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Liver Transplantation for High Risk Hepatocellular Carcinoma After Liver Resection: A Sequential or Salvage Approach?

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Background: Liver transplantation (LT) is the best radical treatment of hepatocellular carcinoma (HCC). Salvage liver transplantation (SalvLT) provides good outcomes for recurrent HCC cases after initial curative liver resection (LR). However, the salvage strategy is not feasible in all situations due to aggressive recurrences. Recently, sequential liver transplantation (SeqLT) was proposed for cases that show adverse pathological features after LR, thus LT is performed pre-emptively before recurrence. In this report, we compared the outcomes of SalvLT and SeqLT for surgical treatment of HCC.

Material/Methods: One hundred and ten cases underwent LR for HCC, then were subjected to either SalvLT (n=91) or SeqLT (n=19), from January 2001 to December 2015. For cases that underwent several LR before LT, we collected the data of the last LR before transplantation. A comparison was made according to pre- and post-transplant clinical and pathological variables. Survival analysis and comparison between both pathways are provided.

Results: The median interval (months) between LR and LT for the SeqLT group and the SalvLT group were 9.6 and 22.2, respectively. ($p=0.01$). The LR histopathological features were similar in both groups. In the SalvLT group, the histopathological comparison between the criteria of last LR and the criteria of liver explants revealed that 14 cases advanced from stage I to stage II, one cases from stage I to stage IIIa, one case from stage I to stage IIIb, one case from stage I to stage IIIc, three cases from stage II to stage IIIb and one case from stage II to stage IIIc. The overall rate of pathological upstaging in the SalvLT group was 27%. The incidence of post-transplant HCC recurrence was 5% (1/19) and 11% (10/91) for the SeqLT and SalvLT groups, respectively ($p=0.4$). The incidence of post-LT in-hospital mortality was 0% among the SeqLT group and 2% (2/91) among the SalvLT group. The estimated rates of five-year overall survival and cancer specific survival for the SeqLT group versus the SalvLT group were (92.3% versus 87.6%; $p=0.4$) and (92.3% versus 91.9%; $p=0.7$), respectively.

Conclusions: The SeqLT approach might be associated with low incidence of cancer recurrence, better overall survival, and less operative mortality. Another possible benefit is the avoidance of aggressive non-transplantable HCC recurrences. More studies and/or randomization are required for high evidence conclusions.

MeSH Keywords: Carcinoma, Hepatocellular • Liver Transplantation • Salvage Therapy

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Background

Hepatocellular carcinoma (HCC) is a major health problem, being the sixth most common diagnosed cancer worldwide and the third most common cause of cancer-related deaths [1]. Liver transplantation (LT) is the best radical treatment option for HCC, as it removes the cancer as well as the pre-cancerous cirrhotic liver [2]. Due to the scarcity of donated organs, either in the context of living or deceased donation, many transplant centers, especially Asian centers, consider liver resection (LR) as the first-line of surgical treatment of early HCC with compensated liver cirrhosis, deferring LT for a salvage strategy if there is disease recurrence or liver failure [3]. However, there have been many controversies and concerns in the LT community regarding the feasibility of salvage LT upon tumor recurrence, including the accepted transplantable tumor criteria, the potential loss of LT option for aggressive recurrences, the difficulty of pre-transplant quantification of tumor burden in a background of a cirrhotic and manipulated liver, and the acceptable recurrence-free duration for consideration of LT, in addition to the safety and technical challenges of the salvage procedure [4–6]. Recently, a sequential LT approach has been proposed, based on a prophylactic strategy for cases that showed adverse pathological features, namely microvascular invasion (mVI) and high grade observed in the initial curative LR specimen. It has been suggested that a pre-emptive LT for this select group of HCC should be pursued without waiting for the almost inevitable recurrence [7–11]. In this report, we retrospectively analyzed and compared the outcome of the aforementioned two proposed approaches over 15 years of experience in a single LT center in Taiwan.

