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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

# Liver Transplantation is Equally Effective as a Salvage Therapy for Patients with Hepatocellular Carcinoma Recurrence Following Radiofrequency Ablation or Liver Resection with Curative Intent

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## ABSTRACT

**Background.** Liver resection (LR) and radiofrequency ablation (RFA) are curative-intent therapies for early stages of hepatocellular carcinoma (HCC). If HCC recurs, salvage liver transplant (SLT) may constitute a treatment option.

**Objective.** We aimed to compare the outcomes of patients transplanted for recurrent HCC after curative-intent therapies with those transplanted as initial therapy.

**Methods.** We conducted a matched-control (1:1) cohort study comparing patients with HCC treated with primary liver transplant (PLT) with SLT after HCC recurrence. Matching was performed according to the size and number of viable tumors at explant pathology following liver transplant.

**Results.** Between November 1999 and December 2014, 687 patients with HCC were listed for transplant at our institution. A total of 559 patients were transplanted; 509 patients were treated with PLT and 50 patients were treated with SLT for HCC recurrence after primary treatment with LR ($n = 25$) or RFA ($n = 25$). The median length of follow-up from transplant was 64 months (0.5–195), and the median time from curative-intent treatment of HCC with RFA or LR to recurrence was 9.5 months (1–36) and 14.5 months (3–143), respectively ($p = 0.04$). The matched cohort was composed of 48 SLT patients (23 LR and 25 RFA) and 48 PLT patients. The 5-year risk of recurrence after LT was 22% in the PLT group versus 32% in the SLT group ($p = 0.53$), while the 5-year actuarial patient survival after PLT was 69% versus 70% in the SLT group ($p = 1$).

**Conclusion.** Liver transplant is an effective treatment for patients with HCC recurrence following RFA or LR. Outcomes are similar in both groups.

Hepatocellular carcinoma (HCC) is the most common primary liver tumor.[1] Treatment options for patients with HCC consider tumor factors, degree of liver disease, patient comorbidities and cancer-related symptoms.[2,3] Patients with early stages of HCC are eligible for curative-intent treatments with radiofrequency ablation (RFA), liver resection (LR), or liver transplantation (LT).[4] RFA can be successful at treating single, small tumors (< 3 cm) in patients with compensated cirrhosis (Child–Pugh A–B), yielding a 5-year survival rate of 55–74%.[5–8] LR is mainly

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offered to patients without portal hypertension and tumors in resectable locations exceeding the RFA size criteria.[4,5] The 5-year survival rates after LR ranges from 50 to 70%.[9–11] Although RFA and LR are potential therapeutic options, HCC recurrence can occur in up to 80–90% of patients.[5,7,10,12]

LT represents the best treatment modality for patients with HCC, but is reserved for multifocal or unresectable tumors in the setting of portal hypertension and significant liver dysfunction.[4] In appropriately selected patients, HCC recurrence after LT can be as low as 5–15%.[1,9,13] However, due to organ shortage and the availability of other, potentially curative, treatments (LR and RFA), not all patients undergo LT. If HCC recurrence occurs after such treatments, salvage liver transplant (SLT) may be considered.[4]

Previous studies reported the outcomes of SLT following recurrent HCC after LR with different results.[12,14–17] Few reports have analyzed the outcomes of SLT after HCC recurrence following curative-intent RFA.[6] From a patients' perspective, it is important to understand the outcomes of SLT following recurrence after potentially curative treatments;[6,12,14] Therefore, we aimed to analyze and compare the outcomes of SLT for recurrent HCC following RFA or LR with patients who had a primary liver transplant (PLT).

## METHODS

### *Study Design*

A prospectively collected database at the University Health Network using the Organ Transplant Tracking Registry software (HKS Medical Information Systems, Omaha, NE, USA) of adult patients receiving LT from November 1999 to December 2014 was retrospectively analyzed. This study was approved by the Research Ethics Board at the Toronto General Hospital (REB#15-9989).

