World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i18.5345

World J Gastroenterol 2014 May 14; 20(18): 5345-5352
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (7): Liver transplant

Liver transplantation for hepatic tumors: A systematic review

Matteo Ravaioli, Giorgio Ercolani, Flavia Neri, Matteo Cescon, Giacomo Stacchini, Massimo Del Gaudio, Alessandro Cucchetti, Antonio Daniele Pinna

Matteo Ravaioli, Giorgio Ercolani, Flavia Neri, Matteo Cescon, Giacomo Stacchini, Massimo Del Gaudio, Alessandro Cucchetti, Antonio Daniele Pinna, Department of General Surgery and Transplantation, Sant'Orsola-Malpighi Hospital, University of Bologna, 40138 Bologna, Italy

Author contributions: All the authors contributed equally to this work; Ercolani G conceived the review; Ravaioli M, Ercolani G and Neri F wrote the manuscript; Ravaioli M and Neri F performed the bibliographical research; Cescon M, Cucchetti A, Del Gaudio M and Pinna AD revised the manuscript.

Correspondence to: Giorgio Ercolani, PhD, Department of General Surgery and Transplantation, Sant'Orsola-Malpighi Hospital, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy. giorgio.ercolani@aosp.bo.it

Telephone: +39-51-6363105 Fax: +39-51-6364819
Received: October 12, 2013 Revised: December 6, 2013
Accepted: January 8, 2014
Published online: May 14, 2014

Abstract

Improvements in the medical and pharmacological management of liver transplantation (LT) recipients have led to a better long-term outcome and extension of the indications for this procedure. Liver tumors are relevant to LT; however, the use of LT to treat malignancies remains a debated issue because 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, 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 a group from the University of S. Francisco (1 lesion < 6.5 cm or up to 3 lesions < 4.5 cm) with satisfying results in terms of recurrence-free survival and the "up-to-seven criteria". Moreover, using these criteria, other transplant groups have recently developed downstaging protocols, including surgical or loco-regional treatments of HCC, which have increased the post-operative survival of recipients. CCA may be treated by LT in patients who cannot undergo liver resection because of underlying liver disease or for anatomical technical challenges. A well-defined protocol of chemoirradiation and staging laparotomy before LT has been developed by the Mayo Clinic, which has resulted in long term disease-free survival comparable to other indications. LT for LM has also been investigated by multicenter studies. It offers a real benefit for metastases from neuroendocrine tumors that are well differentiated and when a major extrahepatic resection is not required. If LT is an option in these selected cases, liver metastases from colorectal cancer is still a borderline indication because data concerning the disease-free survival are still lacking. Hepatoblastoma and hemangioendothelioma represent rare primary tumors for which LT is often the only possible and effective cure because of 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 to balance the chances of cure with actual organ availability.

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

Core tip: This review includes the most relevant outcomes of liver transplantation (LT) for both primary and metastatic tumors. The use of LT for malignancies has been debated because of the recurrence rate caused by the negative impact of immunosuppressive

therapy; however, recent studies show that accurate selection of candidates and pre-LT treatments (surgical, loco-regional or chemotherapeutical) may improve recurrence-free survival. We report the recommendations and accepted guidelines for the use of LT for hepatic tumors and the long term results from the most recent literature; our policy for these indications is also reported.

Ravaioli M, Ercolani G, Neri F, Cescon M, Stacchini G, Del Gaudio M, Cucchetti A, Pinna AD. Liver transplantation for hepatic tumors: A systematic review. *World J Gastroenterol* 2014; 20(18): 5345-5352 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i18/5345.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i18.5345

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 colorectal metastases[1]. After this initial experience, LT was adopted for end-stage liver failure and only in the late 1990s did it become available for patients with hepatocellular carcinoma (HCC), thanks to the results of the Milan study, which established precise criteria for the selection of HCC patients who could undergo liver replacement without the high risk of tumor recurrence[2]. The main problem with LT for liver tumors was the unfavorable post-operative outcome caused by 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, among liver malignancies, HCC became the main indication for LT, even if UNOS (United Network for Organ Sharing)[3] has recently reported malignancies other than HCC as being indicated for LT, including cholangiocarcinoma and Klatskin tumor, hepatoblastoma and hemangioendothelioma, liver metastases from neuroendocrine tumors and few cases of metastases from colorectal cancer.

