REVIEW

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Expanding Indications for Liver Transplant: Tumor and Patient Factors

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During the past few decades, liver transplant has developed from a high-mortality procedure to an almost routine procedure with good survival outcomes. The development of living donor liver transplant has increased the availability of liver grafts, and the scope of indications for liver transplant has been expanding ever since. The aim of this review is to provide an overview of such an expansion of scope. Various criteria have been proposed to expand the eligibility of patients with hepatocellular carcinoma exceeding the Milan criteria for liver transplant. Furthermore, liver transplant is increasingly performed as a treatment modality for cholangiocarcinoma, neuroendocrine liver metastasis and colorectal liver metastasis. The number of elderly patients receiving liver transplant is on the rise. Combined organ transplantation has also been adopted to treat patients with multiple organ failure. Going forward, further development of preoperative noninvasive predictors in tumor, patient and even donor factors is needed to identify patients at risk of poor outcomes and hence optimize patient management. **(Gut Liver, Published online February 28, 2020)**

Key Words: Liver transplant; Hepatocellular carcinoma; Surgical indication

INTRODUCTION

Liver transplant is one of the most effective treatments for irreversible acute or chronic liver failure and liver diseases with different causes when liver resection is contraindicated. During the past four decades, liver transplant has developed from a high-mortality procedure to an almost routine procedure with good survival outcomes, i.e. >80% at 1 year and >70% at 5 years.[1,2] At the same time, living donor liver transplant was developed in the background of organ shortage[3-5] and has greatly expanded the availability of liver grafts. With various methods to increase graft availability together with improvement in patient outcomes, the scope of indications for liver transplant is expanding.

Hepatocellular carcinoma (HCC) is the commonest malignant indication for liver transplant. Starzl *et al*. described the first successful liver transplant as an oncological treatment for hepatoblastoma in 1967.[6] Early attempts at using liver transplant to treat cholangiocarcinoma were disappointing. Better results were reported with more specific patient selection.[7,8] In the past, metastatic liver disease was a contraindication to liver transplant. Nowadays, liver transplant for diseases such as neuroendocrine liver metastasis,[9-11] colorectal liver metastasis,[12,13] etc. is being considered because of the slow-growing nature of these tumors. However, these indications are not favored by the transplant community when the shortage of liver grafts is concerned, especially in Asian places where liver graft shortage is grave (e.g., Hong Kong). In these places, the main concern about offering liver transplant to patients with neuroendocrine or colorectal liver metastasis would be the potential impact on other patients on local liver transplant waiting lists.

Liver transplant is an ultra-major surgery, and hence it was considered to be relatively contraindicated when the patients had high-risk factors for ultra-major surgery.[14] However, with improvement in general outcomes, high-risk patients who have an advanced age, ultra-high Model of End-Stage Liver Disease scores or co-morbidities are now potential candidates for liver transplant. In more extreme cases, combined organ transplant is a measure to treat multiple organ failure.[15-17]

The aim of this review is to give an overview of the expansion of liver transplant indications. In particular, the discussion will focus on the role of tumor factors and patient factors in determining eligibility for liver transplant.

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TUMOR FACTORS

1. HCC exceeding the Milan criteria

Since the introduction of the Milan criteria by Mazzaferro *et al*. in 1996,[18] it has been considered the gold standard for selection of HCC patients for liver transplant. The Milan criteria, defined as the presence of a tumor 5 cm or less in patients with single HCCs and no more than three tumor nodules, each 3 cm or less in diameter in patients with multiple tumors, has been validated by numerous studies over the past years. In a meta-analysis performed in 2011 including 19 studies conducted in 15 years on Milan criteria,[19] it was concluded that significantly increased posttransplant survival was expected for patients who met the Milan criteria when compared with those who did not. A hazard ratio of 1.68 confirmed the inferior survival of patients beyond the Milan criteria when compared with patients within the criteria. However, over the past 20 years, the transplant community has come to realized that the Milan criteria are too restrictive, especially in the context of living donor liver transplant. Numerous centers have attempted to expand the Milan criteria through performing liver transplant for patients beyond the Milan criteria and evaluating the outcomes in these patients. These new criteria are summarized in Table 1.