Patients were divided according to the type of initial treatment received. The PLT group consisted of patients who received LT as initial treatment for HCC, while the SLT group comprised patients who were initially treated (with an intention to cure) with LR or RFA and were transplanted following HCC recurrence.

A preliminary analysis was performed comparing the entire PLT group with the SLT group. Thereafter, to avoid differences in the main confounding factors, a matched-control (1:1) cohort was designed to compare groups. Patients were matched manually based on viable tumor number and largest viable tumor size at the explant pathology. We matched patients with the exact number of viable tumors and to the closest viable tumor size ($\pm$ 1.5 cm).[18,19] All subjects had at least one unique match and the best-fitting match was used.

To determine if time to recurrence after RFA or LR had any impact on recurrence after SLT, patients in the SLT group were divided according to time to recurrence from initial treatment ($< 12$ and $\geq 12$ months).

### *Hepatocellular Carcinoma Diagnosis*

HCC diagnosis was based on the American Association for the Study of Liver Diseases (AASLD) guidelines.[2,3] Computed tomography (CT) or magnetic resonance (MR) were used as imaging techniques. In cases where the diagnosis was not confirmed, a biopsy was obtained.

### *Curative-Intent Treatments*

All patients with a diagnosis of HCC were presented and discussed in a weekly multidisciplinary tumor board and the best treatment option was then offered. The criteria to select patients for each treatment was based on the Barcelona Clinic Liver Cancer Staging System,[4,20] with some modifications outlined below.

### *Radiofrequency Ablation (RFA)*

Patients were considered eligible for RFA under the following conditions: single HCC $< 3$ cm, adequate liver function (Child–Pugh A; patients with higher Child–Pugh scores were selected on a case-by-case basis), no encephalopathy (unless currently well controlled medically) and tumors were amenable to an image-guided procedure. Patients with well controlled and moderate ascites were considered eligible if all other conditions were met. HCCs were mostly treated with LeVeen electrodes (Boston Scientific, Natick, MA, USA) or Cool-tip electrodes (Medtronic, Minneapolis, MN, USA), according to the manufacturers' recommended algorithms.

### *Liver Resection (LR)*

LR was considered in patients with resectable lesions with preserved liver function (Child–Pugh A) and no portal hypertension.[2,3] The preferred approach was an anatomical resection, ensuring a sufficient hepatic remnant to prevent postoperative liver failure.

### *Liver Transplantation (LT)*

LT was offered to those patients who did not fulfill the criteria to undergo RFA or LR. Patients were included on the waiting list if they fulfilled the Extended Toronto

Criteria on preoperative imaging, which includes patients with any size or number of HCC, provided there is no extrahepatic disease, vascular invasion, or cancer-related symptoms and the tumor is not poorly differentiated.[21–23]

All patients with recurrent HCC with eligible criteria for LT were offered an SLT. The selection criteria for patients with recurrent HCC (SLT) were similar to those presenting for PLT with previously untreated tumors. Patients were considered for transplant if HCC recurrence was within the Extended Toronto Criteria, with no contraindications to transplant identified during evaluation. In addition, the initial (previously treated) HCC was not poorly differentiated, had no radiographic vascular invasion, and had an interval time of recurrence of more than 6 months from the initial treatment.

### *Explant Pathology*

All explanted livers were available for analysis. Tumor burden was evaluated based on the number and maximum size of viable tumors.[21]

### *Follow-Up*

After curative intent treatment with LR or RFA, patients were followed with ultrasound (US) and/or CT scan and serum α-fetoprotein (AFP) every 3 months for 2 years, then every 6 months for 3 years, and annually thereafter. Follow-up after LT was based on US and/or thoraco-abdominal CT and AFP every 6 months in the first 2 years of follow-up. Thereafter, CT was performed annually or if symptoms occurred. Tumor recurrence diagnosis was based on imaging, or on biopsy if the image was non-conclusive.