A liver malignancy seems the perfect indication for liver replacement because LT 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 rate of radical hepatic resection in cases of biliary and metastatic tumors, both in pediatric and adult patients.

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

Here, We reviewed the current literature on LT for hepatic tumors systematically, focusing mainly on the topic studies of the recent ten years. We divided the main indications for LT of 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 the 3rd most lethal type[4]. This cancer frequently develops on underlying cirrhosis, 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 sharply[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 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 for patients with the following features: single nodule < 5 cm or up to 3 nodules < 3 cm without macrovascular invasion. These criteria, called the Milan Criteria, were first described by Mazzaferro in 1996[2] and identified a pool of patients who could have excellent recurrence-free survival after LT and an outcome comparable to the other indications of LT.

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

Candidates for LT with HCC often have low MELD scores[10], with relatively preserved hepatic function; therefore, 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 on the waiting list with tumor remaining within the Milan criteria[11-13].

This allocation system required few modifications over the years 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 led many Transplant Centers to suggest new strategies to expand the tumoral criteria to allow more patients to receive LT. In 2001, a research group from the University of California San Francisco reported 5-year survival of 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 a more recent comparative series[16] and led to new studies exploring the opportunity of downstaging the tumor to bring it back within Milan or UCSF criteria. The treatments used for downstaging included resection and locoregional

therapies. In addition, they had the dual advantage of allowing an extension of the pool of candidates for transplantation and the reduction of dropout 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 *vs* patients meeting the criteria from the beginning[17,18]. The downstaging procedures included trans-arterial chemo-embolization (TACE) or radiofrequency ablation (RFA) and, 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 and the downstaging shown to be effective, the 3-mo period before placing the patient in the waiting list allowed exclusion of the more aggressive tumors with a high risk of recurrence after LT.

The good results of downstaging led to a recent consensus conference about LT for HCC to recommend this procedure before LT, although more prospective studies are needed to strengthen the evidence[19]. Similarly, bridging procedures have been recommended for patients with tumors > 2 cm who are likely to wait more than 6 mo for transplantation[19]. Concerning which strategies to adopt, no recommendations can be made because there is no clear evidence that one treatment is preferable 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 overall survival[21].

Recently, a multicenter study was performed to explore retrospectively the chance of survival after LT for HCC beyond the Milan criteria; if the rule of "up to seven" was fulfilled (HCCs with a score of seven, calculated as the sum of the size of the largest tumor in cm and the number of tumors), the 5-year survival could reach 70%. The Metroticket calculator was then created as a statistical tool that 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 centers has not yet been reached as to which survival rate is considered acceptable in balancing the highest chances of cure with 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 the Child-Pugh score of A has traditionally been the selection criterion to identify candidates for surgery, in the recent years other diagnostic tools have been adopted, such as indocyanine green (especially in Japan), measurement of hepatic vein pressure gradient and hepatic elastometry. The policy currently adopted in our center is that cirrhotic 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 esophageal varices at high risk of bleeding are present[23]. More recently, the value of transient elastography, measured using 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 transplantable patients who are not suitable for LT after resection for a variety of 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 of performing an LT after an initial liver resection[27].

New options are offered by downstaging tumors beyond the Milan criteria or by expanding the Milan criteria to increase the pool of potential recipients. To meet the growing demand for organs, programs of living donor transplantation (LDLT) were developed by many transplantation centers. HCC is a good indication for LDLT because the opportunity to have a graft from a relative allows the potential recipients to benefit quickly from a curative treatment while saving organs for the other patients in the 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 detection of more aggressive tumors during an adequately long pre-transplant work-up[31].

The absence of tumor progression during the waiting time still remains the most effective biological selection criteria, allowing transplantion in patients with low risk of tumor recurrence. Furthermore, most of the scientific recommendations define that LDLT should be reserved for 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 for LT; however, the indications, the selection criteria and the minimum waiting time (at least 3 mo) before the surgical procedure should be the same as with deceased-donor livers.

