International Journal of Gastrointestinal Intervention

journal homepage: www.ijgii.org

Original Article

Is hepatocellular carcinoma viability important when using intraoperative blood salvage during liver transplantation?

Ahmed Nasser[1], Victoria Smith[2], Niamh Campbell[1], Michael Devin Rivers-Bowerman[3], Ashley Elispath Stueck[4], Andreu Francesc Costa[3,5], Riley Arseneau[4], Lauren Westhaver[4], and Boris Luis Gala-Lopez[2,5,*]

A B S T R A C T

Background: Intraoperative blood salvage and autotransfusion (IBS) is considered safe in liver transplantation for hepatocellular carcinoma (HCC). However, little is known about the potential impact of the viable tumor burden on recurrence and survival. This study investigated whether the presence of viable HCC during transplantation with IBS impacted HCC recurrence and patient survival.
Methods: A retrospective study was conducted of liver transplants for patients with HCC in Atlantic Canada between 2005 and 2017. Information on locoregional treatment, IBS volume, and explant pathology was collected. Variables were analyzed to identify associations with HCC recurrence and patient survival via parametric and non-parametric tests. The Kaplan-Meier and log-rank tests were used to compare survival.
Results: Sixty-eight subjects were included. IBS was used in 44.1% of the patients, with a median volume of 711 mL. Radiographic total tumor volume correlated well with the actual tumor viable volume (TVV) (Pearson's r = 0.82, $P < 0.01$), but was overestimated by 50% when compared to the actual tumor burden on explant pathology. HCC recurrence was observed in 6 patients, and IBS was used in 5. Patients receiving IBS also had more viable tumors, but not a greater TVV. Overall patient survival did not exhibit significant differences according to the presence of viable tumors, vascular invasion, or satellitosis.
Conclusion: IBS during liver transplantation was associated with significantly higher HCC recurrence in our limited series. However, the volume of viable HCC during the transplant procedure was not associated with any difference in tumor recurrence or patient survival.

Keywords: Carcinoma, hepatocellular; Liver transplantation; Operative blood salvage; Recurrence; Survival

Introduction

Hepatocellular carcinoma (HCC) accounts for 75% of primary liver cancers and is the third leading cause of cancer-related death worldwide.[1,2] The National Cancer Institute estimates that in 2016, 27,170 deaths in the United States were attributed to HCC. The World Health Organization has projected more than 1 million deaths due to HCC in 2030.[3,4] HCC usually occurs due to chronic liver disease and cirrhosis, the causes of which vary across geographic regions due to differences in lifestyle, cultural practices, and genetic factors.[5–7] Alcohol-induced cirrhosis and hepatitis C virus are the etiologies in most patients requiring liver transplantation (LT) in the West, while hepatitis B virus remains the leading cause of cirrhosis in the East.[8] The prognosis for HCC can be poor, and treatment options include surgical resection, systemic therapy, locoregional treatment (LRT) and immunotherapy. These modalities can prolong survival and potentially downstage inoperable HCC.[7]

Orthotopic liver transplant is considered the best therapeutic approach for selected patients with underlying liver cirrhosis and non-resectable HCC.[2,9] The transplant procedure is a complex surgical procedure in which intraoperative hemorrhage remains a

[1]*Faculty of Medicine, Dalhousie University, Halifax, NS, Canada*
[2]*Department of Surgery, Dalhousie University, Halifax, NS, Canada*
[3]*Department of Radiology, Dalhousie University, Halifax, NS, Canada*
[4]*Department of Pathology, Dalhousie University, Halifax, NS, Canada*
[5]*Department of Microbiology & Immunology and Pathology, Beatrice Hunter Cancer Research Institute, QEII Health Science Centre, Dalhousie University, Halifax, NS, Canada*
Received March 29, 2023; Revised June 9, 2023; Accepted June 16, 2023
* Corresponding author. Department of Microbiology & Immunology and Pathology, Beatrice Hunter Cancer Research Institute, QEII Health Science Centre, Dalhousie University, 6-300 Victoria Bldg, 1276 South Park Street, Halifax, NS B3H 2Y9, Canada.
E-mail address: b.gala-lopez@dal.ca (B.L. Gala-Lopez).

pISSN 2636-0004 eISSN 2636-0012 https://doi.org/10.18528/ijgii230020

major complication despite improvements in the management of coagulation disorders associated with liver dysfunction.[10,11] Due to the risk of blood loss, intraoperative blood salvage and autotransfusion (IBS) are frequently incorporated into LT. It has been estimated that IBS is used in more than 85% of all LTs worldwide.[2] This technology reduces allogeneic red cell transfusion when blood loss may exceed 500 mL in adult patients. Relative contraindications to IBS include contamination of the aspirated blood with bowel contents, infection, or tumor cells.[12] During its introduction, there was significant concern about the potential to increase cancer recurrence via the dissemination of malignant cells,[13] as most cases of metastatic disease result from tumor cells detaching from the primary cancer and spreading to distant sites.[13,14] However, multiple studies have demonstrated that IBS is safe during surgery for HCC and other malignancies.[10,15,16]

To date, few studies have analyzed the impact of the actual tumor burden of HCC on cancer recurrence after LT when IBS is used during the transplant procedure. This study investigated whether using IBS during LT in patients with viable HCC was associated with higher cancer recurrence and poorer overall survival.

