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ORIGINAL ARTICLE

# Long-term survival comparison between primary transplant and upfront curative treatment with salvage transplant for early stage hepatocellular carcinoma☆,☆☆

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**Summary** *Background:* Whether primary liver transplantation (PLT) or upfront curative treatment with salvage liver transplantation (SLT) is a better treatment option for early hepatocellular carcinoma (HCC) is controversial. This study aims to compare the long-term survival starting from the time of primary treatment between the two approaches for early HCC using propensity score matching (PSM) analysis.
*Methods:* From 1995 to 2014, 175 patients with early HCC undergoing either PLT (n = 149) or SLT (n = 26) were retrospectively reviewed in a prospectively collected database. Patients' demographic data, tumor characteristics, short-term and long-term outcome were compared between two groups after PSM.
*Results:* After matching, the baseline characteristics were comparable between mPLT group (n = 45) and mSLT group (n = 25). The tumor recurrence rate after transplant was significantly higher in mSLT group than mPLT group (28% vs. 15.6%). Calculating from the time of primary treatment, the 1, 3, and 5-year overall survival rates were comparable between mPLT group (97.8%, 91.1% and 86.3%) and mSLT group (100%, 95% and 85%). However, the 1, 3,

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and 5-year recurrence-free survival rates were significantly better in mPLT group than mSLT group (95.6% vs. 90%, 86.6% vs. 80% and 84.3% vs. 70%). SLT approach and high pre-treatment serum alpha-fetoprotein level (>200 ηg/mL) were poor prognostic factors for recurrence-free survival after transplant.
*Conclusions:* PLT may be a better treatment option for early HCC, whereas SLT approach for HCC should be cautiously considered under the circumstance of organ shortage.


## 1. Introduction

Hepatocellular carcinoma is the commonest primary liver malignancy and it has a global incidence of more than 850,000 new cases annually.[1] Liver resection (LR), radiofrequency ablation (RFA) and primary liver transplantation (PLT) are regarded as curative treatment options for early hepatocellular carcinoma (HCC) within Milan criteria.[2] There are pros and cons associated with these treatment options. PLT seems to be the most effective treatment eliminating both tumor and the underlying chronic liver disease, which is at risk of developing de novo HCC. Nonetheless, the organ shortage, the resulting long waiting time and the high drop-out rate limit its wide application. In contrast, LR and RFA are readily available treatment options and are potentially curative for early HCC in patients with compensated liver function. Long-term favorable survival outcome of these treatment modalities has been reported.[3,4] However, high intrahepatic recurrence (up to 80%) occurs because of intrahepatic metastasis from primary tumor as well as carcinogenesis from the underlying chronic liver disease.[5] Over the years, the approach of upfront LR and salvage liver transplantation (SLT) for intrahepatic recurrence has been practiced in many centers.[6,7]

There are potential advantages associated with upfront LR or RFA and delaying liver transplantation for intrahepatic recurrence (SLT approach). By upfront LR or RFA, a proportion of patients would remain recurrence-free and need no further treatment. In such circumstance, the prestigious source of liver graft can be reserved for other patients who need LT in urgent base. Although technically demanding, SLT approach offers a reasonably good chance of long-term survival for patients with recurrent HCC, which might not be effectively treated by other treatment modalities, namely hepatic re-resection, local ablative therapy and trans-arterial chemoembolization.

Previous studies have reported the survival outcome comparing SLT with PLT with conflicting results.[8–10] One reason was the heterogeneous way of patient grouping for comparison. Moreover, the time point for the calculation of survival was set at the time of transplantation rather than the time of primary treatment, which was inappropriate for SLT approach. Therefore, the present study aims to evaluate the long-term survival outcome starting from the time of primary treatment in patients with early HCC receiving either PLT or SLT approach using propensity score matching (PSM) analysis.

## 2. Methods

### 2.1. Patient selection

From January 1995 to December 2014, 175 adult patients with early HCC received liver transplantation at the Department of Surgery, The University of Hong Kong. Early HCC was defined as those within Milan criteria[11] (single tumor $\leq$ 5 cm, or $\leq$ 3 tumors, each $\leq$ 3 cm). Among these patients, 149 patients received liver transplantation as primary treatment (PLT group), whereas 26 patients underwent upfront LR or RFA and SLT for intrahepatic recurrence (SLT group). In SLT group, tumor status was within Milan criteria at the time of both primary treatment and liver transplantation. Tumor histological examination were performed in all patients in both groups. Patients received liver transplantation for HCC outside Milan criteria, those with incidental finding of HCC in liver explant after transplant and those in whom no HCC was found in primary treatment despite positive findings on preoperative imaging studies were excluded from the present study.