LT FOR CHOLANGIOCARCINOMA

In the 1990s, LT appeared a possible solution for unresectable cholangiocarcinoma (CCA); however, 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%, which was largely inferior to the 50% accepted for other malignant and not-malignant indications for LT. Only a few cases of acceptable 5-year survival (more than 50%) with low post-transplantation tumor recur-

rence rate were reported by the University of Pittsburg[35,36]. Although CCA has long been recognized as a contraindication for LT, in the wake of the promising Pittsburgh results, the Mayo Clinic developed a protocol of strict recipient selection and neoadjuvant chemoirradiation for CCA[37], which produced a very positive outcome and was subsequently adopted by the University of Nebraska[38]. These results suggested that CCA was 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), which showed that although the overall 5-year survival was 39%, the subgroup of patients treated with adjuvant chemoirradiation reached a 5-year survival of 57%[39].

These data were confirmed in a recent review that 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 the 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/m^2 per day). Biliary brachytherapy will then deliver 2000 cGy and finally oral capecitabine (1000 mg/m^2 per die 2 out of every 3 wk) is administered until LT. A staging laparotomy is performed before LT 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 for LT when resective surgery is not an option because of underlying liver disease (primary sclerosing cholangitis; PSC) or anatomically unresectable lesions.

In these cases, LT 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 several advantages over liver resection because 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 from transplantation because they may not tolerate a hepatic resection because of reduced hepatic functional reserve.

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

The first issue is the high drop-out rate, which was shown to be associated with tumor characteristics, such as elevated CA 19.9, radial diameter of the mass > 3 cm and malignant cytology or histology, as well as with patient features, such as a higher MELD score[43]. This observation led to the adoption of the UNOS policy for MELD exception, in which additional MELD scores are assigned to these recipients 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 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 analyzed and no tumors were detected in almost half of them[45]. Although it is not clear whether the absence of tumors was the result of an initial false diagnosis or to the efficacy of the chemoradiation protocol, a more effective tumoral detection is required urgently to avoid unnecessary transplantations.

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

Excellent outcomes of liver resection were also reported by the University of Nagoya, particularly in cases without lymph node metastases and R0 resections; lymph node metastasis is a powerful and independent prognostic factor, which should be utilized to stratify different prognoses 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 the emergence of new alternative medical treatment options means that 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 multicenter study collected data from 35 transplantation centers in 11 European countries for a total of 213 patients operated on between 1982 and 2009[49]. This study reported a satisfactory 5-year survival rate of over 50%, although this was lower than the previously reported overall survival of 80% with the strict

criteria adopted by Mazzaferro[50].

These results, and those from other retrospective studies with fewer patients, established that LT may be performed 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 an unknown primary tumor is not an absolute contraindication for LT); (2) well differentiated tumors, measured with a Ki < 10%; (3) no major extrahepatic resection required; and (4) a follow up time of at least 1-2 years between diagnosis and LT, to assess the biological behavior of the disease.

Additionally, it has been suggested that LT should be an option when other medical treatments are not tolerated or are no longer not effective. This opportunity is supported by evidence that the interval from LM discovery to LT is not associated with a decreased overall survival.

LT for metastases other than NET remains an issue of debate, despite interesting data from recent series. Liver metastases from colorectal cancer currently represent an absolute contraindication for LT because such cases of transplantation from the early 90s reported 5-year survivals of less than 20%. However, some recent advances have been made in terms of improved selection of potential candidates thanks to more sophisticated radiological diagnosis and the use of immunosuppresants, such as mTOR inhibitors, which can help to limit recurrence. Recently, a prospective study described the outcome of 21 LTs for unresectable LM from colorectal cancer performed between 2006 and 2011[54]. The overall survival at 5 years was 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 the presence of progressive disease at the time of LT. It was observed that having more than two negative prognostic factors was associated with 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 study was performed in Norway, where the need for organs is largely covered by donations; however, the international community needs to verify these results on a much larger sample size to determine if a substantial benefit would derive from LT for this kind of malignancy 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 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 with clinical features as well as with technical aspects; however, the conclusion was that improved survival could be obtained if thorough radiological screening was performed and an adequate chemotherapeutic 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 because 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 behavior of this disease. The multifocality of the disease makes a curative resection very rarely possible[59]; therefore, LT becomes an attractive and effective option. Despite the limited experience of LT in this field caused by the rarity of the disease, good outcomes are reported, with a 5-year survival ranging from 53% to 80%, even when vascular and hilar lymph node involvement was present[60]. The main challenge concerning hemangioendothelioma remains the differential diagnosis with hemangiosarcoma, which is particularly important considering the poor outcome related to the latter disease. A recent series from the European Liver Transplant Registry reported an overall survival of about 7 mo after liver transplantation for hemangiosarcoma, making this disease an absolute contraindication for liver transplantation[61]. The immunostaining analysis, together with a 6 mo waiting list observation period, could help in detecting true hemangioendothelioma and avoid unnecessary transplantation. Moreover, an adjuvant protocol of anti-angiogenic chemotherapy could be suggested, considering the vascular nature and the frequent extrahepatic spread of this disease[59].