Methods

This retrospective study included consecutive adult patients undergoing deceased-donor LT for HCC at our hospital, a regional tertiary care referral and transplant center, between 2005 and 2017. Our Research Ethics Board approved the study (file number: 1025307), which was conducted following the Declaration of Helsinki. Patients that were included had signed consent forms to participate in the research. Clinical information was collected from a prospectively maintained database that included pre-transplant, intraoperative, and post-transplant data. All participants had a minimum 3-year follow-up. Any subject with mortality within 30 days of LT was excluded from the study.

Radiographic analysis

Pre-transplant imaging (computed tomography [CT] and magnetic resonance imaging [MRI]) was reviewed independently by two board-certified radiologists (MRB and AC), followed by a consensus to establish a unified assessment of tumor viability before and after LRT. Radiographic total tumor volume (TTV) was calculated as the sum of the individual volume of each viable tumor, assuming that the tumor had a spherical shape, as previously reported.[17] The volume (v) was thus calculated using the formula $v = 4/3\ \pi\ r^3$, where r is the radius of the tumor.

Intraoperative blood salvage

As previously described, IBS was carried out using the CATSmart Continuous Autotransfusion System (Fresenius Kabi AG).[18] Briefly, blood in the surgical field was suctioned into anticoagulated lines with either heparinized saline or acid-citrate dextrose. This mixture was filtered and collected into a reservoir, where red blood cells were separated from whole anticoagulated blood through centrifugation. Red blood cells were finally washed with normal 0.9% saline and then pumped into a bag, ready for re-infusion into the patient (Fig. 1).[12] The decision to use IBS during LT was at the discretion of the surgical team and was not randomized. Patients were divided into two groups according to the use of IBS during their transplant procedure.

Immunosuppressive therapy

As previously described,[19] patients usually receive a treatment protocol targeting interleukin-2, consisting of a combination of basiliximab, tacrolimus, mycophenolate, mofetil, and steroids. Patients were typically switched to sirolimus for long-term maintenance.

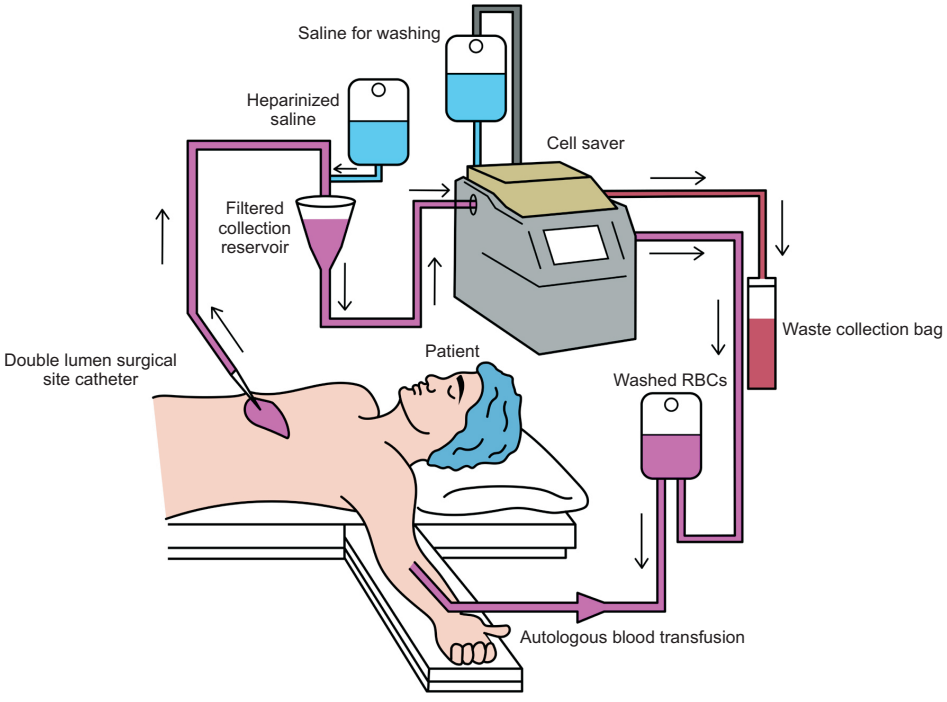

Fig. 1. Diagram of a standard cell saver set up in an operating room. RBCs, red blood cells.

Pathologic analysis

Explant pathology slides for each patient were independently reviewed by a board-certified hepatopathologist (AS). The total number of lesions was documented, and each tumor's percentage of necrosis was calculated. Three-dimensional measurements were performed, and the actual tumor viable volume (TVV) was calculated as the sum of each viable nodule's individual volume, assuming an ellipsoid, as previously reported.[20] The volume (*v*) was thus calculated using the formula $v = 4/3\ \pi\ abc$, where *a*, *b*, and *c* are semi-axis individual radii of the viable HCC. The presence of micro- or macro-vascular invasion and satellitosis was reported for each subject.

Statistical analysis

Categorical variables were compared using Pearson's chi-square test. Continuous variables were expressed as mean ± standard derivation and analyzed using the Student's *t*-test. Non-parametric variables were expressed as the median and interquartile range (IQR) and compared according to their distribution using the Mann-Whitney U test. The Fisher exact-Boschloo unconditional test was used to compare HCC recurrence according to IBS use. Pearson correlation coefficients were used to measure the association between TTV and TVV. Differences in recurrence and survival were analyzed using the Kaplan-Meier method and compared using the log-rank test. The outcome variables in our study were the presence of recurrence and patient survival. Multivariate analyses for recurrence and survival were performed using the logistic and Cox regression methods, respectively. Clinical variables were evaluated independently to identify statistically significant factors. Significant variables for recurrence and survival were then selected and incorporated into the multivariate analyses. A *P*-value below 0.05 was considered to indicate significance at a 95% confidence level. IBM SPSS version 23 (IBM Corp.) and Prism version 9.0 (GraphPad) were used for the analysis.

