

THE EVOLUTION OF CRITERIA FOR LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA: FROM MILAN TO SAN FRANCISCO AND ALL AROUND THE WORLD!

LA EVOLUCIÓN DE LOS CRITERIOS PARA EL TRASPLANTE HEPÁTICO DEL CARCINOMA HEPATOCELULAR:
¿DE MILÁN A SAN FRANCISCO YA TODO EL MUNDO!

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ABSTRACT

Introduction: Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third most common cancer-related cause of death in the world. According to the stage of the disease, each patient is allocated to a different treatment option. Liver transplantation, along with surgical resection, is the only totally therapeutic option and is primarily indicated in HCC patients with underlying cirrhosis. However, the restricted number of liver grafts imposes difficulties in selecting the most suitable patients to receive those limited grafts and therefore certain criteria have been proposed. The Milan criteria are currently the most widely accepted and utilized criteria around the world, despite their restrictiveness. In an attempt to assist HCC patients exceeding them, but with a potential to display acceptable survival outcomes, undergo liver transplantation, research teams worldwide suggest expanded criteria based on their findings. Some of the most broadly known are the University of California, San Francisco (UCSF), Kyoto, Tokyo, Hangzhou and up-to-7 criteria. On the other hand, in order to expand the liver donor pool, grafts may be accepted from living, non-heart beating, elderly, steatotic, or even HCV-infected donors, in addition to the use of split livers with both advantages and disadvantages. The aim of this review is to thoroughly present the current situation of liver transplantation for HCC patients, with a focus on the criteria used and emerging challenges presented. **Core tip:** Hepatocellular carcinoma (HCC) is the third most common malignancy worldwide and liver transplantation represents the treatment of choice, particularly in the setting of cirrhosis. Lack of grafts led to the utilization of certain criteria in order to determine the eligibility of an HCC patient to access the waiting list. The most widely accepted are the Milan criteria, even though they are thought of as too restrictive. Consequently, transplant research groups all over the world published their own criteria, which showed acceptable outcomes. Living donor liver transplantation and other extended-criteria grafts have been proposed as an alternative to reduced donations. **Ziogas IA, Tsoulfas G.** The evolution of criteria for liver transplantation for hepatocellular carcinoma: from Milan to San Francisco and all around the world!

Key words: Hepatocellular carcinoma; HCC; Liver transplantation; Criteria; Milan criteria; UCSF criteria; Expanded criteria. (source: MeSH NLM)

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary neoplasm of the liver (85-90%)¹ and, in spite of the several advances in oncology and surgery we witnessed in the 21th century, it still represents the fifth most frequent carcinoma and the third most common malignancy-related cause of mortality worldwide². It is well known that liver cirrhosis is a major feature usually accompanying HCC (70-90%)², mostly after HBV or HCV infection or even

alcoholic liver disease depending on the geographical parameters. Specifically, the incidence of HCC tends to be higher in Asia (>20/100000) in comparison with North America and Europe (<5/100000)³, but interestingly the development and the establishment of the vaccine against HBV in Asian countries resulted in a prominent decrease in HCC's occurrence during the last decades⁴. On the contrary, it shows an increase over the past years in low-rate countries such as USA, UK and Australia^{1,5} mainly attributed to an increase in HCV incidence and to an improvement in survival of

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cirrhotic patients, thus indicating the significance of further improving the treatment modalities that can be implemented in order to manage this highly fatal type of cancer.

Regarding the available treatment options, there is a wide variety to choose from always depending on the individual parameters of the HCC patient, such as the tumor's characteristics (size and number of neoplastic nodules and invasion of vascular compartments), the liver's functional capacity (Child-Pugh score) and the physiologic reserve (i.e. Eastern Cooperative Group performance status)⁶⁻⁸. The staging system that seems to take all of these aspects into consideration, which is also suggested by the European Association for the Study of the Liver-European Organization for Research and Treatment of Cancer (EASL-EORTC) guidelines, is the Barcelona Clinic Liver Cancer (BCLC) classification (Figure 1)⁹. Nevertheless, the only therapeutic approaches that have shown total cancer remission and cancer-free survival are the surgical resection and orthotopic liver transplantation (OLT), hence indicating that surgery is the cornerstone of HCC treatment.