REFERENCES

1 **Starzl TE**. The saga of liver replacement, with particular reference to the reciprocal influence of liver and kidney transplantation (1955-1967). *J Am Coll Surg* 2002; **195**: 587-610 [PMID: 12437245 DOI: 10.1016/S1072-7515(02)01498-9]

2 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428 DOI: 10.1056/NEJM199603143341104]

3 United Network for Organ Sharing. Available from: URL: http://www.unos.org

4 **Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-2917 [PMID: 21351269 DOI: 10.1002/ijc.25516]

5 **Altekruse SF**, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol* 2009; **27**:

1485-1491 [PMID: 19224838 DOI: 10.1200/JCO.2008.20.7753]
6 **Llovet JM**, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis* 1999; **19**: 329-338 [PMID: 10518312 DOI: 10.1055/s-2007-1007122]
7 **Forner A**, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012; **379**: 1245-1255 [PMID: 22353262 DOI: 10.1016/S0140-6736(11)61347-0]
8 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]
9 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]
10 **Wiesner R**, Edwards E, Freeman R, Harper A, Kim R, Kamath P, Kremers W, Lake J, Howard T, Merion RM, Wolfe RA, Krom R. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology* 2003; **124**: 91-96 [PMID: 12512033 DOI: 10.1053/gast.2003.50016]
11 **Sharma P**, Balan V, Hernandez JL, Harper AM, Edwards EB, Rodriguez-Luna H, Byrne T, Vargas HE, Mulligan D, Rakela J, Wiesner RH. Liver transplantation for hepatocellular carcinoma: the MELD impact. *Liver Transpl* 2004; **10**: 36-41 [PMID: 14755775]
12 **Ravaioli M,** Grazi GL, Ballardini G, Cavrini G, Ercolani G, Cescon M, Zanello M, Cucchetti A, Tuci F, Del Gaudio M, Varotti G, Vetrone G, Trevisani F, Bolondi L, Pinna AD. "Liver transplantation with the Meld system: a prospective study from a single European center." *Am J Transplant* 2006; **6**: 1572-1577 [PMID:16827857 DOI: 10.1111/j.1600-6143.2006.01354.x]
13 **Ravaioli M**, Grazi GL, Ercolani G, Cescon M, Del Gaudio M, Zanello M, Ballardini G, Varotti G, Vetrone G, Tuci F, Lauro A, Ramacciato G, Pinna AD. Liver allocation for hepatocellular carcinoma: a European Center policy in the pre-MELD era. *Transplantation* 2006; **81**: 525-530 [PMID: 16495798 DOI: 10.1097/01.tp.0000198741.39637.44]
14 **Roayaie K**, Feng S. Allocation policy for hepatocellular carcinoma in the MELD era: room for improvement? *Liver Transpl* 2007; **13**: S36-S43 [PMID: 17969067 DOI: 10.1002/lt.21329]
15 **Yao FY**, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; **33**: 1394-1403 [PMID: 11391528 DOI: 10.1053/jhep.2001.24563]
16 **Duffy JP**, Vardanian A, Benjamin E, Watson M, Farmer DG, Ghobrial RM, Lipshutz G, Yersiz H, Lu DS, Lassman C, Tong MJ, Hiatt JR, Busuttil RW. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. *Ann Surg* 2007; **246**: 502-509; discussion 509-511 [PMID: 17717454 DOI: 10.1097/SLA.0b013e318148c704]
17 **Ravaioli M**, Grazi GL, Piscaglia F, Trevisani F, Cescon M, Ercolani G, Vivarelli M, Golfieri R, D'Errico Grigioni A, Panzini I, Morelli C, Bernardi M, Bolondi L, Pinna AD. Liver transplantation for hepatocellular carcinoma: results of down-staging in patients initially outside the Milan selection criteria. *Am J Transplant* 2008; **8**: 2547-2557 [PMID: 19032223 DOI: 10.1111/j.1600-6143.2008.02409.x]
18 **Yao FY**, Kerlan RK, Hirose R, Davern TJ, Bass NM, Feng S, Peters M, Terrault N, Freise CE, Ascher NL, Roberts JP. Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis. *Hepatology* 2008; **48**: 819-827 [PMID: 18688876 DOI: 10.1002/hep.22412]