Several groups have proposed new criteria featuring the expansion of the size and number of tumor nodules accepted on the basis of the Milan criteria. The University of California San Francisco (UCSF) criteria are the earliest and most well-known in this category.[20] In the study, 70 HCC patients receiving liver transplant were retrospectively analyzed. It was found that patients meeting the criterion of solitary tumor ≤6.5 cm or ≤3 nodules with the largest lesion ≤4.5 cm and total tumor diameter ≤8 cm had 1- and 5-year survival rates of 90% and 75.2% respectively; on the other hand, the 1-year survival rate was 50% for patients beyond this criterion. The UCSF criteria were defined on the basis of explant histology findings, so the same group conducted a prospective study to validate the UCSF criteria on the basis of pretransplant imaging.[21] The UCSF criteria were subsequently validated by Patel *et al*. in 2012.[22] It was demonstrated that patients within the Milan criteria and patients within the UCSF criteria had similar overall survival. Thereafter, other criteria including the Hangzhou criteria and the Tokyo criteria were developed and validated over the years.[23-27] The Hangzhou criteria were shown to provide an expansion rate of 51.5% when compared with the Milan criteria, while the overall and tumor-free survival rates were not significantly different.[28]

Portal vein tumor thrombus (PVTT) has been considered a contraindication to liver transplant due to the high risk of post-transplant intrahepatic recurrence or extrahepatic metastasis.[29] However, recent studies in South Korea have expanded the indications for living donor liver transplant to include patients with PVTT.[30-32] Lee *et al*.[32] from Seoul National University Hospital investigated the outcomes of 11 patients diagnosed with HCC and PVTT who had received liver transplant and analyzed the risk factors for recurrence. The 1-, 3-, and 5-year recurrence-free survival rates were 63.3%, 45.5% and 45.5% respectively. Main portal vein invasion and high alpha-fetoprotein×protein induced by vitamin K absence/antagonist-II (AP score) ≥20,000 were identified as significant risk factors for recurrence. It was therefore suggested that living donor liver transplant can be considered as a curative treatment option for patients with PVTT with careful selection of patients with a low AP score and PVTT not extending to the main portal vein. Similarly, studies from Seoul St. Mary's Hospital[30] and Soonchunhyang University Seoul Hospital[31] also concluded that, with careful selection criteria, living donor liver transplant can be offered to patients with PVTT.

Biochemical parameters such as alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) levels are included in several proposed selection criteria.[27,33-35] Serum AFP has been increasingly recognized as a marker for poor prognosis after liver transplant. An AFP level >1,000 ng/mL has been identified as a surrogate for vascular invasion and significant predictor of HCC recurrence after transplant.[36] AFP is therefore incorporated in a few selection criteria including the 5-5-500 rule,[35] which defines the eligibility criteria as tumor diameter ≤5 cm, tumor number ≤5 and serum AFP level ≤500 ng/mL. Using the 5-5-500 rule, the study recorded a 5-year recurrence rate of 7.3% (95% confidence interval, 5.2% to 9.3%), and the rule provided a 19% increase in the number of patients eligible for transplant when compared with the Milan criteria. The 5-year overall survival rate was 75.8% for patients within the 5-5-500 rule. The Samsung criteria[34] have parameters similar to the 5-5-500 rule but the cutoffs are higher, allowing a maximum tumor size of ≤6 cm, tumor number of ≤7 and AFP level of ≤1,000 ng/mL. Interestingly, the 1-, 3-, 5-year overall survival rates of patients meeting the Samsung criteria were 97.9%, 91.5% and 90% respectively, which were higher than those reported in the 5-5-500 study despite much more lenient cutoffs. Further research on AFP cutoff level that would optimize patient outcomes is required. The Kyoto criteria include PIVKA-II level as part of the criteria as PIVKA-II level >400 mAU/mL has been identified as an independent risk factor for postoperative recurrence.