### *Statistical Analysis*

Data are shown as mean ± standard deviation if normally distributed, or median and range in cases of non-normal distribution. Categorical variables were analyzed using the Chi square or Fisher's test, while continuous variables were analyzed using the Student *t* test or Mann–Whitney U test. Patient survival estimates were calculated using the Kaplan–Meier method and compared using the log-rank test. Survival was calculated from both the time of listing and the time of transplant to the time to death, or censored at the last follow-up. Cumulative risk of recurrence was calculated from the time of transplant to the time of recurrence, or censored at the last follow-up. Statistical analysis was performed using SPSS 22.0 software (IBM Corporation, Armonk, NY, USA). Follow-up was performed until September 2016.

## RESULTS

### *Study Population*

Between November 1999 and December 2014, 687 patients with HCC were listed for transplant. A total of 559 patients were transplanted and 128 were de-listed while waiting. Of those transplanted, 509 had an LT as their first treatment of HCC, and hence comprised the PLT group. 50 patients were transplanted for HCC recurrence after primary treatment with LR ($n = 25$) or RFA ($n = 25$), and hence comprised the SLT group (Fig. 1). Each of the 50 patients treated with LR or RFA were eligible for LT at the time of initial treatment. The median follow-up after listing and transplant was 70 months (2–218) and 64 months (0.5–195), respectively.

Details of patients, tumors, and recurrence patterns are outlined in electronic supplementary Table 1. There were significant differences in tumor size and number between the RFA and LR groups. The median time from RFA or LR to recurrence was 9.5 months (1–36) and 14.5 months (3–143), respectively ($p = 0.04$).

### *Salvage Liver Transplantation for Patients in the LR and RFA Groups*

The characteristics after SLT of patients initially treated with LR ($n = 25$) or RFA ($n = 25$) were analyzed, and there were no statistically significant clinical differences between the groups (data not shown).

When comparing patients' outcomes after SLT, 31% of patients treated initially with LR developed HCC recurrence post-transplant, versus 24% of patients treated with RFA ($p = 0.53$). The 1-, 3-, and 5-year cumulative risk of HCC recurrence post-transplant in LR patients was 25, 35, and 35% versus 17, 23, and 32% in patients primarily treated with RFA ($p = 0.61$). The 1-, 3-, and 5-year actuarial survival post-LT for patients with HCC primarily treated with LR was 84, 71, and 71% versus 84, 74, and 68% in patients primarily treated with RFA ($p = 0.49$).

### *Salvage and Primary LT*

The characteristics of patients listed as potential PLT and SLT recipients are summarized in Table 1. There were more patients with alcohol-induced cirrhosis in the PLT group, while the SLT group had more hepatitis B virus patients. The model for end-stage liver disease (MELD) at listing was higher in the PLT group. While awaiting SLT, 26/32 (76.5%) patients who received RFA, and 25/28 (89.3%) patients who received LR, underwent bridging therapies [with RFA, transarterial chemoembolization (TACE), or a combination of both]. The dropout rate was