### 2.2. Management protocol for patient with early HCC within Milan criteria

The diagnosis of HCC was based on the diagnostic criteria for HCC used by the European Association for the Study of the Liver.[12] HCC was diagnosed when the radiologic imaging techniques (spiral contrasted CT scan or contrasted MRI) showed typical features of HCC (contrast enhancement in the arterial phase and rapid wash-out of contrast in the venous/late phase) and/or the serum alpha fetoprotein (AFP) level was elevated (>400 ηg/mL). Percutaneous liver biopsy was not performed in the authors' center because of the risk of needle tract metastasis.

LR was the preferred curative treatment modality in patients with early HCC and preserved liver function in authors' center. The selection criteria and surgical techniques of LR have been described previously.[3] In summary, the extent of resection depended on the anatomical location of the tumor. The aim of surgery was to obtain a 1-cm tumor-free margin after resection. For patients with borderline liver function which precludes curative LR, RFA was considered. Details of techniques of RFA in the authors' center were described previously.[13] The aim of ablation was to achieve complete tumor necrosis with ablation of a 1 cm-margin of non-tumorous tissue. Tru-cut tumor biopsy

was routinely obtained before RFA for detailed tumor histological examination. A spiral contrasted CT scan was performed 4 weeks after the procedure to assess the completeness of ablation. Further RFA was carried out in case of incomplete ablation as shown by CT scan.

For patients with marginal liver function (Child-Pugh class B or C or clinically significant portal hypertension), LT was adopted. Patient evaluation and surgical techniques of LT for early HCC in authors' center was described previously.[14,15] In brief, tumor status was assessed by contrast CT scan or MRI. Bone scan or positron emission tomography (PET) was also performed. Presence of major vascular invasion by tumor and distant metastasis precluded LT. In authors' center, the University of Columbia San Francisco (UCSF) criteria[16] was adopted to enlist patients with HCC. Since Milan criteria was widely adopted worldwide for HCC patients enlisting for LT, the patient selection of the present study was restricted to those within Milan criteria. Model for end-stage liver disease (MELD)[17] was adopted to prioritize deceased donor liver transplantation (DDLT). Bridging therapy using transarterial chemoembolization (TACE), high intensity focused ultrasound (HIFU) or selective internal radiation therapy (SIRT) were considered for tumor control after patients were enlisted. Living donor liver transplantation (LDLT) was considered for patients in a voluntary basis. All living donors were evaluated through a multidisciplinary approach. They should have no medical illnesses that would increase the operative risk and they should not be hepatitis carrier. In terms of recipient—donor matching of liver volume, the authors' center adopted graft weight to estimated standard liver volume ratio as 35% or graft weight to recipient weight ratio as 0.8% for recipients and remnant liver volume as 30% for donors.[14] The waiting time for both DDLT and LDLT was calculated from the time of enlisting to the time of LT.

### 2.3. Surveillance and treatment of recurrence after primary treatment

All patients underwent CT scan of abdomen and thorax and measurement of serum AFP level at 3-month intervals after primary treatment for surveillance of recurrence. The same diagnostic criteria as primary tumor was adopted to define intrahepatic recurrence.[2] PET scan was performed in selected patients with suspicious extrahepatic metastasis. In patients undergone LR or RFA, treatment options for intrahepatic recurrence included SLT, hepatic re-resection, repeated RFA and TACE. The selection criteria for hepatic re-resection and repeated RFA followed that of primary treatment. SLT was considered when intrahepatic recurrence could not be treated by resection or RFA because of tumor location or poor liver function, and the recurrent tumor was still within Milan criteria. The management protocol and treatment strategy for recurrence after SLT were the same as PLT. In case of extrahepatic metastasis, systemic therapy was considered in selected patients.

### 2.4. Short-term outcome

Post-transplant short-term outcome included the duration of stay in intensive care unit, hospital mortality, early significant postoperative complications according to Clavien—Dindo classification[18] and hospital stay. Hospital mortality was defined as patient death within the same admission of transplant.

### 2.5. Long-term outcome

The cumulative long-term overall and recurrence-free survival rates were calculated from the time of primary treatment (LT in PLT group and LR or RFA in SLT group). In SLT group, since all patients recurred after primary treatment (hepatectomy or RFA), the calculation of recurrence-free survival rate was set at the time points whether patients developed tumor recurrence after liver transplantation, and the starting time was that of primary treatment. Hospital deaths were included in the overall survival analysis but were excluded from the recurrence-free survival analysis. Clinicopathologic variables of potential prognostic value were analyzed for their effects on overall and recurrence-free survival.

