World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v21.i42.12071

World J Gastroenterol 2015 November 14; 21(42): 12071-12082
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

2015 Advances in Liver Transplantation

Liver transplantation for hepatocellular carcinoma - factors influencing outcome and disease-free survival

René Fahrner, Felix Dondorf, Michael Ardelt, Yves Dittmar, Utz Settmacher, Falk Rauchfuß

René Fahrner, Felix Dondorf, Michael Ardelt, Yves Dittmar, Utz Settmacher, Falk Rauchfuß, Department of General, Visceral and Vascular Surgery, Jena University Hospital, 07740 Jena, Germany

Author contributions: Fahrner R, Settmacher U and Rauchfuß F designed the review; Fahrner R, Dondorf F, Ardelt M, Dittmar Y and Rauchfuß F performed the review; Fahrner R, Settmacher U and Rauchfuß F analyzed the data; Fahrner R and Rauchfuß F wrote the paper; Dondorf F, Ardelt M, Dittmar Y and Settmacher U revised the paper.

Conflict-of-interest statement: All authors have no conflicts of interest or financial ties to disclose.

Correspondence to: Falk Rauchfuß, MD, MSc, Department of General, Visceral and Vascular Surgery, Jena University Hospital, 07740 Jena, Germany. falk.rauchfuss@med.uni-jena.de
Telephone: +49-3641-9322601
Fax: +49-3641-9322602

Received: April 28, 2015
Peer-review started: May 5, 2015
First decision: July 13, 2015
Revised: August 4, 2015
Accepted: September 14, 2015
Article in press: September 14, 2015
Published online: November 14, 2015

Abstract

Hepatocellular carcinoma is one of the leading causes of cancer-related death worldwide. Liver transplantation can be a curative treatment in selected patients. However, there are several factors that influence disease-free survival after transplantation. This review addresses the pre-, intra- and postoperative factors that influence the risk of tumor recurrence after liver transplantation.

Key words: Hepatocellular carcinoma; Survival; Risk factor; Diagnostics; Recurrence; Liver transplantation

Core tip: Hepatocellular carcinoma is one of the leading causes of cancer-related death worldwide. Liver transplantation can be a curative treatment in selected patients. This review addresses the pre-, intra-, and postoperative factors that influence disease-free survival and the risk of tumor recurrence after liver transplantation. Furthermore, novel diagnostic methods are presented and discussed.

Fahrner R, Dondorf F, Ardelt M, Dittmar Y, Settmacher U, Rauchfuß F. Liver transplantation for hepatocellular carcinoma - factors influencing outcome and disease-free survival. *World J Gastroenterol* 2015; 21(42): 12071-12082 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i42/12071.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i42.12071

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide[1,2]. Most HCC co-occurs with liver cirrhosis, and the etiology of liver cirrhosis leading to HCC differs among global regions, *e.g.*, hepatitis C virus infection in North

Table 1 Overview of the selection criteria for liver transplantation

Name	Criteria	Ref.
Milan	1 tumor < 5 cm in diameter or ≤ 3 tumor nodules, each ≤ 3 cm in diameter No extrahepatic manifestation No vascular invasion	Mazzaferro *et al*[7]
Up-to-seven criteria ("new Milan")	Seven as the sum of the size of the largest tumor (in cm) and the number of tumors	Mazzaferro *et al*[166]
Kyoto	≤ 10 tumors, all ≤ 5 cm in diameter PIVKA-II > 400 mAU/mL	Takada *et al*[167]
UCSF	Solitary tumor ≤ 6.5 cm or ≤ 3 nodules with largest lesion ≤ 4.5 cm and total tumor diameter ≤ 8 cm No gross vascular invasion	Yao *et al*[9]
Shanghai Fudan	Solitary tumor ≤ 9 cm in diameter or ≤ 3 lesions with the largest ≤ 5 cm and total tumor diameter ≤ 9 cm	Fan *et al*[168]
Hangzhou	Total tumor diameter ≤ 8 cm or Total tumor diameter more than 8 cm with histopathological grade I or Ⅱ and preoperative α-fetoprotein ≤ 400 ng/mL	Zheng *et al*[169] Lee *et al*[170]
Asan	Largest tumor diameter ≤ 5 cm Hepatocellular carcinoma number ≤ 6 No gross vascular invasion	

America, Europe, and Japan and hepatitis B virus infection in China, South Korea, and Taiwan[1].

Depending on hepatic function, liver transplantation (LT) is a curative option for selected HCC patients. However, the recurrence rate after LT is reported to be between 5% and 23%[3-6].

This review addresses the issue of HCC recurrence after LT and is subdivided into three sections: preoperative, intraoperative, and postoperative factors.

PREOPERATIVE FACTORS

Size and number of HCC nodules

In 1996, Mazzaferro *et al*[7] introduced the Milan criteria (MC), which showed a survival benefit in HCC patients with one tumor nodule < 5 cm diameter or three tumor nodules with a maximum diameter < 3 cm for each nodule. The MC remain the gold standard for decision-making in LT settings for HCC patients.

The MC have been challenged by different authors and work-groups aiming at an expansion of the criteria (see Table 1). However, there is only a consensus that "modest expansion of the criteria should consider the dynamics of the waiting list and whether a worse prognosis could be tolerated, if there is no prejudice for patients without HCC"[4].

What we do know is the so-called "Metroticket paradigm": the larger the tumor burden, the lower the post-transplant expected survival. However, reliance on tumor size and number of nodules is not the most ideal approach because biological parameters, such as the response to local-ablative therapy or tumor grading, are not included.

In practice, there are two important pipelines in liver allocation: center-based allocation, meaning that a graft is offered to a center that chooses the ideal recipient for a donor organ, and MELD-based allocation, which involves a waiting list where patients with a high MELD score receive an organ sooner than patients with a low MELD score. This is important in HCC patients because most have good hepatic function and subsequently a low MELD score. These patients have the chance of requesting an "exceptional" MELD score when fulfilling certain criteria. This phenomenon brings us back to the MC: in most countries around the world, the MC is the deciding tool for an exceptional MELD request (see Table 2).

However, there is increasing evidence that a decision on organ allocation based only on radiological findings does not reflect the reality of tumor biology. A large single-center study of over 800 patients undergoing LT because of HCC revealed that in addition to tumor size, other clinicopathological parameters are helpful and necessary to identify patients with a lower risk of tumor recurrence[8]. Varona *et al*[5] showed that the French prognostic model, including pre-transplant α-fetoprotein (AFP), tumor size, and number of nodules, was better at detecting patients with HCC recurrence after LT than the MC or up-to-7 criteria. Yao *et al*[9] showed that expanded tumor size had no negative effect on patient survival or tumor recurrence. In conclusion, the development of the MC was an important step towards improved outcome after LT in HCC, but these criteria are likely too narrow, and further adaptations are necessary.

AFP

The biomarker AFP, which is encoded in humans by the AFP gene located on chromosome 4[10-12], is a frequently used serum parameter for the detection of HCC. Unfortunately, the sensitivity of AFP is limited because non-tumor liver diseases are also associated with high serum AFP levels[13,14], and AFP levels are not always increased in HCC[15]. Generally speaking, the higher the tumor differentiation, the lower the AFP level. However, elevated AFP levels predict HCC

Table 2 Overview of prioritization systems in different transplant regions worldwide

Region	Country	Basic listing	Standard exception	Patient benefit
Eurotransplant	Germany		1 tumor > 2 and < 5 cm up to 3 tumors > 1 and < 3 cm	Initial listing with MELD 22; upgrading every 3 mo by 10% mortality risk
	The Netherlands		1 tumor > 2 and < 5 cm up to 3 tumors > 1 and < 3 cm	Initial listing with MELD 20; upgrading every 3 mo by 10% mortality risk However, "test of time": patient must have been on the waiting list for 6 mo prior
	Austria	Possible (if Milan criteria are met); however, irrelevant with center-based allocation	No	
Europe	United Kingdom	Single lesion < 5 cm Up to 5 lesions < 3 cm Single lesion between 5 and 7 cm without progression over 6 mo No extrahepatic tumor No macrovascular invasion AFP < 1000 U/L		No prioritization on the waiting list
	France	Complex French Liver Allocation Score under consideration of Lab-MELD-Scores Tumor stage (T2 ranked higher than T1) Elapsed waiting time Distance between donor and Recipient hospital		
	Switzerland		1 tumor > 2 and < 5 cm up to 3 tumors > 1 and < 3 cm	Lab-MELD + 1.5 points per month
North America	United States		1 tumor > 2 and < 5 cm up to 3 tumors > 1 and < 3 cm	Initial listing with MELD 22; upgrading every 3 mo by 10% mortality risk
South America	Brazil		1 tumor < 5 cm up to 3 tumors of less than 3 cm each	Initial listing with 20 points, increase to 24 points after 3 mo and 29 points after 6 mo

recurrence in a multi-predictive model, together with elevated liver enzymes, lactate dehydrogenase, small resection margins, and advanced tumor stage[16]. In an analysis of approximately 1500 patients with liver cirrhosis, AFP levels showed a sensitivity of 99% and a specificity of approximately 72% to detect HCC in combination with ultrasound[17]. Recently, several studies showed that during hepatitis treatment, AFP levels were helpful to detect HCC development[18-20].

The recurrence of HCC after LT is a problem; therefore, patients with a high risk of recurrence must be detected. A retrospective cohort study showed that a combination of biomarkers, such as AFP and the MC, was more sensitive for predicting tumor recurrence than the MC alone[21]. In a multivariate analysis, AFP was the only pre-transplant predictor of HCC recurrence and mortality in a cohort of 1074 patients transplanted for HCC[22]. Grąt *et al*[23] analyzed 121 patients undergoing LT for HCC and demonstrated that the combination of up-to-7 criteria and University of California, San Francisco (UCSF) criteria with AFP levels less than 100 ng/mL was associated with a minimized risk for tumor recurrence. Previously, in a small cohort of 20 patients, a cut-off level of 100 ng/mL for AFP was shown to be a predictor for HCC recurrence after LT[24].

AFP remains the gold standard biomarker for HCC detection and a prognostic marker for post-transplant tumor recurrence, particularly in combination with other morphological tumor criteria or diagnostic tools.