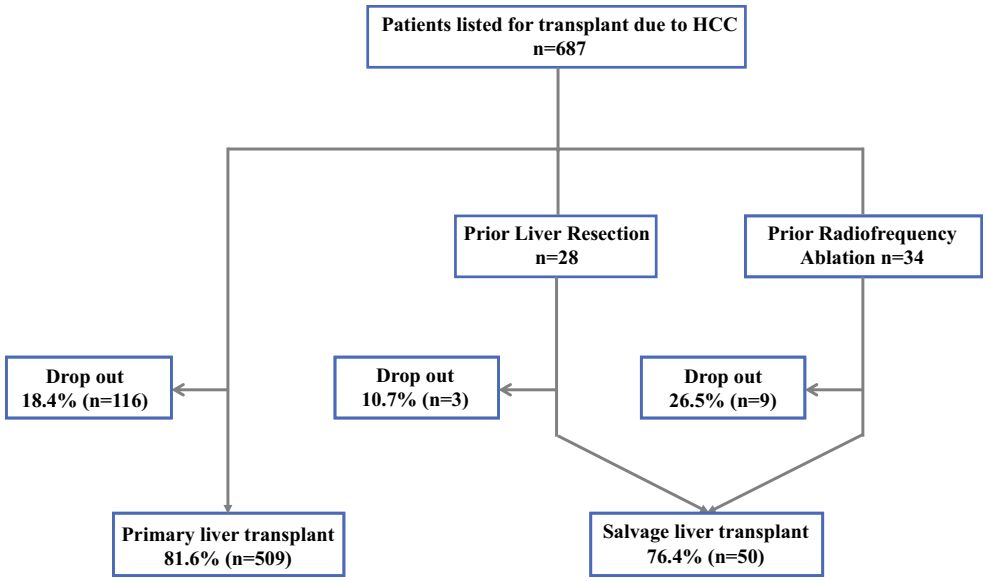


**FIG. 1** Study population classified by treatment type. *HCC* hepatocellular carcinoma

18.4% in the PLT group versus 20.6% in the SLT group ($p = 0.43$). Most patients were delisted due to HCC progression. The 1-, 3-, and 5-year actuarial survival from the time of listing was similar between the PLT and SLT groups ($p = 0.31$) (Fig. 2a).

The characteristics of transplanted patients are summarized in Table 1. Explant pathology showed a larger tumor size in the PLT group. Due to bridging therapy, some patients had no viable tumor on explant pathology after LT.

Following LT, 17.3% of patients in the PLT group and 28% of patients in the SLT group developed HCC recurrence ($p = 0.06$). The 1-, 3-, and 5-year cumulative risk of recurrence was 13, 17, and 18% in the PLT group versus 21, 29, and 33% in the SLT group ($p = 0.04$) (Fig. 2b). The 1-, 3- and 5-year actuarial survival after PLT was 86, 77, and 73% versus 84, 72, and 69% in the SLT group ($p = 0.34$) (Fig. 2c).

### *Outcomes of the Matched-Control Cohort*

Forty-eight patients were successfully matched between the PLT and SLT groups. Characteristics of both cohorts are summarized in Table 2. After matching, 20.8% of patients in the PLT group developed HCC recurrence versus 27.1% of patients in the SLT group ($p = 0.47$) (Table 2). Both the cumulative risk of recurrence after LT ($p = 0.53$) (Fig. 3a) and the actuarial survival ($p = 0.1$) (Fig. 3b) were similar between the PLT and SLT groups.

### *Post-Transplant Outcomes in Early (< 12 Months) and Late (≥ 12 Months) Recurrence After Curative Intent Treatment*

After initial curative-intent treatment with RFA or LR, 42% (21/50) of patients relapsed in < 12 months, while 58% (29/50) relapsed after 12 months. The 5-year cumulative risk of recurrence after SLT between groups was 41% versus 28% ($p = 0.56$) (electronic supplementary Fig. 1a), while the 5-year survival was 59% versus 76% ($p = 0.81$) (electronic supplementary Fig. 1b). HCC recurrence was the most common cause of death in the early recurrence group, while infectious and cardiac causes predominated in the late recurrence group (electronic supplementary Table 2).

## DISCUSSION

This is the first intention-to-treat study comparing the outcomes of PLT and SLT for the management of HCC. Since patients with early-stage HCC may be offered RFA or LR,[2,3] we combined patients who received either curative intent treatment to simulate a 'real-world' scenario and assess the outcomes of SLT after HCC recurrence following potentially curative therapies. SLT for HCC recurrence following intent to cure with LR or RFA treatments provided comparable outcomes to PLT. Therefore, we believe SLT should be offered to patients with liver recurrence following their initial treatment of HCC.