### 2.6. Statistical analysis

All data were prospectively collected by a research assistant and computerized in a database. Statistical analysis was performed by Chi-square test with Yates' correction or the Fisher's exact test to compare categorical variables and Mann—Whitney U test to compare continuous variables. The comparison of patient demographics and tumor characteristics between groups was made at the time of primary treatment. Propensity scores were generated using a multivariable logistic regression model based on the selected co-variables which were associated with the treatment approaches. Matching process using the nearest neighboring method was performed to match patients in PLT and SLT groups in 2:1 ratio. The process of sampling without replacement was adopted. After PSM, the paired *t*-test and the Wilcoxon signed rank test are used for comparing differences in continuous variables, whereas McNemar's test was used to compare categorical variables.[19,20] Univariate analysis using Cox proportional hazards regression model were performed to identify the significant prognostic factors affecting overall and disease-free survival rates. Results of the univariate analysis were presented as hazard ratio with a corresponding 95% confidence interval. Cumulative overall and disease-free survival rates were computed by the Kaplan—Meier method and compared by Log-rank test between mPLT and mSLT groups. All the survival rates were calculated starting at the time of primary treatment. All statistical tests were two-sided and a significant difference was considered when $P < 0.05$. All analyses were performed on an intention-to-treat basis. SPSS version 24.0 statistical software (SPSS, Chicago, Illinois, US) was used for statistical analyses.

## 3. Results

### 3.1. At the time of primary treatment

The patient demographics and tumor characteristics of PLT and SLT groups were shown in Table 1. There was no

**Table 1** Patient demographics and tumor characteristics of PLT group and SLT group at the time of primary treatment before and after propensity score matching.

| Characteristics | Before matching | | | After matching | | |
|---|---|---|---|---|---|---|
| | PLT group (n = 125) | SLT group (n = 26) | *P* value | mPLT group (n = 45) | mSLT group (n = 25) | *P* value |
| Age | 54 (30–68) | 51 (35–63) | 0.208 | 53 (30–58) | 50 (36–61) | 0.061 |
| Male:female | 100:25 | 23:3 | 0.464 | 38:7 | 22:3 | 0.834 |
| Hepatitis B viral infection | 99 (79.2) | 23 (88.5) | 0.414 | 36 (80) | 22 (88) | 0.861 |
| Hepatitis C viral infection | 18 (14.4) | 3 (11.5) | 0.942 | 6 (13.3) | 3 (12) | 1.000 |
| Child-Pugh classification | | | 0.001[a] | | | 0.855 |
| Class A | 54 (43.2) | 21 (80.8) | | 37 (82.2) | 20 (80) | |
| Class B | 41 (32.8) | 5 (19.2) | | 9 (17.7) | 5 (20) | |
| Class C | 30 (24) | 0 | | 0 | 0 | |
| MELD | 12 (6–59) | 8 (6–14) | <0.001[a] | 8 (6–25) | 8 (6–14) | 0.093 |
| Size of largest tumor (cm) | 2.5 (1–5) | 2.7 (1–5) | 0.141 | 2 (1–5) | 2.8 (1–4.6) | 0.727 |
| No. of tumor nodules | | | 0.001[a] | | | 0.063 |
| One | 91 (72.8) | 18 (69.2) | | 37 (82.2) | 18 (72) | |
| Two | 29 (23.2) | 5 (19.2) | | 5 (11.1) | 5 (20) | |
| Three | 5 (4) | 3 (11.5) | | 3 (6.6) | 2 (8) | |
| Serum AFP level (ηg/ml) | 20 (1–11,210) | 47 (4–25,550) | 0.035[a] | 21 (3–1443) | 35 (4–2555) | 0.081 |
| Tumor differentiation | | | 0.482 | | | 0.523 |
| Well-differentiated | 44 (35.2) | 7 (26.9) | | 17 (37.7) | 7 (28) | |
| Moderately differentiated | 67 (53.6) | 17 (65.3) | | 25 (55.5) | 17 (68) | |
| Poorly differentiated | 5 (4) | 2 (7.6) | | 3 (6.6) | 1 (4) | |
| Microvascular invasion | 30 (24) | 5 (19.2)[b] | 0.281 | 11 (24.4) | 5 (20)[b] | 0.124 |
| Presence of satellite nodules | 1 (0.8) | 0 | 1.000 | 1 (2.2) | 0 | 1.000 |