Response to bridging

To avoid tumor progression and waitlist drop-off, patients waiting for LT undergo local bridging therapies[25] such as transarterial chemoembolization (TACE), which has been shown to be effective and was first proposed as a treatment option in 1977[26]. TACE produces a combination of localized chemotherapy and ischemia by occluding feeding vessels with concomitant tumor necrosis[27]. Other bridging treatments are selective internal irradiation (SIRT) or radiofrequency ablation (RFA)[28,29]. The question of who is likely to benefit from locoregional therapy remains controversial, but, currently, the proposed optimal candidates for TACE have almost normal liver function, a tumor localized to the liver, an estimated survival of 16 mo[30], tumors > 3 cm in size, and signs of hypervascularization[31]. Some authors noted that poor liver function, vascular invasion, extrahepatic tumor load, bilobar tumors, arterioportal fistula, portal vein thrombosis, or renal dysfunction are contraindications for TACE[30,32]. A systematic review analyzed the different techniques and substances used for TACE[33]. Doxorubicin, epirubicin, or cisplatin alone or in combination are used as local chemotherapy. In addition to these drugs, lipiodol, gelatin sponge particles, or beads are injected after

the chemotherapeutic substance to embolize the tumor-supplying artery. This should be performed in a selective or superselective manner to avoid damage to the nontumorous liver[31,33]. Acute liver failure, acute renal failure, gastrointestinal bleeding, and abscess formation are side effects of TACE, and a treatment related mortality rate of 2.4% was reported[33], mainly because of liver failure. The timing of TACE before LT remains unclear[34]. Decaens *et al*[35] showed that TACE only had a beneficial effect in patients with a waiting time longer than 4 mo. Others showed a positive effect of TACE on survival and tumor recurrence in patients with at least 6 mo on the waiting list[34,36]. The complete response is reported to be up to 30%[37], but rates of progressive disease following treatment have been reported to be 20%[38]. Overall, several studies have demonstrated that TACE prior to LT was associated with a good response rate for advanced tumor stages with acceptable survival rates after LT of 40% to 90% after at least 4 years, even in patients with HCC outside the MC[39-43]. A recently published study investigated 204 patients with HCC undergoing LT and showed reduced survival in patients with TACE prior to transplantation. The authors concluded that this might be because of a higher amount of pulmonary and distant metastasis[44]. Although most results appear promising, there are no controlled prospective trials to investigate the benefits of TACE prior to LT; thus, this issue remains controversial.

In contrast to TACE, SIRT is more effective in cases of large and multifocal HCC[28]. Negative side effects are rare[45-47]. Portal vein thrombosis is not an absolute contraindication for selective internal irradiation and, therefore, offers an alternative to TACE[48]. Selective internal irradiation leads to downstaging or tumor size reduction in 32% to 56% of patients with HCC[49,50]. Selective internal irradiation therapy is useful in bridging patients with HCC until LT[49,51].

During local tumor therapy with RFA, the tumor is destroyed because of local hyperthermia or chemical injury. RFA is performed percutaneously or during a surgical procedure[29]. Thus far, RFA has been shown to be a safe and effective procedure as a bridging therapy prior to transplantation[29,52-55]. A combination of different bridging therapies, such as RFA and TACE, are safe and effective regarding tumor necrosis[56]. However, a Cochrane analysis demonstrated that there is a lack of randomized clinical trials and no evidence demonstrating the superiority of RFA for bridging therapy over no intervention, chemotherapy, or transplantation[57].

Positron emission tomography

Positron emission tomography (PET) measures the metabolic activity of tumor tissue. In most oncologic cases, the tracer ^{18}F-fluorodeoxyglucose (^{18}F-FDG), an analog of glucose, is used[58].

The role of ^{18}F-FDG-PET as a diagnostic tool in HCC patients is controversial. One of the first studies dealing with PET in HCC was published by Teefey *et al*[59]. In this work, ultrasound, computed tomography, magnet resonance imaging, and PET were compared. PET showed the worst sensitivity but displayed good specificity. A Chinese group noted the value of PET scans for the diagnosis of HCC lymph node metastases in a pre-transplant setting and for the detection of tumor recurrence after LT[60]. A study by Lee *et al*[61] showed an excellent predictive value for the ratio of the maximum standard uptake volume of the tumor to the maximum standard uptake volume of non-tumoral liver tissue, which predicted tumor recurrence after LT. Similar results were confirmed by several workgroups[62-66].

In non-transplant settings, ^{18}F-FDG-PET is useful for estimating tumor differentiation[67], the probability of microvascular invasion[68], the diagnosis of bone metastases[69,70], and the estimation of tumor-free or overall survival[67,71-77].

One major issue is the dependency of PET results on tumor grade. Well-differentiated tumors have nearly the same metabolic activity as the surrounding liver tissue and, therefore, have similar tracer uptake.

However, as shown above, ^{18}F-FDG-PET correlated well with microvascular invasion and post-transplant outcome. ^{18}F-FDG-PET is a good marker for the biological behavior of HCC[58]. Therefore, ^{18}F-FDG-PET appears to be a promising approach to evaluate the aforementioned findings using a prospective approach.

Metabolomics, proteomics, and transcriptomics

AFP is the standard serum biomarker for the detection of HCC. As previously mentioned, AFP is not specific for HCC, and, therefore, diagnosis on the basis of this biomarker is limited. However, until now, no other marker has replaced AFP as the new standard in routine clinical use. To overcome this dilemma, new and more sensitive markers have been investigated using metabolomic, transcriptomic, and proteomic techniques.

Metabolomics is a global unbiased analysis of biomarkers that identifies small molecular metabolites reflecting normal biological or pathological processes in biological fluids, tissues, organs, and organisms[78-81]. Metabolomics can measure the metabolite complements in living and diseased systems[81]. In contrast, proteomics is able to analyze all proteins within a biological system[82].

Thus far, several metabolites have been investigated and proposed as potential biomarkers for HCC, such as the aspartate metabolism pathway[83], 1-methyladenosine[81], and aberrant lipid metabolism[84]. Urinary liquid chromatography-hybrid triple quadrupole linear ion trap mass spectrometry (LC-QTRAP MS) revealed that butyrylcarnitine and hydantoin-5-propionic acid were markers to distinguish patients with HCC from patients with liver cirrhosis without HCC[85]. Huang *et*

al[86] showed that betaine and propionylcarnitine in tissue and serum could distinguish HCC from hepatitis or cirrhosis better than AFP alone. A combination of metabolomics and transcriptomics reported reduced cellular glucose levels and reduced metabolites of cellular energy production in HCC[87]. A proteomic analysis detected 87 differently expressed proteins in patients with early HCC recurrence involved in catalytic pathways, signal transduction, and cell organization[88] and quantified novel phosphorylation sites that might be important for tumor progression in HCC[89]. The fields of metabolomics, transcriptomics, and proteomics are still emergent fields in cancer research. For most candidate metabolites or proteins, a definite role in HCC development and tumor progression is unclear, and further investigations are required. To date, there is no clinically available biomarker for HCC detection other than AFP.

MicroRNAs

MicroRNAs (miRNAs) are small noncoding RNA molecules that are not transcribed into proteins but are important for regulating the stability and translation of protein-coding messenger RNAs[90,91]. miRNAs were first described in 1993[92,93]; since then, hundreds of miRNAs have been identified. miRNAs play an important role in tumorigenesis[94-96]. In HCC, a number of miRNAs have been identified with partially prognostic significance[90,97,98]. These miRNAs can be downregulated, *e.g.*, miR-122[99,100] and miR-199[101,102], or up-regulated, *e.g.*, miR-21[103], miR-221[104,105], and miR-222[104,106,107]. This is only a partial list of the previously reported miRNAs. Therefore, miRNAs could be important diagnostic and therapeutic targets in the future of cancer and HCC therapy.

Circulating tumor cells

Despite the radical resection of localized HCC with hepatectomy or LT, postoperative tumor recurrence and metastasis are frequently observed[108,109], with the transplanted liver the most frequent site of early recurrence[110]. After access of the primary tumor cells to the blood stream, circulating tumor cells (CTCs) are postulated to be responsible for tumor recurrence and tumor metastasis after complete surgical resection[110-113]. Several methods have been investigated in the past to detect CTCs, mainly based on the identification of tumor-specific antigens or epithelial cell surface antigens that are present on the primary tumor[114,115]. One of the most frequently used markers for the detection of circulating tumor cells is the epithelial cell adhesion molecule, which is only expressed on a small proportion of HCC tumors[116]. In addition, in one-third of patients, only low numbers of CTCs are detectable[117]. Therefore, this technique is not suitable for the routine detection of HCC CTCs[118]. Novel approaches to detect CTCs showed promising results[119,120], but until CTC detection is able to guide the therapy of HCC patients, further basic and clinical research is required.

INTRAOPERATIVE FACTORS

Ischemia time

Intraoperative factors are less likely to be associated with tumor recurrence in the long-term. However, there is some evidence that ischemia times play a significant role in the recurrence of HCC.

A recent published study by Nagai *et al*[121] showed a significant effect of both cold (CIT) and warm ischemia time (WIT) on post-transplant HCC recurrence. In the multivariate analysis, a CIT of more than 10 h and a WIT of more than 50 min were risk factors for the development of a recurrent HCC[121]. These results were confirmed by a Munich workgroup[122].

This observation is explained by ischemia-reperfusion injury, which leads to hepatic microcirculatory barrier dysfunction and activates cell signals related to invasion and migration[121]. Furthermore, a cellular cascade leading to angiogenesis, cellular proliferation, and growth is activated by ischemia.

This theory was confirmed by an analysis by Croome *et al*[123], who showed an inferior outcome in HCC patients who received an organ from a donor who underwent cardiac death. These grafts are exposed to additional WIT.

Transfusion

Bleeding during LT remains a major problem, and sometimes large amounts of blood products are required[124-127]. Over the last decades, there has been a significant reduction in the need for transfusions[128]. Several studies have shown that blood loss and transfusion during LT were associated with decreased overall survival and increased complications[129,130]. In addition, perioperative transfusion is associated with earlier tumor recurrence and cancer-related mortality in colorectal cancer resection[131-135] and liver resection for colorectal liver metastases[136,137]. Shiba *et al*[138] showed that a reduction of blood supply during liver resection for HCC was associated with increased survival. In a meta-analysis of 5635 patients undergoing surgery for HCC, survival, tumor recurrence, and complications were negatively correlated with blood transfusion[139]. However, the use of intraoperative autotransfusion during liver surgery because of malignancy showed no negative effects in terms of survival or tumor dissemination[140,141]. Several studies have investigated the safety of blood salvage autotransfusion regarding tumor recurrence during LT in HCC patients. The authors concluded that in cases where nonruptured HCC tumor cells were filtered, or particularly when a leukocyte depletion filter was used, there was no increase in risk of tumor

recurrence[142-144].