OLT has the theoretical advantage of simultaneously treating HCC and cirrhosis at the same time, and as such it would be the ideal treatment in a fictitious world of graft abundance. Unfortunately, it is evident that there is a great absence of donor organs worldwide and consequently potential transplant candidates should firstly undergo an objective prioritization process in order to determine the ones with the greatest potential to benefit from OLT and thus allocate liver grafts accordingly. Although Dr. Thomas Starzl carried out the first human liver transplantation in 1963, it was not until the 1990s that Mazzaferro et al published the famous Milan criteria for liver transplantation¹⁰. These were the findings, that in combination with Bismuth's studies^{11,12}, achieved the establishment of OLT as the appropriate therapy for patients with small HCC and cirrhosis. Therefore, they facilitated the transition of liver transplantation from the experimental level to the current life-saving procedure for a continuously increasing number of liver failure patients.

New challenges have emerged, though, over the past years in regard to liver transplantation, especially associated with the attempt of increasing the liver donor pool, as deceased donor liver transplantation (DDLT)-the standard option-does not seem to fulfill the need for liver grafts. Living donor liver transplantation (LDLT) has gained a great deal of attention, especially in eastern countries, and its results seem promising.

Split liver transplantation (SLT) is also an alternative option by which more recipients can benefit from a single donor organ and its effects, especially in the pediatric population in need, have been tremendous. Moreover, many HCC patients with advanced stage tumor receive pre-transplant treatments in order to meet certain criteria for OLT (downstaging strategy) or receive bridging therapy, while on the waiting list, so as to have the course of their disease remain constant. Last but not least, new anti-HCV therapies have a significant effect in liver transplant candidates and recipients with HCV-related liver disease.

On the whole, the constant need for prioritization and the accompanying advances in liver surgery and research need to be followed by the establishment and the subsequent transformation of liver transplantation criteria. Thus, the aim of this review is to thoroughly describe the evolution of those criteria (Table 1) and OLT in general.

DIFFERENT CRITERIA AND EVOLUTION MILAN CRITERIA

The Milan criteria proposed by Mazzaferro et al in 1996¹⁰ are the most broadly accepted ones worldwide. Specifically, the achievement of 85% and 92% 4-year overall and recurrence-free survival, respectively, led to their adoption by the United Network for Organ Sharing (UNOS) as the criteria of choice for objectively choosing the suitable early-HCC patients for liver transplantation. According to the Milan criteria patients receiving liver transplantation should have a single tumor ≤ 5 cm in diameter or no more than three nodules ≤ 3 cm in diameter and no evidence of vascular or extrahepatic invasion. Although these findings correlated with great survival and oncologic outcomes, they seem to be quite restrictive and only a small portion of the HCC patients that could benefit from liver transplantation does fulfill them. Additionally, the whole biological course of such a unique and heterogeneous type of cancer cannot be simply assessed only by size and number. Thus, a great deal of experts in liver transplantation proposed their own expanded criteria, many of which incorporate the evaluation of certain biological markers. Nevertheless, this consecutive tendency for expanding them cannot always be followed by an adequate evidential value, as most studies are retrospective cohorts and there is a profound absence of outside validation¹³. In general, the "metro ticket paradigm" perfectly describes the current situation: the longer distance we cover away

from the conventional criteria, the higher the price we will have to pay in terms of increased recurrence¹⁴.

