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**Liver transplantation for hepatic tumors: a systematic review**

Ravaioli M *et al*. treatment of liver tumors with transplantation

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**Abstract**

The improvement in medical and pharmacological management of liver transplantation (LT) recipients has led to a better long term outcome and extension of the indications to this procedure. Liver tumors have a relevant rationale to LT, however indication for malignancies still remains a debated issue due to the high risk of recurrence. In this review we considered LT for hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), liver metastases (LM) and other rare tumors. We reviewed the literature about these topics, focusing on the past 10 years. The highly selected Milan criteria of LT for HCC (single nodule < 5 cm or up to 3 nodules < 3 cm) have been recently extended by the group of the University of S. Francisco (1 lesion < 6.5 cm or up to 3 lesions < 4.5 cm) with satisfying results of recurrence-free survival as well as by the “up-to-seven criteria”. Moreover other transplant groups have recently developed downstaging protocols, including surgical or loco-regional treatments of HCC, which have showed efficacy in increasing the post-operative survival of recipients initially out of these criteria. CCA has become an indication to LT in patients who cannot undergo liver resection due to underlying liver disease or to anatomical technical challanges. A well-defined protocol of chemoirradiation and staging laparotomy before LT has been developped by the Mayo Clinic which allows to obtain long term results in disease-free survival comparable to other indications. LT for LM has also been investigated by multiple center studies. It offers a real benefit for metastases from neuroendocrine tumors which are well differentiated and when a major extrahepatic resection is not required. If LT is an option in these selected cases, liver metastases from colo-rectal cancer is still a borderline indication since data about the disease-free survival are still lacking. Hepatoblastoma and hemagioendothelioma represent rare primary tumors for which LT is often the only possible and effective cure due to the frequent multifocal, intrahepatic nature of the disease. LT is a very promising procedure for both primary and secondary liver malignancies, however it needs an accurate evaluation of the costs and benefits for each indication in order to balance the chances of cure with the actual organ availability.

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**Key words:** Liver transplantation; Liver cancer; Hepatocellular carcinoma; Cholangiocarcinoma; Neuroendocrine carcinoma; Liver metastases; Hepatoblastoma; Hemangioendothelioma

**Core tip:** This review includes the most relevant outcome of liver transplantation (LT) for both primary and metastatic tumors. The indications to LT for malignancies has been debated because of the recurrence rate due to the negative impact of immunosuppressive therapy; however recent studies show that an accurate selection of the candidates and pre-LT treatments (surgical, loco-regional or chemotherapeutical) may improve the recurrence-free survival. We report the recommendations and accepted guidelines to LT for hepatic tumors and the long term results from the most recent literature; our policy for these indications is also reported.

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**Introduction**

The first cases of liver transplantation (LT) reported in the literature were performed for liver tumors; in fact among the first seven liver transplantation recipients there were patients with duct cell carcinoma and colo-rectal metastases[1] . After this initial experience, LT was adopted for end-stage liver failure and only in the late 1990s it became available for patients with hepatocellular carcinoma (HCC) thanks to the results of the Milan study, which established precise criteria for the selection of HCC who could undergo liver replacement without the high risk of tumor recurrence[2]. The main problem with LT for liver tumors was the unfavourable post-operative outcome due to the tumor recurrence, which was drastically reduced for HCC patients meeting the Milan criteria; these selection criteria produced similar survivals among patients with and without HCC.

Therefore, HCC became the main indication for LT, even if UNOS (United Network for Organ Sharing)[3] has recently reported malignancies other than HCC as indication for LT, including colangiocarcinoma and Klatskin tumor, hepatoblastoma and hemangioendothelioma, liver metastases from neuroendocrine tumors and few cases of metastases from colo-rectal cancer.

A liver malignancy seems the perfect indication for liver replacement as it allows the most radical intervention, although the post-operative immunosuppressive therapy may increase the risk of tumor recurrence. On the other hand, the improvement of surgical resective techniques allows a high radicality rate with hepatic resection in case of biliary and metastatic tumors, both in pediatric and adult patients.