POSTOPERATIVE FACTORS

Immunosuppression

There is a relationship between the inflammatory state and carcinogenesis[7,145]. Pro-inflammatory cells and cytokines play a pivotal role in tumor growth, tumor invasion, and tumor spread[146,147]. Therefore, immunosuppression after transplantation can modify the inflammatory state and influence tumor recurrence. Most immunosuppression has a negative effect on the outcome of patients with HCC undergoing LT. Steroids[148], basiliximab[149], and calcineurin inhibitors (CNIs)[150] are postulated to be associated with an increased risk of HCC recurrence. In contrast, several studies reported that mammalian target of rapamycin inhibitors (mTORi) have positive effects on tumor recurrence and are favored drugs in HCC patients after LT[151-153]. A meta-analysis of five studies demonstrated a decreased recurrence rate and increased recurrence-free and overall survival in patients with sirolimus-based immunosuppression compared to patients with CNIs[154]. One reason for the positive effect of mTOR could be the inhibition of the phosphatidylinositol 3 phosphate kinase (PI3K)/Akt/mTOR pathway, which is a key regulator of the cell cycle and is responsible for cell proliferation and cancer[155]. However, thus far, randomized controlled prospective studies with long-term follow-up investigating the influence of this immunosuppression treatment are lacking[156].

Adjuvant treatment

Even after the use of a potentially curative treatment for gastrointestinal tumors, adjuvant therapy is used in most cases depending on the tumor stage. For HCC, this concept was not accepted for a long time[157]. A review by Duvoux *et al*[158] identified the problem with adjuvant therapy protocols after LT: most studies were small and retrospective with a low level of evidence. The authors concluded that the homogeneous and ethical selection of patients with a high risk of recurrence, stratification by confounding factors such as pre-transplant therapies and post-transplant immunosuppression, relevant endpoints focusing on recurrence, and appropriate follow-up are key points for appropriate studies on this issue. Similar conclusions were drawn 2 years later by Fujiki *et al*[159].

Even recently published trials lack the inclusion of a sufficient number of patients. A study by Teng *et al*[160] showed a beneficial effect of sorafenib in a case-control study. However, sorafenib was used in only 11 patients with HCC beyond the MC in either a curative intervention (n = 5) or a palliative regime after LT. Another prospective trial showed a benefit of sorafenib application after LT in seven patients with HCC beyond the MC compared to a historic control group[161].

The increased toxicity of sorafenib in patients after LT should be taken into account. This increased toxicity, which is not mechanistically understood, should lead to a dose reduction in affected patients[162].

In addition to sorafenib, Licartin has been proposed as a potential adjuvant treatment for HCC[158,159]. One Chinese study evaluated Licartin, an ^{131}I-radiolabeled murine monoclonal antibody, in a transplantation setting with excellent results regarding the tumor recurrence rate and the overall survival in the treatment group[163]. Additional data or even multicenter data for Licartin after LT are unfortunately still lacking.

Some authors have used conventional chemotherapy protocols for the treatment of HCC after LT. Zhang *et al*[164] showed good short-term (1 year) results for a treatment protocol using the FOLFOX regime. The overall survival was even better in the midterm (3 years), but the recurrence rate did not differ significantly from the control after this time period. Wu *et al*[165] performed a randomized three-arm study and showed that the gemcitabine regimen and conventional chemotherapy significantly improved the survival rate and disease free survival rate of HCC patients who had major vascular invasion and/or microvascular invasion after LT compared to a best supportive care group.

In summary, the best approach for adjuvant treatment protocols has not been identified. Large, prospective, randomized studies should be performed in the future.

CONCLUSION

LT is the treatment of choice for selected patients with HCC. There are several factors that should be taken into account, particularly in preoperative settings. The previously used selection criterion of pure morphometric variables should be modified to include biological parameters, which offer a better risk stratification for tumor recurrence.

In addition to intraoperative parameters that influence the post-transplant prognosis (ischemia times, transfusion), immunosuppression is an important tool to prevent or at least reduce the recurrence of HCC. Adjuvant protocols have not yet been established for HCC.

REFERENCES

1 **Park JW**, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, Kudo M, Johnson P, Wagner S, Orsini LS, Sherman M. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int* 2015; **35**: 2155-2166 [PMID: 25752327 DOI: 10.1111/liv.12818]

2 **Diamond DL**, Proll SC, Jacobs JM, Chan EY, Camp DG, Smith RD, Katze MG. HepatoProteomics: applying proteomic technologies to the study of liver function and disease. *Hepatology* 2006; **44**: 299-308 [PMID: 16871559 DOI: 10.1002/hep.21318]

3 **Piras-Straub K**, Khairzada K, Gerken G, Saner F, Treckmann J, Paul A, Canbay A, Herzer K. Glutamate dehydrogenase and alkaline phosphatase as very early predictors of hepatocellular

carcinoma recurrence after liver transplantation. *Digestion* 2015; **91**: 117-127 [PMID: 25662469 DOI: 10.1159/000370212]
4 **Dutkowski P**, Linecker M, DeOliveira ML, Müllhaupt B, Clavien PA. Challenges to liver transplantation and strategies to improve outcomes. *Gastroenterology* 2015; **148**: 307-323 [PMID: 25224524 DOI: 10.1053/j.gastro.2014.08.045]
5 **Varona MA**, Soriano A, Aguirre-Jaime A, Garrido S, Oton E, Diaz D, Portero J, Bravo P, Barrera MA, Perera A. Risk factors of hepatocellular carcinoma recurrence after liver transplantation: accuracy of the alpha-fetoprotein model in a single-center experience. *Transplant Proc* 2015; **47**: 84-89 [PMID: 25645778 DOI: 10.1016/j.transproceed.2014.12.013]
6 **Pecchi A**, Besutti G, De Santis M, Del Giovane C, Nosseir S, Tarantino G, Di Benedetto F, Torricelli P. Post-transplantation hepatocellular carcinoma recurrence: Patterns and relation between vascularity and differentiation degree. *World J Hepatol* 2015; **7**: 276-284 [PMID: 25729483 DOI: 10.4254/wjh.v7.i2.276]
7 **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]
8 **Agopian VG**, Harlander-Locke M, Zarrinpar A, Kaldas FM, Farmer DG, Yersiz H, Finn RS, Tong M, Hiatt JR, Busuttil RW. A novel prognostic nomogram accurately predicts hepatocellular carcinoma recurrence after liver transplantation: analysis of 865 consecutive liver transplant recipients. *J Am Coll Surg* 2015; **220**: 416-427 [PMID: 25690672 DOI: 10.1016/j.jamcollsurg.2014.12.025]
9 **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]
10 **Tomasi TB**. Structure and function of alpha-fetoprotein. *Annu Rev Med* 1977; **28**: 453-465 [PMID: 67821 DOI: 10.1146/annurev.me.28.020177.002321]
11 **Mizejewski GJ**. Alpha-fetoprotein structure and function: relevance to isoforms, epitopes, and conformational variants. *Exp Biol Med* (Maywood) 2001; **226**: 377-408 [PMID: 11393167]
12 **Harper ME**, Dugaiczyk A. Linkage of the evolutionarily-related serum albumin and alpha-fetoprotein genes within q11-22 of human chromosome 4. *Am J Hum Genet* 1983; **35**: 565-572 [PMID: 6192711]
13 **Nicholson JK**, Lindon JC. Systems biology: Metabonomics. *Nature* 2008; **455**: 1054-1056 [PMID: 18948945 DOI: 10.1038/4551054a]
14 **Arakaki AK**, Skolnick J, McDonald JF. Marker metabolites can be therapeutic targets as well. *Nature* 2008; **456**: 443 [PMID: 19037294 DOI: 10.1038/456443c]
15 **Gonzalez SA**. Novel biomarkers for hepatocellular carcinoma surveillance: has the future arrived? *Hepatobiliary Surg Nutr* 2014; **3**: 410-414 [PMID: 25568864 DOI: 10.3978/j.issn.2304-3881.2014.07.06]
16 **Wang ZX**, Jiang CP, Cao Y, Zhang G, Chen WB, Ding YT. Preoperative serum liver enzyme markers for predicting early recurrence after curative resection of hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int* 2015; **14**: 178-185 [PMID: 25865691]
17 **Chang TS**, Wu YC, Tung SY, Wei KL, Hsieh YY, Huang HC, Chen WM, Shen CH, Lu CH, Wu CS, Tsai YH, Huang YH. Alpha-Fetoprotein Measurement Benefits Hepatocellular Carcinoma Surveillance in Patients with Cirrhosis. *Am J Gastroenterol* 2015; **110**: 836-844; quiz 845 [PMID: 25869392 DOI: 10.1038/ajg.2015.100]
18 **Kim GA**, Seock CH, Park JW, An J, Lee KS, Yang JE, Lim YS, Kim KM, Shim JH, Lee D, Lee HC. Reappraisal of serum alpha-foetoprotein as a surveillance test for hepatocellular carcinoma during entecavir treatment. *Liver Int* 2015; **35**: 232-239 [PMID: 24576055 DOI: 10.1111/liv.12516]
19 **Wong GL**, Chan HL, Tse YK, Chan HY, Tse CH, Lo AO, Wong VW. On-treatment alpha-fetoprotein is a specific tumor marker for hepatocellular carcinoma in patients with chronic hepatitis B receiving entecavir. *Hepatology* 2014; **59**: 986-995 [PMID: 24123097 DOI: 10.1002/hep.26739]
20 **Shim JJ**, Kim JW, Lee CK, Jang JY, Kim BH. Oral antiviral therapy improves the diagnostic accuracy of alpha-fetoprotein levels in patients with chronic hepatitis B. *J Gastroenterol Hepatol* 2014; **29**: 1699-1705 [PMID: 24730702 DOI: 10.1111/jgh.12612]
21 **Chaiteerakij R**, Zhang X, Addissie BD, Mohamed EA, Harmsen WS, Theobald PJ, Peters BE, Balsanek JG, Ward MM, Giama NH, Moser CD, Oseini AM, Umeda N, Venkatesh S, Harnois DM, Charlton MR, Yamada H, Satomura S, Algeciras-Schimnich A, Snyder MR, Therneau TM, Roberts LR. Combinations of biomarkers and Milan criteria for predicting hepatocellular carcinoma recurrence after liver transplantation. *Liver Transpl* 2015; **21**: 599-606 [PMID: 25789635 DOI: 10.1002/lt.24117]
22 **Macdonald B**, Sewell JL, Harper AM, Roberts JP, Yao FY. Liver transplantation for hepatocellular carcinoma: analysis of factors predicting outcome in 1074 patients in OPTN Region 5. *Clin Transplant* 2015; **29**: 506-512 [PMID: 25777321 DOI: 10.1111/ctr.12542]
23 **Grąt M**, Kornasiewicz O, Lewandowski Z, Hołówko W, Grąt K, Kobryń K, Patkowski W, Zieniewicz K, Krawczyk M. Combination of morphologic criteria and α-fetoprotein in selection of patients with hepatocellular carcinoma for liver transplantation minimizes the problem of posttransplant tumor recurrence. *World J Surg* 2014; **38**: 2698-2707 [PMID: 24858191 DOI: 10.1007/s00268-014-2647-3]
24 **Guzman G**, Alagiozian-Angelova V, Layden-Almer JE, Layden TJ, Testa G, Benedetti E, Kajdacsy-Balla A, Cotler SJ. p53, Ki-67, and serum alpha feto-protein as predictors of hepatocellular carcinoma recurrence in liver transplant patients. *Mod Pathol* 2005; **18**: 1498-1503 [PMID: 16007066 DOI: 10.1038/modpathol.3800458]
25 **Freeman RB**, Steffick DE, Guidinger MK, Farmer DG, Berg CL, Merion RM. Liver and intestine transplantation in the United States, 1997-2006. *Am J Transplant* 2008; **8**: 958-976 [PMID: 18336699 DOI: 10.1111/j.1600-6143.2008.02174.x]
26 **Yamada R**, Sato M, Kawabata M, Nakatsuka H, Nakamura K, Takashima S. Hepatic artery embolization in 120 patients with unresectable hepatoma. *Radiology* 1983; **148**: 397-401 [PMID: 6306721 DOI: 10.1148/radiology.148.2.6306721]
27 **Lesurtel M**, Müllhaupt B, Pestalozzi BC, Pfammatter T, Clavien PA. Transarterial chemoembolization as a bridge to liver transplantation for hepatocellular carcinoma: an evidence-based analysis. *Am J Transplant* 2006; **6**: 2644-2650 [PMID: 16939518 DOI: 10.1111/j.1600-6143.2006.01509.x]
28 **Lau WY**, Lai EC, Leung TW. Current role of selective internal irradiation with yttrium-90 microspheres in the management of hepatocellular carcinoma: a systematic review. *Int J Radiat Oncol Biol Phys* 2011; **81**: 460-467 [PMID: 20888138 DOI: 10.1016/j.ijrobp.2010.06.010]
29 **DuBay DA**, Sandroussi C, Kachura JR, Ho CS, Beecroft JR, Vollmer CM, Ghanekar A, Guba M, Cattral MS, McGilvray ID, Grant DR, Greig PD. Radiofrequency ablation of hepatocellular carcinoma as a bridge to liver transplantation. *HPB* (Oxford) 2011; **13**: 24-32 [PMID: 21159100 DOI: 10.1111/j.1477-2574.2010.00228.x]
30 **de Lope CR**, Tremosini S, Forner A, Reig M, Bruix J. Management of HCC. *J Hepatol* 2012; **56** Suppl 1: S75-S87 [PMID: 22300468 DOI: 10.1016/S0168-8278(12)60009-9]
31 **Pompili M**, Francica G, Ponziani FR, Iezzi R, Avolio AW. Bridging and downstaging treatments for hepatocellular carcinoma in patients on the waiting list for liver transplantation. *World J Gastroenterol* 2013; **19**: 7515-7530 [PMID: 24282343 DOI: 10.3748/wjg.v19.i43.7515]
32 **Molla N**, AlMenieir N, Simoneau E, Aljiffry M, Valenti D, Metrakos P, Boucher LM, Hassanain M. The role of interventional radiology in the management of hepatocellular carcinoma. *Curr Oncol* 2014; **21**: e480-e492 [PMID: 24940108 DOI: 10.3747/