UNIVERSITY OF CALIFORNIA SAN FRANCISCO (UCSF) CRITERIA

In an effort to expand the Milan criteria, a retrospective study by Yao et al¹⁵ reported that patients with larger lesions could also exhibit improved survival with OLT. To elaborate this, they proposed the University of California San Francisco (UCSF) criteria, according to which patients could undergo OLT if they presented with a single lesion ≤ 6.5 cm in diameter or ≤ 3 lesions with the largest one ≤ 4.5 cm in diameter and an overall tumor diameter ≤ 8 cm. Significantly, the 1- and 5-year survival rates were 90% and 75.2%, respectively. In addition, the group of HCC patients exceeding the Milan, but fulfilling the UCSF criteria showed 86% 2-year survival percentage. Even though their data were based on histopathological examination of the explanted hepatic lesion, Yao et al¹⁶ also validated the UCSF criteria in accordance to pre-OLT imaging reporting a 5-year recurrence-free survival of 80.7%. Notably, the rate of expansion beyond the Milan criteria was 16.3%¹⁷.

PITTSBURGH CRITERIA

In an attempt to improve the predictive values of cancer-free survival in HCC patients receiving OLT, Marsh et al¹⁸ evaluated the association between the pathologic tumor-node-metastasis (pTNM) staging system and cancer-free survival, which led to the recognition of the no contact point. Instead they came up with a modification of the pTNM criteria, the so-called Pittsburgh criteria, according to which the prognosis can be determined by assessing the depth of vascular invasion, lymph node status, lobar distribution, as well as size of the largest lesion, although the number of nodules did not seem to play a key role. Unfortunately, the major limitation of this system is that metastasis to lymph nodes or invasion of vessels cannot be easily determined preoperatively, hence it did not gain wide acceptance.

UNIVERSITY CLINIC OF NAVARRA CRITERIA

In 2001, Herrero et al¹⁹ reported that patients with HCC and cirrhosis could benefit from OLT, as long as they presented with a solitary tumor ≤ 6 cm or up to three nodules ≤ 5 cm in diameter. These are the University Clinic of Navarra (CUN) criteria and the aforementioned study showed that the estimated 1-, 3- and 5-year survival rates were 87%, 79% and 79%, respectively, while the 1-, 2- and 3-year actuarial recurrence-free survival ones were 87%, 82% and

70%, respectively. Interestingly, bilobar disease, viral etiology of cirrhosis, invasion of vessels and TNM stage IV were significant characteristics of patients displaying a decreased recurrence-free survival. An important recommendation from Herrero et al is that HCC patients with radiological TNM stage IV should not be considered for OLT. The CUN criteria also exhibited an expansion estimate of 19.6% beyond the Milan criteria¹⁷.

MOUNT-SINAI CRITERIA

Roayaie et al²⁰ attempted another criteria expansion at Mount-Sinai, New York arguing that the number of lesions should not be taken into consideration. In other words, the proposed criteria included patients with any number of nodules, as long as the diameter of each one was 5-7 cm. They demonstrated a 5-year recurrence rate of 55%, which unfortunately falls short of that of the Milan criteria.

EDMONTON CRITERIA

On a similar pattern, Kneteman et al²¹ suggested an extended version of OLT criteria consisting of a solitary nodule < 7.5 cm, or any number of lesions with a size < 5 cm for each one. The demonstrated 4-year survival was 82.9% in comparison with the 87.4% of the Milan criteria arm of the study.

DALLAS CRITERIA

Onaca et al²² analyzed data from 1206 HCC patients from the International Registry of Hepatic Tumors in Liver Transplantation and suggested that more patients could benefit from OLT if the criteria expanded to one nodule ≤ 6 cm in diameter, or two to four lesions each one ≤ 5 cm in diameter. Survival rates were similar to that of the Milan criteria, as 5-year recurrence-free survival was 63.9% for a single tumor 5.1-6.0 cm in diameter and 64.6% for 2-4 lesions, with the largest being 3.1-5.0 cm, versus the 61.8% observed in those fulfilling the Milan criteria.