Continuous variables are expressed as median with range.
Categorical variables are expressed as number of patients (percentage).
MELD, model for end-stage liver disease; AFP, alpha fetoprotein.
[a] Statistically significant.
[b] Presence of microvascular invasion referred to the tumor status at the time of liver resection and this cannot be adequately assessed in patients undergone RFA.

statistically significant difference in age, sex, proportion of patients with hepatitis B or C viral infection between the two groups. Patients in PLT group had significantly worse liver function than SLT group, in terms of Child-Pugh classification and MELD score. The maximal tumor size was similar between the two groups. More patients in SLT group had multiple tumors (up to 3 tumors) than those in PLT group. The preoperative serum AFP level was significantly higher in SLT group (median = 47 ηg/ml) than PLT group (median = 20 ηg/ml). The pathological characteristics of tumor was similar between two group with regards to the tumor differentiation, presence of microvascular invasion and satellites nodules.

PSM was performed to match the preoperative factors that were significantly different between PLT and SLT groups. These factors included MELD score, number of tumor nodules and pre-treatment serum AFP level. There were 45 patients in mPLT (matched primary liver transplant) group matching with 25 patients in mSLT (matched salvage liver transplant) group and the patient demographic and tumor characteristics of two matched groups were shown in Table 1. Essentially, all the patient demographic and tumor characteristics were comparable between the two matched groups (mPLT and mSLT groups).

### 3.2. Recurrence after primary treatment in mSLT group

In mSLT group, 15 patients underwent LR, whereas 10 patients received RFA. Major and minor hepatectomy were performed in 4 patients (right hepatectomy, n = 3; left hepatectomy plus caudate lobectomy, n = 1) and 11 patients (segmentectomy, n = 10; left lateral sectionectomy, n = 1), respectively. For patients undergone RFA, it was performed through percutaneous (n = 4), laparaoscopic (n = 2) and open approach (n = 4). Complete ablation was achieved in all patients as shown by postoperative CT scan performed one month after the procedure. Following primary treatment (LR or RFA), patients in mSLT group developed intrahepatic recurrence within Milan criteria at the median interval of 17 months (range: 6–122 months). Eleven patients (44%) developed early recurrence within one year, whereas 14 patients (56%) had late recurrence occurring more than one year.

### 3.3. At the time of liver transplantation

The operative details of both groups at the time of liver transplantation were shown in Table 2. There was no

**Table 2** Operative details of mPLT group and mSLT group at the time of liver transplantation.

| Parameters | mPLT group (n = 45) | mSLT group (n = 25) | *P* value |
|---|---|---|---|
| Waiting time on transplant list (days) | 42 (1–288) | 30 (5–260) | 0.728 |
| LDLT:DDLT | 35:10 | 20:5 | 0.898 |
| Donor sex (male:female) | 32:13 | 10:15 | 0.756 |
| Donor age (years) | 37 (16–67) | 35 (18–57) | 0.779 |
| Donor body weight (kg) | 57.8 (41–80) | 59.8 (49–78) | 0.509 |
| GW (gm) | 675 (265–1800) | 607 (455–1990) | 0.176 |
| GRWR | 1 (0.5–2.1) | 0.9 (0.6–2.4) | 0.236 |
| GW to ESLV (%) | 60 (28–126) | 52 (39–118) | 0.174 |
| Blood transfusion (unit) | 3 (2–40) | 3 (0–25) | 0.964 |
| Graft cold ischemic time (min) | 124 (62–610) | 116 (60–600) | 0.143 |
| Recipient warm ischemic time (min) | 51 (25–102) | 45 (30–82) | 0.075 |
| Operative time (min) | 610 (300–1120) | 735 (385–1100) | 0.087 |

Continuous variables are expressed as median with range.
Categorical variables are expressed as number of patients.
LDLT, living donor liver transplant; DDLT, deceased donor liver transplant; GW, graft weight; GRWR, graft to recipient weight ratio; ESLV, estimated standard liver volume.

significant difference in waiting time on transplant list in both groups. The proportion of patients receiving LDLT was similar in both groups. Other parameters were similar between two groups, including donor characteristics, graft weight, operative time, requirement of blood transfusion, graft cold ischemic time and recipient warm ischemic time.