Down-staging has been proposed as a method to expand the eligibility of HCC patients for liver transplant. Down-staging can be defined as a reduction in tumor burden using locoregional therapy to reduce tumor stage to within eligibility criteria for liver transplant. A meta-analysis performed by Parikh *et al*.[37] reported that the pooled success rate of down-staging was 48% and the pooled posttransplant HCC recurrence rate was 16%. In an intention-to-treat analysis,[38] it was found that successful down-staging of HCC to within the Milan criteria resulted in a 5-year survival rate of 77.8%, which is comparable to the 81% reported in patients already within the Milan criteria without

Table 1. Expansion in Liver Transplant for HCC Exceeding the Milan Criteria

Strategy	Criteria and validation studies	Key points
The gold standard	Milan criteria[18]	Single tumor ≤5 cm, or
	Validation: meta-analysis of 25 studies by Mazzaferro *et al.*[19]	No more than 3tumor nodules, each ≤3 cm
		No extrahepatic manifestations
		No evidence of gross vascular invasion
Expansion in size and number	University of California, San Francisco (UCSF) Criteria[20]	Solitary tumor ≤6.5 cm, or
	Validation: Yao *et al.*,[21] Patel *et al.*,[22] Unek *et al.*[114]	≤3 Nodules with the largest lesion ≤4.5 cm and total tumor diameter ≤8 cm
	Hangzhou Criteria[27]	One of the following two items;
	Validation: Xu *et al.*[28]	Total tumor diameter ≤8 cm
		Total tumor diameter >8 cm, with histopathologic grade I or II and preoperative AFP level ≤400 ng/mL, simultaneously
	Tokyo Criteria (5-5 rule)[26]	≤5 Nodules
	Validation: Togashi *et al.*[115]	Maximum tumor diameter of 5 cm
	Asan Criteria[24]	Largest tumor diameter ≤5 cm
	Validation: Bonadio *et al.*[116]	HCC number ≤6
		No gross vascular invasion
	Up-to-seven criteria (new Milan criteria)[25]	Size of largest tumor (in cm) plus number of tumors ≤7
	Validation: de Ataide *et al.*[117]	
Presence of portal vein invasion	Seoul St. Mary's Hospital[30]	Segmental portal vein tumor thrombus is acceptable, especially when AFP <100 ng/mL
		Lobar portal vein tumor thrombus remains a contraindication to liver transplant
	Seoul National University Hospital[32]	Living donor liver transplant could be considered if
		- portal vein tumor thrombus does not extend into the main portal vein
		- AFP×PIVKA-II score is not high (≤20,000)
	Soonchunhyang University Seoul Hospital[31]	Living donor liver transplant could be considered if
		- portal vein tumor thrombus is less than Vp4 type (presence of tumor thrombus in the main truck of the portal vein or a portal vein branch contralateral to the primarily involved lobe, or both)
		- showed good response to radiotherapy down-staging
Addition of biochemical markers	5-5-500 Rule[35]	Nodule size ≤5 cm in diameter
		Nodule number ≤5
		AFP ≤500 ng/mL
	Kyoto Criteria[33]	≤10 Tumor nodules, and all ≤5 cm, and PIVKA-II
	Validation: Kaido *et al.*[118]	≤400 mAU/mL
	Samsung Criteria[34]	Maximal tumor size ≤6 cm
		Tumor number ≤7
		AFP levels ≤1,000 ng/mL
Down-staging	Parikh *et al.*,[37] Lei *et al.*,[119] Yao *et al.*[38]	The success rate of down-staging to within Milan criteria exceeds 40%[37]
		Recipients who meet Milan or UCSF criteria after successful down-staging achieve similar results to recipients fulfilling the criteria without down-staging[38,119]

HCC, hepatocellular carcinoma; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

down-staging. These results have demonstrated that down-staging may be a potential method to further expand liver transplant indications in HCC patients beyond defined criteria.