Results

Between 2005 and 2017, 77 patients underwent deceased-donor LT for HCC. Of these, nine were excluded, four due to insufficient follow-up and five due to in-hospital mortality. As a result, 68 subjects were included in the study and divided into IBS (n = 30) and non-IBS (n = 38) groups (Fig. 2). The mean follow-up period was 66.5 ± 11.1 months. The baseline characteristics of the patients in both groups were comparable, with similar natural

Table 1 Patients' Baseline Characteristics

	IBS group (n = 30)	Non-IBS group (n = 38)	*P*-value
Age (yr)	64.2 ± 6.3	66.7 ± 5.5	0.10
Sex (M/F)	18/12	30/8	0.11
Cirrhosis etiology			
HBV	2 (6.7)	3 (7.8)	
HCV	16 (53.3)	23 (60.5)	
Alcohol	4 (13.3)	5 (13.2)	
NASH/NAFLD	3 (10.0)	2 (5.3)	
Others	5 (16.7)	5 (13.2)	
Natural MELD at transplant (point)	8 (5–30)	10 (5–21)	0.48
Locoregional bridge therapy	23 (76.7)	33 (86.8)	0.344
TACE	14	23	
RFA	3	3	
Y90	0	1	
Combination	9	4	
Nil	4	7	
TTV (cm^3)	15.3 ± 17.6	11.5 ± 15.1	0.14
AFP (μg/L)	10.8 (1.0–342.0)	14.6 (2.0–3,395.0)	0.53
HCC recurrence	5 (16.7)	1 (2.6)	0.03*

Values are presented as mean ± standard deviation, number only, number (%), or median (interquartile range).
IBS, intraoperative blood salvage and autotransfusion; M, male; F, female; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease; MELD, Model for End-Stage Liver Disease; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; Y90, yttrium-90 radioembolization; TTV, total tumor volume; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma.
*Fisher exact-Boschloo unconditional test.

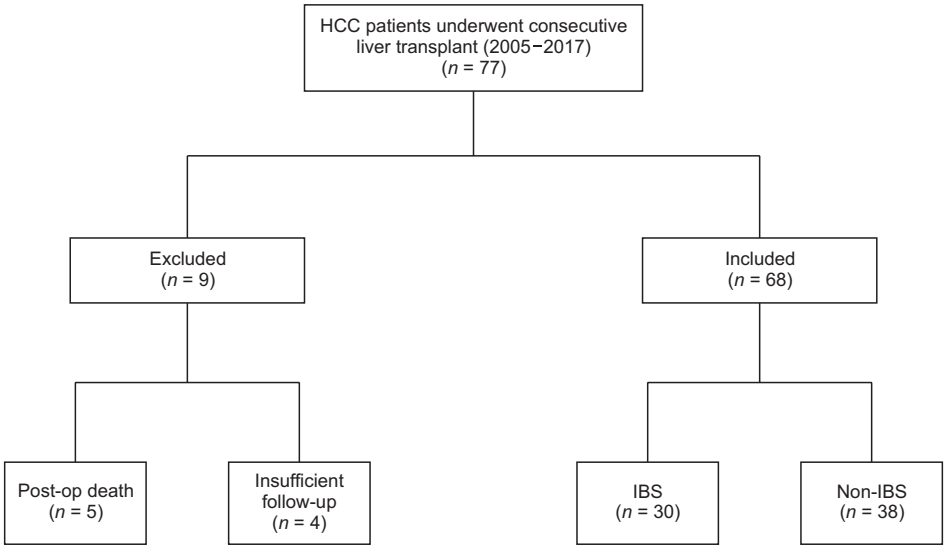

Fig. 2. Flow chart for patient selection. HCC, hepatocellular carcinoma; IBS, intraoperative blood salvage and autotransfusion.

Model for End-Stage Liver Disease scores, a similar proportion of LRT, and similar mean TTV and median alpha-fetoprotein (AFP) levels (Table 1). The specific distribution of LRTs per group is also described in Table 1. Patients in both groups had similar platelet counts and mean platelet volumes during transplantation. However, the subjects in the non-IBS group required significantly higher volumes of packed red cell transfusions than those in the IBS group (median: 582.5 vs. 2,100.0 mL, $P < 0.01$) (Table 2).

Explant pathology analysis revealed that 56 (82.3%) study subjects had viable HCC. Of these, 44 (78.6%) had received bridging LRT. Only 11 patients (19.6%) receiving LRT had complete tumor necrosis (TVV = 0 cm^3). Patients in the IBS group had a median of 2 (IQR, 1–14) viable tumors versus 1 (IQR, 1–4) in the non-IBS group ($P < 0.01$); nonetheless, there were no significant differences in the size of nodules, TVV, and presence of vascular invasion or satellitosis (Table 3). A close correlation was observed between radiological TTV and pathological TVV (Pearson's r = 0.82, $P < 0.01$), but the paired analysis demonstrated a radiological tumor burden overestimation of about 50% (12.0 ± 15.0 cm^3 vs. 6.4 ± 10.0 cm^3; $P < 0.01$) (Fig. 3).