Material and Methods

Patient population and inclusion criteria

After the approval of the hospital IRB (No. 102-5206B), we retrospectively reviewed the data of adult patients (18 years and older) who underwent LT for HCC in the period between January 2001 and December 2015 in Chang Gung Memorial Hospital, Kaohsiung, Taiwan. The diagnosis of HCC was based on typical radiological enhancement criteria in contrast enhanced CT or MRI in the context of a clinical scenario of hepatitis B or hepatitis C or patients presenting with impaired liver functions on regular check-ups, all according to EASL and AASLD guidelines [12,13]. In case of atypical imaging criteria or discrepant clinical and imaging data, a pre-transplant biopsy was employed. The decision of LT was based on case fitness into Milan Criteria (MC) up to June 2006. Thereafter, University of California San Francisco (UCSF) criteria were adopted to assign HCC cases for LT. We included only cases that underwent secondary LT, i.e., LT after a previous curative LR. Beyond criteria

cases, either MC or UCSF criteria, found on histopathological examination of LR specimens were not excluded from the study so long as they were amenable to subsequent LT. Tumor recurrence was identified on follow-up contrast enhanced CT/MRI and/or progressively elevated alpha-feto protein (AFP), while liver failure was diagnosed if there were manifestations of end stage liver disease (ESLD). Cases that presented with beyond criteria tumor recurrence after LR were subjected to downstaging loco-regional therapies (LRT) and the decision of LT was decided upon the response. All cases underwent living donor LT.

Identification of study groups

We identified 532 cases of HCC who were subjected to LT in the study period. Among them, 392 cases underwent primary LT, while 140 cases underwent secondary LT (i.e., after curative LR). After the exclusion of 29 cases due to absence of pathological data of the last LR specimen, and one case of post-hepatectomy liver failure with subsequent urgent LT, 110 HCC cases that underwent secondary LT were included. We assigned secondary LT cases to either the sequential LT (SeqLT) group or the salvage LT (SalvLT) group on a retrospective basis for the purpose of this study. The cases that received LT following curative LR and before development of tumor recurrence or liver decompensation constituted the SeqLT group (n=19), while cases that received LT upon recurrence of HCC or liver failure constituted the SalvLT group (n=91). The sequential strategy was employed for cases that showed adverse pathological features on the last LR specimen, including positive mVI (n=13), beyond MC resected tumor (n=3), progressive cirrhosis with patient's concern (n=2), and one case that experienced repeated recurrences, last within the vicinity of IVC, though R0 resection was achieved.

SalvLT was decided for recurrent tumors within MC/UCSF criteria and “beyond MC/UCSF criteria” cases if successfully downstaged to “within criteria” status after LRT or cases that showed the likelihood of non-viability of tumor on pre-transplant imaging even if exceeded Milan/UCSF criteria [2]. Among the SalvLT group, LT was indicated due to tumor recurrence (n=87) and hepatic decompensation (n=4). Patient enrollment flow chart is shown in Figure 1.

Study information

Collected data included patients' demographics (age and gender), clinical and pathological data of pre-transplant LR (primary underlying liver disease, type of resection, status of resection margins, mVI, and TNM stage), clinical data of LT (time interval between last LR and LT, radiological staging of the recurrent tumor, and fitness into Milan and UCSF criteria), pathological data of the explanted livers (mVI, histopathological grade and TNM stage, Milan criteria, and UCSF criteria pathological

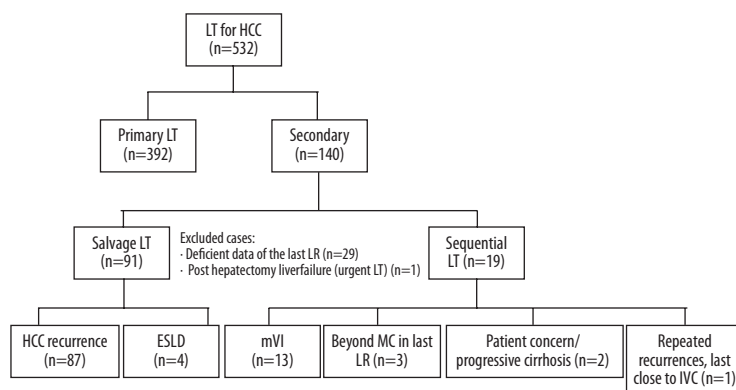


Figure 1. Diagram of study inclusion and exclusion criteria and enrollment into study groups.

