1 (10.0)	1.0	-	1.0	-
Number of instrumentation					
<4	0 (0.0)	&&	<0.001	&&	<0.001
= 4	9 (24.3)	1.34 (0.59 – 3.02)	0.479	7.96 (1.68 – 37.6)	0.009
>4	10 (20.4)	1.0	-	1.0	-
Number of decompression					
0	5 (20.0)	1.01 (0.35 – 2.94)	0.977	0.91 (0.04 – 22.1)	0.957
1	6 (18.1)	1.0	-	1.0	-
>1	8 (20.0)	1.44 (0.55 – 3.75)	0.456	13.5 (1.00 – 182.0)	0.050
Total tokuhashi score	-	1.13 (0.98 – 1.32)	0.092	1.17 (0.86 – 1.61)	0.308
Total blood loss ^c (mL)	-	0.93 (0.61 – 1.43)	0.741	0.51 (0.15 – 1.65)	0.259
General condition					
Poor	5 (26.3)	1.81 (0.50 – 6.55)	0.363	3.16 (0.25 – 40.3)	0.374
Moderate	4 (11.8)	1.0	-	1.0	-
Good	10 (22.2)	1.46 (0.48 – 4.40)	0.504	2.83 (0.44 – 18.2)	0.272
No. of extra spinal met					
=>3 lesions	10 (23.8)	2.18 (0.70 – 6.85)	0.180	2.07 (0.44 – 9.71)	0.358
1-2 lesions	3 (13.6)	1.0	-	1.0	-
0 lesions	6 (17.6)	1.62 (0.45 – 5.79)	0.458	0.45 (0.08 – 2.71)	0.386
No. Of vertebral body mets					
=>3 lesions	12 (16.4)	1.0	-	1.0	-
2 lesions	3 (21.4)	1.22 (0.47 – 3.18)	0.677	1.17 (0.15 – 9.26)	0.878
1 lesion	4 (36.4)	2.55 (0.85 – 7.69)	0.097	5.62 (0.68 – 46.6)	0.100
Mets to major internal organs					
Non-removable	7 (15.2)	1.0	-	1.0	-
Removable	3 (33.3)	1.48 (0.52 – 4.20)	0.456	6.74 (0.74 – 51.1)	0.090
None	9 (20.9)	1.72 (0.67 – 4.42)	0.259	5.84 (0.85 – 40.3)	0.073

^asHR hazard ratio with death without progression as competing.

^bCI confidence interval.

^cThe unadjusted/adjusted HR (95% CI) and P value were computed based on the ln transformation of total blood loss.

&&very small sHR due to no PD events.

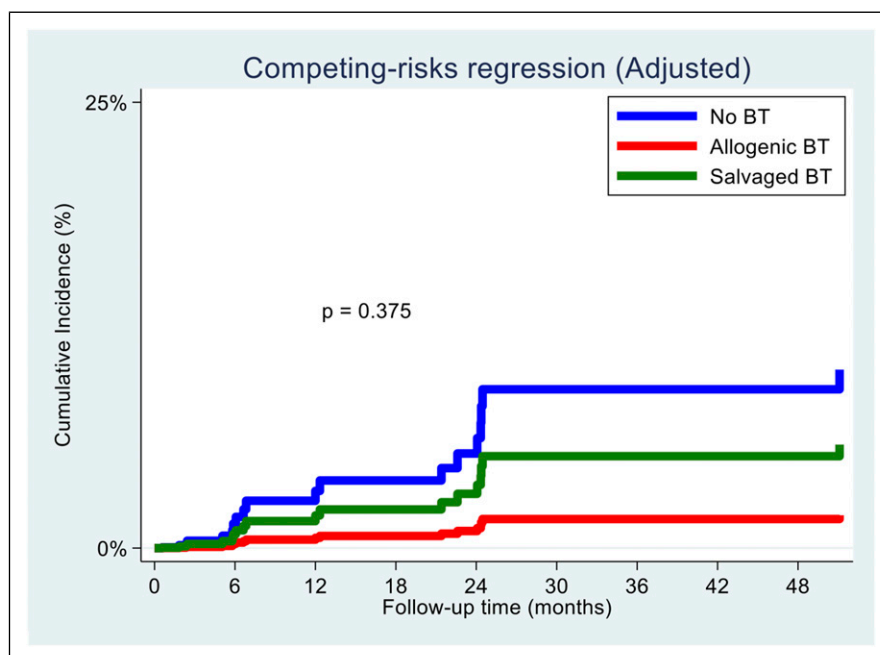


Figure 3. Cumulative incidence of tumour progression for all blood transfusion (BT) types.

Table 5. Complications According to Transfusion Types.

	No BT (n = 26)	Allogenic BT (n = 39)	Salvaged BT (n = 33)	Unadjusted P Value
Surgical site-infection (SSI), n (%)	5 (5.1)	1 (3.8)	1 (2.6)	0.430
Infections other than SSI, n (%)	26 (26.5)	3 (11.5)	14 (35.9)	0.092
Medical complications, n (%)	39 (39.8)	9 (34.6)	16 (41.0)	0.814
Surgical site recurrence, n (%)	4 (4.1)	0 (0.0)	1 (2.6)	0.209
Recurrence requiring operation, n (%)	3 (3.1)	0 (0.0)	1 (2.6)	0.329
Days of SHDICU stay, median (IQR)	2 (2)	2 (1)	2 (2)	0.168
Total length of stay, median (IQR)	18 (28)	13.5 (14)	20.5 (33)	0.064