2. Cholangiocarcinoma

Cholangiocarcinoma is a malignant tumor of the biliary system and is the second commonest primary liver cancer after HCC.[39] Depending on its location, it can be classified as hilar cholangiocarcinoma, intrahepatic cholangiocarcinoma or distal cholangiocarcinoma (mid-third and lower-third of the bile duct).[40]

Hilar cholangiocarcinoma carries a poor prognosis; the overall survival was reported to be between 12 and 24 months.[41]Although the most promising treatment is complete resection with negative oncological margin, this could only be achieved in one-third of the patients.[42-44] The low resection rate gave rise to the concept of treating these patients with liver transplant, which would be a cure for patients with unresectable hilar cholangiocarcinoma or insufficient liver reserve. However, early attempts of liver transplant alone as treatment of cholangiocarcinoma resulted in disappointing results, with a 5-year survival of 23% to 30% only.[45,46]

Neoadjuvant therapy before liver transplant has been shown to result in improved survival outcomes. Nebraska University was among the first to offer neoadjuvant therapy to patients with hilar cholangiocarcinoma before liver transplant.[47] Although the number of patients in the study was small (n=17), this was the first study to report favorable long-term survival in selected patients with unresectable hilar cholangiocarcinoma; 45% of the transplant recipients were alive with a median follow-up period of 7.5 years. The Mayo Clinic group reported their series with neoadjuvant therapy followed by liver transplant in 2000.[7] This led to the development of the Mayo Clinic protocol, which includes selection of patients without evidence of metastatic or nodal disease, neoadjuvant high-dose radiotherapy, and operative staging followed by liver transplant.[48] With the neoadjuvant protocol consisting of a combination of external beam and transcatheter radiation with intravenous 5-fluorouracil, only one out of 11 transplant recipients had tumor relapse. It was thus concluded that liver transplant in combination with preoperative irradiation and chemotherapy might be a potential treatment for patients with early-stage cholangiocarcinoma. In an early study comparing liver resection and liver transplant, the 5-year survival rate was 21% in the resection group and 82% in the transplant group with neoadjuvant chemoradiation.[49] More recent publications from the Mayo Clinic reported 2- and 5-year recurrence-free survival rates of 78% and 65% respectively[50] with the adoption of the Mayo Clinic protocol. Hong *et al*.[51] identified the lack of neoadjuvant and adjuvant therapy as an independent predictor of tumor recurrence after liver transplant for cholangiocarcinoma.

The Mayo Clinic protocol has received criticism as it includes two separate components which may affect survival results, namely, strict selection criteria and neoadjuvant therapy. A study by Mantel *et al*. investigated the effect of strict selection on patient survival. They looked into the survival outcomes in patients who were selected based on the Mayo Clinic protocol and received no neoadjuvant therapy.[52] The 5-year survival of this subgroup of patients was 59%, suggesting that selection criteria alone could result in improved survival when compared with results reported by early studies.

Table 2 is a summary of survival outcomes of liver transplant for hilar cholangiocarcinoma in studies with different neoadjuvant and selection protocols. As shown, combination of strict selection criteria and neoadjuvant therapy may achieve acceptable long-term survival in patients with hilar cholangiocarcinoma. Hence, hilar cholangiocarcinoma should not be an absolute contraindication to liver transplant. However, most of the studies were retrospective in nature and had small sample sizes. Further studies are required to elucidate the effect of neoadjuvant therapy followed by liver transplant on survival outcomes. In fact, this is already under investigation in the TRANSPHIL study (Randomized Prospective Multicentric Study: Liver Resection versus Radio-chemotherapy-Transplantation for Hilar Cholangiocarcinoma), which is expected to be completed in 2021. Furthermore, most of the studies were conducted in the West–in the East, liver transplant has not been widely adopted as a treatment of cholangiocarcinoma. Future studies exploring liver transplant as a treatment option for cholangiocarcinoma in Eastern populations would provide more evidence on the efficacy of this treatment modality.

Intrahepatic cholangiocarcinoma is a contraindication to liver transplant at most liver transplant centers around the world[53] because of the very poor outcomes in the early experience of liver transplant for this disease.[54,55] A Spanish multicenter study reported a reasonable outcome with a 73% 5-year survival[8] in a subgroup of very early intrahepatic cholangiocarcinoma (≤2 cm). However, the number of patients with this stage of disease was limited. In the same cohort, the outcome for combined HCC-cholangiocarcinoma had a better survival outcome, i.e. comparable with HCC patients. The authors concluded that a preoperative biopsy resulting in a diagnosis of combined HCC-cholangiocarcinoma should not exclude patients from liver transplant.