Since the pool of deceased donors is not sufficient to meet the need of organs, it is particularly important to employ the resective strategy whenever possible, leaving LT as an option in the case of unresectable liver tumor (due to diffuse localization or advanced hepatic disease), post-operative liver failure or in the case of disease recurrence after liver resection (salvage transplantation).

We systematically reviewed the current literature on LT for hepatic tumors focusing mainly on the topic studies of the recent ten years. We devided the main indications to LT for hepatic tumors as follows: HCC, cholangiocarcinoma, liver metastases and other rare liver tumors.

**LT for hepatocellular carcinoma**

Hepatocellular carcinoma is the 6th most common cancer and at the 3rd position as the most lethal one[4]. This cancer frequently develops on underlying chirrosis, in particular when the cause is hepatitis B or C; despite the advent of vaccination and new antiviral therapies, the incidence of HCC is increasing at high rate[5].

Different staging systems for HCC have been proposed, but the most widely adopted is the BCLC (Barcelona Clinic Liver Cancer), which not only stratifies the patients according to the outcome, but also indicates the best treatment option considering the different stages of tumor and hepatic disease[6-9].

According to the BCLC classification, LT should be reserved to patients with the following features: single nodule < 5 cm or up to 3 nodules < 3 cm without macrovascular invasion. These criteria, called Milan Criteria, were first described by Mazzaferro in 1996[2] and identified a pool of patients who could have an excellent recurrence-free survival after LT and an outcome comparable to the other indication of LT.

The pre-operative selection criteria help to reduce the risk of tumor recurrence after LT, but they limit the numbers of possible candidates to LT, in particular if the waiting time is long and during that time a disease progression develops. For these reasons many patients are currently excluded from the chance of transplantation.

Since candidates to LT with HCC often have low MELD scores[10], with a quite preserved hepatic function, UNOS and other European allocation systems created a new policy for organ allocation to these patients. They were given additional escalating scores according to the time spent in waiting list with tumor remaining within Milan criteria[11-13].

This allocation system required few modifications over the years, in order to reach a balance in waiting list mortality between possible recipients with and without HCC[14].

The excellent results yielded by the adoption of Milan Criteria lead many Transplant Centers to suggest new strategies to expand the tumoral criteria in order to allow more patients to receive LT. In 2001, the research group from the University of California San Francisco reported a 5-year survival over 70% by slightly expanding the tumor criteria (1 lesion < 6.5 cm or up to 3 lesions < 4.5 cm)[15]. This good outcome was confirmed in more recent comparative series[16] and led to new studies exploring the opportunity of downstaging the tumor in order to bring it back within Milan or UCSF criteria. The treatments used for downstaging were both resection and locoregional therapies and they had the dual advantage of allowing an extention of the pool of candidates to transplantation and the reduction of drop-out in the waiting list. Among the various retrospective data, only two prospective studies reported comparable survival after LT in patients initially out of Milan criteria versus patients meeting the criteria from the beginning[17,18]. The downstaging procedures included TACE or RFA and in order to proceed to LT a total necrosis of the treated lesions had to be diagnosed at the pre-LT imaging. If an accurate diagnosis could be performed the downstaging showed effective and the 3-mo period before placing the patient in the waiting list allowed to exclude the more aggressive tumors with a high risk of recurrence after LT.

The good results of downstaging lead a recent consensus conference about LT for HCC to recommend this procedure before LT, although more prospective studies are needed to strenghten the evidence[19]. Similarly bridging procedures have been recommended for patients with tumors > 2 cm who are likely to wait more than 6 mofor transplantation[19]. Concerning to the strategies to adopt, no recommendations can be made since there is no clear evidence that one treatment is preferred over the others[20], although a combination of the different locoregional therapies might have a beneficial effect on slowing down the progression rate of the tumor and increasing the overall survival[21].