HCC recurrence was documented in 6 (8.9%) patients. Of these, 5 (83.3%) received IBS (5 out of 29 [17.2%] within the IBS group), and 1 (16.7%) in the non-IBS group (1 out of 38 [2.6%] within the non-IBS group) ($P = 0.03$). This resulted in shorter disease-free survival (Fig. 4, log-rank $P = 0.02$). However, tumor viability was not independently associated with recurrence. Logistic regression analysis revealed that the pre-transplant platelet count was a significant predictor of recurrence (odds ratio = 1.0226; 95% confidence interval, 0.005859–0.038899, $P < 0.05$). Univariate analysis of each variable showed that no other clinical variables had statistically significant relationships with recurrence. Table 4 summarizes the general characteristics of these six subjects with

Table 2 Intraoperative Hematologic Parameters

	IBS group (n = 30)	Non-IBS group (n = 38)	P-value
Platelet count ($\times 10^9$/L)	99.67 ± 62.2	100.2 ± 48.5	0.97
Platelet volume (fL)	10.8 (7.6–3.2)	9.8 (7.0–13.2)	< 0.01
Packed red cell volume (mL)	582.5 (0–8,925.0)	2,100.0 (0–26,250.0)	< 0.01
IBS volume (mL)	711.0 (75.0–5,200.0)	-	-

Values are presented as mean ± standard deviation or median (interquartile range).
IBS, intraoperative blood salvage and autotransfusion.

Table 3 Histopathologic Tumor Characteristics

	IBS group (n = 30)	Non-IBS group (n = 38)	P-value
Patients with viable tumors	21 (70.0)	35 (92.1)	0.05
Number of viable nodules	2 (1–14)	1 (1–4)	< 0.01
Size of largest viable nodule (cm)	2.8 (0.9–7.1)	2.7 (1.2–6.0)	0.38
TVV (cm^3)	8.7 ± 13.0	5.7 ± 8.9	0.32
Vascular invasion	21 (70.0)	26 (68.4)	0.89
Satellitosis	9 (30.0)	10 (26.3)	0.79

Values are presented as number (%), median (interquartile range), or mean ± standard deviation.
IBS, intraoperative blood salvage and autotransfusion; TVV, tumor viable volume.

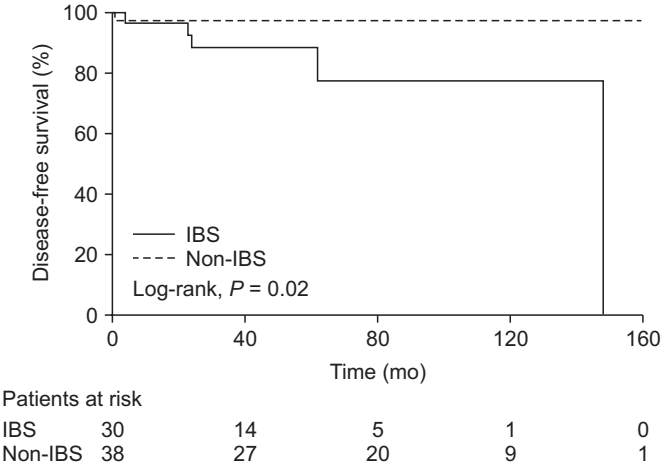

Fig. 4. Disease-free survival analysis for patients undergoing liver transplant for hepatocellular carcinoma comparing patients by use of IBS (n = 68). The curves were compared using the log-rank test at a 95% confidence interval. IBS, intraoperative blood salvage and autotransfusion.

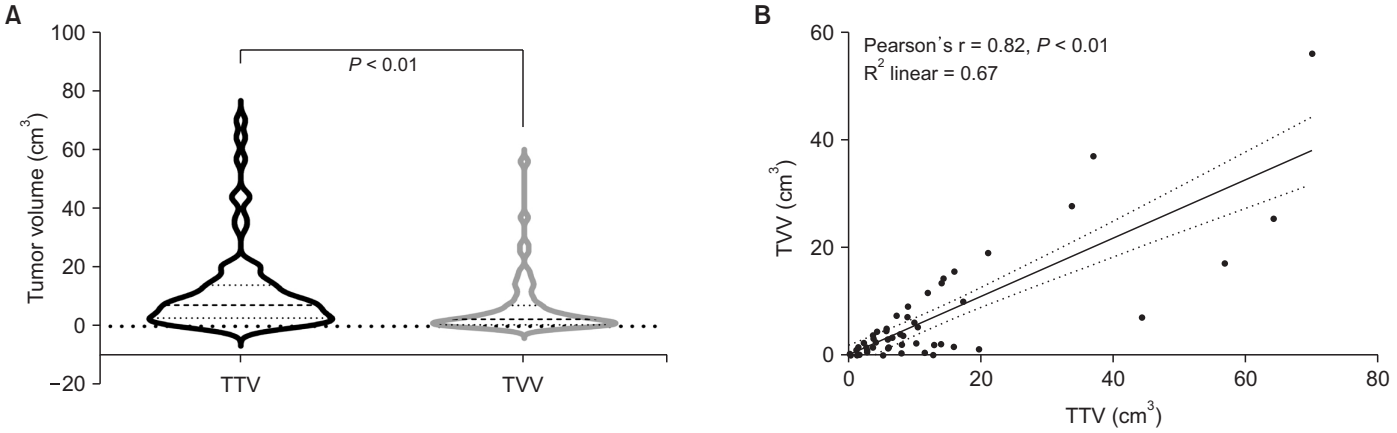

Fig. 3. Comparison of mean TTV calculated immediately before transplant and the actual mean TVV found on explant pathology (n = 68). (A) Overestimation of tumor burden on radiology versus actual TVV on pathology. (B) Pearson correlation coefficients of TTV versus TVV at a 95% confidence interval. TTV, total tumor volume; TVV, tumor viable volume.

recurrence. All six cases of documented recurrence were local in the transplanted liver.

