

Oncologic Safety of Irradiated-only Autologous Blood Transfusion in Liver Transplantation for Hepatocellular Carcinoma: A Single-Center Cohort Study

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Background. Liver transplantation for hepatocellular carcinoma (HCC) is highly transfusion-demanding, and intraoperative cell salvage is used to limit allogeneic blood exposure. This study aimed to assess the oncologic safety of transfusion of irradiated-only autologous red blood cells during liver transplantation for HCC. **Methods.** This single-center retrospective cohort included all patients who underwent liver transplantation for HCC between 2010 and 2022. Among the 135 patients, 97 received autologous transfusion of irradiated red blood cells collected through intraoperative cell salvage; the remaining 38 did not. No leukocyte depletion filters were used. The primary outcome was HCC recurrence; secondary outcomes were overall survival and transfusion requirements. **Results.** The median follow-up time was 9.7 y. HCC recurrence occurred in 15.5% of patients in the autotransfusion group compared with 21.1% in the nonautotransfusion group ($P = 0.44$). Kaplan-Meier analyses revealed no significant differences in recurrence-free or overall survivals between the 2 groups. Multivariable Cox regression adjusted for the Model for End-Stage Liver Disease score, tumor burden, Milan criteria, and microvascular invasion revealed that autotransfusion was not associated with recurrence or mortality. Patients in the autotransfusion group had significantly higher exposure to allogeneic blood products. **Conclusions.** Intraoperative autotransfusion of irradiated red blood cells without leukocyte depletion filters appears oncologically safe during liver transplantation for HCC, although the single-center, retrospective design and small control group warrant cautious interpretation and confirmation in larger multicenter studies. As tertiary transplant centers already use blood irradiators for immunocompromised patients, these findings support irradiation as a practical alternative to filtration.

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All procedures were performed in accordance with the ethical standards of our Institutional Ethics Committee and the 1964 Helsinki and the 2008 Istanbul declaration and its subsequent amendments or comparable ethical standards. The study also fulfills all points of the Strengthening the Reporting of Observational Studies in Epidemiology checklist.

Research data supporting this publication are available on demand to the authors.

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INTRODUCTION

Liver transplantation (LT) is a well-established treatment for cirrhotic patients with hepatocellular carcinoma (HCC), especially those who meet the Milan criteria. By treating both the tumor and the cirrhotic liver, it provides excellent long-term results.¹ LT is a surgical procedure that can be associated with major blood loss,² resulting from a combination of precipitating factors including portal hypertension, coagulopathy, breaches in collateral circulation, and the need to perform complex vascular anastomoses. Consequently, LT frequently requires the transfusion of large volumes of blood products.

In this context, the principles of patient blood management (PBM) have gained prominence as a multidisciplinary, evidence-based strategy to optimize care for patients who may require transfusion.³ A cornerstone of PBM is reducing exposure to allogeneic blood products, which are associated with risks such as transfusion-related immunomodulation and pulmonary complications, postoperative infections linked to multiple transfusion-related manipulations, and thromboembolic events.⁴ Therefore, minimizing allogeneic transfusion is particularly relevant in LT and may also reduce the substantial direct and downstream costs related to allogeneic blood use.

Intraoperative cell salvage (IOCS) has therefore emerged as an important PBM tool.⁵ IOCS involves collecting, processing, and reinfusing the patient's own red blood cells (RBCs) that are salvaged from the surgical field. This technique significantly reduces the need for allogeneic transfusion.⁶ However, the use of IOCS in oncologic surgery has long been debated because of the theoretical risk of reinfusing viable tumor cells. To mitigate this risk, many institutions have adopted the use of leukocyte depletion filters (LDFs), as these filters can physically trap circulating malignant cells.⁷ Several studies on autotransfusion using LDFs during LT have shown no increase in recurrence, including 2 large Korean cohorts demonstrating safety, even in patients with advanced HCC.^{8,9} However, the exact oncologic efficacy of LDF remains partly theoretical and could be incomplete in case of high HCC cell loads.¹⁰

Irradiation of salvaged blood has been proposed as an alternative method to inactivate potential tumor cells.¹¹ Experimental models suggest that irradiation doses around 25–50 Gy impair tumor-cell proliferation without compromising RBC viability.^{11,12} Some advocate irradiation as the most effective method to reduce the risk of tumor-cell dissemination associated with autotransfusion,¹³ but, so far, no study has specifically evaluated posttransplantation HCC recurrence rate after the autotransfusion of irradiated RBC without LDF use during LT. One may argue that irradiation is more expensive than LDF. However, irradiators that are available on the market, although expensive at purchase, can be used for several years, whereas several filters may be required for 1 LT procedure. In addition, the use of LDFs is occasionally limited by technical issues, such as difficult purging, filter damage, increased contamination risk, loss of transfusion volume, or the need for a relatively slow transfusion rate. In our center, LDF costs ~3–6 times more than irradiation (€60 per filter for 1–2 units versus €10 per irradiation, billed to insurance; context-specific). LDFs (eg, PALL RS01/RS02) handle max 2 units (~300–500 mL capacity, Hct ~55%–60% post-wash) but cause substantial autologous loss (~70–130 mL