### 3.4. Short-term outcome

The short-term outcome was assessed both at the time of primary and liver transplantation. At the time of primary treatment, mPLT group had longer intensive care unit stay, more early postoperative complications and longer hospital stay than mSLT group (Table 3). At the time of liver transplantation, the duration of intensive care unit stay was similar in both groups. There was no hospital mortality in both groups. However, in PLT group before matching, there is one hospital mortality (0.8%). More patients in mPLT group developed early postoperative complications than mSLT group (55% vs. 20%). Majority of them suffered from pulmonary complications, wound infection and intra-abdominal collection requiring radiological intervention. Patients in mPLT group developed more severe post-operative complications (Clavien–Dindo grade IIIa or above) than those in mSLT group (17.7% vs. 8%). The median hospital stay was similar between mPLT group and mSLT group (16 days vs. 12 days) (Table 4).

### 3.5. Long-term outcome

With median follow-up of 73 months, the overall tumor recurrence rate following transplantation was higher in

**Table 3** Short-term outcome of mPLT group and mSLT group following primary treatment.

| Parameters | mPLT group (n = 45) | mSLT group[a] (n = 25) | *P* value |
|---|---|---|---|
| Intensive care unit stay (days) | 4 (3–19) | 1 (0–5) | 0.003[b] |
| Hospital mortality | 0 | 0 | 1.000 |
| Early postoperative complications | 25 (55) | 7 (28) | 0.021[b] |
| Pulmonary complications | 23 | 3 | |
| Wound infection | 2 | – | |
| Intraabdominal collection/abscess | 3 | 4 | |
| Intraabdominal bleeding | 5 | – | |
| Vascular complications | 1 | – | |
| Renal failure | 3 | – | |
| Opportunistic infection | 1 | – | |
| Severe postoperative complications[c] | 8 (17.7) | 1 (4) | 0.037[b] |
| Hospital stay (days) | 14 (7–105) | 8 (3–26) | 0.001[b] |

Continuous variables are expressed as median with range.
Categorical variables are expressed as number of patients.
[a] Primary treatment included hepatectomy and radiofrequency ablation in mSLT group.
[b] Statistically significant.
[c] Clavien–Dindo grade IIIa or above.

**Table 4** Short-term outcome of mPLT group and mSLT group following liver transplantation.

| Parameters | mPLT group (n = 45) | mSLT group (n = 25) | *P* − value |
|---|---|---|---|
| Intensive care unit stay (days) | 4 (3−19) | 3 (2−7) | 0.310 |
| Hospital mortality | 0[c] | 0 | 1.000 |
| Early postoperative complications | 25 (55) | 5 (20) | 0.001[a] |
| Pulmonary complications | 23 | 3 | |
| Wound infection | 2 | − | |
| Intraabdominal collection/abscess | 3 | 2 | |
| Intraabdominal bleeding | 5 | − | |
| Vascular complications | 1 | − | |
| Renal failure | 3 | − | |
| Opportunistic infection | 1 | − | |
| Severe postoperative complications[b] | 8 (17.7) | 2 (8) | 0.046[a] |
| Hospital stay (days) | 14 (7−105) | 12 (8−30) | 0.064 |

Continuous variables are expressed as median with range.
Categorical variables are expressed as number of patients.
[a] Statistically significant.
[b] Clavien−Dindo grade IIIa or above.
[c] There is one hospital mortality in PLT group before matching (0.8%).

mSLT group than mPLT group (28% vs. 15.5%). There was higher proportion of patients in mSLT group developing extrahepatic metastases than those in mPLT group (20% vs. 8.8%). These patients were mainly treated by systemic therapy (Table 5). Calculating from the time of primary treatment, the 1, 3, and 5-year overall survival rates were comparable between mPLT group (97.8%, 91.1% and 86.3%) and mSLT group (100%, 95% and 85%) ($P = 0.611$) (Fig. 1a). However, the 1, 3, and 5-year recurrence-free survival rates were significantly better in mPLT group (95.6%, 86.6% and 84.3%) than mSLT group (90%, 80% and 70%). ($P = 0.049$) (Fig. 1b) On univariate analysis of potential prognostic factors affecting overall survival, high pre-treatment serum AFP (>200 ηg/mL) was associated with poor overall survival (Table 6). Regarding potential prognostic factors affecting recurrence-free survival, univariate analysis identified three poor prognostic factors, which were SLT approach, high pre-treatment serum AFP (>200 ηg/mL) and microvascular invasion of tumor (Table 7).