co.21.1829]
33 **Marelli L**, Stigliano R, Triantos C, Senzolo M, Cholongitas E, Davies N, Tibballs J, Meyer T, Patch DW, Burroughs AK. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. *Cardiovasc Intervent Radiol* 2007; **30**: 6-25 [PMID: 17103105 DOI: 10.1007/s00270-006-0062-3]
34 **Galuppo R**, McCall A, Gedaly R. The role of bridging therapy in hepatocellular carcinoma. *Int J Hepatol* 2013; **2013**: 419302 [PMID: 24455285 DOI: 10.1155/2013/419302]
35 **Decaens T**, Roudot-Thoraval F, Bresson-Hadni S, Meyer C, Gugenheim J, Durand F, Bernard PH, Boillot O, Boudjema K, Calmus Y, Hardwigsen J, Ducerf C, Pageaux GP, Dharancy S, Chazouilleres O, Dhumeaux D, Cherqui D, Duvoux C. Impact of pretransplantation transarterial chemoembolization on survival and recurrence after liver transplantation for hepatocellular carcinoma. *Liver Transpl* 2005; **11**: 767-775 [PMID: 15973710 DOI: 10.1002/lt.20418]
36 **Cescon M**, Cucchetti A, Ravaioli M, Pinna AD. Hepatocellular carcinoma locoregional therapies for patients in the waiting list. Impact on transplantability and recurrence rate. *J Hepatol* 2013; **58**: 609-618 [PMID: 23041304 DOI: 10.1016/j.jhep.2012.09.021]
37 **Millonig G**, Graziadei IW, Freund MC, Jaschke W, Stadlmann S, Ladurner R, Margreiter R, Vogel W. Response to preoperative chemoembolization correlates with outcome after liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl* 2007; **13**: 272-279 [PMID: 17256758 DOI: 10.1002/lt.21033]
38 **Forner A**, Ayuso C, Varela M, Rimola J, Hessheimer AJ, de Lope CR, Reig M, Bianchi L, Llovet JM, Bruix J. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma: are response evaluation criteria in solid tumors reliable? *Cancer* 2009; **115**: 616-623 [PMID: 19117042 DOI: 10.1002/cncr.24050]
39 **Jang JW**, You CR, Kim CW, Bae SH, Yoon SK, Yoo YK, Kim DG, Choi JY. Benefit of downsizing hepatocellular carcinoma in a liver transplant population. *Aliment Pharmacol Ther* 2010; **31**: 415-423 [PMID: 19821808 DOI: 10.1111/j.1365-2036.2009.04167.x]
40 **Graziadei IW**, Sandmueller H, Waldenberger P, Koenigsrainer A, Nachbaur K, Jaschke W, Margreiter R, Vogel W. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. *Liver Transpl* 2003; **9**: 557-563 [PMID: 12783395 DOI: 10.1053/jlts.2003.50106]
41 **Otto G**, Herber S, Heise M, Lohse AW, Mönch C, Bittinger F, Hoppe-Lotichius M, Schuchmann M, Victor A, Pitton M. Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma. *Liver Transpl* 2006; **12**: 1260-1267 [PMID: 16826556 DOI: 10.1002/lt.20837]
42 **Chapman WC**, Majella Doyle MB, Stuart JE, Vachharajani N, Crippin JS, Anderson CD, Lowell JA, Shenoy S, Darcy MD, Brown DB. Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. *Ann Surg* 2008; **248**: 617-625 [PMID: 18936575 DOI: 10.1097/SLA.0b013e31818a07d4]
43 **Bargellini I**, Vignali C, Cioni R, Petruzzi P, Cicorelli A, Campani D, De Simone P, Filipponi F, Bartolozzi C. Hepatocellular carcinoma: CT for tumor response after transarterial chemoembolization in patients exceeding Milan criteria--selection parameter for liver transplantation. *Radiology* 2010; **255**: 289-300 [PMID: 20308465 DOI: 10.1148/radiol.09090927]
44 **Li HL**, Ji WB, Zhao R, Duan WD, Chen YW, Wang XQ, Yu Q, Luo Y, Dong JH. Poor prognosis for hepatocellular carcinoma with transarterial chemoembolization pre-transplantation: retrospective analysis. *World J Gastroenterol* 2015; **21**: 3599-3606 [PMID: 25834326 DOI: 10.3748/wjg.v21.i12.3599]
45 **Hilgard P**, Hamami M, Fouly AE, Scherag A, Müller S, Ertle J, Heusner T, Cicinnati VR, Paul A, Bockisch A, Gerken G, Antoch G. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. *Hepatology* 2010; **52**: 1741-1749 [PMID: 21038413 DOI: 10.1002/hep.23944]
46 **Sangro B**, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, Paprottka PM, Fiore F, Van Buskirk M, Bilbao JI, Ettorre GM, Salvatori R, Giampalma E, Geatti O, Wilhelm K, Hoffmann RT, Izzo F, Iñarrairaegui M, Maini CL, Urigo C, Cappelli A, Vit A, Ahmadzadehfar H, Jakobs TF, Lastoria S. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology* 2011; **54**: 868-878 [PMID: 21618574 DOI: 10.1002/hep.24451]
47 **Salem R**, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, Atassi B, Baker T, Gates V, Miller FH, Sato KT, Wang E, Gupta R, Benson AB, Newman SB, Omary RA, Abecassis M, Kulik L. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010; **138**: 52-64 [PMID: 19766639 DOI: 10.1053/j.gastro.2009.09.006]
48 **Iñarrairaegui M**, Thurston KG, Bilbao JI, D'Avola D, Rodriguez M, Arbizu J, Martinez-Cuesta A, Sangro B. Radioembolization with use of yttrium-90 resin microspheres in patients with hepatocellular carcinoma and portal vein thrombosis. *J Vasc Interv Radiol* 2010; **21**: 1205-1212 [PMID: 20598574 DOI: 10.1016/j.jvir.2010.04.012]
49 **Kulik LM**, Atassi B, van Holsbeeck L, Souman T, Lewandowski RJ, Mulcahy MF, Hunter RD, Nemcek AA, Abecassis MM, Haines KG, Salem R. Yttrium-90 microspheres (TheraSphere) treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. *J Surg Oncol* 2006; **94**: 572-586 [PMID: 17048240 DOI: 10.1002/jso.20609]
50 **Vouche M**, Kulik L, Atassi R, Memon K, Hickey R, Ganger D, Miller FH, Yaghmai V, Abecassis M, Baker T, Mulcahy M, Nayar R, Lewandowski RJ, Salem R. Radiological-pathological analysis of WHO, RECIST, EASL, mRECIST and DWI: Imaging analysis from a prospective randomized trial of Y90 ± sorafenib. *Hepatology* 2013; **58**: 1655-1666 [PMID: 23703789 DOI: 10.1002/hep.26487]
51 **Saraswat VA**, Pandey G, Shetty S. Treatment algorithms for managing hepatocellular carcinoma. *J Clin Exp Hepatol* 2014; **4**: S80-S89 [PMID: 25755616 DOI: 10.1016/j.jceh.2014.05.004]
52 **Fontana RJ**, Hamidullah H, Nghiem H, Greenson JK, Hussain H, Marrero J, Rudich S, McClure LA, Arenas J. Percutaneous radiofrequency thermal ablation of hepatocellular carcinoma: a safe and effective bridge to liver transplantation. *Liver Transpl* 2002; **8**: 1165-1174 [PMID: 12474157 DOI: 10.1053/jlts.2002.36394]
53 **Lu DS**, Yu NC, Raman SS, Limanond P, Lassman C, Murray K, Tong MJ, Amado RG, Busuttil RW. Radiofrequency ablation of hepatocellular carcinoma: treatment success as defined by histologic examination of the explanted liver. *Radiology* 2005; **234**: 954-960 [PMID: 15681691 DOI: 10.1148/radiol.2343040153]
54 **Mazzaferro V**, Battiston C, Perrone S, Pulvirenti A, Regalia E, Romito R, Sarli D, Schiavo M, Garbagnati F, Marchianò A, Spreafico C, Camerini T, Mariani L, Miceli R, Andreola S. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. *Ann Surg* 2004; **240**: 900-909 [PMID: 15492574]
55 **Sala M**, Llovet JM, Vilana R, Bianchi L, Solé M, Ayuso C, Brú C, Bruix J. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. *Hepatology* 2004; **40**: 1352-1360 [PMID: 15565564 DOI: 10.1002/hep.20465]
56 **Ashoori N**, Paprottka P, Trumm C, Bamberg F, Kolligs FT, Rentsch M, Reiser MF, Jakobs TF. Multimodality treatment with conventional transcatheter arterial chemoembolization and radiofrequency ablation for unresectable hepatocellular carcinoma. *Digestion* 2012; **85**: 18-26 [PMID: 22156507 DOI: 10.1159/000334714]
57 **Weis S**, Franke A, Mössner J, Jakobsen JC, Schoppmeyer K. Radiofrequency (thermal) ablation versus no intervention or other interventions for hepatocellular carcinoma. *Cochrane*