Recently a multicenter study was performed in order to explore retrospectively the chance of survival after LT for HCC beyond Milan criteria; if the rule of “up to seven” was fulfilled (HCCs with seven as the sum of the size of the largest tumour in cm and the number of tumours) the 5-year survival could reach 70%. The Metroticket calculator was then created as a statistical tool which could predict the 5-year survival of any given patient on the basis of morphological and pathologic characteristics: total size of the nodules, size of the largest nodule and presence or absence of vascular invasion (if available)[22]. Although the prediction of survival has recently become more accurate and precise, an agreement among the centers has not yet been reached as to which survival rate is to be considered acceptable in balancing the highest chances of cure with the actual organ availability.

Hepatic resection should be considered whenever possible, because for some patients it can be a curative procedure, without hampering the chance of a LT in the case of post-operative liver failure (*i.e.* the so-called “salvage transplantation”). Although a Child-Pugh A has traditionally been the selection criteria to identify candidates to surgery, in the recent years other diagnostic tools have been adopted as indocyanine green (especially in Japan), measurement of hepatic vein pressure gradient and hepatic elastometry. The policy currently adopted in our center is that chirrotic patients undergo hepatic resection if the Child-Pugh score is A, the MELD score is below 12, platelet count is over 50000/μl and no oesophageal varices at high risk of bleeding are present[23]. More recently, the value of transient elastography measured with Fibro Scan was effective to predict the risk of liver failure after hepatic resection for HCC[24].

In our experience a series of transplantable patients undergoing hepatic resection developed post-operative liver failure or HCC recurrence, and finally received a salvage transplantation. The outcomes obtained with this procedure were comparable to those achieved with primary LT[25,26].

The main limit of this strategy is the number of actually transplantable patients, who are not suitable for LT after resection for many reasons (tumor recurrence out of the conventional criteria, death during the waiting time, too sick, advanced age or other comorbidities). Currently one debated issue is how to predict the impossibility to perform a LT after an initial liver resection[27].

The new options offered by downstaging tumors beyond Milan criteria or by expanding Milan criteria increase the pool of potential recipients. In order to meet the growing demand of organs, the programs of living donor transplantation (LDLT) were developed by many transplantation centers. HCC is a good indication for LDLT since the opportunity to have a graft from a relative allows the potential recipients to shortly benefit of a curative treatment while saving organs for the other patients in waiting list.

Although some studies reported a higher risk of tumor recurrence with the use of partial grafts from living donors[28-30], this result is partly linked to a fast track effect, which prevents from detecting more aggressive tumors during an adequatlely long pre-transplant work-up[31].

The absence of tumor progression during the waiting time still remains the most effective biological selection criteria, allowing to transplant patients with low risk of tumor recurrence. Furthermore, most of the scientific reccomendations define that LDLT should be reserved to HCC patients who have an expected 5-year survival similar to comparably staged patients receiving a deceased-donor liver[19].

In conclusion, LDLT seem to offer many advantages for HCC cases suitable to LT, but the indications, the selection criteria and a minimum waiting time (at least 3 mo) before the surgical procedure should be the same such as with the deceased-donor liver.

**LT FOR CHOLANGIOCARCINOMA**

Although in the 1990s LT appeared a possible solution for unresectable cholangiocarcinoma (CCA) the initial clinical experience yielded very poor results in term of both overall and recurrence free survival[32-34]. In these early reports, the 5-year survival ranged between 18% and 38%, largely inferior to the 50% accepted for other malignant and not-malignant indications for LT. Only few cases of acceptable 5-year survival (more than 50%) with low post-transplantation tumor recurrence rate were reported by the University of Pittsburg[35,36]. Although CCA has been recognized for a long time a contraindication for LT, on the wake of the promising Pittsburgh results, the Mayo Clinic developed a protocol of strict recipient selection and neoadjuvant chemoirradiation for CCA[37] which prompted very positive outcome being subsequently adopted by the University of Nebraska[38]. These results suggested that CCA could no longer be an absolute contraindication for LT. A meta-analysis was conducted on 605 patients who underwent LT for CCA in 14 American and European centers (from 1997 to 2009) and it showed that although the overall 5-year survival was 39%, the subgroup of patients treated with adjuvant chemoirradiation reached a 5-year suvival of 57%[39].