status) and survival data (follow-up duration, tumor recurrence data, overall survival, recurrence-free survival, and cancer specific survival). All patients were followed for at least one year after LT or to the date of death.

Surgical procedure, immunosuppression and follow-up

All cases underwent LDLT. Donors were selected from candidates who expressed their willingness of living donation, provided that they were between 18 and 60 years old and within the 5th degree of consanguinity to the recipients. The standard surgical techniques and perioperative care have been described in previous publications [2,14]. All liver explants were examined consecutively by two experienced hepatopathologists using sliced specimen at 1-cm thickness. Tumor number, size, grade, and the presence of mVI were also provided. The standard immunosuppression protocol after LDLT involved induction of basiliximab (Simulect; Novartis Pharma AG, Basel, Switzerland). Steroid therapy consisted of intraoperative I.V. methylprednisolone (500 mg) followed by 20 mg/day (switched to oral prednisolone 20 mg/day once the patient could tolerate oral medication), which was gradually tapered and discontinued over three months if no acute cellular rejection occurred. Patients who showed stable vital signs and renal function were given tacrolimus (Prograf; Fujisawa, Kerry, Ireland) at a dose to maintain trough levels at 5–10 ng/mL during the first week after LDLT. In addition, mycophenolate mofetil (CellCept; Roche, Humacao, Puerto Rico) was continuously administered at 0.5–1 gm/day. An m-TOR inhibitor was used in selective cases for renal sparing and anti-tumor effects. After discharge, all recipients were examined for HCC recurrence by ultrasonography and alpha-fetoprotein (AFP) every three months.

Statistical analysis

Categorical variables are presented as number (%) of cases while numerical variables are presented as mean ($\pm$ standard deviation) for normally distributed variables or median

(interquartile range) for non-normally distributed variables. We used Pearson's chi-square test to compare categorical variables and either Student *t*-test or Mann-Whitney's test to compare numerical variables between study groups. Survival rates were estimated using the Kaplan-Meier method and survival curves were compared using the log-rank test. All cases were followed for at least one year. All tests were two-sided with a level of significance set at $p < 0.05$. All analyses and plots were performed with SPSS 20.0 software (SPSS, Chicago, IL, USA).

Results

The demographic and clinical criteria of the whole study population and both study groups are presented in Table 1. The mean age was 52.2 ± 8.5 years; the patients in the SeqLT group were younger than those in the SalvLT group. Male to female ratio was 5.2 to 1. Hepatitis B viral (HBV) disease was the most frequent underlying liver disease in both groups. The median (range) total follow-up duration for the whole study group was 81 months (15–222) months.

The relevant clinical, histopathological, and staging criteria encountered at the time of last LR are shown in Table 2. The median duration elapsed between the date of last LR and the date of LT was 9.2 months (interquartile range 4.4–15.2) for the SeqLT and 22.2 months (IQR 11.1–38) for the SalvLT, respectively ($p = 0.01$). Within the whole study group, 13 cases underwent more than one LR before LT. Of note that the histopathological data of 15 cases (14 in SalvLT, one in SeqLT) was deficient and they are not included in the analysis shown in Table 2. The incidence of mVI was higher in the SeqLT (55%) than the SalvLT (41%) group ($p = 0.4$). The incidence of beyond criteria cases was more than 30% and comparable between both groups. The SeqLT group showed 38% of cases containing more than one tumor mass in the resected specimen, the corresponding incidence in the SalvLT group was 18% ($p = 0.1$). The incidence of resected specimens with total tumor diameter

Table 1. Demographic and clinical criteria of the entire study group and both study cohorts.