Previous reports on the outcomes of SLT after LR have reported different outcomes.[6,14,16] Adam et al. suggested that the results of SLT were inferior to those of PLT,[14]

**TABLE 1** Characteristics of PLT and SLT groups

| Characteristics | PLT ($n = 625$) | SLT ($n = 62$) | $p$ |
|---|---|---|---|
| *Demographics* | | | |
| Male (*n*) | 84% (524) | 85.7% (54) | 0.72 |
| Median age (years) | 58.1 (19.1–71.4) | 57.5 (41.8–69.2) | 0.74 |
| *Liver disease* (*n*) | | | |
| NASH | 1.9% (12) | 3.2% (2) | 0.04 |
| HCV | 51.9% (323) | 52.4% (33) | |
| HBV | 20.3% (126) | 33.3% (21) | |
| Alcohol | 14.8% (92) | 4.8% (3) | |
| Other | 11.4% (58) | 8% (4) | |
| *Listing data* | | | |
| Median wait time (months) | 5.4 (0.03–86.1) | 5.4 (0.01–21.1) | 0.74 |
| Median MELD at the time of listing | 11 (6–35) | 8 (6–19) | $< 0.001$ |
| Median serum AFP (ng/mL) at the time of listing | 12 (2–93,787) | 11 (1–1094) | 0.51 |
| Median number of maximum tumours | 2 (1–12) | 2 (0–10) | 0.26 |
| Median size of largest maximum tumour (cm) | 2.9 (1–24) | 2.5 (1–14.3) | 0.01 |
| In-Milan criteria | 62.4% (385) | 61.3% (38) | 0.86 |
| Bridged to transplant (*n*) | 60.7% (379) | 84.1% (53) | |
| RFA | 63.3% (240) | 79.2% (42) | 0.05 |
| TACE | 26.4% (100) | 20.8% (11) | |
| PEI | 5% (19) | 0% (0) | |
| Radioactivity | 5.3% (19) | 0% (0) | |
| *De-listed patients* (*n*) | 18.4% (115) | 20.6% (13) | 0.67 |
| Causes of de-listing | | | |
| Tumor progression | 84.8% (95) | 84.6% (11) | 0.43 |
| Liver decompensation | 12.5% (14) | 7.7% (1) | |
| Other causes | 2.7% (3) | 7.7% (1) | |
| | $n = 509$ | $n = 50$ | |
| *Transplanted patients* | | | |
| Median wait times (months) | 5 (0.03–61.4) | 6.4 (0.01–20.3) | 0.53 |
| *Explant pathology* | | | |
| Median number of viable tumuors | 2 (1–100) | 2 (0–20) | 0.66 |
| Median size of largest viable tumour (cm) | 2.7 (0–33) | 2 (0–15) | 0.025 |
| Tumour differentiation (*n*) | | | |
| Well | 18% (80) | 26.8% (11) | 0.06 |
| Moderate | 72.1% (320) | 73.2% (30) | |
| Poor | 9.9% (44) | 0% (0) | |
| Vascular invasion (*n*) | | | |
| Yes | 27.1% (138) | 34% (17) | 0.52 |
| Not assessed | 4.9% (25) | 6% (3) | |

*NASH* non Alcoholic steatohepatitis, *HCV* Hepatitis C Virus, *HBV* Hepatitis B Virus, *MELD* Model for end-stage liver disease, *AFP* alpha fetoprotein, *TACE* transarterial chemoembolization, *PEI* percutaneous alcohol injection, *RFA* radiofrequency ablation

while other studies have suggested that SLT for HCC recurrence following LR is feasible and good post-transplant outcomes can be achieved.[6,10,12,16,17] However, the majority of studies focused on the outcomes of patients with recurrence following LR rather than RFA. Many studies were confounded by including patients transplanted for liver decompensation after resection rather than tumor recurrence. Finally, none of these studies attempted to match cancer recurrence risk factors in the comparison groups.