Database Syst Rev 2013; **12**: CD003046 [PMID: 24357457 DOI: 10.1002/14651858.CD003046.pub3]

58 **Asman Y**, Evenson AR, Even-Sapir E, Shibolet O. [18F]fludeoxyglucose positron emission tomography and computed tomography as a prognostic tool before liver transplantation, resection, and loco-ablative therapies for hepatocellular carcinoma. *Liver Transpl* 2015; **21**: 572-580 [PMID: 25644857 DOI: 10.1002/lt.24083]

59 **Teefey SA**, Hildeboldt CC, Dehdashti F, Siegel BA, Peters MG, Heiken JP, Brown JJ, McFarland EG, Middleton WD, Balfe DM, Ritter JH. Detection of primary hepatic malignancy in liver transplant candidates: prospective comparison of CT, MR imaging, US, and PET. *Radiology* 2003; **226**: 533-542 [PMID: 12563151 DOI: 10.1148/radiol.2262011980]

60 **Wang XL**, Li H, Wang QS, Zhang XL. Clinical value of pre- and postoperative 18F-FDG PET/CT in patients undergoing liver transplantation for hepatocellular carcinoma. *Nan Fang Yi Ke Da Xue Xuebao* 2006; **26**: 1087-1091, 1095 [PMID: 16939890]

61 **Lee JW**, Paeng JC, Kang KW, Kwon HW, Suh KS, Chung JK, Lee MC, Lee DS. Prediction of tumor recurrence by 18F-FDG PET in liver transplantation for hepatocellular carcinoma. *J Nucl Med* 2009; **50**: 682-687 [PMID: 19372474 DOI: 10.2967/jnumed.108.060574]

62 **Kornberg A**, Freesmeyer M, Bärthel E, Jandt K, Katenkamp K, Steenbeck J, Sappler A, Habrecht O, Gottschild D, Settmacher U. 18F-FDG-uptake of hepatocellular carcinoma on PET predicts microvascular tumor invasion in liver transplant patients. *Am J Transplant* 2009; **9**: 592-600 [PMID: 19191771 DOI: 10.1111/j.1600-6143.2008.02516.x]

63 **Kornberg A**, Küpper B, Thrum K, Katenkamp K, Steenbeck J, Sappler A, Habrecht O, Gottschild D. Increased 18F-FDG uptake of hepatocellular carcinoma on positron emission tomography independently predicts tumor recurrence in liver transplant patients. *Transplant Proc* 2009; **41**: 2561-2563 [PMID: 19715974 DOI: 10.1016/j.transproceed.2009.06.115]

64 **Kornberg A**, Küpper B, Tannapfel A, Büchler P, Krause B, Witt U, Gottschild D, Friess H. Patients with non-[18 F]fludeoxyglucose-avid advanced hepatocellular carcinoma on clinical staging may achieve long-term recurrence-free survival after liver transplantation. *Liver Transpl* 2012; **18**: 53-61 [PMID: 21850692 DOI: 10.1002/lt.22416]

65 **Cascales Campos P**, Ramirez P, Gonzalez R, Febrero B, Pons JA, Miras M, Sanchez Bueno F, Robles R, Parrilla P. Value of 18-FDG-positron emission tomography/computed tomography before and after transarterial chemoembolization in patients with hepatocellular carcinoma undergoing liver transplantation: initial results. *Transplant Proc* 2011; **43**: 2213-2215 [PMID: 21839236 DOI: 10.1016/j.transproceed.2011.05.023]

66 **Pant V**, Sen IB, Soin AS. Role of ^{18}F-FDG PET CT as an independent prognostic indicator in patients with hepatocellular carcinoma. *Nucl Med Commun* 2013; **34**: 749-757 [PMID: 23689586 DOI: 10.1097/MNM.0b013e3283622eef]

67 **Han JH**, Kim DG, Na GH, Kim EY, Lee SH, Hong TH, You YK. Evaluation of prognostic factors on recurrence after curative resections for hepatocellular carcinoma. *World J Gastroenterol* 2014; **20**: 17132-17140 [PMID: 25493027 DOI: 10.3748/wjg.v20.i45.17132]

68 **Ahn SY**, Lee JM, Joo I, Lee ES, Lee SJ, Cheon GJ, Han JK, Choi BI. Prediction of microvascular invasion of hepatocellular carcinoma using gadoxetic acid-enhanced MR and (18)F-FDG PET/CT. *Abdom Imaging* 2015; **40**: 843-851 [PMID: 25253426 DOI: 10.1007/s00261-014-0256-0]

69 **Choi C**, Seong J. Predictive factors of palliative radiotherapy response and survival in patients with spinal metastases from hepatocellular carcinoma. *Gut Liver* 2015; **9**: 94-102 [PMID: 25071067 DOI: 10.5009/gnl14009]

70 **Seo HJ**, Kim GM, Kim JH, Kang WJ, Choi HJ. ^{18}F-FDG PET/CT in hepatocellular carcinoma: detection of bone metastasis and prediction of prognosis. *Nucl Med Commun* 2015; **36**: 226-233 [PMID: 25460306 DOI: 10.1097/MNM.0000000000000246]

71 **Simoneau E**, Hassanain M, Madkhali A, Salman A, Nudo CG, Chaudhury P, Metrakos P. (18)F-Fluorodeoxyglucose positron-emission tomography could have a prognostic role in patients with advanced hepatocellular carcinoma. *Curr Oncol* 2014; **21**: e551-e556 [PMID: 25089106 DOI: 10.3747/co.21.1959]

72 **Lee JW**, Yun M, Cho A, Han KH, Kim do Y, Lee SM, Lee JD. The predictive value of metabolic tumor volume on FDG PET/CT for transarterial chemoembolization and transarterial chemotherapy infusion in hepatocellular carcinoma patients without extrahepatic metastasis. *Ann Nucl Med* 2015; **29**: 400-408 [PMID: 25652647 DOI: 10.1007/s12149-015-0956-8]

73 **Ma W**, Jia J, Wang S, Bai W, Yi J, Bai M, Quan Z, Yin Z, Fan D, Wang J, Han G. The prognostic value of 18F-FDG PET/CT for hepatocellular carcinoma treated with transarterial chemoembolization (TACE). *Theranostics* 2014; **4**: 736-744 [PMID: 24883123 DOI: 10.7150/thno.8725]

74 **Sabet A**, Ahmadzadehfar H, Bruhman J, Sabet A, Meyer C, Wasmuth JC, Pieper CC, Biersack HJ, Ezziddin S. Survival in patients with hepatocellular carcinoma treated with 90Y-microsphere radioembolization. Prediction by 18F-FDG PET. *Nuklearmedizin* 2014; **53**: 39-45 [PMID: 24777354 DOI: 10.3413/Nukmed-0622-13-09]

75 **Hayakawa N**, Nakamoto Y, Nakatani K, Hatano E, Seo S, Higashi T, Saga T, Uemoto S, Togashi K. Clinical utility and limitations of FDG PET in detecting recurrent hepatocellular carcinoma in postoperative patients. *Int J Clin Oncol* 2014; **19**: 1020-1028 [PMID: 24366329 DOI: 10.1007/s10147-013-0653-3]

76 **Song HJ**, Cheng JY, Hu SL, Zhang GY, Fu Y, Zhang YJ. Value of 18F-FDG PET/CT in detecting viable tumour and predicting prognosis of hepatocellular carcinoma after TACE. *Clin Radiol* 2015; **70**: 128-137 [PMID: 25459673 DOI: 10.1016/j.crad.2014.09.020]

77 **Ochi H**, Hirooka M, Hiraoka A, Koizumi Y, Abe M, Sogabe I, Ishimaru Y, Furuya K, Miyagawa M, Kawasaki H, Michitaka K, Takada Y, Mochizuki T, Hiasa Y. (18)F-FDG-PET/CT predicts the distribution of microsatellite lesions in hepatocellular carcinoma. *Mol Clin Oncol* 2014; **2**: 798-804 [PMID: 25054048 DOI: 10.3892/mco.2014.328]