No significant differences in patient survival were found between the IBS and the non-IBS group (log-rank, $P = 0.50$), even in subgroup analyses of patients with viable tumors on explantation ($P = 0.72$), with macro- or micro-vascular invasion ($P = 0.78$), or with satellitosis ($P = 0.80$) (Fig. 4). Additionally, no clinical variables were identified as statistically significant for survival in the univariate Cox regression analysis. To explore the possible association between the viable tumor burden and patient survival, we stratified patients into three groups: TVV < 5 cm^3, TVV 5–10 cm^3, and TVV >10 cm^3. The overall survival in the groups with TVV < 5 cm^3 and > 10 cm^3 was similar; however, poorer survival was observed in patients with TVV between 5 and 10 cm^3 (log-rank, $P = 0.05$) (Fig. 5).

Table 4 Summary of Six Patients Exhibiting Hepatocellular Carcinoma Recurrence after Liver Transplantation

ID	LRT	TTV (cm^3)	AFP (μg/L)	IBS	TVV (cm^3)	Vascular invasion	Satellitosis	TTR (mo)	Survival (mo)	Status
11	Yes	3.9	5	Yes	0	Yes	Yes	30.0	41	Deceased
30	Yes	8.6	10	Yes	0	No	No	65.0	99	Deceased
34	Yes	2.9	49	Yes	0.6	Yes	Unknown	5.3	8	Deceased
37	Yes	11.6	4	Yes	0.6	Yes	No	13.5	16	Deceased
49	Yes	9.1	1,786	No	9.1	Yes	Yes	21.1	43	Deceased
76	Yes	0.2	6	Yes	0	No	No	24.0	42	Alive

LRT, locoregional treatment; TTV, total tumor volume; AFP, alpha-fetoprotein; IBS, intraoperative blood salvage and autotransfusion; TVV, tumor viable volume; TTR, time to recurrence.