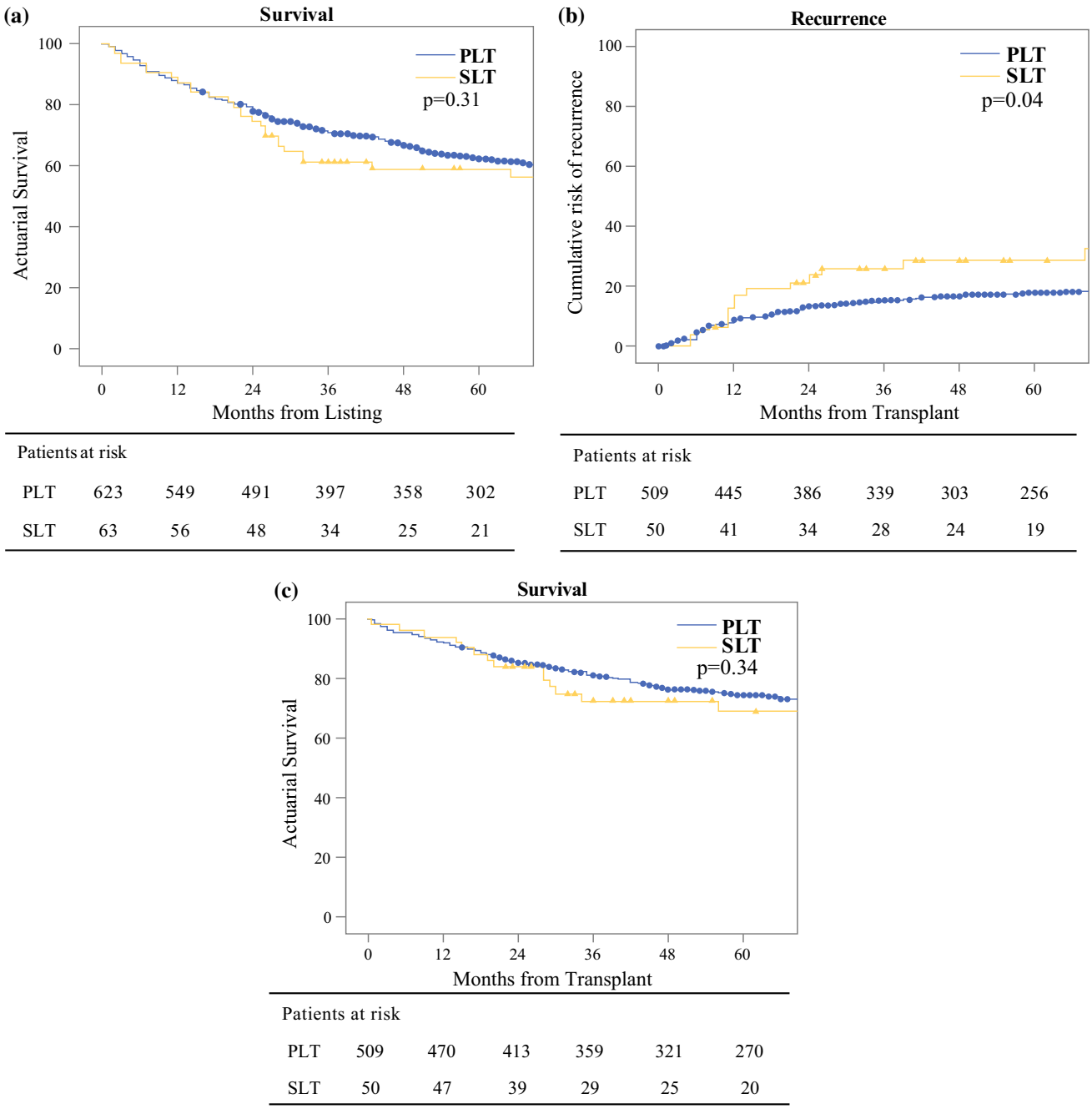


**FIG. 2** Actuarial patient survival and cumulative risk of recurrence in the unmatched cohort. **a** Intention-to-treat actuarial survival analysis (from the time of listing); **b** cumulative risk of recurrence (from the time of transplant); **c** actuarial survival (from the time of transplant). *PLT* primary liver transplant, *SLT* salvage liver transplant