These data were confirmed in a recent review which summarized the results of LT for CCA comparing the survival rates of studies performed before and after the development of the “Mayo protocol” [40]. The 5–year survival was 17-35% in the early years (1987-2002) while it ranged from 21% to 82% in recent years (2004-2012). Five-year survival rates were 71%-82% when considering only studies in which recipients were treated with neo-adjuvant therapy.

The neo-adjuvant treatment scheme first described by the Mayo Clinic consists of extended beam radiation (4500 cGy/d for 15 d) and protracted intra-venous infusion of 5-FU (225 mg/m2 per day). Biliary brachitherapy will then deliver 2000 cGy and finally oral capecitabine (1000 mg/m2 per die 2 out of every 3 wk) is administered until LT. A staging laparotomy is performed before LT in order to rule out the presence of intra or extrahepatic metastases and lymph node metastases. The timing of this procedure is still debated[41].

Both intra- and extrahepatic CCA could represent indications to LT when resective surgery is not an option because of underlying liver disease (PSC) or anatomically unresectable lesions.

In these cases liver transplantation could offer better results than palliative therapy if the following conditions are respected: (1) the radial diameter of the intrahepatic mass is under 3 cm; and (2) staging laparotomy is performed and no extrahepatic or lymph node metastases are detected[42].

LT has certaintly several advantages over liver resection since it allows a potential complete resection when the anatomical location of the lesion would not allow a radical resection. Patients with underlying disease (as PSC) would particularly benefit the transplantation as they may not tolerate an hepatic resection because of the reduced hepatic functional reserve.

Although encouraging long term results have been obtained some problems have raised which need to be addressed before this disease can become a routine indication for LT.

A first issue is the high drop-out rate which was shown to be associated to tumor characteristics, like elevated CA 19.9, radial diameter of the mass > 3 cm and malignant citology or histology, as well as to patient features, like a higher MELD score[43]. This observation lead to the adoption of the UNOS policy for MELD exception, in which additional MELD scores are assigned to these recipients in order to adjust their gravity for the increased risk of drop-out from the waiting list every 3 mo [44]. In a recent paper from the Mayo Clinic the main predictors of drop-out were identified as CA 19.9 > 500 U/mL, a mass diameter > 3 cm, bioptic evidence of malignancy and MELD score > 20; all these parameters are available before LT and can therefore be used to guide the patient enrollment in the protocol.

In a Mayo Clinic series published in 2005 the explanted livers of patients who underwent LT after the chemoradiation protocol were analysed and no tumor was detected in almost half of them[45]. Although it is not clear whether the absence of tumor was due to an initial false diagnosis or to the efficacy of the chemoradiation protocol, a more effective tumoral detection is strongly needed in order to avoid unnecessary transplantations.

A recent series from the University of Seoul showed that an accurate preoperative staging and biliary drainage associated to portal embolization could allow extended hepatectomy for CCA. In these cases if R0 was obtained, 5-year survival could reach 50%[46]. The main poor prognostic factors were the same that would contraindicate LT. Therefore it can be concluded that the Mayo Protocol is effective for certain cases of CCA, especially when the liver function is deteriorated due to the underlying hepatic disease. However hepatic resection is still the main therapeutic strategy which not only allows satisfying survival results but also saves organs for patients with hepatic failure who do not have an alternative treatment other than LT.

An excellent outcome with the liver resection was also reported by the University of Nagoya in particular in the cases without lymph node metastases and R0 resections; the lymph node metastasis is a powerful and independent prognostic factor, which should be utilized to stratify different prognosis and treatments[47].

**LT for Liver Metastases**

LT for hepatic metastases has been mainly proposed for unresectable neuroendocrine liver tumors (NET)[48]. The main debate about the adoption of LT in the treatment of unresectable metastases from NET is that the real survival benefit of LT over other therapies is unknown and since new alternative medical treatment options are emerging, a current comparative analysis is needed. Moreover the relative rarity of the disease accounts for the small number of patients in each center. Recently a multicentric study collected data from 35 transplantation centers on 11 European countries for a total of 213 patients operated between 1982 and 2009[49]. This study reports a satisfying 5-year survival rate of over 50% although lower than the previously reported overall survival of 80% with the strict criteria adopted by Mazzaferro[50].