## 4. Discussion

This retrospective cohort study demonstrates that, using PSM analysis, the overall survival is comparable between PLT and SLT, when the survival is calculated from the time of primary treatment. However, the recurrence-free survival is significantly better in PLT than SLT. Both approaches seem to be viable treatment option for early HCC. Nonetheless, under the circumstance of organ shortage, SLT approach should be cautiously considered in view of high recurrence rate.

Survival comparison between PLT and SLT, particularly recurrence-free survival, has been reported by various retrospective studies with conflicting results.[8,21,22] A meta-analysis focusing on this issue has shown that the overall survival was comparable between PLT and SLT.[23] However, these studies have limitation of adopting the timing of transplantation as the starting point of the calculation of patients' survival. This is particularly unrealistic and unfair

**Table 5** Tumor recurrence after transplantation in mPLT group and mSLT group.

| Parameters | mPLT group (n = 45) | mSLT group (n = 25) | *P* value |
|---|---|---|---|
| Tumor recurrence pattern | | | 0.042[a] |
| No recurrence | 38 (84.4) | 18 (72) | |
| Intrahepatic recurrence | 3 (6.6) | 1 (4) | |
| Extrahepatic recurrence | 4 (8.8) | 5 (20) | |
| Both intrahepatic and extrahepatic recurrence | 2 (4.4) | 1 (4) | |
| Treatment modality for recurrence | | | |
| Hepatic resection | 1 (0.6) | − | |
| Radiofrequency ablation | 1 (0.6) | 1 (3.8) | |
| Transarterial chemoembolization | 2 (2.6) | 1 (3.8) | |
| Systemic therapy | 1 (0.6) | 4 (16) | |
| No active treatment | 2 (2.6) | 1 (3.8) | |

Categorical variables are expressed as number of patients (percentage).
[a] Statistically significant.

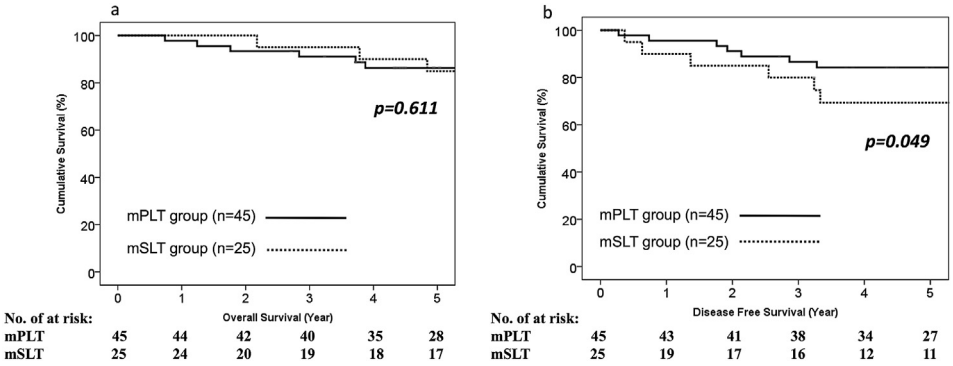


**Figure 1** (a) Overall survival rates in matched PLT group and matched SLT group (b) Recurrence-free survival rate in matched PLT group and matched SLT group.

for SLT approach as those patients received upfront curative treatment (LR) at the starting point of HCC treatment. Hence, to make a reasonable survival comparison between PLT and SLT approaches, the starting point of survival calculation should be that of primary treatment, i.e. transplantation in PLT and LR in SLT. This essential information is rarely reported in the literature. Fuks et al[24] carried out an intention-to-treat analysis comparing PLT and upfront LR with SLT for recurrence and the overall and disease-free survival were found to be similar between the two groups. However, another intention-to-treat analytical study by Bhangui et al[25] showed better overall and disease-free survival in PLT than LR with SLT. One of the reason for this discrepancy was the heterogeneous way of patient grouping for analysis, in which PLT and SLT groups was not comparable with each other. It is, however, unrealistic and unethical to carry out randomized controlled trial for this topic. Thus, the present study utilizes PSM analysis to provide valuable information on the long-term survival outcome starting from the time of primary treatment in patients with early HCC between PLT and SLT approaches. Such information is rarely reported in the literature. Because of intrinsic selection bias between the two approaches in the authors' center, patients in PLT group had significantly worse liver function, whereas patients in SLT group had potentially more aggressive tumors (multiple tumors and high pre-treatment AFP level). After PSM, the baseline demographic and tumor characteristics were comparable between two matched groups. This allowed fair comparison of long-term outcome between the two matched groups.