priming/hold-up), plus frequent replacement in high-bleed cases. Irradiation (Gammacell 3000 Elan, 30.5 Gy) takes ~15 min (dose rate ~2–3 Gy/min), enabling rapid reinfusion (>100 mL/min); LDF limits flow to 20–50 mL/min (clogging/backpressure), necessitating parallel allogeneic blood in major hemorrhage. Additional LDF issues include purging difficulties, rupture risk, contamination, and ~5–10 min extra setup. Overall, irradiation offers cost/logistic advantages in high-volume centers while maintaining rapid preoperative hemoglobin delivery, supporting its evaluation as sole decontamination.

In this study, as a first step for finding the best technique to be used in this context, we therefore aimed at retrospectively determining the oncologic safety of autotransfusion of irradiated RBC during LT by comparing the HCC recurrence rate between patients having received such autotransfusion and those who did not. Our secondary objectives were to assess several aspects of transfusion outcomes.

MATERIALS AND METHODS

The Ethics Committee of the University Hospital of Liege (Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège, Belgium; internal reference: 2024/36; Chairperson: Pr D. Ledoux) approved this retrospective observational study and waived informed consent in accordance with the Belgian legislation (Law of May 7, 2004, on experiments on human subjects). The study was conducted and reported in accordance with the Declaration of Helsinki and the Istanbul Declaration, and it fulfilled all points of the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Patients

Data were retrospectively collected from the medical records of all adult patients who underwent LT for HCC at the University Hospital of Liege, Belgium, between January 2010 and October 2022. In accordance with Belgian transplant policy, eligibility for LT in patients with HCC was primarily assessed using the Milan criteria (single tumor ≤5 cm in diameter, or up to 3 tumors, each ≤3 cm in diameter, with no evidence of macrovascular invasion or extrahepatic spread).¹⁴ Patients fulfilling validated other extended criteria, such as the up-to-7 criteria (sum of the diameter [in cm] of the largest tumor and the number of tumors must be ≤7). For a single lesion, this means the diameter of the tumor must be ≤7 cm. These criteria also require the absence of macrovascular invasion and extrahepatic spread, similar to the Milan criteria), and could also be listed when expected posttransplant outcomes were deemed acceptable.¹⁵ Patients who died within 3 mo of surgery from any cause or who underwent redo LT were excluded.

Cell Salvage and Irradiation Protocol

In this center, a cell salvage device is routinely set up for all LT procedures, including those performed for HCC. Salvaged blood is collected intraoperatively and processed using a blood salvage system (Xtra Autotransfusion System, LivaNova PLC, United Kingdom). RBCs are separated by centrifugation, washed with isotonic saline, and transferred to a sterile reinfusion bag. Before autologous

transfusion, each unit is systematically irradiated using an external gamma irradiator (Gammacell 3000 Elan, Nordion, Canada) at a dose of 30.5 Gy. Irradiated salvaged RBCs are reinfused only if intraoperative blood loss provides sufficient aspirated volume (~800–1000 mL minimum for Xtra system) and hemoglobin concentration in aspirated blood (which fluctuates during surgery) to yield a usable washed RBC culot after centrifugation, and if the salvage circuit functions appropriately. Otherwise, processed RBCs are discarded.

Transfusion decisions by the anesthesiologist were based on standard hemoglobin thresholds (7 or 7.5 g/dL, adjusted higher for cardiac/renal comorbidities per Association for the Advancement of Blood & Biotherapies guidelines) and cell saver feasibility. Patients in the non-autotransfusion (NAT) group ($n = 38$) mostly had limited perioperative hemorrhage, yielding insufficient aspirated volume for a transfusable culot (dysfunction rare but possible) and/or no transfusion indication despite processing. This is consistent with higher preoperative hemoglobin (13.85 [12.03–14.8] versus 12.20 [10.5–14.1] g/dL in IAT, $P = 0.005$; Table 1), reflecting lower anemia risk during

surgery. Salvaged blood was thus not reinfused, according to international guidelines (eg, Association for the Advancement of Blood & Biotherapies restrictive strategy, TRIGGER trial) to avoid overtransfusion.

No LDF is applied at any point in the process. For the present analysis, patients were therefore classified into 2 groups: the irradiated autotransfusion (IAT) group, in whom irradiated salvaged RBCs were reinfused, and the NAT group, in whom salvaged RBCs were not reinfused.

Study Endpoints

The primary endpoints of this study were the overall incidence of HCC recurrence during follow-up, documented by imaging or histological confirmation, the cumulative incidence of HCC recurrence at 1, 2, and 3 y after LT and recurrence-free survival (RFS). The secondary endpoints included the need for allogeneic blood product transfusions (RBCs, fresh frozen plasma, and platelets) and patients' overall survival (OS). Follow-up for time-to-event analyses was censored administratively on November 1, 2025; all RFS and OS analyses therefore used individual

TABLE 1.