These results and those emerged from other retrospective studies with less patients allow to establish that LT can be suggested when[51-53]: (1) the disease is limited to the liver or the primary tumor is detected and removed (the primary tumor should be removed before LT, but unknown primary tumor is not an absolute contraindication to LT); (2) well differentiated tumors, measured with a Ki < 10%; (3) no major extrahepatic resection is needed; and (4) at least a follow up time of 1-2 years between the diagnosis and the LT, in order to assess the biological behavior of the disease.

Additionally it is suggested that LT should be proposed as an option when other medical treatment are not tollerated or not effective any longer. This opportunity is supported by the evidence that the interval from LM discovery to LT is not associated to a decreased overall survival.

LT for other metastases different from NET still remains a debated iusse, even if interesting data came from recent series. Liver metastases from colo-rectal cancer represent nowadays an absolute contraindication to LT since cases of transplantation for such indications from the early 90s reported 5-year survival of less than 20%. However some recent advances have been made in term of improved selection of potential candidates thanks to more sofisticated radiological diagnosis and owing to the use of immunosuppresants like mTOR inhibitors which can help to limit the recurrence. Recently, a prospective study decribed the outcome of 21 LT for unresectable LM from colorectal cancer performed between 2006 and 2011[54]. The overall survival at 5 years was of 60%, and the major prognostic factors were maximal tumor diameter over 5.5 cm, less than 2 years from surgery of the primary cancer, CEA levels over 80 mcg/L and presence of progressive disease at the time of LT. It was observed that having more than two negative prognostic factors was associated to a significantly worse outcome. Although the recurrence rate was almost universal after LT, the overall survival was much better than any other treatment option even when considering resectable LM[55]. The Norwegian situation of organ donation in which the need for organs is largely covered, allowed the performance of this study; before approving the opportunity of this indication for LT the international community needs to verify on a much larger sample size that a substantial benefit would derive from LT for this kind of malignancies and to establish inclusion criteria for the potential recipients.

**LT for rare Liver Tumors**

Hepatoblastoma represents the most frequent hepatic primary tumor in children with a growing incidence in the last decades[56]. Unfortunately this disease often presents at the diagnosis with a diffuse pattern for which surgical resection is not possible; in these cases LT is the only option.

A recent review from the data of LT performed in United States between 1988 and 2010 revealed a satisfying 5-year survival exceeding 75% for children suffering from hepatoblastoma, with a recurrence rate up to 16%. It appeared that it was associated to clinical features as well as to technical aspects, but the conclusion was that an improved survival could be obtained if a thorough radiological screening was performed and an adequate chemotherapic protocol was applied[57].

Hepatic hemangioendothelioma is also a rare malignancy derived from endothelial cells, which often presents as multifocal disease (in 81% of patients) or with extrahepatic metastases[58]. It has an intermediate prognosis between benign hemangioma and malignant angiosarcoma, with a survival rate of less than 50% without therapy[59].

Tumor resection is the gold standard treatment since poor results have been reported with chemotherapy or radiotherapy; however hepatic resection is not indicated if the tumor cannot be completely removed because of the aggressive biological behaviour of this disease. Since the multifocality of the disease makes a curative resection very rarely possible[59], LT becomes an attractive effective option. The limited experience of LT on this field due to the rarity of the disease reported good outcome with a 5-year survival ranging from 53% to 80%, even when vascular and hilar lymphnodal involvement was present[60]. The main challange about hemangioendothelioma remains the differential diagnosis with hemangiosarcoma which is particularly important considering the poor outcome related to the latter disease. Recent series from the European Liver Transplant Registry reported an overall survival about 7 mo after liver transplantation for hemangiosarcoma, making this disease an absoute contraindication to liver transplantation[61]. The immunostaining analysis together with a 6 mo wait-list observation period could help in detecting true hemangioendothelioma and avoid useless transplantation. Moreover, an adjuvant protocol of anti-angiogenetic chemotherapy could be suggested considering the vascular nature and the frequent extrahepatic spread of this disease[59].

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