An important finding of the present study is that the 5-year overall survival rate was comparable between PLT and SLT (86.3% vs. 85%) but the 5-year recurrence-free survival

**Table 6** Univariate analysis of potential prognostic factors affecting overall survival.

| Variables | HR (95% CI) | *P* value |
|---|---|---|
| Sex (female) | 3.265 (0.327—6.987) | 0.252 |
| Age (>50 years) | 1.123 (0.453—1.863) | 0.662 |
| Hepatitis B viral infection | 1.182 (0.370—2.197) | 0.714 |
| Hepatitis C viral infection | 2.635 (0.819—2.491) | 0.741 |
| Child-Pugh grading | 1.891 (0.699—2.346) | 0.842 |
| MELD (>10) | 0.946 (0.457—1.612) | 0.412 |
| Tumor size (>3 cm) | 1.431 (0.567—1.789) | 0.454 |
| Multiple tumors | 1.663 (0.786—2.802) | 0.363 |
| Microvascular invasion | 2.046 (0.729—3.267) | 0.257 |
| Tumor differentiation | 0.926 (0.157—2.833) | 0.661 |
| Serum AFP level (>200 ηg/ml) | 3.845 (1.158—4.232) | 0.023* |
| SLT approach | 1.224 (0.961—3.757) | 0.116 |
| Post-transplant complications | 1.394 (0.569—2.191) | 0.748 |
| LDLT as type of transplant | 1.794 (0.976—3.768) | 0.283 |
| Waiting time on list (>5 days) | 0.692 (0.313—1.528) | 0.230 |
| Donor age (>50 years) | 1.735 (0.895—3.682) | 0.270 |
| Graft weight to recipient ESLV (<40%) | 2.312 (0.571—3.160) | 0.782 |
| Graft cold ischemic time (>110 min) | 0.930 (0.654—2.025) | 0.862 |
| Recipient warm ischemic time (>55 min) | 0.682 (0.512—1.483) | 0.768 |
| Blood transfusion (>5 units) | 0.678 (0.547—2.384) | 0.769 |

HR, hazard ratio; CI, confidence interval; MELD, model for end-stage liver disease; AFP, alpha fetoprotein; LR, liver resection; RFA, radiofrequency ablation; SLT, salvage liver transplant, LDLT, living donor liver transplant.
*Statistically significant ($P < 0.05$).

**Table 7** Univariate analysis of potential prognostic factors affecting recurrence-free survival.

| Variables | HR (95% CI) | *P* value |
|---|---|---|
| Sex (female) | 1.674 (0.653–4.225) | 0.234 |
| Age (>50 years) | 0.251 (0.493–1.668) | 0.854 |
| Hepatitis B viral infection | 0.873 (0.291–2.187) | 0.686 |
| Hepatitis C viral infection | 1.569 (0.284–3.535) | 0.844 |
| Child-Pugh grading | 0.568 (0.278–1.471) | 0.874 |
| MELD (>10) | 0.543 (0.443–1.382) | 0.586 |
| Tumor size (>3 cm) | 0.827 (0.306–1.764) | 0.491 |
| Multiple tumors | 1.301 (0.824–2.873) | 0.307 |
| Microvascular invasion | 2.771 (0.750–3.341) | 0.047* |
| Tumor differentiation | 2.569 (0.778–6.291) | 0.433 |
| Serum AFP level (>200 ηg/ml) | 2.562 (1.287–4.881) | 0.025* |
| SLT approach | 2.653 (1.243–7.342) | 0.046* |
| Post-transplant complications | 0.781 (0.615–1.870) | 0.892 |
| LDLT as type of transplant | 1.036 (0.707–3.133) | 0.261 |
| Waiting time on list (>5 days) | 0.549 (0.245–1.519) | 0.283 |
| Donor age (>50 years) | 1.256 (0.912–3.595) | 0.161 |
| Graft weight to recipient ESLV (<40%) | 0.529 (0.613–2.823) | 0.703 |
| Graft cold ischemic time (>110 min) | 0.910 (0.502–1.396) | 0.841 |
| Recipient warm ischemic time (>55 min) | 0.822 (0.462–1.648) | 0.561 |
| Blood transfusion (>5 units) | 1.234 (0.692–2.674) | 0.176 |

HR, hazard ratio; CI, confidence interval; MELD, model for end-stage liver disease; AFP, alpha fetoprotein; LR, liver resection; RFA, radiofrequency ablation; SLT, salvage liver transplant, LDLT, living donor liver transplant.
*Statistically significant ($P < 0.01$).

rate was significantly better in PLT than SLT (84.3% vs. 70%) for early HCC. This finding agrees with another report by Shan et al[26] in which SLT resulted in higher risk of tumor recurrence and death than PLT using PSM analysis. Although both approaches are feasible and practical for patients with early HCC, SLT should be considered cautiously, especially in patients with high pre-treatment AFP level. In the present study, pre-treatment serum AFP level was a poor prognostic factor for both overall and recurrence-free survival. The finding of this surrogate maker for tumor aggressiveness agrees with other studies[27–29] which incorporate serum AFP level into prognostic scoring systems in predicting recurrence after transplantation.