Variable	Whole group	SalvLT	SeqLT	<i>p</i>
Number	110	91	19	
Age (y)	51±9	53±8	49±9.6	0.02
Male (%)	84%	82%	98%	0.4
Underlying disease n (%)				
HBV	78 (76%)	62 (73%)	16 (95%)	
HCV	21	20	1	
B+C	6	4	2	
Non-viral	5	5	–	
Total Follow up duration (months), median (range)	81 (2–246)	80 (2–246)	70 (16–200)	1
Post-LT follow up duration (months), median (range)	43 (0.4–184)	52 (0.4–180)	61 (14–184)	0.3

Table 2. Clinical, histopathological, and staging criteria of the last liver resection (SalvLT vs. SeqLT).

Variable	SalvLT (n=77)*	SeqLT (n=18)*	<i>P</i>
LR number >1, n (%)	9 (11.6%)	4 (22%)	0.4
Resection type (anatomical/non-anat.)	60/17	15/3	0.8
Positive resection margins, n (%)	3 (3.8%)	0	
Tumor number >1 n (%)	14 (18%)	7 (38%)	0.1
Maximal tumor diameter > 5 cm, n (%)	18 (23%)	4 (22%)	0.8
Total tumor diameter > 10 cm, n (%)	4 (5%)	2 (11%)	0.6
Positive mVI, n (%)	32 (41%)	10 (55%)	0.4
TNM, n (%)			0.7
Stage I	31 (40%)	7 (39%)	
Stage II	41 (53%)	9 (50%)	
Stage IIIa	5 (7%)	2 (11%)	
Beyond Milan, n (%)**	24 (31%)	7 (39%)	0.7
Beyond UCSF, n (%)**	18 (23%)	5 (28%)	0.9

mVI – microvascular invasion; LR – liver resection; SeqLT – sequential group; SalvLT – salvage group; SD – standard deviation; UCSF – University of California San Francisco. (*) For this analysis, 15 cases were excluded (14 in SalvLT and 1 in SeqLT) due to incomplete LR data. (**) On histopathological examination of LR specimens.

exceeding 10 cm was 5% and 11% in the SalvLT and SeqLT groups, respectively ($p=0.6$). TNM/AJCC stage II was the most frequent stage in both groups' resected specimens. Stage distribution was nearly equal among both groups.

The clinical and surgical variables of LT are provided in Table 3. Both groups had similar MELD scores. Among the whole study group, 92 cases (84%) were within Child-Turcotte-Pough

(CTP) A category, 14 cases were Child B, and four cases were Child C. The median level of alpha-feto protein (AFP) before LT didn't exceed the normal value (<20 ng/mL) in both groups. Five cases among the SalvLT group were beyond criteria (both MC and UCSF) as determined on pre-LT imaging. Pre-operative LRT was significantly more employed in the SalvLT group (88% versus 53%, $p=0.001$). No LRT was given after last LR in the SeqLT group. The median (mL) intraoperative blood loss was

Table 3. Liver transplantation variables.

Variable	Whole group (n=110)		SalvLT (n=91)		SeqLT (n=19)		P
Time between last LR and LT, Median (IQR) (months)	15	(10–33)	22.2	(11–38)	8.9	(4–15)	0.01
CTP score, mean $\pm$ SD	5.6 $\pm$ 1.4		5.6 $\pm$ 1.3		5.8 $\pm$ 1.7		0.5
MELD score, mean $\pm$ SD	8 $\pm$ 3		8 $\pm$ 3		8 $\pm$ 7		0.6
Pre-LT AFP (ng/ml), median (IQR)	7.7	(3–18.9)	8.5	(3.3–21.5)	3.3	(3–13)	0.1
Pre-LT LRT, n (%)	90	(81.8%)	80	(88%)	10	(53%)	0.001
Pre-LT imaging/beyond MC, n (%) [*]	–		5	(5.5%)	–		
Pre-LT imaging/beyond UCSF, n (%) [*]	–		5	(5.5%)	–		
Blood loss/LT, ml, median (IQR)	1300 (600–2500)		1500 (700–2500)		1000 (450–1950)		0.6
In-hospital mortality	2		2		0		
Post-LT recurrence, n (%)	11	(10%)	10	(11%)	1	(5%)	0.4