19 **Clavien PA**, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol* 2012; **13**: e11-e22 [PMID: 22047762 DOI: 10.1016/S1470-2045(11)70175-9]
20 **Oliveri RS**, Wetterslev J, Gluud C. Transarterial (chemo) embolisation for unresectable hepatocellular carcinoma. *Cochrane Database Syst Rev* 2011; (**3**): CD004787 [PMID: 21412886 DOI: 10.1002/14651858.CD004787.pub2]
21 **Ni JY**, Liu SS, Xu LF, Sun HL, Chen YT. Meta-analysis of radiofrequency ablation in combination with transarterial chemoembolization for hepatocellular carcinoma. *World J Gastroenterol* 2013; **19**: 3872-3882 [PMID: 23840128 DOI: 10.3748/wjg.v19.i24.3872]
22 **Mazzaferro V**, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T, Roayaie S, Schwartz ME, Grazi GL, Adam R, Neuhaus P, Salizzoni M, Bruix J, Forner A, De Carlis L, Cillo U, Burroughs AK, Troisi R, Rossi M, Gerunda GE, Lerut J, Belghiti J, Boin I, Gugenheim J, Rochling F, Van Hoek B, Majno P. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009; **10**: 35-43 [PMID: 19058754 DOI: 10.1016/S1470-2045(08)70284-5]
23 **Cescon M**, Colecchia A, Cucchetti A, Peri E, Montrone L, Ercolani G, Festi D, Pinna AD. Value of transient elastography measured with FibroScan in predicting the outcome of hepatic resection for hepatocellular carcinoma. *Ann Surg* 2012; **256**: 706-712; discussion 712-713 [PMID: 23095613 DOI: 10.1097/SLA.0b013e3182724ce8]
24 **Cucchetti A,** Ercolani G, Vivarelli M, Cescon M, Ravaioli M, Ramacciato G, Grazi GL, Pinna AD. "Is portal hypertension a contraindication to hepatic resection?" *Ann Surg* 2009; **250**: 922-928 [PMID: 19855258 DOI: 10.1097/SLA.0b013e3181b977a5]
25 **Del Gaudio M**, Ercolani G, Ravaioli M, Cescon M, Lauro A, Vivarelli M, Zanello M, Cucchetti A, Vetrone G, Tuci F, Ramacciato G, Grazi GL, Pinna AD. Liver transplantation for recurrent hepatocellular carcinoma on cirrhosis after liver resection: University of Bologna experience. *Am J Transplant* 2008; **8**: 1177-1185 [PMID: 18444925 DOI: 10.1111/j.1600-6143.2008.02229.x]
26 **Cucchetti A**, Vitale A, Del Gaudio M, Ravaioli M, Ercolani G, Cescon M, Zanello M, Morelli MC, Cillo U, Grazi GL, Pinna AD. Harm and benefits of primary liver resection and salvage transplantation for hepatocellular carcinoma. *Am J Transplant* 2010; **10**: 619-627 [PMID: 20121741 DOI: 10.1111/j.1600-6143.2009.02984.x]
27 **Fuks D**, Dokmak S, Paradis V, Diouf M, Durand F, Belghiti J. Benefit of initial resection of hepatocellular carcinoma followed by transplantation in case of recurrence: an intention-to-treat analysis. *Hepatology* 2012; **55**: 132-140 [PMID: 21932387 DOI: 10.1002/hep.24680]
28 **Fisher RA**, Kulik LM, Freise CE, Lok AS, Shearon TH, Brown RS, Ghobrial RM, Fair JH, Olthoff KM, Kam I, Berg CL. Hepatocellular carcinoma recurrence and death following living and deceased donor liver transplantation. *Am J Transplant* 2007; **7**: 1601-1608 [PMID: 17511683 DOI: 10.1111/j.1600-6143.2007.01802.x]
29 **Hwang S**, Lee SG, Joh JW, Suh KS, Kim DG. Liver transplantation for adult patients with hepatocellular carcinoma in Korea: comparison between cadaveric donor and living donor liver transplantations. *Liver Transpl* 2005; **11**: 1265-1272 [PMID: 16184545 DOI: 10.1002/lt.20549]
30 **Vakili K**, Pomposelli JJ, Cheah YL, Akoad M, Lewis WD, Khettry U, Gordon F, Khwaja K, Jenkins R, Pomfret EA. Living donor liver transplantation for hepatocellular carcinoma: Increased recurrence but improved survival. *Liver Transpl* 2009; **15**: 1861-1866 [PMID: 19938113 DOI: 10.1002/lt.21940]
31 **Olthoff KM**, Merion RM, Ghobrial RM, Abecassis MM, Fair JH, Fisher RA, Freise CE, Kam I, Pruett TL, Everhart JE,