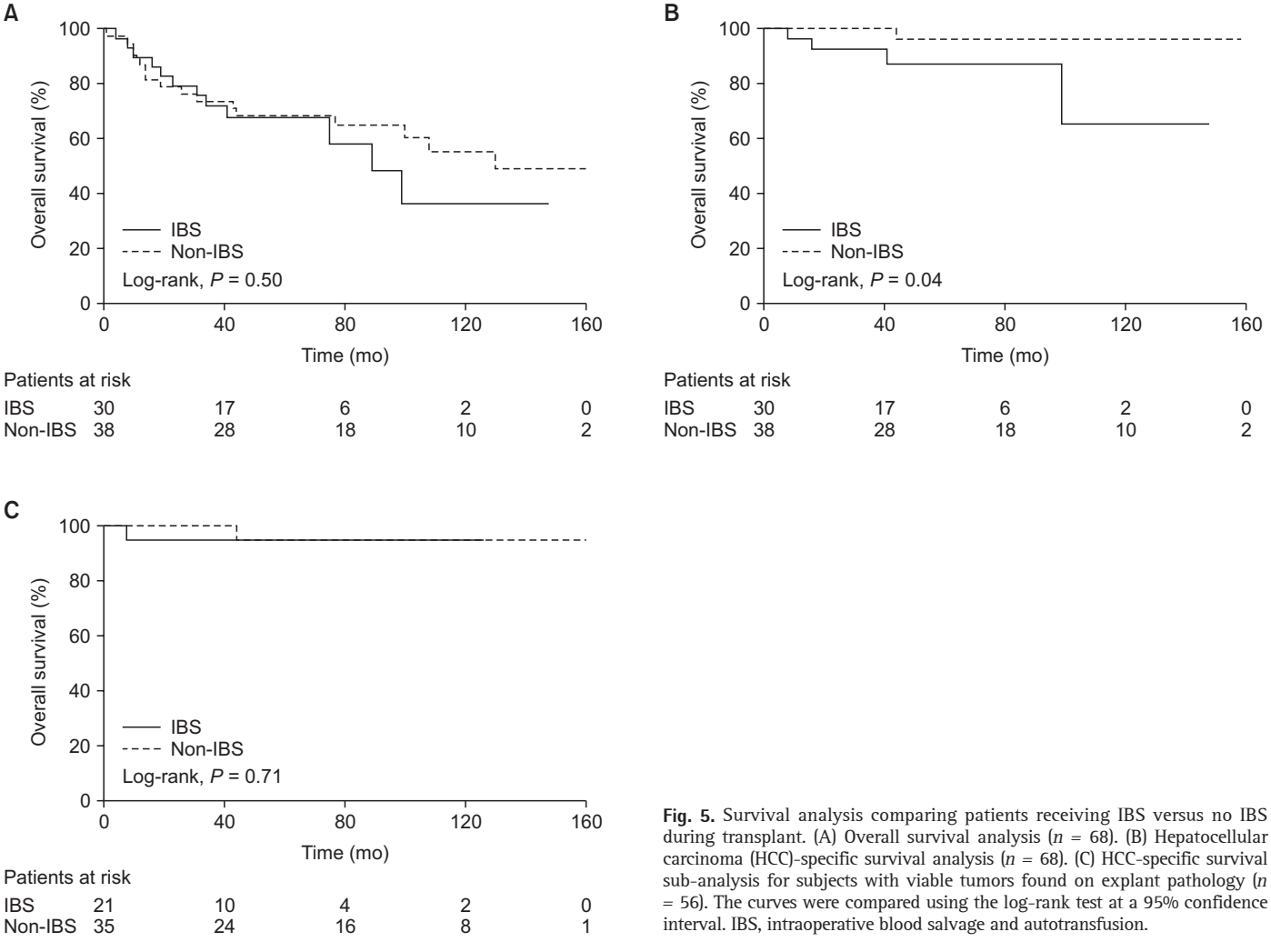

Fig. 5. Survival analysis comparing patients receiving IBS versus no IBS during transplant. (A) Overall survival analysis ($n = 68$). (B) Hepatocellular carcinoma (HCC)-specific survival analysis ($n = 68$). (C) HCC-specific survival sub-analysis for subjects with viable tumors found on explant pathology ($n = 56$). The curves were compared using the log-rank test at a 95% confidence interval. IBS, intraoperative blood salvage and autotransfusion.

Discussion

LT is the preferred treatment for patients with early-stage HCC and liver cirrhosis. In the last decade, the proportion of cases of HCC undergoing LT has tripled, and HCC has become the leading indication for transplantation.[21] Despite strict selection criteria, HCC recurrence still takes place in about 15% to 20% of these patients.[22,23] Debate has continued for years about the intrinsic risk of performing IBS in cancer patients due to the theoretical risk of increased recurrence.[13] IBS is frequently used in LT, which is often performed in a setting of portal hypertension, intra-abdominal varices, and clotting dysfunction associated with liver failure.[2,11,24] The surgery is also highly complex, involving major blood vessel dissection, which increases the risk of potential hemorrhage and extensive allogenic blood transfusion.[25,26] Numerous studies have demonstrated that IBS had no significant impact on cancer recurrence or patient survival.[13,16,27–29] However, there is a paucity of data in the literature regarding the potential impact of the viable tumor burden on long-term results. Our study demonstrated that IBS could be safely used without severely impacting the outcomes after LT.

In our series, IBS was used in 43.3% of patients, significantly reducing the required transfusion volume of allogeneic blood products. Transfusions can be lifesaving; however, they carry a host of possible life-threatening reactions such as acute lung injury, metabolic derangements, circulatory overload, sepsis, hemolysis, anaphylaxis and, more rarely, graft-versus-host reaction.[26] Since donated blood is also a scarce commodity, the use of IBS may be a feasible option in some cases.[2] Thus, IBS is beneficial not only because it is cost-effective, but also because it prevents the deleterious reactions associated with allotransfusion.[24]

Platelets have been reported to interact with HCC cells and alter their microenvironment, promoting progression, recurrence, and metastasis.[30,31] However, the real impact of platelets remains unclear, as multiple publications have reported thrombocytopenia to be both detrimental and advantageous to tumourigenesis.[32] In this series, we recorded the platelet count and the mean platelet volume at the time of LT. We observed that pre-transplant platelet volume was significantly higher in the IBS group ($P < 0.01$), but we did not demonstrate any correlation between this variable and cancer recurrence. However, the pre-transplant platelet count was found to be a significant predictor of HCC recurrence ($P < 0.05$), similar to recently published research by Xia et al,[33] who found that a preoperative platelet count above 75×10^9/L is associated with an increased risk of HCC recurrence after living-donor LT.

Overall, this cohort had a significant correlation between radiographic TTV and pathologic TVV. Nonetheless, we observed a 50% overestimation of the radiological tumor burden with respect to the actual viable HCC volume found on explant analysis. This likely resulted from the spherical volume calculation employed in the radiographic analysis, whereas the pathologic analysis used a more accurate ellipsoid assumption. Indeed, ellipsoid tumoral morphology was recently reported as a better predictor of cancer recurrence and hence, a more objective criterion for HCC patient selection for transplantation.[20] Tumor necrosis post-LRT may also have been underestimated by CT/MRI, contributing to increased radiographic TTV relative to pathologic TTV.

Cancer recurrence is the main determinant of long-term success in HCC patients after LT. Our study observed a lower recurrence rate than has been reported in the literature.[20,21] One of our main study variables was the presence of viable tumors on explant pathology, as this is traditionally associated with poor outcomes.[34,35] In our series, subjects receiving IBS had more viable tumors on explant but did not have a larger TVV. Despite the presence of viable HCC, there was no significant difference in cancer recurrence or the survival of study participants. This observation also held true when patients underwent IBS and was independent of the existence of macro- and micro-vascular invasion or satellitosis, which supports previous reports concluding that this technology is safe in the field of transplantation.[10,16,36] Interestingly, five out of six patients with cancer recurrence in this series had received IBS, but only two of those subjects had viable tumors at transplant. The one patient with recurrent HCC in the non-IBS group had a significant tumor burden, as shown by a TTV and TVV of 9.1 cm^3, an AFP level of 1,786 µg/L, and the presence of vascular invasion and satellitosis. Finally, we analyzed the impact of the actual viable tumor burden on survival by stratifying TVV in different ranges. Although we observed significantly lower survival in the TVV = 5–10 cm^3 stratum, this was not consistent in the group with a larger (> 10 cm^3) viable tumor burden, and hence, difficult to interpret. Most likely, this finding can be attributed to a small sample size. A larger multi-center dataset may provide a more realistic answer to these questions.