Patients, HCC, and donor characteristics at the time of surgery

Variables	N = 135	NAT group (N = 38)	IAT group (N = 97)	P
Age, y	70 (64–73)	70 (65.25–75.5)	70 (64–73)	0.64
Sex (male)	111 (82.2)	32 (84.2)	79 (81.4)	0.81
Cause of HCC				0.65
Post-toxic (alcohol)	61 (45.2)	16 (42.1)	45 (46.4)	
NASH	15 (11.1)	4 (10.5)	11 (11.3)	
Primary biliary disease	3 (2.2)	1 (2.6)	2 (2.1)	
Viral	26 (19.3)	8 (21.1)	18 (18.6)	
Healthy liver	2 (1.5)	1 (2.6)	1 (1)	
Post-toxic and NASH	5 (3.7)	2 (5.3)	3 (3.1)	
Post-toxic and viral	16 (11.9)	3 (7.9)	13 (13.4)	
Post-toxic, viral, and NASH	3 (2.2)	1 (2.6)	2 (2.1)	
Undetermined	2 (1.5)	2 (5.3)	0 (0)	
NASH and viral	1 (0.7)	0 (0)	1 (1)	
Other	1 (0.7)	0 (0)	1 (1)	
Child-Pugh Score				0.09
A	84 (62.2)	26 (70.3)	56 (58.3)	
B	42 (31.1)	7 (18.9)	35 (36.5)	
C	9 (6.67)	4 (10.8)	5 (5.2)	
MELD score	11 (8–14)	9 (7–13)	11 (9–15)	0.053
Hemoglobin, g/dL	12.50 (11.2–14.45)	13.85 (12.03–14.8)	12.20 (10.5–14.1)	0.005
Platelets, $10^3/\mu\text{L}$	100 (63–143)	116.5 (94.75–162.5)	87 (56–125)	0.008
No. nodes	1 (1–3)	2 (1–3)	1 (1–2)	0.066
Size of largest node, mm	29 (21.5–40)	29.5 (25–38.7)	28.0 (21–40)	0.053
Milan criteria (in)	103 (76.3)	25 (65.8)	78 (81.2)	0.07
Up to 7 criteria (in), Milan criteria (out)	30 (22.2)	12 (31.6)	18 (18.6)	0.11
AFP, ng/mL	10.1 (4.1–61.4)	14.3 (6.4–78.6)	9.45 (3.82–53.6)	0.16
Microvascular invasion	25 (18.5)	7 (18.4)	18 (18.6)	0.98
Lymphovascular invasion	13 (9.6)	5 (13.2)	8 (8.2)	0.51
Waiting time for transplant, d	123 (63.5–204)	131 (64–194)	115 (66–206)	0.96
Age of the donor, y	58.5 (48–69)	60 (52–71)	58 (48–68)	0.63

Data are expressed as median (IQR) or n (%).

P values are from the Mann-Whitney U test for continuous variables and chi-square test or the Fisher exact test for categorical variables, as appropriate.

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; IAT, irradiated autotransfusion; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; NAT, nonautotransfusion.

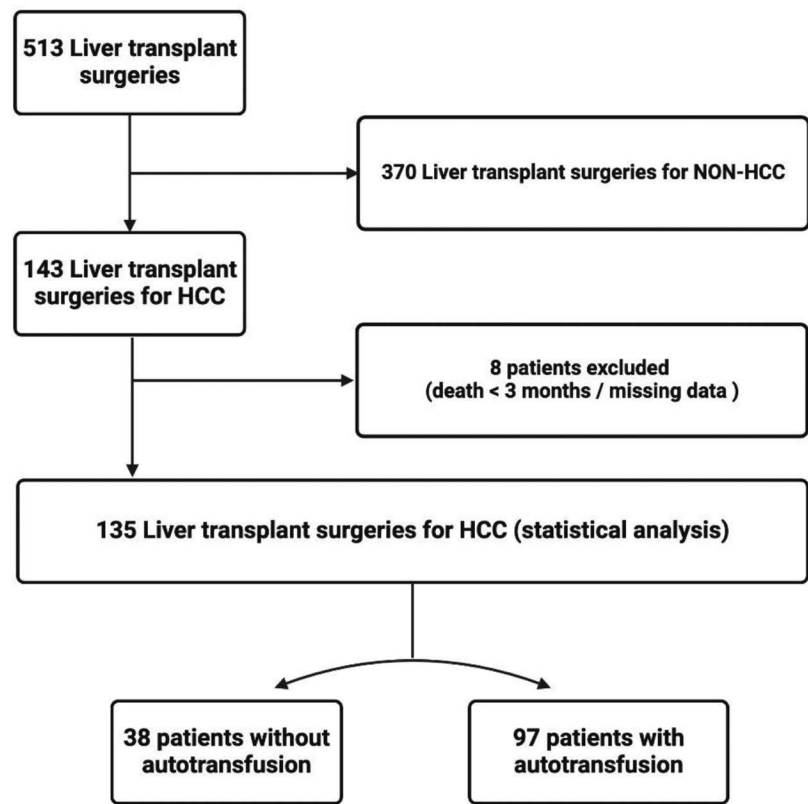


FIGURE 1. Flowchart. HCC, hepatocellular carcinoma.

follow-up times from transplantation to recurrence or death, whichever came first. Kaplan-Meier curves were plotted up to 10 y after LT to match the main clinical endpoints, although statistical analyses used the entire available follow-up.