Hulbert-Shearon TE, Gillespie BW, Emond JC. Outcomes of 385 adult-to-adult living donor liver transplant recipients: a report from the A2ALL Consortium. *Ann Surg* 2005; **242**: 314-323, discussion 323-325 [PMID: 16135918]
32 **Pichlmayr R**, Weimann A, Klempnauer J, Oldhafer KJ, Maschek H, Tusch G, Ringe B. Surgical treatment in proximal bile duct cancer. A single-center experience. *Ann Surg* 1996; **224**: 628-638 [PMID: 8916878 DOI: 10.1097/00000658-199611000-00007]
33 **Becker NS**, Rodriguez JA, Barshes NR, O'Mahony CA, Goss JA, Aloia TA. Outcomes analysis for 280 patients with cholangiocarcinoma treated with liver transplantation over an 18-year period. *J Gastrointest Surg* 2008; **12**: 117-122 [PMID: 17963015 DOI: 10.1007/s11605-007-0335-4]
34 **Robles R**, Figueras J, Turrión VS, Margarit C, Moya A, Varo E, Calleja J, Valdivieso A, Valdecasas JC, López P, Gómez M, de Vicente E, Loinaz C, Santoyo J, Fleitas M, Bernardos A, Lladó L, Ramírez P, Bueno FS, Jaurrieta E, Parrilla P. Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. *Ann Surg* 2004; **239**: 265-271 [PMID: 14745336 DOI: 10.1097/01.sla.0000108702.45715.81]
35 **Urego M**, Flickinger JC, Carr BI. Radiotherapy and multimodality management of cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 1999; **44**: 121-126 [PMID: 10219804 DOI: 10.1016/S0360-3016(98)00509-4]
36 **Iwatsuki S**, Todo S, Marsh JW, Madariaga JR, Lee RG, Dvorchik I, Fung JJ, Starzl TE. Treatment of hilar cholangiocarcinoma (Klatskin tumors) with hepatic resection or transplantation. *J Am Coll Surg* 1998; **187**: 358-364 [PMID: 9783781 DOI: 10.1016/S1072-7515(98)00207-5]
37 **De Vreede I**, Steers JL, Burch PA, Rosen CB, Gunderson LL, Haddock MG, Burgart L, Gores GJ. Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoirradiation for cholangiocarcinoma. *Liver Transpl* 2000; **6**: 309-316 [PMID: 10827231]
38 **Sudan D**, DeRoover A, Chinnakotla S, Fox I, Shaw B, McCashland T, Sorrell M, Tempero M, Langnas A. Radiochemotherapy and transplantation allow long-term survival for nonresectable hilar cholangiocarcinoma. *Am J Transplant* 2002; **2**: 774-779 [PMID: 12243499 DOI: 10.1034/j.1600-6143.2002.20812.x]
39 **Gu J**, Bai J, Shi X, Zhou J, Qiu Y, Wu Y, Jiang C, Sun X, Xu F, Zhang Y, Ding Y. Efficacy and safety of liver transplantation in patients with cholangiocarcinoma: a systematic review and meta-analysis. *Int J Cancer* 2012; **130**: 2155-2163 [PMID: 21387295 DOI: 10.1002/ijc.26019]
40 **Schmeding M**, Neumann UP. Liver transplantation for intra- and extrahepatic cholangiocarcinoma. *Ann Transplant* 2013; **18**: 1-8 [PMID: 23792495 DOI: 10.12659/AOT.883789]
41 **Gores GJ**, Darwish Murad S, Heimbach JK, Rosen CB. Liver transplantation for perihilar cholangiocarcinoma. *Dig Dis* 2013; **31**: 126-129 [PMID: 23797134 DOI: 10.1159/000347207]
42 **Gores GJ**, Nagorney DM, Rosen CB. Cholangiocarcinoma: is transplantation an option? For whom? *J Hepatol* 2007; **47**: 455-459 [PMID: 17697722 DOI: 10.1016/j.jhep.2007.07.003]
43 **Darwish Murad S**, Kim WR, Therneau T, Gores GJ, Rosen CB, Martenson JA, Alberts SR, Heimbach JK. Predictors of pretransplant dropout and posttransplant recurrence in patients with perihilar cholangiocarcinoma. *Hepatology* 2012; **56**: 972-981 [PMID: 22290335 DOI: 10.1002/hep.25629]
44 **Darwish Murad S**, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, Botha JF, Mezrich JD, Chapman WC, Schwartz JJ, Hong JC, Emond JC, Jeon H, Rosen CB, Gores GJ, Heimbach JK. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. *Gastroenterology* 2012; **143**: 88-98.e3; quiz e14 [PMID: 22504095 DOI: 10.1053/j.gastro.2012.04.008]