Another role of liver transplant in this group of diseases is the liver transplant for patients with primary sclerosing cholangitis (PSC). Historically, PSC patients who developed cholangiocarcinoma while waiting for liver transplant had a poor prognosis and this is a relative contraindication to liver transplant in many programs. However, it was reported that the incidentally discovered tumors in the setting of PSC had good results without recurrence.[7,56]

Table 2. Survival Outcomes of Liver Transplant for Hilar Cholangiocarcinoma in Studies with Different Neoadjuvant and Selection Protocols

Center	Author	Year	Neoadjuvant protocol	Selection criteria	Survival
University of Cincinnati	Meyer *et al.*[45]	2000	None of the patient received neoadjuvant therapy prior to LT	Selection criteria was not adopted.	1-, 2-, 5-Year survival: 72%, 48% and 23% respectively
University of Nebraska Medical Center	Sudan *et al.*[47]	2002	6,000 cGy biliary brachytherapy Intravenous infusion of 5-fluorouracil (300 mg/m^2/day)	Patients with no evidence of extrahepatic tumor.	Survival rate was 45% with a median follow-up of 7.5 years
Multicenter in Spain	Robles *et al.*[46]	2004	None of the patient received neoadjuvant therapy prior to LT	Selection criteria was not adopted.	1-, 3-, 5-Year survival was 82%, 53%, and 30% respectively
Mayo Clinic	Darwish Murad *et al.*[50]	2012	External beam radiotherapy (99%) with sensitizing chemotherapy (5-fluorouracil) (98%) Additional brachytherapy (75%) Additional maintenance chemotherapy (oral capecitabine) (65%)	Patients outside UNOS criteria (tumor >3 cm, transperitoneal tumor biopsy or metastatic disease or with prior malignancy) was found to have significantly worse recurrence-free survival (hazard ratio, 2.98)	2-, 5-Year post transplantation recurrence-free survival rates: 78% and 65%
Europe Liver Transplant Registry	Mantel *et al.*[52]	2016	Patients not undergoing neoadjuvant chemoradiation therapy were included in the study	Patients were selected according to the Mayo Clinic protocol: - Tumor size <3 cm - Absence of distant metastasis - No lymph node metastasis	5-Year survival: 59%

LT, liver transplant; UNOS, United Network of Organ Sharing.

3. Neuroendocrine liver metastasis

Neuroendocrine tumor metastasis localized to the liver is an indication for liver transplant as it is slow-growing and has lower oncological aggressiveness compared with HCC.[9] In view of the scarcity of donated organs and improved results of non-surgical treatment of neuroendocrine liver metastasis, the controversy over patient selection and timing for liver transplant continues. Patients who have neuroendocrine liver metastasis usually receive multimodal treatment including a combination of surgical resection, systemic chemotherapy, radiofrequency ablation, and transarterial chemoembolization. While complete resection is considered the only curative treatment, theoretically liver transplant would be the best treatment. It would be important to exclude other extrahepatic metastases–distant lymph nodes (20% to 30%), peritoneal carcinomatosis (10% to 33%), lungs (3% to 5%), and bones (1% to 6%).[57]

In a study comparing transplant with non-transplant treatment, the two groups of patients had similar 5-year overall survival but the transplant group had better 5-year disease-free survival (50% vs 34%).[58,59] There is the criticism that comparison of patients from the date of liver transplant is unfair as these patients had already undergone other therapy;[60] comparison at the time of diagnosis or the detection of uncontrolled disease would be fairer.

A systematic review conducted by Moris *et al*. in 2017 summarized 64 studies evaluating the outcomes of liver transplant for neuroendocrine tumor liver metastasis.[61] Pancreas was the found to be the most common primary tumor site. The overall recurrence rate after liver transplant ranged from 31.3% to 56.8%. The 5-year overall survival rate ranged from 50% in multicenter studies to 70.7% in aggregated data from 57 single-center studies. The authors thus concluded that liver transplant offered survival benefits to patients with diffuse neuroendocrine metastases to the liver without extrahepatic disease. They further recommended that strict selection of patients would be required in order to optimize outcomes in the face of organ shortage.