The following variables were retrospectively collected from the medical records: demographic data (age and sex); cause of the underlying liver disease; Model for End-Stage Liver Disease (MELD) score and Child-Pugh score; tumor burden information from the surgical pathologic report (number and size of nodules, Milan criteria and up-to-7 status); pretransplant hemoglobin, platelets, and alpha-fetoprotein plasma concentration; waiting time for transplant and donor age; presence of microvascular and lymphovascular invasions, IOCS, and autotransfusion data (treated blood volumes and transfused volumes); and intraoperative use of blood products (RBC, fresh frozen plasma, platelets).

Recurrence and survival data were collected through elements of the longitudinal follow-up available in the institutional database.

Statistical Analysis

Quantitative variables were summarized as median (interquartile range) and categorical variables were summarized as counts (percentages). Between-group comparisons were performed using the Fisher exact test for categorical variables and the Mann-Whitney *U* test or Student *t* test for continuous variables, as appropriate and according to data distribution. Normality of distributions was checked using the Shapiro-Wilk test.

RFS and OS were estimated using Kaplan-Meier curves and compared using log-rank tests. To evaluate the independent impact of autologous transfusion on oncologic outcomes, Cox proportional hazards models

TABLE 2.
Recurrence of cancer and death

Variables	N = 135	NAT group (N = 38)	IAT group (N = 97)	P
Recurrence of cancer	23 (17.0)	8 (21.1)	15 (15.5)	0.437
Time before recurrence, d	811 (472.5–1396)	811 (458.5–1230)	872 (628–1396)	0.392
Death at the end of follow-up	47 (34.8)	17 (44.74)	30 (30.93)	0.160
Time before death, d	1395 (933.5–2447)	1196 (941.8–2404)	1414 (944–2483)	0.811

Data are expressed as median (P25–P75) and as counts (%).
IAT, irradiated autotransfusion; NAT, nonautotransfusion.