New technologies may also provide alternative ways to assess HCC viability during liver transplants. One such technology is the quantification of circulating cell-free DNA (cfDNA, also known as liquid biopsy), which has shown clinical value in the field of oncology for detecting early recurrence.[4,37] Although still experimental, combining IBS with cfDNA as a real-time estimator of circulating HCC cells could be an exciting area of research. Another attractive avenue of investigation would be microarray analysis and next-generation sequencing in IBS fluids to quantify gene transcription and discover genes and gene modifiers associated with HCC recurrence. Increasing clinical evidence suggests that this technique may enhance the precision of cancer prognostication in these patients.[38,39]

This study has addressed the concern of increased HCC recurrence and decreased survival due to the use of IBS during LT through an analysis of the real tumor burden. Although we found a statistically significantly higher risk of cancer recurrence in the IBS group, it was not linked to HCC viability. We believe our results are inconclusive due to the limited sample size, the retrospective nature of the study, and the lack of randomization in the use of IBS. Still, these findings certainly prompt larger prospective multi-center studies, in which more accurate modern technology can also be incorporated to measure circulating HCC cells at the time of transplant.

Funding

This research was supported by the Department of Surgery at Dalhousie University.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

This research has been presented at the Department of Surgery

2021 Research Symposium, Dalhousie University.

ORCID

Ahmed Nasser, https://orcid.org/0000-0002-4415-1260
Victoria Smith, https://orcid.org/0000-0003-1930-8024
Niamh Campbell, https://orcid.org/0009-0004-3762-5378
Michael Devin Rivers-Bowerman, https://orcid.org/0000-0001-5871-4530
Ashley Elispath Stueck, https://orcid.org/0000-0002-0328-6687
Andreu Francesc Costa, https://orcid.org/0000-0003-1683-8230
Riley Arseneau, https://orcid.org/0000-0003-1379-1211
Lauren Westhaver, https://orcid.org/0000-0003-1197-2377
Boris Luis Gala-Lopez, https://orcid.org/0000-0003-1179-2085