The reported prognostic factors for tumor recurrence and poor overall survival were age >50 years, symptomatic tumor, primary tumor in the pancreas or a non-gastrointestinal location, non-carcinoid tumor, high Ki-67 index, involvement of liver more than 50%, and poor tumor differentiation.[9-11,59,62] The Milan criteria group thus suggested the "Milan Criteria in case of Neuroendocrine Tumor (Milan-NET)" in 2007.[62] The inclusion criteria for liver transplant include confirmed histology of low-grade (G1/G2 grading according to the World Health Organization classification) neuroendocrine tumor, primary tumor removed with curative resection, metastatic diffusion to liver parenchyma ≤50%, stable disease for at least 6 months before liver transplant, and age ≤55 years. Application of the Milan-NET criteria resulted in 5-year and 10-year survival rates of 97% and 89% respectively.[63] The same study also compared transplant for neuroendocrine liver metastasis and transplant for HCC and found comparable results between them.

The data presented above suggested that stringent criteria for selection of patients with good prognostic factors for liver transplant would result in favorable long-term survival comparable with that of HCC patients. On the other hand, disease down-staging[64] and transplant delay[62] were also proposed. From current evidence, neuroendocrine tumor is not an absolute indication for liver transplant. However, liver transplant for neuroendocrine liver metastasis was still uncommonly performed due to limited available data. In addition, most of the studies identifying prognostic variables and evaluating survival outcomes in the context of liver transplant for neuroendocrine metastasis were retrospective in nature. Future prospective studies with larger sample sizes are needed to further optimize the patient selection criteria for liver transplant for metastatic neuroendocrine tumors so that the benefit of liver transplant for this subgroup of patients can be maximized.

4. Colorectal liver metastasis

Colorectal cancer is one of the commonest cancer and a leading cause of cancer-related morbidity and death.[65] Liver metastases are commonly detected as synchronous or metachronous lesions.[66] Early attempts of liver transplant for these patients were disappointing. The first and largest published series from University of Vienna reported that the overall survival rates at 1, 3 and 5 years were 76%, 32% and 12% respectively.[67,68] Other early studies in the 1990s also reported poor overall survival.[69,70]

In 2013, Hagness *et al*.[12] from reported the outcomes of liver transplant for colorectal liver metastasis at Oslo University Hospital. Unlike Asian regions, Norway had a surplus of deceased donor liver grafts and the average waiting time for liver transplant was less than 1 month.[12,13] A substantial number of liver grafts were exported to other liver transplant centers. They performed liver transplant for patients who met these three criteria: their primary tumors had been excised, their metastatic disease was confined to the liver, and they had undergone at least 6 weeks of chemotherapy. The overall survival rates at 1, 3 and 5 years were 95%, 68% and 60% respectively. Although the overall survival results were encouraging, almost all these patients had disease recurrence after 2 years from liver transplant. Risk factors for poor survival were largest tumor diameter, carcinoembryonic antigen, time from primary surgery, and nonresponse to chemotherapy. Four years later, Toso *et al*.[13] reported a series of 12 liver transplants for colorectal liver metastasis at four European centers. The overall survival rates at 1, 3, and 5 years were 83%, 62%, and 50% respectively, and only half of their patients had disease recurrence. Most of the patients who had synchronous metastasis received chemotherapy. All patients received a complex chemotherapy regimen and responded to chemotherapy. Predictive factors for poor disease-free survival

were upfront transplant, salvage transplant, and vena cava involvement.

Liver transplant for colorectal liver metastasis is still highly controversial. With further improvement of chemotherapy, the results of treatment of colorectal liver metastasis may further improve. The role of liver transplant in the management of this disease will be redefined in the future.

5. Other neoplasms

Hepatoblastoma is the most common primary liver malignancy in children. The major treatment modalities for hepatoblastoma are chemotherapy and liver resection. However, for tumors involving all four sections, centrally located tumor which is not feasible for resection, portal vein, and hepatic vein involvement, liver transplant would be indicated.[71,72] Long-term survival was reported to be 85%–90%.[73]