78 **Fahrner R**, Beyoğlu D, Beldi G, Idle JR. Metabolomic markers for intestinal ischemia in a mouse model. *J Surg Res* 2012; **178**: 879-887 [PMID: 22947700 DOI: 10.1016/j.jss.2012.08.011]

79 **Wang TJ**, Larson MG, Vasan RS, Cheng S, Rhee EP, McCabe E, Lewis GD, Fox CS, Jacques PF, Fernandez C, O'Donnell CJ, Carr SA, Mootha VK, Florez JC, Souza A, Melander O, Clish CB, Gerszten RE. Metabolite profiles and the risk of developing diabetes. *Nat Med* 2011; **17**: 448-453 [PMID: 21423183 DOI: 10.1038/nm.2307]

80 **Sun JL**, Zhang SK, Chen JY, Han BZ. Metabolic profiling of Staphylococcus aureus cultivated under aerobic and anaerobic conditions with (1)H NMR-based nontargeted analysis. *Can J Microbiol* 2012; **58**: 709-718 [PMID: 22571732 DOI: 10.1139/w2012-046]

81 **Wang X**, Zhang A, Sun H. Power of metabolomics in diagnosis and biomarker discovery of hepatocellular carcinoma. *Hepatology* 2013; **57**: 2072-2077 [PMID: 23150189 DOI: 10.1002/hep.26130]

82 **Tsai TH**, Song E, Zhu R, Di Poto C, Wang M, Luo Y, Varghese RS, Tadesse MG, Ziada DH, Desai CS, Shetty K, Mechref Y, Ressom HW. LC-MS/MS-based serum proteomics for identification of candidate biomarkers for hepatocellular carcinoma. *Proteomics* 2015; **15**: 2369-2381 [PMID: 25778709 DOI: 10.1002/pmic.201400364]

83 **Darpolor MM**, Basu SS, Worth A, Nelson DS, Clarke-Katzenberg RH, Glickson JD, Kaplan DE, Blair IA. The aspartate metabolism pathway is differentiable in human hepatocellular carcinoma: transcriptomics and (13) C-isotope based metabolomics. *NMR Biomed* 2014; **27**: 381-389 [PMID: 24497316 DOI: 10.1002/nbm.3072]

84 **Patterson AD**, Maurhofer O, Beyoglu D, Lanz C, Krausz KW, Pabst T, Gonzalez FJ, Dufour JF, Idle JR. Aberrant lipid metabolism in hepatocellular carcinoma revealed by plasma metabolomics and lipid profiling. *Cancer Res* 2011; **71**: 6590-6600

[PMID: 21900402 DOI: 10.1158/0008-5472.CAN-11-0885]
85 **Shao Y**, Zhu B, Zheng R, Zhao X, Yin P, Lu X, Jiao B, Xu G, Yao Z. Development of urinary pseudotargeted LC-MS-based metabolomics method and its application in hepatocellular carcinoma biomarker discovery. *J Proteome Res* 2015; **14**: 906-916 [PMID: 25483141 DOI: 10.1021/pr500973d]
86 **Huang Q**, Tan Y, Yin P, Ye G, Gao P, Lu X, Wang H, Xu G. Metabolic characterization of hepatocellular carcinoma using nontargeted tissue metabolomics. *Cancer Res* 2013; **73**: 4992-5002 [PMID: 23824744 DOI: 10.1158/0008-5472.CAN-13-0308]
87 **Beyoğlu D**, Imbeaud S, Maurhofer O, Bioulac-Sage P, Zucman-Rossi J, Dufour JF, Idle JR. Tissue metabolomics of hepatocellular carcinoma: tumor energy metabolism and the role of transcriptomic classification. *Hepatology* 2013; **58**: 229-238 [PMID: 23463346 DOI: 10.1002/hep.26350]
88 **Taoka M**, Morofuji N, Yamauchi Y, Ojima H, Kubota D, Terukina G, Nobe Y, Nakayama H, Takahashi N, Kosuge T, Isobe T, Kondo T. Global PROTOMAP profiling to search for biomarkers of early-recurrent hepatocellular carcinoma. *J Proteome Res* 2014; **13**: 4847-4858 [PMID: 24967658 DOI: 10.1021/pr500262p]
89 **Xu B**, Wang F, Song C, Sun Z, Cheng K, Tan Y, Wang H, Zou H. Large-scale proteome quantification of hepatocellular carcinoma tissues by a three-dimensional liquid chromatography strategy integrated with sample preparation. *J Proteome Res* 2014; **13**: 3645-3654 [PMID: 24972180 DOI: 10.1021/pr500200s]
90 **Zhu Z**, Zhang X, Wang G, Zheng H. Role of MicroRNAs in Hepatocellular Carcinoma. *Hepat Mon* 2014; **14**: e18672 [PMID: 25337143 DOI: 10.5812/hepatmon.18672]
91 **Li X**, Yang W, Lou L, Chen Y, Wu S, Ding G. microRNA: a promising diagnostic biomarker and therapeutic target for hepatocellular carcinoma. *Dig Dis Sci* 2014; **59**: 1099-1107 [PMID: 24390674 DOI: 10.1007/s10620-013-3006-1]
92 **Lee RC**, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell* 1993; **75**: 843-854 [PMID: 8252621]
93 **Wightman B**, Ha I, Ruvkun G. Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans. *Cell* 1993; **75**: 855-862 [PMID: 8252622]
94 **Calin GA**, Croce CM. MicroRNA signatures in human cancers. *Nat Rev Cancer* 2006; **6**: 857-866 [PMID: 17060945 DOI: 10.1038/nrc1997]
95 **Esteller M**. Non-coding RNAs in human disease. *Nat Rev Genet* 2011; **12**: 861-874 [PMID: 22094949 DOI: 10.1038/nrg3074]
96 **Ling H**, Fabbri M, Calin GA. MicroRNAs and other non-coding RNAs as targets for anticancer drug development. *Nat Rev Drug Discov* 2013; **12**: 847-865 [PMID: 24172333 DOI: 10.1038/nrd4140]
97 **Varnholt H**. The role of microRNAs in primary liver cancer. *Ann Hepatol* 2008; **7**: 104-113 [PMID: 18626426]
98 **Li W**, Xie L, He X, Li J, Tu K, Wei L, Wu J, Guo Y, Ma X, Zhang P, Pan Z, Hu X, Zhao Y, Xie H, Jiang G, Chen T, Wang J, Zheng S, Cheng J, Wan D, Yang S, Li Y, Gu J. Diagnostic and prognostic implications of microRNAs in human hepatocellular carcinoma. *Int J Cancer* 2008; **123**: 1616-1622 [PMID: 18649363 DOI: 10.1002/ijc.23693]
99 **Gramantieri L**, Ferracin M, Fornari F, Veronese A, Sabbioni S, Liu CG, Calin GA, Giovannini C, Ferrazzi E, Grazi GL, Croce CM, Bolondi L, Negrini M. Cyclin G1 is a target of miR-122a, a microRNA frequently down-regulated in human hepatocellular carcinoma. *Cancer Res* 2007; **67**: 6092-6099 [PMID: 17616664 DOI: 10.1158/0008-5472.CAN-06-4607]
100 **Tsai WC**, Hsu PW, Lai TC, Chau GY, Lin CW, Chen CM, Lin CD, Liao YL, Wang JL, Chau YP, Hsu MT, Hsiao M, Huang HD, Tsou AP. MicroRNA-122, a tumor suppressor microRNA that regulates intrahepatic metastasis of hepatocellular carcinoma. *Hepatology* 2009; **49**: 1571-1582 [PMID: 19296470 DOI: 10.1002/hep.22806]
101 **Murakami Y**, Yasuda T, Saigo K, Urashima T, Toyoda H, Okanoue T, Shimotohno K. Comprehensive analysis of microRNA expression patterns in hepatocellular carcinoma and non-tumorous tissues. *Oncogene* 2006; **25**: 2537-2545 [PMID: 16331254 DOI: 10.1038/sj.onc.1209283]
102 **Jiang J**, Gusev Y, Aderca I, Mettler TA, Nagorney DM, Brackett DJ, Roberts LR, Schmittgen TD. Association of MicroRNA expression in hepatocellular carcinomas with hepatitis infection, cirrhosis, and patient survival. *Clin Cancer Res* 2008; **14**: 419-427 [PMID: 18223217 DOI: 10.1158/1078-0432.CCR-07-0523]
103 **Meng F**, Henson R, Wehbe-Janek H, Ghoshal K, Jacob ST, Patel T. MicroRNA-21 regulates expression of the PTEN tumor suppressor gene in human hepatocellular cancer. *Gastroenterology* 2007; **133**: 647-658 [PMID: 17681183 DOI: 10.1053/j.gastro.2007.05.022]
104 **Garofalo M**, Di Leva G, Romano G, Nuovo G, Suh SS, Ngankeu A, Taccioli C, Pichiorri F, Alder H, Secchiero P, Gasparini P, Gonelli A, Costinean S, Acunzo M, Condorelli G, Croce CM. miR-221& amp; 222 regulate TRAIL resistance and enhance tumorigenicity through PTEN and TIMP3 downregulation. *Cancer Cell* 2009; **16**: 498-509 [PMID: 19962668 DOI: 10.1016/j.ccr.2009.10.014]
105 **Gramantieri L**, Fornari F, Ferracin M, Veronese A, Sabbioni S, Calin GA, Grazi GL, Croce CM, Bolondi L, Negrini M. MicroRNA-221 targets Bmf in hepatocellular carcinoma and correlates with tumor multifocality. *Clin Cancer Res* 2009; **15**: 5073-5081 [PMID: 19671867 DOI: 10.1158/1078-0432.CCR-09-0092]
106 **Coulouarn C**, Factor VM, Andersen JB, Durkin ME, Thorgeirsson SS. Loss of miR-122 expression in liver cancer correlates with suppression of the hepatic phenotype and gain of metastatic properties. *Oncogene* 2009; **28**: 3526-3536 [PMID: 19617899 DOI: 10.1038/onc.2009.211]
107 **Wong QW**, Ching AK, Chan AW, Choy KW, To KF, Lai PB, Wong N. MiR-222 overexpression confers cell migratory advantages in hepatocellular carcinoma through enhancing AKT signaling. *Clin Cancer Res* 2010; **16**: 867-875 [PMID: 20103675 DOI: 10.1158/1078-0432.CCR-09-1840]
108 **Fan ST**, Mau Lo C, Poon RT, Yeung C, Leung Liu C, Yuen WK, Ming Lam C, Ng KK, Ching Chan S. Continuous improvement of survival outcomes of resection of hepatocellular carcinoma: a 20-year experience. *Ann Surg* 2011; **253**: 745-758 [PMID: 21475015 DOI: 10.1097/SLA.0b013e3182111195]
109 **Portolani N**, Coniglio A, Ghidoni S, Giovanelli M, Benetti A, Tiberio GA, Giulini SM. Early and late recurrence after liver resection for hepatocellular carcinoma: prognostic and therapeutic implications. *Ann Surg* 2006; **243**: 229-235 [PMID: 16432356 DOI: 10.1097/01.sla.0000197706.21803.a1]
110 **Zhang Y**, Li J, Cao L, Xu W, Yin Z. Circulating tumor cells in hepatocellular carcinoma: detection techniques, clinical implications, and future perspectives. *Semin Oncol* 2012; **39**: 449-460 [PMID: 22846862 DOI: 10.1053/j.seminoncol.2012.05.012]
111 **Alix-Panabières C**, Pantel K. Circulating tumor cells: liquid biopsy of cancer. *Clin Chem* 2013; **59**: 110-118 [PMID: 23014601 DOI: 10.1373/clinchem.2012.194258]
112 **Nguyen DX**, Bos PD, Massagué J. Metastasis: from dissemination to organ-specific colonization. *Nat Rev Cancer* 2009; **9**: 274-284 [PMID: 19308067 DOI: 10.1038/nrc2622]
113 **Toso C**, Mentha G, Majno P. Liver transplantation for hepatocellular carcinoma: five steps to prevent recurrence. *Am J Transplant* 2011; **11**: 2031-2035 [PMID: 21831154 DOI: 10.1111/j.1600-6143.2011.03689.x]
114 **Jacob K**, Sollier C, Jabado N. Circulating tumor cells: detection, molecular profiling and future prospects. *Expert Rev Proteomics* 2007; **4**: 741-756 [PMID: 18067413 DOI: 10.1586/14789450.4.6.741]
115 **Attard G**, de Bono JS. Utilizing circulating tumor cells: challenges and pitfalls. *Curr Opin Genet Dev* 2011; **21**: 50-58 [PMID: 21112767 DOI: 10.1016/j.gde.2010.10.010]
116 **de Boer CJ**, van Krieken JH, Janssen-van Rhijn CM, Litvinov SV. Expression of Ep-CAM in normal, regenerating, metaplastic, and neoplastic liver. *J Pathol* 1999; **188**: 201-206 [PMID: 10398165]
117 **Sun YF**, Xu Y, Yang XR, Guo W, Zhang X, Qiu SJ, Shi RY, Hu B, Zhou J, Fan J. Circulating stem cell-like epithelial cell adhesion molecule-positive tumor cells indicate poor prognosis of hepatocellular carcinoma after curative resection. *Hepatology* 2013; **57**: 1458-1468 [PMID: 23175471 DOI: 10.1002/hep.26151]