References

1. Sherman M, Burak K, Maroun J, Metrakos P, Knox JJ, Myers RP, et al. Multidisciplinary Canadian consensus recommendations for the management and treatment of hepatocellular carcinoma. *Curr Oncol.* 2011;18:228-40.
2. Ozer Etik D, Suna N, Boyacioglu AS. Management of hepatocellular carcinoma: prevention, surveillance, diagnosis, and staging. *Exp Clin Transplant.* 2017;15(Suppl 2):31-5.
3. Inchingolo R, Posa A, Mariappan M, Spiliopoulos S. Locoregional treatments for hepatocellular carcinoma: current evidence and future directions. *World J Gastroenterol.* 2019;25:4614-28.
4. von Felden J, Garcia-Lezana T, Schulze K, Losic B, Villanueva A. Liquid biopsy in the clinical management of hepatocellular carcinoma. *Gut.* 2020;69:2025-34.
5. Baskiran A, Akbulut S, Sahin TT, Koc C, Karakas S, Ince V, et al. Effect of HBV-HDV co-infection on HBV-HCC co-recurrence in patients undergoing living donor liver transplantation. *Hepatol Int.* 2020;14:869-80.
6. Sun S, Li Y, Han S, Jia H, Li X, Li X. A comprehensive genome-wide profiling comparison between HBV and HCV infected hepatocellular carcinoma. *BMC Med Genomics.* 2019;12:147.
7. Duffy AG, Ulahannan SV, Makorova-Rusher O, Rahma O, Wedemeyer H, Pratt D, et al. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. *J Hepatol.* 2017;66:545-51.
8. Shukla A, Vadeyar H, Rela M, Shah S. Liver transplantation: east versus west. *J Clin Exp Hepatol.* 2013;3:243-53.
9. Moon DB, Lee SG. Liver transplantation. *Gut Liver.* 2009;3:145-65.
10. Muscari F, Suc B, Vigouroux D, Duffas JP, Migueres I, Mathieu A, et al. Blood salvage autotransfusion during transplantation for hepatocarcinoma: does it increase the risk of neoplastic recurrence? *Transpl Int.* 2005;18:1236-9.
11. Dai WC, Chok KSH, Sin SL, Chan ACY, Cheung TT, Wong TCL, et al. Impact of intraoperative blood transfusion on long-term outcomes of liver transplantation for hepatocellular carcinoma. *ANZ J Surg.* 2018;88:E418-23.
12. Klein AA, Bailey CR, Charlton AJ, Evans E, Guckian-Fisher M, McCrossan R, et al. Association of anaesthetists guidelines: cell salvage for peri-operative blood conservation 2018. *Anaesthesia.* 2018;73:1141-50.
13. Wu WW, Zhang WY, Zhang WH, Yang L, Deng XQ, Ou MC, et al. Survival analysis of intraoperative blood salvage for patients with malignancy disease: a PRISMA-compliant systematic review and meta-analysis. *Medicine (Baltimore).* 2019;98:e16040.
14. Akbulut S, Kayaalp C, Yilmaz M, Ince V, Ozgor D, Karabulut K, et al. Effect of autotransfusion system on tumor recurrence and survival in hepatocellular carcinoma patients. *World J Gastroenterol.* 2013;19:1625-31.
15. Araujo RL, Pantanali CA, Haddad L, Rocha Filho JA, D'Albuquerque LA, Andraus W. Does autologous blood transfusion during liver transplantation for hepatocellular carcinoma increase risk of recurrence? *World J Gastrointest Surg.* 2016;8:161-8.
16. Foltys D, Zimmermann T, Heise M, Kaths M, Lautem A, Wisser G, et al. Liver transplantation for hepatocellular carcinoma--is there a risk of recurrence caused by intraoperative blood salvage autotransfusion? *Eur Surg Res.* 2011;47:182-7.
17. Toso C, Trotter J, Wei A, Bigam DL, Shah S, Lancaster J, et al. Total tumor volume predicts risk of recurrence following liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl.* 2008;14:1107-15.
18. Florio G, Valbonesi M, Lercari G, Frisoni R, Pollicardo N, Beraudo S. The Fresenius continuous autotransfusion system (CATS): preliminary studies and application. *Int J Artif Organs.* 1996;19:431-4.
19. Murali AR, Chandra S, Stewart Z, Blazar BR, Farooq U, Ince MN, et al. Graft versus host disease after liver transplantation in adults: a case series, review of literature, and an approach to management. *Transplantation.* 2016;100:2661-70.
20. Kashkoush S, El Moghazy W, Kawahara T, Gala-Lopez B, Toso C, Kneteman NM. Three-dimensional tumor volume and serum alpha-fetoprotein are predictors of hepatocellular carcinoma recurrence after liver transplantation: refined selection criteria. *Clin Transplant.* 2014;28:728-36.
21. Yang JD, Larson JJ, Watt KD, Allen AM, Wiesner RH, Gores GJ, et al. Hepatocellular carcinoma is the most common indication for liver transplantation and placement on the waitlist in the United States. *Clin Gastroenterol Hepatol.* 2017;15:767-75.e3.
22. Filgueira NA. Hepatocellular carcinoma recurrence after liver transplantation: risk factors, screening and clinical presentation. *World J Hepatol.* 2019;11:261-72.
23. Mehta N, Dodge JL, Roberts JP, Yao FY. Validation of the prognostic power of the RETREAT score for hepatocellular carcinoma recurrence using the UNOS database. *Am J Transplant.* 2018;18:1206-13.
24. Waters JH, Donnenberg AD. Blood salvage and cancer surgery: should we do it? *Transfusion.* 2009;49:2016-8.
25. Makowka L, Stieber AC, Sher L, Kahn D, Mieles L, Bowman J, et al. Surgical technique of orthotopic liver transplantation. *Gastroenterol Clin North Am.* 1988;17:33-51.
26. Hendrickson JE, Hillyer CD. Noninfectious serious hazards of transfusion. *Anesth Analg.* 2009;108:759-69.
27. Pinto MA, Chedid MF, Sekine L, Schmidt AP, Capra RP, Prediger C, et al. Intraoperative cell salvage with autologous transfusion in liver transplantation. *World J Gastrointest Surg.* 2019;11:11-8.
28. Han S, Kim G, Ko JS, Sinn DH, Yang JD, Joh JW, et al. Safety of the use of blood salvage and autotransfusion during liver transplantation for hepatocellular carcinoma. *Ann Surg.* 2016;264:339-43.
29. Tomimaru Y, Eguchi H, Marubashi S, Wada H, Kobayashi S, Tanemura M, et al. Advantage of autologous blood transfusion in surgery for hepatocellular carcinoma. *World J Gastroenterol.* 2011;17:3709-15.
30. Pang Q, Zhang JY, Song SD, Qu K, Xu XS, Liu SS, et al. Central obesity and nonalcoholic fatty liver disease risk after adjusting for body mass index. *World J Gastroenterol.* 2015;21:1650-62.
31. Pavlovic N, Rani B, Gerwins P, Heindryckx F. Platelets as key factors in hepatocellular carcinoma. *Cancers (Basel).* 2019;11:1022.
32. Peng W, Li C, Zhang X, Wen T, Chen Z. The impact of thrombocytopenia on prognosis of HBV-related small hepatocellular carcinoma: a propensity score matching analysis. *World J Surg Oncol.* 2021;19:46.
33. Xia W, Ke Q, Wang Y, Wang W, Zhang M, Shen Y, et al. Predictive value of pretransplant platelet to lymphocyte ratio for hepatocellular carcinoma recurrence after liver transplantation. *World J Surg Oncol.* 2015;13:60.
34. Montalti R, Mimmo A, Rompianesi G, Di Gregorio C, Serra V, Cautero N, et al. Absence of viable HCC in the native liver is an independent protective factor of tumor recurrence after liver transplantation. *Transplantation.* 2014;97:220-6.
35. Chan KM, Yu MC, Chou HS, Wu TJ, Lee CF, Lee WC. Significance of tumor necrosis for outcome of patients with hepatocellular carcinoma receiving locoregional therapy prior to liver transplantation. *Ann Surg Oncol.* 2011;18:2638-46.
36. Kim JM, Kim GS, Joh JW, Suh KS, Park JB, Ko JS, et al. Long-term results for living donor liver transplant recipients with hepatocellular carcinoma using intraoperative blood salvage with leukocyte depletion filter. *Transpl Int.* 2013;26:84-9.
37. Ng KT, Lo CM, Wong N, Li CX, Qi X, Liu XB, et al. Early-phase circulating miRNAs predict tumor recurrence and survival of hepatocellular carcinoma patients after liver transplantation. *Oncotarget.* 2016;7:19824-39.
38. Marsh JW, Finkelstein SD, Demetris AJ, Swalsky PA, Sasatomi E, Bandos A, et al. Genotyping of hepatocellular carcinoma in liver transplant recipients adds predictive power for determining recurrence-free survival. *Liver Transpl.* 2003;9:664-71.
39. Das T, Diamond DL, Yeh M, Hassan S, Bryan JT, Reyes JD, et al. Molecular signatures of recurrent hepatocellular carcinoma secondary to hepatitis C virus following liver transplantation. *J Transplant.* 2013;2013:878297.