AFP – α -fetoprotein; CTP – Child-Turcotte-Pugh score; HBV – hepatitis B virus; HCV – hepatitis C virus; IQR – interquartile range; LT – liver transplantation; MELD – model for end stage liver disease; Pre-LT LRT – pre-transplant locoregional therapy; SD – standard deviation; UCSF – University of California San Francisco. (^{*}) Salvage group only.

more in the SalvLT versus the SeqLT (1,500 cc versus 1,000 cc, $p=0.6$). In-hospital mortality occurred in two cases (2%) in the SalvLT group within the first 30 days after LT, while none of the SeqLT group experienced this event. The incidence of post-LT disease recurrence was 11% (10/91) and 5% (1/19) in the SalvLT and SeqLT groups, respectively ($p=0.4$).

LR-LT histopathological correlation and upstaging

Correlation of histopathological examination between last LR specimens and the explanted livers at LT revealed that for the SeqLT group, there were no residual lesions in 15 cases, while residual liver cell dysplasia was evident in four cases.

Upon histopathological analysis of the explanted livers of the SalvLT group, 34% (31/91) of cases appeared to harbor mVI, though 12 of these cases were devoid of mVI at the time of the last LR. Thirty-five cases (38%) were beyond MC, though 11 of them were within MC at time of the last LR. Twenty-eight cases (31%) were beyond UCSF criteria though none of them were within UCSF at last LR. Regarding the cases that received SalvLT due to hepatic decompensation ($n=4$), no residual HCC was found but dysplastic nodules were found in only one of them. According to AJCC/TNM staging system, 14 cases advanced from stage I to II, one cases from stage I to stage IIIa, one case from stage I to stage IIIb, one case from stage I to stage IIIc, three cases from stage II to stage IIIb and one case from stage II to stage IIIc. The overall rate of pathological upstaging in the SalvLT group was 27%.

The post-LT recurrence group

Only one case from the SeqLT (5.8%) witnessed post-LT tumor recurrence (lung metastases) 43 months after LT and succumbed to it 10 months later with total follow-up duration of 53 months from the date of the last LR. The patient was 36-years-old, HBV (+) and had LR for three HCC nodules with maximal size of 3.3 cm and none had mVI. This patient received SeqLT due to the largest tumor close vicinity to the IVC. The time interval between LR and LT was less than four months. The explanted liver of this patient was clear of any residual disease or dysplasia.

Among the SalvLT, 10 cases (11%) had disease recurrence (distant metastases/4 loco-regional/5, combined/1) at a median of 12 months (range 3–31) months after LT. Seven cases succumbed to their recurrent disease within a range of 6–18 months after evidence of recurrence. Among the remaining three surviving cases, one case had local recurrence into the graft and was treated with TACE for two sessions. The pathological criteria of last LR specimens of those 10 patients revealed that four cases harbored mVI, and one case had positive resection margin. No specific adverse features were evident in the LR specimens of the other five cases, but mVI was evident in the liver explants of three of them, and beyond MC tumor burden was evident in the other two cases.

Survival outcomes

For the whole group, the one-, three-, five- and 10-year overall survival (OS) rates were 100%, 94%, 88%, and 78%, respectively.