45 **Rea DJ**, Heimbach JK, Rosen CB, Haddock MG, Alberts SR, Kremers WK, Gores GJ, Nagorney DM. Liver transplantation with neoadjuvant chemoradiation is more effective than resection for hilar cholangiocarcinoma. *Ann Surg* 2005; **242**: 451-458; discussion 458-461 [PMID: 16135931 DOI: 10.1097/01.sla.0000179678.13285.fa]
46 **Lee SG**, Song GW, Hwang S, Ha TY, Moon DB, Jung DH, Kim KH, Ahn CS, Kim MH, Lee SK, Sung KB, Ko GY. Surgical treatment of hilar cholangiocarcinoma in the new era: the Asan experience. *J Hepatobiliary Pancreat Sci* 2010; **17**: 476-489 [PMID: 19851704 DOI: 10.1007/s00534-009-0204-5]
47 **Aoba T**, Ebata T, Yokoyama Y, Igami T, Sugawara G, Takahashi Y, Nimura Y, Nagino M. Assessment of nodal status for perihilar cholangiocarcinoma: location, number, or ratio of involved nodes. *Ann Surg* 2013; **257**: 718-725 [PMID: 23407295 DOI: 10.1097/SLA.0b013e3182822277]
48 **Pavel M**, Baudin E, Couvelard A, Krenning E, Öberg K, Steinmüller T, Anlauf M, Wiedenmann B, Salazar R. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. *Neuroendocrinology* 2012; **95**: 157-176 [PMID: 22262022 DOI: 10.1159/000335597]
49 **Le Treut YP**, Grégoire E, Klempnauer J, Belghiti J, Jouve E, Lerut J, Castaing D, Soubrane O, Boillot O, Mantion G, Homayounfar K, Bustamante M, Azoulay D, Wolf P, Krawczyk M, Pascher A, Suc B, Chiche L, de Urbina JO, Mejzlik V, Pascual M, Lodge JP, Gruttadauria S, Paye F, Pruvot FR, Thorban S, Foss A, Adam R. Liver transplantation for neuroendocrine tumors in Europe-results and trends in patient selection: a 213-case European liver transplant registry study. *Ann Surg* 2013; **257**: 807-815 [PMID: 23532105 DOI: 10.1097/SLA.0b013e31828ee17c]
50 **Mazzaferro V**, Pulvirenti A, Coppa J. Neuroendocrine tumors metastatic to the liver: how to select patients for liver transplantation? *J Hepatol* 2007; **47**: 460-466 [PMID: 17697723 DOI: 10.1016/j.jhep.2007.07.004]
51 **Le Treut YP**, Grégoire E, Belghiti J, Boillot O, Soubrane O, Mantion G, Cherqui D, Castaing D, Ruszniewski P, Wolf P, Paye F, Salame E, Muscari F, Pruvot FR, Baulieux J. Predictors of long-term survival after liver transplantation for metastatic endocrine tumors: an 85-case French multicentric report. *Am J Transplant* 2008; **8**: 1205-1213 [PMID: 18444921 DOI: 10.1111/j.1600-6143.2008.02233.x]
52 **Gedaly R**, Daily MF, Davenport D, McHugh PP, Koch A, Angulo P, Hundley JC. Liver transplantation for the treatment of liver metastases from neuroendocrine tumors: an analysis of the UNOS database. *Arch Surg* 2011; **146**: 953-958 [PMID: 21844436 DOI: 10.1001/archsurg.2011.186]
53 **Nguyen NT**, Harring TR, Goss JA, O'Mahony CA. Neuroendocrine Liver Metastases and Orthotopic Liver Transplantation: The US Experience. *Int J Hepatol* 2011; **2011**: 742890 [PMID: 22254141 DOI: 10.4061/2011/742890]
54 **Hagness M**, Foss A, Line PD, Scholz T, Jørgensen PF, Fosby B, Boberg KM, Mathisen O, Gladhaug IP, Egge TS, Solberg S, Hausken J, Dueland S. Liver transplantation for nonresectable liver metastases from colorectal cancer. *Ann Surg* 2013; **257**: 800-806 [PMID: 23360920 DOI: 10.1097/SLA.0b013e3182823957]
55 **Primrose JN**. Surgery for colorectal liver metastases. *Br J Cancer* 2010; **102**: 1313-1318 [PMID: 20424612 DOI: 10.1038/sj.bjc.6605659]
56 **Spector LG**, Birch J. The epidemiology of hepatoblastoma. *Pediatr Blood Cancer* 2012; **59**: 776-779 [PMID: 22692949 DOI: 10.1002/pbc.24215]
57 **Cruz RJ**, Ranganathan S, Mazariegos G, Soltys K, Nayyar N, Sun Q, Bond G, Shaw PH, Haberman K, Krishnamurti L, Marsh JW, Humar A, Sindhi R. Analysis of national and single-center incidence and survival after liver transplantation for hepatoblastoma: new trends and future opportunities. *Surgery* 2013; **153**: 150-159 [PMID: 23331862 DOI: 10.1016/j.surg.2012.11.006]
58 **Mehrabi A**, Kashfi A, Fonouni H, Schemmer P, Schmied BM, Hallscheidt P, Schirmacher P, Weitz J, Friess H, Buchler