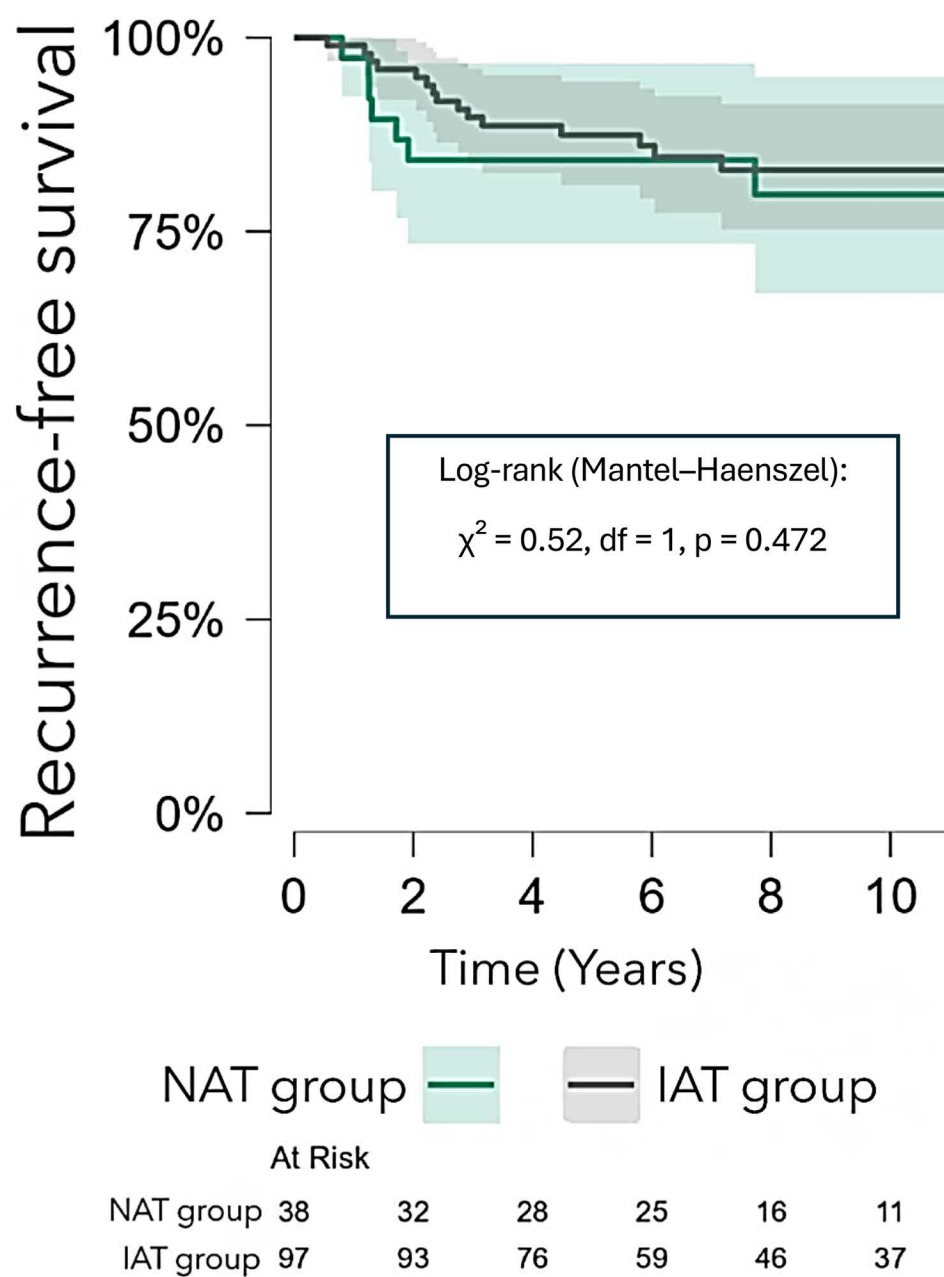


FIGURE 2. Kaplan-Meier curves for recurrence-free survival up to 10 y after liver transplantation for HCC according to intraoperative autotransfusion. Event = HCC recurrence. Shaded areas represent 95% confidence intervals. The log-rank test compares recurrence-free survival between IAT and NAT groups. HCC, hepatocellular carcinoma; IAT, irradiated autotransfusion; NAT, nonautotransfusion.

were fitted for both RFS and OS, adjusting for MELD score, tumor burden, Milan criteria, and microvascular invasion.

The minimally adjusted model included covariates that were imbalanced between groups at baseline, such as MELD score at listing and number of tumor nodules. The clinically adjusted model incorporated established prognostic factors for HCC recurrence, namely Milan status and microvascular invasion. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported, and the proportional hazards assumption was verified for each model. All analyses were performed using the JASP software (JASP Team, version 0.95.2, University of Amsterdam, the Netherlands).

RESULTS

Between January 2010 and October 2022, 512 LTs were performed at our institution, 143 of which concerned patients having HCC. The final cohort used in this study consisted of 135 patients (8 patients were excluded because of death within <3 mo after LT or underwent redo LT), including 97 patients who received intraoperative autologous transfusion of irradiated RBC through IOCS (IAT group), whereas 38 did not receive autotransfusion (NAT group; Figure 1).

Patients and Surgery Characteristics

The baseline characteristics of the patients are summarized in Table 1. Age, sex distribution, cause of HCC,

TABLE 3.
Multivariable Cox regression for recurrence-free and overall survival

Outcome	Model (adjustment)	Variable	Hazard ratio	95% CI lower	95% CI upper
Recurrence-free survival	Minimal (MELD, nodules) <i>P</i> = 0.97	Irradiated autologous transfusion	0.976	0.287	3.314
		MELD	0.977	0.866	1.103
		No. nodules	0.888	0.551	1.431
Recurrence-free survival	Clinical (MELD, nodules, Milan, MVI) <i>P</i> = 0.83	Irradiated autologous transfusion	0.862	0.223	3.336
		MELD	0.966	0.852	1.096
		No. nodules	0.685	0.354	1.324
		MILAN criteria IN	0.497	0.139	1.778
		Microvascular invasion	1.454	0.578	3.656
Overall survival	Minimal (MELD, nodules) <i>P</i> = 0.27	Irradiated autologous transfusion	1.488	0.738	3.003
		MELD	0.927	0.838	1.025
		No. nodules	1.326	0.951	1.849
Overall survival	Clinical (MELD, nodules, Milan, MVI) <i>P</i> = 0.38	Irradiated autologous transfusion	1.391	0.668	2.895
		MELD	0.930	0.839	1.031
		No. nodules	1.051	0.704	1.568
		MILAN criteria IN	0.371	0.145	0.949
		Microvascular invasion	0.923	0.461	1.847

Data are presented as hazard ratios with 95% CIs from Cox proportional hazards models, minimally adjusted for MELD and number of nodules, and clinically adjusted for MELD, number of nodules, Milan criteria, and microvascular invasion.

CI, confidence interval; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; MVI, microvascular invasion.

Child-Pugh score distribution, and the alpha-fetoprotein plasma concentration were similar between groups. The MELD scores showed a nonsignificant trend toward higher values in the IAT group (9 [7–13] versus 11 [9–15], respectively; *P* = 0.053) at the time of LT. Waiting time before LT and donor age were also comparable between groups.

Median preoperative hemoglobin was higher in the NAT than in the IAT group (13.85 [12.03–14.8] and 12.20 [10.5–14.1] g/dL, *P* = 0.005), as was the platelet count (116.5 [94.75–162.5] and 87 [56–125] × 10³/mm³, *P* = 0.008).