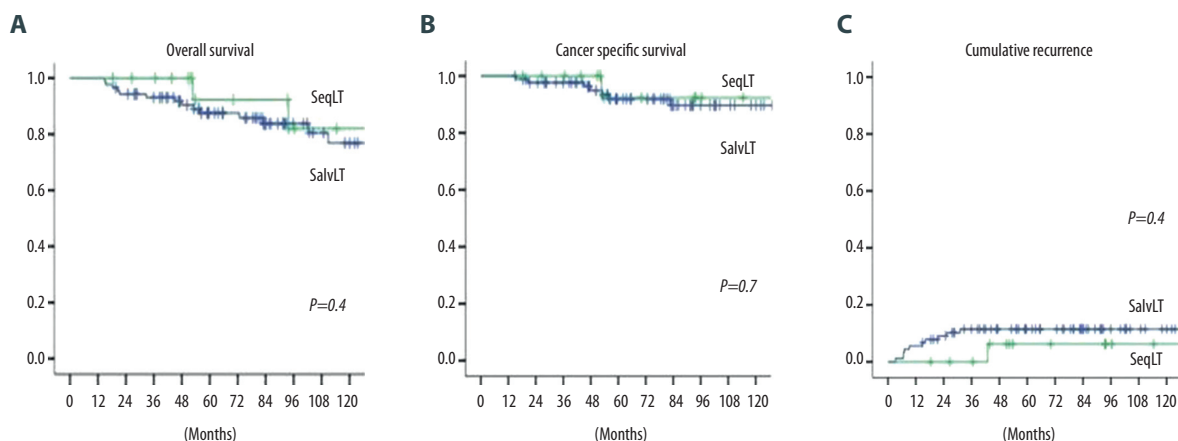


Figure 2. Kaplan Meier survival curves for the study groups. (A) overall survival rates. (B) cancer specific corresponding survival rates. (C) The cumulative recurrence rates.

The corresponding recurrence-free survival (RFS) rates were 95%, 87%, 86%, and 77%, respectively. Likewise, the cancer specific survival rates were 100%, 98%, 92%, and 90%, respectively.

Comparison of survival rates between both study groups is shown in Figure 2. The five-year OS rates were 92% and 88% for SeqLT and SalvLT, respectively ($p=0.4$). The five-year cancer specific survival rates, estimated as the time from the date of last LR to the date of post-LT HCC recurrence related mortality, were both 92% for the SeqLT and the SalvLT groups ($p=0.7$). The five-year cumulative recurrence rates for the SeqLT group and the SalvLT group were 6.2% and 11.5%, respectively ($p=0.4$).

Discussion

The current worldwide problem of organ shortage has led most transplant centers, especially in Asian countries, to pursue curative LR for early cases of HCC and perform LT on a rescue basis when the patient develops local recurrence. Though LR had been validated as an accepted alternative for early HCC cases in a context of organ shortage, it has been plagued by high incidence of recurrence reaching up to 80% in some series [15-18]. Moreover, the risk of non-transplantable tumor recurrences has been reported to be between 20% and 80%, putting those patients on the risk of potential loss of LT chance and hence dismal prognosis [10,19].

Meanwhile, the salvage strategy has the advantages of best management of the donor pool, delaying the administration of immunosuppressive drugs as much as possible, and allowing the time factor to help select cases with indolent tumors characterized by delayed non-aggressive recurrences [4]. This roadmap of SalvLT should, as its name implies, be aiming at survival rates as good as primary LT for HCC. However, the

absence of consensus about the salvageable tumor criteria for LT, the unpredictable pattern of HCC recurrence after initial LR especially in a cirrhotic liver with risk of upstaging, the reduced accuracy of pre-transplant work-up for assessment of tumor burden, the biological behavior in the context of a cirrhotic liver with previous locoregional therapies, and the reluctance of some patient to follow a protracted strict follow-up program after LR, are all drawbacks of the SalvLT pathway [6,15].