Discussion

Patient blood management strategies in recent years have emphasised the use of salvaged blood transfusion for MSTs.^{22,23} SBT has shown to be safe, with minimal to no tumour cells present in the salvaged blood after passage through a leukocyte depletion filter.²⁵ Previously, retrospective studies^{29,35} have also highlighted the advantages of SBT to reduce ABT without an increase in overall costs for the patients. SBT has been used extensively in other oncological procedures such as GI or gynaecological conditions.^{18,19}

Despite the above advantages, there still remains a major reluctance in the uptake of SBT in clinical practice, which can be due to the current lack of long term prospective clinical studies establishing the clinical safety profile of SBT for MSTs patients. In the present study, we manage to establish how SBT is an effective tool for use in MSTs, without increase in risk of death or tumour progression in MSTs patients, on long term clinical follow-up. This is especially

important since blood loss is a significant concern in MSTs, with studies showing pooled mean blood loss in MSTs patients to be up to 2180 mLs.⁶ Previously, the main method of blood transfusion has been the use of ABT, but studies have shown an increase in complications in patients with ABT. In a multicentre prospective review of 1601 patients by the American College of Surgeons National Quality Improvement Program database,³⁶ 623 patients (38.9%) received packed cell transfusion, and those who had a transfusion had significantly higher complication rate when compared to non-transfused patients, (22.3% vs 15.0%, $P = 0.00$). Vinas-Rios et al^{13,37} also found ABT to be an independent risk factor for higher risks of complications while Purvis et al³⁷ found that a liberal transfusion policy was associated with an independently higher risk of perioperative morbidity and increasing perioperative costs.

To date, this is the first long-term study to compare prospectively the survival and tumour progression results in patients undergoing MSTs who received SBT. There was no

significant difference in the oncological characteristics of the three groups [Tables 1 and 2]. Overall, SBT was associated with a decreased risk of death compared to ABT and NBT in univariate analysis, and comparable OS outcomes on long term follow-up in multivariate analysis. As mentioned in previous studies,^{38,39} the improved OS for SBT compared to ABT can be theoretically attributed to ABT-related immunosuppression which increase the likelihood of postoperative complications in such as infection reduces overall survival. Immunosuppression is unlikely to happen with SBT, resulting in better survival.

Our study also used the recently established tumour vascularity model³² which divides group of tumours based on their vascularity to show the correlation between tumour vascularity and OS as well as TP. As established in previous studies,^{32,40} tumour vascularity was shown to be a significant risk factor in OS, with highly vascular tumours showing significant increase in risk of death. Tumour vascularity did not show significant influence on TP on competing risks analysis. Our study did not find any factor that had significant association with TP. This is supported by studies^{41,42} which showed that TP is usually due to inherent primary tumour characteristics and also affected by ongoing genetic mutations that leads to local and distant progression. As established by our previous basic science publications,^{25,26} salvaged blood has no viable tumour cells after passing through a filter, and hence is unlikely to affect TP.

One interesting finding in our study is that every unit increase in the natural log scale of blood loss was associated with a decreased risk of death [Adjusted HR 0.58; 95% CI 0.36-0.96; $P = 0.03$]. This is also supported by a decreased risk of death with greater number of instrumentation in our study, though not significant [Adjusted HR 0.45; 95% CI 0.13-1.53; $P = 0.203$]. These findings can possibly be explained by the undertaking of larger debulking surgeries such as partial or near total corpectomy for certain tumours subgroups,⁴³ with greater number of instrumentation, which can aid in more extensive removal of tumour material and hence leading to improved OS. In such cases, the surgery itself may be curative.

The absence of any complications from SBT, and overall comparable trend of OS and TP to ABT during the 4 year follow-up period in our study highlights the long term safety profile of SBT for use in MSTs. From our knowledge, the usage of SBT in MSTs has yet to be established in clinical practices around the world due to the theoretical concerns of tumour seeding. In MSTs, patient blood management (PBM) is an important concept to improve outcomes and readmission free survival. Hence, the utilisation of SBT as a form of intra-operative PBM will only help in overall management of blood loss, improvement in outcomes and reduction in length of hospital stay.

Limitations

This prospective study is the first to highlight the long term safety profile of SBT in MSTs patients but it also faces some

limitations. Firstly, this study was not randomised as it is not ethically reasonable to control the treatment which each group of patients received since each patient was managed according to their clinical presentation based on department treatment protocols. Secondly, the relatively small number of patients in each BT subgroup makes it difficult to generalise our results to all MSTs patients. However, further propensity matched studies from large tumour databases can be done to validate the findings of our present prospective study.

Conclusion

SBT has shown to be promising and useful in the intra-operative blood management of MSTs patients. It has comparable overall survival, as well as tumour progression outcomes to those who received ABT. Complication rates of patients who received SBT are also comparable to those who received ABT or NBT.

The utilisation of SBT in MSTs can help to reduce ABT requirement and its related risks, improving overall outcomes of patients with MSTs. SBT should be incorporated to the practice of MSTs surgeons around the world, as part of PBM protocols, which have shown to benefit morbidity and mortality of MSTs patients.

Declaration of Conflicting Interests

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ORCID iDs

Naresh Kumar  <https://orcid.org/0000-0003-4538-5031>

Si Jian Hui  <https://orcid.org/0000-0001-5355-497X>

Rohan Parihar  <https://orcid.org/0000-0003-0766-7054>

Jiong Hao Tan  <https://orcid.org/0000-0002-9237-2586>

Supplemental Material

Supplemental material for this article is available online.

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