In the present analysis, patients transplanted for liver decompensation were excluded to accurately assess the oncological outcomes. The 5-year survival of listed patients in the SLT and PLT groups was similar. Both groups had a comparable number of dropouts, mostly due to tumor progression. After the groups were matched, the outcomes of SLT were similar to those of PLT. SLT offered a 5-year survival of 70%, which is within the accepted minimal 5-year survival of 50–60%.[24] Recurrence was also similar between the PLT and SLT groups. Our results are consistent with a recent intention-to-treat subgroup from a meta-analysis showing a comparable 5-year overall survival for SLT and PLT (62% vs. 63%, respectively).[25]

**TABLE 2** Characteristics of the PLT and SLT matched cohort

| Characteristics | PLT ($n = 48$) | SLT ($n = 48$) | $p$ |
|---|---|---|---|
| *Demographics* | | | |
| Male (*n*) | 79.2% (38) | 87.5% (42) | 0.27 |
| Median age (years) | 58.2 (43.7–68.7) | 57.5 (41.8–69.2) | 0.82 |
| *Liver disease* (*n*) | | | |
| NASH | 2.1% (1) | 4.2% (2) | 0.09 |
| HCV | 50% (25) | 50% (25) | |
| HBV | 18.8% (9) | 35.4% (17) | |
| Alcohol | 12.5% (6) | 2.1% (1) | |
| Other | 14.6% (7) | 6.3% (3) | |
| *Transplant data* | | | |
| Median wait time (Months) | 3.4 (0.2–52) | 6.4 (0.01–20.3) | 0.16 |
| Median MELD at the time of LT | 12.5 (7–29) | 8 (6–19) | $< 0.001$ |
| Median serum AFP (ng/mL) at the time of LT | 9 (3–20,303) | 9 (1–161) | 0.88 |
| *Explant pathology* | | | |
| Median number of viable tumours | 2 (0–20) | 2 (0–20) | 1 |
| Median size of largest viable tumour (cm) | 1.8 (0–7.5) | 2 (0–8) | 0.8 |
| Tumour differentiation (*n*) | | | |
| Well | 33.3% (14) | 28.2% (11) | 0.31 |
| Moderate | 61.9% (26) | 71.8% (28) | |
| Poor | 4.8% (2) | 0% (0) | |
| Vascular invasion (*n*) | | | |
| Yes | 19.8% (19) | 31.5% (15) | 0.18 |
| No | 60.4% (29) | 62.5% (30) | |
| Not assessed | 0% (0) | 6% (3) | |

*NASH* non alcoholic steatohepatitis, *HCV*: Hepatitis C Virus, *HBV* Hepatitis B Virus, *MELD* Model for end-stage liver disease, *AFP* Alpha fetoprotein

Early recurrence (< 12 months) after cancer treatments has been described as a surrogate marker for tumor aggressiveness.[12] Our data support this hypothesis as the risk of recurrence after SLT was 41% in patients with early recurrence compared with 28% in those with late recurrence. The very nature of selecting recurrent HCC tumors after RFA or LR in the SLT group may be selecting more aggressive tumor biology. Due to the relatively small sample size (leading to a type II error), we were unable to find statistically significant differences.

In the last decade, RFA has been shown to be an effective and curative treatment for early HCC.[2,5–8] In most jurisdictions, RFA has become the preferred treatment for patients with single HCC $\leq$ 2 cm who are not granted MELD exception points and whose calculated MELD score is usually very low, precluding listing for an organ transplant.[24] Therefore, RFA seems an adequate treatment, with the caveat that tumor recurrence after ablation is high and the optimal treatment after recurrence is not well described.[2,5–8] There is scarce information on the outcomes of SLT for recurrent HCC after RFA. In their series, N'Kontchou et al. reported 21 patients who were transplanted for HCC recurrence following RFA, and found similar outcomes to patients who were primarily transplanted.[6] Similarly, our results suggest that the results after SLT for recurrent HCC following RFA (5-year survival of 68%) are satisfactory and comparable with PLT. Therefore, SLT post-RFA treatment may represent a good option.