Over the past few years, some reports have explored the principle of sequential LT (other nomenclature in the literature; pre-emptive, de principe, ab initio) which is based on initial LR followed by LT for tumors showing pathological features notorious of high risk of recurrence, namely mVI, high grade, short interval recurrences, and progressive cirrhosis. Nevertheless, this sequential approach has its concerns in the LT community and literature, since many of the clinicopathological factors that underlie the need for a pre-emptive LT are in fact the same factors that may be associated with a high risk of recurrence after LT [8-10,19-21].

In our retrospective study, we compared the aforementioned two proposed pathways over 15 years. The main difference between our study and previous studies that assessed the same issue was that we included cases that were beyond MC on histopathological analysis of the last LR. More than 30% of patients in either group of our study were beyond MC at the time of last LR. In addition, 5.5% of cases in the SalvLT group had been transplanted with “beyond MC and UCSF” recurrences. We didn’t exclude beyond criteria cases from the analysis for two reasons. The first reason was the growing evidence of multifactorial contribution to the survival outcome other than the mere size and number of HCC lesions, including histopathological, biological, and genetic factors. The second was due to the effect of pre-transplant LRT that modify

the static morphological criteria, by inducing tumor necrosis, partially or completely [3].

In our study, nearly both study groups harbored similar adverse pathological features. The incidence of mVI in the SeqLT group, detected in specimens of last LR, was 55% and in the SalvLT group, whereas-detected in liver explants was 41%. Similar incidence of beyond criteria cases, as previously shown, occurred in both study groups, too. However, the five-year overall survival and cancer-specific survival rates were not significantly different between both strategies. Though the five-year cumulative recurrence rate was higher in the SalvLT group, it didn't reach statistical significance.

There might be a survival advantage, if larger sample size, in favor of the subgroup that showed positive mVI in the LR mass, since the sequential pathway had 100% five-year OS, as compared to 80% for the salvage pathway ($p=0.1$). Also, the stage-specific survival comparison between both pathways for early stage (TNM/AJCC stage I and II) was in favor of the sequential pathway, though not reaching statistical significance.

Recently, two comparative studies addressed the outcome of sequential and the salvage pathways. A prospective validation of sequential (*ab initio*) pathway at Barcelona clinic on an intention-to-treat (ITT) basis was provided. They performed sequential LT for 17 high risk cases with positive mVI and/or satellite nodules upon analysis of resected specimens, while 11 low risk cases without adverse pathological features were transplanted on salvage basis, all within MC at initial LR. No statistically significant difference could be found between both study groups, the five-year OS being both 81.8% and 82.4% for the salvage and sequential (*ab initio*) pathways, respectively ($p=0.7$) [21]. The second comparative study by Tribillon et al. entailed ITT and per-protocol analyses. In the per-protocol analysis, 60 cases received sequential (*De Principe*) LT, while 40 cases were transplanted on salvage basis. A statistically significant superior survival rates in favor of the sequential group were evident. The five-year OS rates were 84.6% and 74.8% for the sequential (*de principe*) and the salvage pathways, respectively. ($p=0.01$) [10]. The hallmark difference between both studies and our study is the inclusion of beyond MC and mVI (+) cases equally among both groups in our study.

Cancer recurrence after LT is a grave complication with very limited treatment options and it is one of the major concerns about the sequential pathway, since select cases for this pathway already harbored adverse pathological factors notorious of recurrence. In our study, >50% of cases in the SeqLT group showed mVI, a percent comparable to that found in the aforementioned two studies. The recurrence rates after LT in our study was 5% and 11% for the SeqLT and SalvLT groups, respectively ($p=0.4$). The recurrence rate in the Tribillon et al. study

was quite higher for both the *De Principe* (8%) and the salvage (17.5%) pathways ($p=0.2$). In the Barcelona study, 11% (2/17) of high risk cases transplanted *ab initio* developed recurrence, as compared to 18% (2/11) recurrence after SalvLT for the low risk group [21]. Although the criteria of both groups in our study were different than that of the previous two studies, the SeqLT approach was associated with lower risk of recurrence. Again, more studies are needed to corroborate this finding.