118 **Zhang Y**, Shi ZL, Yang X, Yin ZF. Targeting of circulating hepatocellular carcinoma cells to prevent postoperative recurrence and metastasis. *World J Gastroenterol* 2014; **20**: 142-147 [PMID: 24415867 DOI: 10.3748/wjg.v20.i1.142]

119 **Morris KL**, Tugwood JD, Khoja L, Lancashire M, Sloane R, Burt D, Shenjere P, Zhou C, Hodgson C, Ohtomo T, Katoh A, Ishiguro T, Valle JW, Dive C. Circulating biomarkers in hepatocellular carcinoma. *Cancer Chemother Pharmacol* 2014; **74**: 323-332 [PMID: 24923562 DOI: 10.1007/s00280-014-2508-7]

120 **Liu HY**, Qian HH, Zhang XF, Li J, Yang X, Sun B, Ma JY, Chen L, Yin ZF. Improved method increases sensitivity for circulating hepatocellular carcinoma cells. *World J Gastroenterol* 2015; **21**: 2918-2925 [PMID: 25780289 DOI: 10.3748/wjg.v21.i10.2918]

121 **Nagai S**, Yoshida A, Facciuto M, Moonka D, Abouljoud MS, Schwartz ME, Florman SS. Ischemia time impacts recurrence of hepatocellular carcinoma after liver transplantation. *Hepatology* 2015; **61**: 895-904 [PMID: 25099130 DOI: 10.1002/hep.27358]

122 **Kornberg A**, Witt U, Kornberg J, Friess H, Thrum K. Extended Ischemia Times Promote Risk of HCC Recurrence in Liver Transplant Patients. *Dig Dis Sci* 2015; **60**: 2832-2839 [PMID: 25630421 DOI: 10.1007/s10620-015-3541-z]

123 **Croome KP**, Wall W, Chandok N, Beck G, Marotta P, Hernandez-Alejandro R. Inferior survival in liver transplant recipients with hepatocellular carcinoma receiving donation after cardiac death liver allografts. *Liver Transpl* 2013; **19**: 1214-1223 [PMID: 23907778 DOI: 10.1002/lt.23715]

124 **Ozier Y**, Albi A. Liver transplant surgery and transfusion. *Int Anesthesiol Clin* 2004; **42**: 147-162 [PMID: 15205645]

125 **Hendriks HG**, van der Meer J, Klompmaker IJ, Choudhury N, Hagenaars JA, Porte RJ, de Kam PJ, Slooff MJ, de Wolf JT. Blood loss in orthotopic liver transplantation: a retrospective analysis of transfusion requirements and the effects of autotransfusion of cell saver blood in 164 consecutive patients. *Blood Coagul Fibrinolysis* 2000; **11** Suppl 1: S87-S93 [PMID: 10850571]

126 **Navarro F**, Le Moine MC, Fabre JM, Belghiti J, Cherqui D, Adam R, Pruvot FR, Letoublon C, Domergue J. Specific vascular complications of orthotopic liver transplantation with preservation of the retrohepatic vena cava: review of 1361 cases. *Transplantation* 1999; **68**: 646-650 [PMID: 10507483]

127 **Bennett-Guerrero E**, Feierman DE, Barclay GR, Parides MK, Sheiner PA, Mythen MG, Levine DM, Parker TS, Carroll SF, White ML, Winfree WJ. Preoperative and intraoperative predictors of postoperative morbidity, poor graft function, and early rejection in 190 patients undergoing liver transplantation. *Arch Surg* 2001; **136**: 1177-1183 [PMID: 11585512]

128 **Coêlho GR**, Feitosa Neto BA, de G Teixeira CC, Marinho DS, Rangel ML, Garcia JH. Single-center transfusion rate for 555 consecutive liver transplantations: impact of two eras. *Transplant Proc* 2013; **45**: 3305-3309 [PMID: 24182806 DOI: 10.1016/j.transproceed.2013.07.062]

129 **de Boer MT**, Christensen MC, Asmussen M, van der Hilst CS, Hendriks HG, Slooff MJ, Porte RJ. The impact of intraoperative transfusion of platelets and red blood cells on survival after liver transplantation. *Anesth Analg* 2008; **106**: 32-44, table of contents [PMID: 18165548 DOI: 10.1213/01.ane.0000289638.26666.ed]

130 **Cacciarelli TV**, Keeffe EB, Moore DH, Burns W, Busque S, Concepcion W, So SK, Esquivel CO. Effect of intraoperative blood transfusion on patient outcome in hepatic transplantation. *Arch Surg* 1999; **134**: 25-29 [PMID: 9927126]

131 **Acheson AG**, Brookes MJ, Spahn DR. Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer surgery: a systematic review and meta-analysis. *Ann Surg* 2012; **256**: 235-244 [PMID: 22791100 DOI: 10.1097/SLA.0b013e31825b35d5]

132 **Amato A**, Pescatori M. Perioperative blood transfusions for the recurrence of colorectal cancer. *Cochrane Database Syst Rev* 2006; (**1**): CD005033 [PMID: 16437512 DOI: 10.1002/14651858.CD005033.pub2]

133 **Burrows L**, Tartter P. Effect of blood transfusions on colonic malignancy recurrent rate. *Lancet* 1982; **2**: 662 [PMID: 6125797]

134 **Chung M**, Steinmetz OK, Gordon PH. Perioperative blood transfusion and outcome after resection for colorectal carcinoma. *Br J Surg* 1993; **80**: 427-432 [PMID: 8192723]

135 **Vamvakas EC**. Perioperative blood transfusion and cancer recurrence: meta-analysis for explanation. *Transfusion* 1995; **35**: 760-768 [PMID: 7570938]

136 **Schiergens TS**, Rentsch M, Kasparek MS, Frenes K, Jauch KW, Thasler WE. Impact of perioperative allogeneic red blood cell transfusion on recurrence and overall survival after resection of colorectal liver metastases. *Dis Colon Rectum* 2015; **58**: 74-82 [PMID: 25489697 DOI: 10.1097/DCR.0000000000000233]

137 **Hallet J**, Tsang M, Cheng ES, Habashi R, Kulyk I, Hanna SS, Coburn NG, Lin Y, Law CH, Karanicolas PJ. The Impact of Perioperative Red Blood Cell Transfusions on Long-Term Outcomes after Hepatectomy for Colorectal Liver Metastases. *Ann Surg Oncol* 2015; **22**: 4038-4045 [PMID: 25752895 DOI: 10.1245/s10434-015-4477-4]

138 **Shiba H**, Ishida Y, Fujiwara Y, Wakiyama S, Gocho T, Ito R, Sakamoto T, Tsutsui N, Iida T, Matsumoto M, Furukawa K, Haruki K, Hirohara S, Misawa T, Yanaga K. Practice to minimize the use of blood products improve outcome after hepatic resection for hepatocellular carcinoma. *Hepatogastroenterology* 2013; **60**: 1681-1683 [PMID: 24634937]

139 **Liu L**, Wang Z, Jiang S, Shao B, Liu J, Zhang S, Zhou Y, Zhou Y, Zhang Y. Perioperative allogenenic blood transfusion is associated with worse clinical outcomes for hepatocellular carcinoma: a meta-analysis. *PLoS One* 2013; **8**: e64261 [PMID: 23741309 DOI: 10.1371/journal.pone.0064261]

140 **Zulim RA**, Rocco M, Goodnight JE, Smith GJ, Krag DN, Schneider PD. Intraoperative autotransfusion in hepatic resection for malignancy. Is it safe? *Arch Surg* 1993; **128**: 206-211 [PMID: 8381647]