Not surprisingly, the LR group had a larger proportion of multifocal tumors and tumors had a larger size compared with the RFA group. The current guidelines do not provide a clear cut-off for tumor size when offering LR,[2,3] and some studies have shown good results with resection of multifocal HCC.[26,27] Therefore, at our institution, we offer LR to patients without portal hypertension and resectable tumors. Interestingly, time to recurrence was longer in patients treated with LR compared with RFA. The recurrence pattern post-LR was concordant with a previous single-center study including more than 600 patients.[28] Post-transplant outcomes (survival and tumor recurrence) following SLT after LR or RFA were comparable.

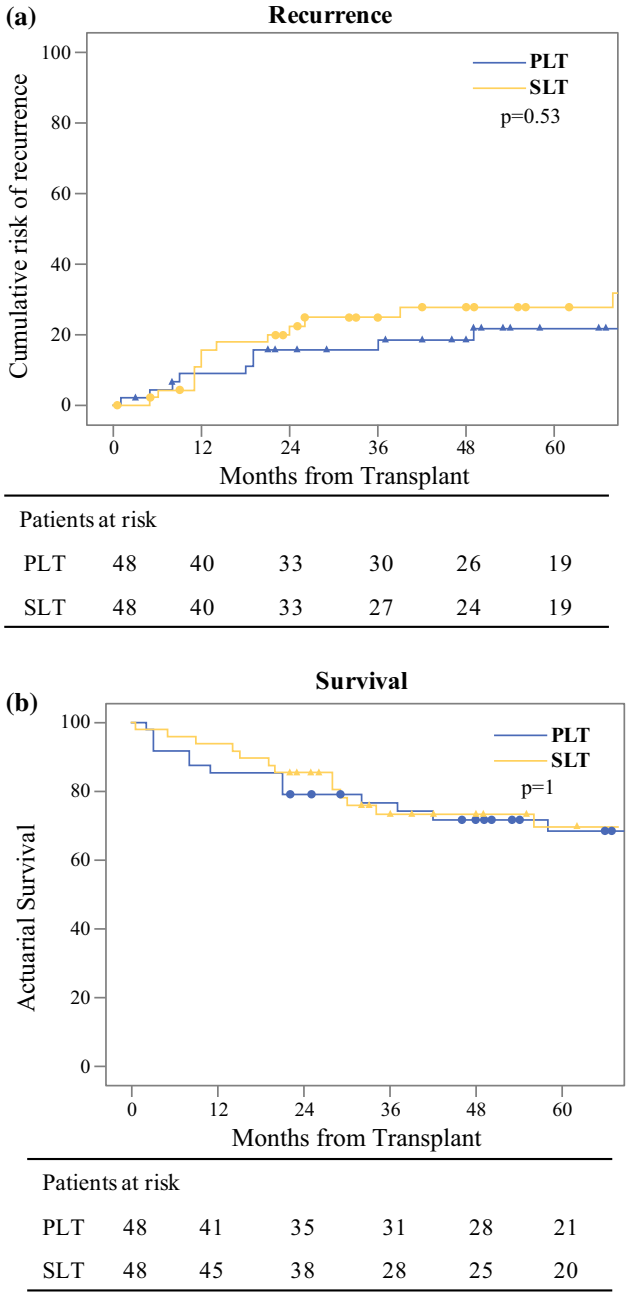


**FIG. 3** Actuarial patient survival and cumulative risk of recurrence in the matched cohort. **a** Cumulative risk of recurrence (from the time of transplant); **b** actuarial survival (from the time of transplant). *PLT* primary liver transplant, *SLT* salvage liver transplant

Our study had several limitations. The current study sample size is relatively small, increasing the risk of type I and II errors. We did not have access to the whole cohort of patients since the time of LR or RFA, therefore the analysis examined events after listing. Some data were collected retrospectively. Nevertheless, our study provides important information on the results of SLT for HCC recurrence following intention-to-cure treatments.

## CONCLUSION

SLT is a potential therapy for HCC recurrence following intent to cure with LR or RFA. The results are similar to PLT, with a 5-year survival of 70%. Further studies are warranted to examine on an intention-to-treat basis from the time of LR and RFA.

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