An important finding in our study was related to the concept of upstaging. Histopathological correlation of resected and explanted specimens in our study revealed upstaging of 27% (21/77) of cases in the SalvLT group. Among them, seven cases experienced upstaging from early (stages I and II) to late (stage III). These cases may represent a subgroup that has lost a chance of LT at an early stage. However, an ITT analysis is the best to address this point.

The test of time for an HCC to express its aggressiveness or indolence is a consistent tool in several studies. A waiting time of 6–12 months had been proposed to allow natural selection of cases that would recur at an earlier time. In our study, the median waiting time for the SeqLT group was less than 12 months; however, this duration was not reflected in an increased recurrence rate among this group. Also, the recurrence rates among salvageable cases that had been waiting either for more or less than 12 months were comparable. All these remarks would suggest that the time factor alone was not the only determinant factor of outcome, in view of the different modalities in the locoregional armamentarium that could modify, over the time of waiting, the morphological burden of the tumor as well as its internal environment by inducing tumor necrosis [22]. However, based on evidence in several studies, it is prudent to wait for at least 4–6 months after LR before enlistment a case of HCC for LT [21,23,24].

Application of the secondary LT strategies must take into account the demanding secondary surgery, especially in the setting of living donation, since the procedure is challenging due to previous surgeries and locoregional therapies with resultant adhesions and tissue friability, in addition to the inherent challenges of the LDLT procedure including short vascular stumps and complex biliary anastomoses. Indeed, the final outcome in our the center showed that the incidence of surgical mortality have dropped from 8% to 2% over a consecutive 100 cases of salvage LT [25], and in this study we had two surgical mortalities among the SalvLT group and none in the SeqLT group. However, the sequential pathway in our study was associated with more vascular and biliary complications, while more blood loss occurred during the salvage procedure. A larger sample size is needed for more precise comparison. The operative morbidities among the previous two comparative studies were not provided [10,21].

An important advantage of the sequential pathway is the avoidance of protracted time of strict follow-up after LR in a subset of patients, since adherence to 3–6 months visits is a must in the salvage pathway. Inability to follow a strict prolonged follow-up schedule was found to be a cause of failure of the salvage pathway [9].

LT rescuing post-hepatectomy liver failure represents a very special situation when SalvLT is considered on an urgent life-saving basis for a patient who wouldn't otherwise be considered initially for LT due to beyond criteria tumor burden [26]. Though we excluded such cases from our study, this situation, though rarely encountered in view of proper pre-operative assessment and more conservative resections, does exist and a decision-making largely depends on the availability of a willing non-coerced donor, as well as tumor and patient conditions. Due to the dismal overall prognosis, major vascular invasion and uncontrollable sepsis are the absolute contraindications for LT in this situation.

Obviously, our study lacked an intention-to-treat basis. So, the patients whose tumors progressed while waiting for LT were not included in the analysis. Since many cases had the last LR outside our center and then were referred for LT, some pathological and clinical data were missing, that's why as many as 29 cases were discarded from the analysis at the beginning of the study, otherwise they could add to the robustness of

the analysis. The retrospective nature of the study is another limitation. Though it is extremely difficult to do a randomized controlled trial to compare both study arms, it will be the most precise tool to conclude the best way of management of early cases of HCC with compensated cirrhosis. Also, the heterogeneity of patient allocation to a sequential pathway over 15 years is evident, that's because of absence of consensus about the indications of such pathway.

Conclusions

The sequential approach for high risk HCC cases might be associated with less cumulative recurrence rate as compared to the salvage approach. Other possible practical benefits of the sequential pathway may be the avoidance of an unpredictable aggressive recurrence, avoidance of protracted waiting time and loss of follow-up, and overcoming the shortcomings of pre-LT work-up. The adoption of secondary LT by its two pathways, i.e., SeqLT and SalvLT, should be in specialized centers due to the demanding surgery. Still, more studies and/or randomization are required for highre evidence conclusions.

Conflict of interest

None.

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