Regarding tumor burden, the median number of HCC nodules was 1 [1–3] for the whole group of recruited patients, 2 [1–3] in the NAT group and 1 [1–2] (*P* = 0.57), and the size of the largest nodule showed a nonsignificant trend toward larger ones in the NAT group, with a value of 29.5 [25.0–38.7] mm in that group and 28.0 [21.0–40.0] mm in the IAT group (*P* = 0.053). Microvascular invasion was present in 18.4% of the NAT patients and 18.6% of IAT patients (*P* = 0.98), and lymphovascular invasion in 13.2% and 8.2%, respectively (*P* = 0.51).

At the time of surgery, 65.8% of NAT and 81.2% of IAT patients met the Milan criteria (*P* = 0.07), whereas 31.6% and 18.6% were within the up-to-7 criteria (out of Milan criteria), respectively (*P* = 0.11).

Primary Outcome

At the time of analysis, the median follow-up time for the cohort was 9.7 [5.9–12.3] y. Overall, HCC recurrence occurred in 23 of the 135 recruited patients (17.0%), including 8 of the 38 patients in the NAT group (21.1%) and 15 of the 97 patients in the IAT group (15.5%; *P* = 0.437; Table 2). The median time before HCC recurrence was 811 [458.5–1230] d in the NAT group and 872 [628–1396] d in the IAT group (*P* = 0.392).

The cumulative recurrence rates at 1, 2, and 3 y were 7.9%, 18.4%, and 23.7% in the NAT group, compared with 6.2%, 10.3%, and 13.4% in the IAT group (log-rank *P* = 0.472; Figure 2). Kaplan-Meier curves were displayed up to 10 y after LT and showed no significant difference in RFS between groups (log-rank *P* = 0.472; Figure 2), whereas the Cox regression models used the entire follow-up until the common censoring date. In multivariable Cox

TABLE 4.
Autotransfusion data and allogeneic transfusion parameters

Variables	N = 135	NAT group (N = 38)	IAT group (N = 97)	<i>P</i>
Autotransfusion parameters				
Blood volume treated, mL	1000 (600–1800)	500 (400–800)	1300 (900–2025)	<0.001
Washed red blood cells transfused, mL	408 (0–724)	0 (0–0)	477 (300–845)	<0.001
Allogeneic transfusion				
Erythrocytes	29 (21.5)	2 (5.3)	27 (28.7)	0.003
Fresh frozen plasma	38 (28.1)	4 (10.5)	34 (36.2)	0.004
Platelets	22 (16.3)	3 (7.9)	19 (20.2)	0.021

Data are expressed as median (P25–P75) and as counts (%).

IAT, irradiated autotransfusion; NAT, nonautotransfusion.