Epithelioid hemangioendothelioma is a rare tumor of vascular origin. Some hepatic epithelioid hemangioendotheliomas behave similarly to benign hepatic hemangiomas, whereas others have a clinical course resembling highly aggressive angiosarcoma.[74] With data from United Network for Organ Sharing (UNOS), Rodriguez *et al*.[74] analyzed the outcomes in 110 hemangioendothelioma patients having liver transplant between 1987 and 2005. The 1- and 5-year patient survival rates were 80% and 64% respectively and the 1- and 5-year graft survival rates were 70% and 55% respectively.[74] A more recent study conducted by Lai *et al*. demonstrated even more favorable survival outcomes. They retrospectively analyzed data from 1984 to 2014 in the European Liver Transplant Registry and found that the 1-, 5- and 10-year overall survival rates in the 149 patients having liver transplant for hepatic hemangioendothelioma were 88.6%, 79.5% and 74.4% respectively. They also identified the following three independent risk factors for recurrence: macrovascular invasion, hilar lymph node invasion, and a wait for transplant of ≤120 days.[75] These studies confirmed the value of liver transplant for patients with hemangioendothelioma. Unresectable hemangioendothelioma should therefore not be a contraindication to liver transplant. Prospective analyses are needed to determine the independent risk factors for survival of this subgroup of patients and to identify patients at risk of recurrence after liver transplant.

PATIENT FACTORS

1. Age

Advanced age was considered a relative contraindication to liver transplant as it is a major risk factor in many chronic diseases.[76] However, as the population continues to age and good antiviral treatment delayed cirrhosis process, the proportion of elderly patients requiring liver transplant is expected to increase.[77-79] Compared to the young, elderly patients more commonly present with co-morbidities including cardiovascular diseases, diabetes mellitus, renal insufficiency and pulmonary diseases, which adversely affect long-term prognosis.[80] However, elderly recipients have been reported to display a lower rate of rejection with respect to immune senescence,[81,82] which may indicate a favorable effect on graft survival.

There have been a few studies conducted to compare elderly and young transplant recipients in terms of postoperative outcomes and long-term survival.[81-87] The results reported were inconsistent, which was likely in part due to the heterogeneity of age cutoffs for the elderly and non-elderly (varying between 60 and 75 years). Some studies reported comparable patient and graft survival rates between the two groups,[82,83,85] while some reported significantly worse survival in the elderly group.[81,84,86,87]

One of the studies reporting inferior outcomes in elderly transplant recipients was a large retrospective study conducted by the University of California. The study compared 3,711 transplant recipients aged ≥60 years and 11,966 recipients younger than 60 years.[87] It was found that age ≥70 years was independently associated with an increased risk of graft loss (hazard ratio, 1.65; 95% confidence interval, 1.08 to 1.82; $p<0.001$). However, the increased risk was attenuated in elderly patients with a Model of End-Stage Liver Disease score <28. It was thus concluded that patients should not be excluded solely because of age. Similarly, preoperative intensive care unit admission,[85] fulminant hepatic failure,[85] pretransplant hospital admission[86] and high bilirubin level[86] were identified as independent risk factors for inferior outcomes in elderly patients.

Currently in the literature, the results of studies of liver transplant for the elderly are inconsistent. However, almost all studies concluded that age alone should not be an exclusion factor for liver transplant. For optimization of patient selection and graft allocation, further prospective studies should be conducted to identify the risk factors in elderly patients.

2. Co-morbidity

Patients with failure of another organ in addition to the liver may need a transplant simultaneous with liver transplant. Combined liver and kidney transplantation was probably the commonest combined organ transplant performed (6.8% of all liver transplants in the United States).[16] Hepatorenal syndrome together with preexisting kidney disease, are common indications for combined liver and kidney transplant; these include chronic glomerulonephritis, diabetic nephropathy, polycystic kidney disease, calcineurin inhibitor toxicity and hypertensive kidney disease.[88] A study by Schmitt *et al*.[89] demonstrated that patients with renal failure on hemodialysis had more survival benefit from combined liver-kidney transplants when compared with patients with renal failure but not on hemodialysis. For patients with renal failure but not on hemodialysis, there was no increase in survival when comparing combined liver-kidney transplants to liver transplants alone.