Theoretically, patients with early HCC should have excellent post-LT outcome provided that the donor supply is unlimited. However, limited organ supply in Asia–Pacific region restricts the efficacy of PLT in the authors' center. With the expected high drop-out rate, just a few proportion of waitlisted patients can be benefited from LT. In the authors' center, due to potentially high mortality and morbidity of PLT, majority of patients with early HCC and preserved liver function received LR or RFA as first curative treatment and SLT was offered in case of tumor recurrence within selection criteria. Therefore, an intention-to-treat analysis on both PLT and SLT approaches may be another better way to evaluate and compare each of their efficacies. A recent report by de Haas et al.[30] has clearly pointed out that the intention-to-treat 5-year recurrence-free survival of SLT approach was 60% and the ultimate success rate of SLT strategy is 56%.

The present study represents one of the largest series of SLT for early HCC within Milan criteria in the world. The 5-year recurrence-free survival result of 70% of SLT group is either comparable to or even better than the other reported series.[24,25,31,32] And this reported long-term disease-free survival outcome is again better than the other treatment options for recurrent HCC (hepatic re-resection, RFA, TACE) in one previous series from the authors' center.[33] Such excellent result reflects the aggressiveness surgical approach with coherent patients' follow-up in the authors' center.

One argument against the practice of SLT is that the total tumor burden might exceed that of Milan criteria if the initial tumor burden at the time of primary treatment is included, suggesting that SLT might have more aggressive tumor than PLT. This argument is valid but the situation is unavoidable, and there is no current guideline on the criteria of total tumor burden for SLT approach. In the present study, all patients in SLT group had at least 6 months' recurrence-free period after the primary treatment before they were enlisted for SLT (median time to tumor recurrence = 17 months). It has been suggested that early recurrent tumor imposes poor outcome after SLT than late recurrent tumor.[34] Because of small patient number in the present study, the prognostic effect of the timing of tumor recurrence cannot be further evaluated.

Unlike previous studies, the authors' center adopts both LR and RFA as the primary curative treatment modalities for early HCC in SLT approach. A recent randomized trial from the authors' center has shown that both long-term overall and disease-free survival rates were similar between LR and RFA for early HCC.[4] Hence, the tumor clearance effect of both LR and RFA seems to be similar. A recent matched-control study by Muaddi et al.[35] has shown that SLT is equally effective for patients with tumor recurrence following LR or RFA with curative intent. Similar

result is also reported by a meta-analysis on the efficacy of SLT approach using loco-regional therapy.[36]

The fact that postoperative complication rate is significantly lower in mSLT group than mPLT group (20% vs. 55%) is worth noting. Such result is in contrast with the finding of a report by Hu et al.[23] that SLT was associated with increased bleeding complication, comparing to PLT. It is generally believed that vascular adhesion from previous LR together with a degree of portal hypertension may increase the risk of bleeding during SLT. One approach is to adopt laparoscopic LR as primary treatment to minimize the degree of vascular adhesion.[37] In the present study, 42.3% of patients in SLT group had RFA as primary treatment. This relatively less invasive procedure led to the minimal vascular adhesion during SLT. Together with relatively low MELD of patients, the complication rate was then relatively low in SLT group.

Small patient number and the resulting type II error is the main limitation of the present study. Furthermore, patients were accumulated over two decades and this might lead the historic bias in terms of imaging technology, surgical techniques and perioperative patient care. Another limitation is the per treatment analytic approach in the present study. There was selection bias in SLT approach and the percentage of patients' drop-out while on SLT waiting list was missing. Since both PLT and SLT approaches involve patients' drop-out, large-scale intention-to-treat study involving homogenous group of patients would be the preferred approach.

In conclusion, using propensity score matching analysis, PLT may be a better treatment option for early HCC, whereas SLT approach for HCC should be cautiously considered under the circumstance of organ shortage.

## Disclosure of conflict of interest

The authors declare that they have no competing interests.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.asjsur.2018.08.008.

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