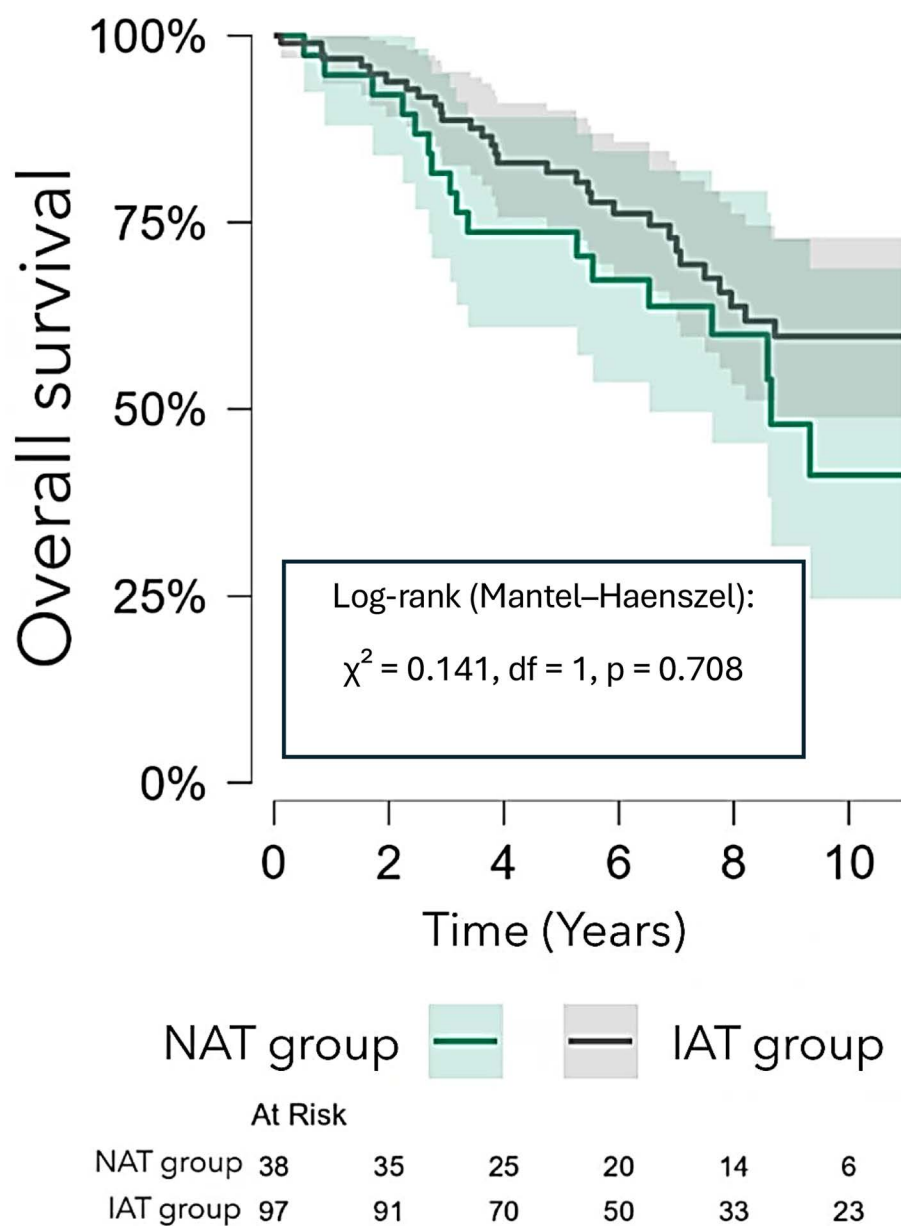


FIGURE 3. Kaplan-Meier curves for overall survival up to 10 y after liver transplantation for HCC according to intraoperative autotransfusion. Event = death from any cause. Shaded areas represent 95% confidence intervals. The log-rank test compares recurrence-free survival between IAT and NAT groups. HCC, hepatocellular carcinoma; IAT, irradiated autotransfusion; NAT, nonautotransfusion.

regression analyses, autotransfusion did not adversely affect RFS, with adjusted HRs near unity in both models (minimal model: HR, 0.98; 95% CI, 0.29-3.31; $P = 0.97$; clinical model: HR, 0.86; 95% CI, 0.22-3.34, $P = 0.83$; Table 3).

Secondary Outcomes

Autotransfusion parameters and transfusion outcomes are summarized in Table 4. The median blood volume processed in the IAT group was 1300 mL (900–2025) as compared with 500 mL (400–800) in the NAT group ($P < 0.001$), yielding 477 mL (300–845) of washed, irradiated RBCs in the IAT group compared with 0 mL in the NAT group.

Concerning allogeneic transfusion, 2 of 38 patients (5.3%) in the NAT group and 27 of 97 patients (28.7%) in the IAT group received allogeneic erythrocyte transfusion ($P = 0.003$). Fresh frozen plasma was administered to 4 NAT patients (10.5%) versus 34 IAT patients (36.2%; $P = 0.004$), and platelet transfusion was required in 3 NAT patients (7.9%) versus 19 IAT patients (20.2%; $P = 0.021$). At the end of follow-up, 47 of 135 patients (34.8%) had died, including 17 of the NAT patients (44.74%) and 30 of the IAT patients (30.93%; $P = 0.160$; Table 3). The median time to death was 1196 [941.8–2404] d in the NAT group and 1414 [944–2483] d in the IAT group ($P = 0.811$). HCC-related mortality occurred in 13 patients (9.6% of the cohort), with similar proportions in the NAT and IAT groups (10.5% versus 9.3%, $P = 1.00$). Kaplan-Meier

curves showed no significant difference in OS between groups (log-rank $P = 0.708$; Figure 3), and multivariable Cox regression confirmed that autotransfusion was not associated with lower OS (minimal model: adjusted HR, 1.49; 95% CI, 0.74-3.00; $P = 0.27$; clinical model: adjusted HR, 1.39; 95% CI, 0.67-2.90; $P = 0.38$; Table 3).

DISCUSSION

This retrospective single-center cohort study evaluated the oncologic safety of intraoperative autotransfusion of irradiated RBC without LDF during LT for HCC. During more than a decade of practice, with a median follow-up time of 9.7 y, autotransfusion of irradiated-only RBC was not associated with higher HCC recurrence or mortality compared with no autotransfusion. RFS and OS curves, as well as multivariable Cox models adjusted for established prognostic factors (MELD, tumor burden, Milan criteria, microvascular invasion), consistently showed no adverse oncologic signal related to irradiated-only autologous transfusion.

Beyond HCC, the role of IOCS in LT remains heterogeneous across centers. Some programs use IOCS routinely as part of a comprehensive PBM strategy,^{3,16,17} whereas others either restrict its use to selected high-risk cases or do not use it at all, often because of concerns about cost, logistics, or theoretical oncologic risks. Recent systematic reviews suggest that intraoperative blood salvage can reduce allogeneic RBC transfusion requirements in liver resection and transplantation without compromising clinical outcomes,^{8,9,18,19} but its uptake in daily practice is still far from universal.