141 **Fujimoto J**, Okamoto E, Yamanaka N, Oriyama T, Furukawa K, Kawamura E, Tanaka T, Tomoda F. Efficacy of autotransfusion in hepatectomy for hepatocellular carcinoma. *Arch Surg* 1993; **128**: 1065-1069 [PMID: 8396388]

142 **Liang TB**, Li DL, Liang L, Li JJ, Bai XL, Yu W, Wang WL, Shen Y, Zhang M, Zheng SS. Intraoperative blood salvage during liver transplantation in patients with hepatocellular carcinoma: efficiency of leukocyte depletion filters in the removal of tumor cells. *Transplantation* 2008; **85**: 863-869 [PMID: 18360269 DOI: 10.1097/TP.0b013e3181671f2e]

143 **Muscari F**, Suc B, Vigouroux D, Duffas JP, Migueres I, Mathieu A, Lavayssiere L, Rostaing L, Fourtanier G. Blood salvage autotransfusion during transplantation for hepatocarcinoma: does it increase the risk of neoplastic recurrence? *Transpl Int* 2005; **18**: 1236-1239 [PMID: 16221153 DOI: 10.1111/j.1432-2277.2005.00207.x]

144 **Akbulut S**, Kayaalp C, Yilmaz M, Ince V, Ozgor D, Karabulut K, Eris C, Toprak HI, Aydin C, Yilmaz S. Effect of autotransfusion system on tumor recurrence and survival in hepatocellular carcinoma patients. *World J Gastroenterol* 2013; **19**: 1625-1631 [PMID: 23538988 DOI: 10.3748/wjg.v19.i10.1625]

145 **Sotiropoulos GC**, Molmenti EP, Lösch C, Beckebaum S, Broelsch CE, Lang H. Meta-analysis of tumor recurrence after liver transplantation for hepatocellular carcinoma based on 1,198 cases. *Eur J Med Res* 2007; **12**: 527-534 [PMID: 18024261]

146 **Balkwill F**, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001; **357**: 539-545 [PMID: 11229684 DOI: 10.1016/S0140-6736(00)04046-0]

147 **Mantovani A**, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008; **454**: 436-444 [PMID: 18650914 DOI: 10.1038/nature07205]

148 **Xing T**, Huang L, Yu Z, Zhong L, Wang S, Peng Z. Comparison of steroid-free immunosuppression and standard immunosuppression for liver transplant patients with hepatocellular carcinoma. *PLoS One* 2013; **8**: e71251 [PMID: 23940730 DOI: 10.1371/journal.pone.0071251]

149 **Lee JY**, Kim YH, Yi NJ, Kim HS, Lee HS, Lee BK, Kim H, Choi YR, Hong G, Lee KW, Suh KS. Impact of immunosuppressant

therapy on early recurrence of hepatocellular carcinoma after liver transplantation. *Clin Mol Hepatol* 2014; **20**: 192-203 [PMID: 25032186 DOI: 10.3350/cmh.2014.20.2.192]

150 **Vivarelli M**, Cucchetti A, La Barba G, Ravaioli M, Del Gaudio M, Lauro A, Grazi GL, Pinna AD. Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors: reassessment of risk factors for tumor recurrence. *Ann Surg* 2008; **248**: 857-862 [PMID: 18948815 DOI: 10.1097/SLA.0b013e3181896278]

151 **Cholongitas E**, Mamou C, Rodríguez-Castro KI, Burra P. Mammalian target of rapamycin inhibitors are associated with lower rates of hepatocellular carcinoma recurrence after liver transplantation: a systematic review. *Transpl Int* 2014; **27**: 1039-1049 [PMID: 24943720 DOI: 10.1111/tri.12372]

152 **Toso C**, Merani S, Bigam DL, Shapiro AM, Kneteman NM. Sirolimus-based immunosuppression is associated with increased survival after liver transplantation for hepatocellular carcinoma. *Hepatology* 2010; **51**: 1237-1243 [PMID: 20187107 DOI: 10.1002/hep.23437]

153 **Ferreiro AO**, Vazquez-Millán MA, López FS, Gutiérrez MG, Diaz SP, Patiño MJ. Everolimus-based immunosuppression in patients with hepatocellular carcinoma at high risk of recurrence after liver transplantation: a case series. *Transplant Proc* 2014; **46**: 3496-3501 [PMID: 25498079 DOI: 10.1016/j.transproceed.2014.08.045]

154 **Menon KV**, Hakeem AR, Heaton ND. Meta-analysis: recurrence and survival following the use of sirolimus in liver transplantation for hepatocellular carcinoma. *Aliment Pharmacol Ther* 2013; **37**: 411-419 [PMID: 23278125 DOI: 10.1111/apt.12185]

155 **Sahin F**, Kannangai R, Adegbola O, Wang J, Su G, Torbenson M. mTOR and P70 S6 kinase expression in primary liver neoplasms. *Clin Cancer Res* 2004; **10**: 8421-8425 [PMID: 15623621 DOI: 10.1158/1078-0432.CCR-04-0941]

156 **Schnitzbauer AA**, Zuelke C, Graeb C, Rochon J, Bilbao I, Burra P, de Jong KP, Duvoux C, Kneteman NM, Adam R, Bechstein WO, Becker T, Beckebaum S, Chazouillères O, Cillo U, Colledan M, Fändrich F, Gugenheim J, Hauss JP, Heise M, Hidalgo E, Jamieson N, Königsrainer A, Lamby PE, Lerut JP, Mäkisalo H, Margreiter R, Mazzaferro V, Mutzbauer I, Otto G, Pageaux GP, Pinna AD, Pirenne J, Rizell M, Rossi G, Rostaing L, Roy A, Turrion VS, Schmidt J, Troisi RI, van Hoek B, Valente U, Wolf P, Wolters H, Mirza DF, Scholz T, Steininger R, Soderdahl G, Strasser SI, Jauch KW, Neuhaus P, Schlitt HJ, Geissler EK. A prospective randomised, open-labeled, trial comparing sirolimus-containing versus mTOR-inhibitor-free immunosuppression in patients undergoing liver transplantation for hepatocellular carcinoma. *BMC Cancer* 2010; **10**: 190 [PMID: 20459775 DOI: 10.1186/1471-2407-10-190]

157 **Schlitt HJ**, Schnitzbauer AA. Hepatocellular carcinoma: agents and concepts for preventing recurrence after curative treatment. *Liver Transpl* 2011; **17** Suppl 3: S10-S12 [PMID: 21850696 DOI: 10.1002/lt.22411]

158 **Duvoux C**, Kiuchi T, Pestalozzi B, Busuttil R, Miksad R. What is the role of adjuvant therapy after liver transplantation for hepatocellular carcinoma? *Liver Transpl* 2011; **17** Suppl 2: S147-S158 [PMID: 21714065 DOI: 10.1002/lt.22367]

159 **Fujiki M**, Aucejo F, Kim R. Adjuvant treatment of hepatocellular carcinoma after orthotopic liver transplantation: do we really need this? *Clin Transplant* 2013; **27**: 169-177 [PMID: 23216662 DOI: 10.1111/ctr.12042]

160 **Teng CL**, Hwang WL, Chen YJ, Chang KH, Cheng SB. Sorafenib for hepatocellular carcinoma patients beyond Milan criteria after orthotopic liver transplantation: a case control study. *World J Surg Oncol* 2012; **10**: 41 [PMID: 22339891 DOI: 10.1186/1477-7819-10-41]

161 **Shetty K**, Dash C, Laurin J. Use of adjuvant sorafenib in liver transplant recipients with high-risk hepatocellular carcinoma. *J Transplant* 2014; **2014**: 913634 [PMID: 24818010 DOI: 10.1155/2014/913634]

162 **Castelli G**, Burra P, Giacomin A, Vitale A, Senzolo M, Cillo U, Farinati F. Sorafenib use in the transplant setting. *Liver Transpl* 2014; **20**: 1021-1028 [PMID: 24809799 DOI: 10.1002/lt.23911]

163 **Xu J**, Shen ZY, Chen XG, Zhang Q, Bian HJ, Zhu P, Xu HY, Song F, Yang XM, Mi L, Zhao QC, Tian R, Feng Q, Zhang SH, Li Y, Jiang JL, Li L, Yu XL, Zhang Z, Chen ZN. A randomized controlled trial of Licartin for preventing hepatoma recurrence after liver transplantation. *Hepatology* 2007; **45**: 269-276 [PMID: 17256759 DOI: 10.1002/hep.21465]

164 **Zhang Q**, Chen H, Li Q, Zang Y, Chen X, Zou W, Wang L, Shen ZY. Combination adjuvant chemotherapy with oxaliplatin, 5-fluorouracil and leucovorin after liver transplantation for hepatocellular carcinoma: a preliminary open-label study. *Invest New Drugs* 2011; **29**: 1360-1369 [PMID: 21809025 DOI: 10.1007/s10637-011-9726-1]

165 **Wu J**, Sun H, Han Z, Peng Z. A single center experience: post-transplantation adjuvant chemotherapy impacts the prognosis of hepatocellular carcinoma patients. *Chin Med J* (Engl) 2014; **127**: 430-434 [PMID: 24451946]

166 **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]

167 **Takada Y**, Uemoto S. Liver transplantation for hepatocellular carcinoma: the Kyoto experience. *J Hepatobiliary Pancreat Sci* 2010; **17**: 527-532 [PMID: 19707711 DOI: 10.1007/s00534-009-0162-y]

168 **Fan J**, Zhou J, Xu Y, Qiu SJ, Wu ZQ, Yu Y, Huang XW, Tang ZY, Wang YQ. [Indication of liver transplantation for hepatocellular carcinoma: Shanghai Fudan Criteria]. *Zhonghua Yixue Zazhi* 2006; **86**: 1227-1231 [PMID: 16796876]

169 **Zheng SS**, Xu X, Wu J, Chen J, Wang WL, Zhang M, Liang TB, Wu LM. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. *Transplantation* 2008; **85**: 1726-1732 [PMID: 18580463 DOI: 10.1097/TP.0b013e31816b67e4]

170 **Lee SG**, Hwang S, Moon DB, Ahn CS, Kim KH, Sung KB, Ko GY, Park KM, Ha TY, Song GW. Expanded indication criteria of living donor liver transplantation for hepatocellular carcinoma at one large-volume center. *Liver Transpl* 2008; **14**: 935-945 [PMID: 18581465 DOI: 10.1002/lt.21445]

P- Reviewer: Massironi S **S- Editor**: Ma YJ **L- Editor**: Filipodia
E- Editor: Ma S

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327