MW, Schmidt J. Primary malignant hepatic epithelioid hemangioendothelioma: a comprehensive review of the literature with emphasis on the surgical therapy. *Cancer* 2006; **107**: 2108-2121 [PMID: 17019735 DOI: 10.1002/cncr.22225]

59 **Ercolani G**, Grazi GL, Pinna AD. Liver transplantation for benign hepatic tumors: a systematic review. *Dig Surg* 2010; **27**: 68-75 [PMID: 20357454 DOI: 10.1159/000268628]

60 **Grossman EJ**, Millis JM. Liver transplantation for non-hepatocellular carcinoma malignancy: Indications, limitations, and analysis of the current literature. *Liver Transpl* 2010; **16**: 930-942 [PMID: 20677284 DOI: 10.1002/lt.22106]

61 **Orlando G**, Adam R, Mirza D, Soderdahl G, Porte RJ, Paul A, Burroughs AK, Seiler CA, Colledan M, Graziadei I, Garcia Valdecasas JC, Pruvot FR, Karam V, Lerut J. Hepatic hemangiosarcoma: an absolute contraindication to liver transplantation--the European Liver Transplant Registry experience. *Transplantation* 2013; **95**: 872-877 [PMID: 23354302 DOI: 10.1097/TP.0b013e318281b902]

P- Reviewers: Gong NQ, Tashiro H
S- Editor: Ma YJ **L- Editor**: Stewart G **E- Editor**: Liu XM

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Fax: +852-65557188
Telephone: +852-31779906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com

ISSN 1007-9327