The rising global incidence of HCC, particularly in the context of nonalcoholic steatohepatitis (NASH),²⁰ underscores the urgent need to optimize both the safety and the efficiency of LT. As more centers face increasing caseloads, the ability to save blood products while ensuring oncologic safety becomes increasingly relevant. In oncologic surgery, IOCS has long been debated because of the theoretical risk of reinfusing viable tumor cells mobilized during tumor manipulation. LDF has become the most widely adopted strategy to mitigate this risk, and multiple experimental and clinical studies indicate that LDFs markedly reduce tumor-cell contamination and that cancer recurrence rates are not higher with IOCS than with conventional allogeneic transfusion. However, filtration does not guarantee complete removal of malignant cells under high tumor-cell loads, and several *in vitro* studies have found residual tumor cells after LDF use,^{10,21-23} whereas irradiation can inactivate nucleated cells and has been proposed as an additional or alternative method of decontamination.¹¹ Despite its theoretical efficiency, no clinical data were available regarding its use as the sole method of oncologic safety during IOCS in LT.^{24,25} This study provides clinical evidence that irradiation alone, without LDF, does not compromise oncologic outcomes in patients transplanted for HCC.

At the University Hospital of Liege, intraoperative autotransfusion of centrifuged, washed, and irradiated RBCs without LDFs have been systematically implemented for LT in patients with HCC since 2010. The central dose usually used for every patient is 30.5 Gy. This dose is in accordance with current guidelines recommending an

irradiation dose between 25 and 45 Gy.^{11,12,26-29} In the present cohort, patients in the IAT group had higher MELD scores and greater intraoperative bleeding, reflected by higher use of both salvaged and allogeneic blood products, yet their recurrence rates and survival outcomes were comparable with those of NAT patients. These findings are in line with published series and meta-analyses showing that intraoperative blood salvage autotransfusion does not increase HCC recurrence after LT and may even be associated with recurrence rates that are equal to or slightly lower than those of strategies based solely on allogeneic transfusion. In this context, our results support the use of IOCS in LT for HCC and suggest that an irradiation-based protocol can be applied safely in centers where this technology is available. In most tertiary care and transplant centers, dedicated blood irradiators are already available as part of routine transfusion support for immunocompromised patients, where irradiation of cellular blood components is recommended to prevent transfusion-associated graft-versus-host disease. Therefore, implementing an irradiation-based IOCS protocol generally does not require new technology but rather an organizational adaptation of existing infrastructure. Given the absence of any oncologic penalty in our high-bleeding IAT group, there is no oncologic rationale to avoid IOCS in HCC LT, and its use could reasonably be extended to most, if not all, eligible LT procedures in this setting, and, in centers with the necessary infrastructure, irradiation could be a feasible and effective alternative to LDF. However, LDF is more accessible and widely used, which may limit generalizability.^{8,9,19}

Two limitations must be acknowledged. First, this single-center retrospective study was not statistically powered to detect small differences in HCC recurrence rates between groups. The control (NAT) group was small ($n = 38$, only 8 recurrences [21.1%]) compared with the IAT group ($n = 97$, 15 recurrences [15.5%]; $P = 0.437$), limiting conclusions on safety. Given the overall recurrence rate of 17% (3-y cumulative incidence ~15%–20%), a sensitivity power analysis (2-sample proportions test, $\alpha = 0.05$, 80% power) shows our design reliably detects only large between-group differences—from baseline ~17% risk to ~41% (absolute Δ ~24 percentage points). Smaller differences, including the modest numerical trends in our data (eg, wide CIs: RFS clinical model HR 0.86 [0.22-3.34], $P = 0.83$; OS 1.39 [0.67-2.90], $P = 0.38$), cannot be excluded. Second, despite adjustment for key prognostic factors (MELD, tumor burden, Milan criteria, microvascular invasion), unmeasured confounders cannot be ruled out, and the small sample size further limits HR precision.

Designing a randomized controlled trial to compare irradiated IOCS, filtered IOCS, and no IOCS in LT for HCC would be challenging both ethically and logistically. Large sample sizes would be required to detect modest differences in recurrence, and clinicians may be reluctant to withhold IOCS in high-risk bleeding situations or to randomize patients between different decontamination methods when experimental data suggest that both filtration and irradiation are effective. In practice, high-quality observational studies and multicenter registries are likely to provide the main evidence base for guiding IOCS strategies in HCC transplantation. Against this background, the present cohort adds clinically relevant data supporting the

oncologic safety of irradiation-based IOCS without LDF in routine practice and underscores the need for collaborative prospective studies to refine blood management strategies in this population.

In summary, intraoperative autotransfusion of irradiated RBCs without LDFs appears oncologically safe during LT for HCC, although our single-center cohort with a small control group warrants cautious interpretation and confirmation in larger multicenter studies. In this study, recurrence rates were consistent with established benchmarks, and exposure to allogeneic blood products was significantly reduced. Although LDF remains the most widely used safeguard, systematic irradiation is a biologically robust alternative for tertiary centers with the appropriate infrastructure. These findings support integrating irradiation-based protocols into PBM strategies and provide a strong rationale for conducting prospective, multicenter studies to confirm their safety and guide future oncologic LT practices.

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