A well-established advantage of combined liver and kidney

transplant is an immunoprotective effect of the transplanted kidney from the liver allograft when both organs come from the same donor.[90,91] The possible mechanism has not been clearly elucidated, but it has been suggested that the liver absorbs lymphocytotoxic antibodies, promotes antibody phagocytosis by Kupffer cells, and secretes soluble human leukocyte antigens. A pretransplant cross-match is not routinely performed and cases of conversion of a positive to a negative cross-match post-transplant have been described. The most common indication for combined liver and kidney transplant in children is inherited hepatic metabolic abnormalities such as primary hyperoxaluria.[92] Kitajima *et al*.[93] reported that a sequential liver-kidney transplant from a single living donor achieved an excellent overall survival rate of 92.3% in 10 years.

Combined heart and liver transplant was described for patients with familial amyloid polyneuropathy (FAP). In this group of patients, the liver produces the majority of the transthyretin that is involved in the cause of amyloid deposition.[94] Cardiac cirrhosis is the most common hepatic diagnosis in patients with coronary heart disease.[17] Other indications of combined heart and liver transplant include familial hypercholesterolemia, beta-thalassemia,[95] hemochromatosis,[96] alcoholic cardiomyopathy, cryptogenic cirrhosis with underlying cardiomyopathy and glycogen storage disease.[97] Combined liver and lung transplantation were reported to be performed in cystic fibrosis patients.[98] Together with the experience and advancement, the use of liver transplant in these patients are likely to be expanded.

3. Expanding graft availability in low deceased donor rate regions

Despite high demand, a severe shortage of suitable allografts limits the use of liver transplant for the treatment of different etiologies of liver diseases. The condition in Asian centers including Hong Kong is different from Scandinavian countries described–having a surplus in liver grafts is a kind of luxury. Expanding the indications for liver transplant affects patients who were already on list. Resistance would be encountered if the outcome of new indications were not proven to be good enough. On the other hand, living donor liver transplant and multiple other strategies were developed to further increase organ supply. Close relatives are the commonest living donor but their ABO blood group may not be compatible. ABO-incompatible living donor liver transplant protocols with the use of rituximab and plasma exchange were reported by multiple living donor liver transplant centers.[99-101] Donor exchange programs were also aimed at resolving the incompatible relative problem.[102,103] Domino liver transplant, with the example of FAP graft, were reported to have comparable short term results with deceased donor liver transplant.[104] However, the *de novo* development of FAP within various periods has been described.[105]

Another strategy to expand the donor pool is utilization of extended criteria donor grafts, e.g. donation after circulatory death,[106] steatotic[107] and elderly grafts,[108,109] etc. Liver transplant service could only be expanded with the expansion of indication together with graft availability.

Although the number of cadaveric organ donations has not increased in most Asian places, South Korea has recently succeeded in increasing the rate of organ donation by introducing several systems, such as incentive programs, an organ procurement organization, a donor registry, and a system to facilitate potential donor referral.[110] With these measures, the number of braindead donors increased from 50 in 2003 to 367 in 2013. This experience may help other Asian regions to improve their organ donation rates.[111]

4. Extension of deceased donor criteria

Extension of deceased donor criteria may be a potential method to expand liver transplant indications. Liver grafts from DCD are a potential source of organ growth in the West. Croome *et al*. compared DCD and donation after brain death (DBD) in terms of liver transplant recipient survival. The 1-, 3- and 5-year survival rates were 92.3%, 86.1% and 80.3% respectively in the DCD group and 92.3%, 85.1% and 79.5% respectively in the DBD group (p=0.27).[112] The use of organs from DCD may be a method to alleviate organ shortages in Asian regions. DCD is still limited in Asia. However, in Mainland China, DCD has been the sole legal source of donor organs since 2015. A study found that DCD was associated with a higher risk of early allograft dysfunction.[113] Future studies are required to evaluate the outcomes of DCD liver transplant and explore the possibility of adopting DCD grafts as a method of increasing graft supply in Asia.

CONCLUSION

The scope of indications for liver transplant has been gradually expanding over the decades. Going forward, further development of preoperative noninvasive predictors in tumor, patient and even donor factors is needed to identify patients at risk of poor outcomes. Stringently relaxed criteria for liver transplant will be the way to go. The significance of development of tools that can accurately predict outcomes lies not only in patient consultation and management but also in implementation of policies and guidelines in the future.

CONFLICTS OF INTEREST

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

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