TOKYO CRITERIA

During the last decade, Asian centers showed an increased interest in expanding the Milan criteria. It was the University of Tokyo²³, specifically, that laid the foundation for LDLT by introducing historically the first criteria for this operation. The so-called 5-5 rule indicated that HCC patients are eligible for LDLT if they have ≤ 5 tumors not exceeding a diameter of 5cm. This study reported a 5-year overall and recurrence-free survival of 75% and 90%, respectively. Another study incorporating 139 HCC patients receiving LDLT from 1996 until 2015 showed that overall and recurrence-

free survival were similar between patients meeting Milan and Tokyo criteria²⁴. Shindoh et al proposed another subset of criteria based on the Tokyo ones²⁵. In other words, the additional prerequisites they added to the Tokyo criteria were a serum a-fetoprotein (AFP) level ≤ 250 ng/mL and a serum Des-Gamma-carboxy prothrombin (DCP) level, a serum marker of primary HCC²⁶, ≤ 450 mAU/mL. The observed 5-year overall and recurrence-free survival were 84% and 96.8%, respectively.

KYOTO CRITERIA

Another group, also from Japan, proposed the Kyoto criteria²⁷, which suggest that LDLT can be effectively performed in HCC patients with ≤ 10 nodules all of which are ≤ 5 cm in diameter and with a serum DCP ≤ 400 mAU/mL. The 125 patients included displayed a 5-year overall survival rate of 86.7%, while patients exceeding the Milan but meeting the Kyoto criteria showed a 7.3% 5-year recurrence rate in comparison with the 9.7% of the patients meeting the Milan criteria. These criteria were also recently prospectively evaluated exhibiting a 5-year overall survival rate and recurrence rate of 82% and 7%, respectively, thus highlighting that by this expansion more patients could benefit from LDLT with acceptable outcomes²⁸.

KYUSHU UNIVERSITY INDICATIONS

Additionally, another Japanese team of researchers, this time from Kyushu University, in an effort to evaluate the extent that liver transplantation criteria could be expanded, treated 60 HCC patients with LDLT [29]. The inclusion criteria were the absence of both extrahepatic metastases and vascular invasion, without preclusion of patients in regard to number or size of HCC lesions; for the record more than half of them exceeded the Milan criteria (67%). Their conclusions were that patients with DCP > 300 mAU/mL and > 5 cm in diameter will have a significantly worse prognosis and increased recurrence percentage.

HANGZHOU CRITERIA

A Chinese research team established a new subset of HCC patient selection for OLT criteria, the Hangzhou criteria³⁰. These consist of a) an overall tumor diameter ≤ 8 cm, or b) > 8 cm with a histopathological grade I or II and pre-transplantation AFP ≤ 400 ng/mL. The reported 1-, 3-, 5-year overall survival and cancer-free recurrence estimates were 92.8%, 70.7%, 70.7%, and 83.7%, 65.6%, 62.4%, respectively. Interestingly, there was no statistically significant difference between the patients meeting the Hangzhou and the Milan criteria as to survival rates. A recent study evaluating

the percentage of expansion beyond the Milan criteria reported that patients fulfilling those criteria exhibited the highest expansion rate (51.5%) among those tested, while type a presented with markedly increased survival rates compared to type b¹⁷. In 2015, Xiao et al³¹ proposed a combination of the Hangzhou criteria with the measurement of Neutrophil-lymphocyte ratio (NLR). It is widely known that elevation of this marker correlates with worse prognosis of HCC, and as a result they demonstrated that patients with NLR ≤ 4 and within the Hangzhou criteria exhibit the best prognosis and recommend these criteria as the gold-standard for the mainland of China.

ASAN CRITERIA

The Asian tradition of expanding the Milan criteria, especially in HCC patients undergoing LDLT, was carried on by the Asan Medical Center in South Korea. In particular, the Asan criteria, which are based on explant pathology just as the UCSF criteria, includes ≤ 5 cm in diameter, ≤ 6 nodules and no gross invasion of the vessels³². The 1-, 3- and 5-year overall survival rates according to the Asan criteria were 88.1%, 81.9% and 76.3%, respectively. When compared to Milan and UCSF, Asan criteria displayed similar survival rates. An advantage of these criteria is that their application by preoperative assessment was markedly associated with the survival and recurrence rates as to the histopathological evaluation of the explanted specimen. This shows that patient selection could be also partially based on pre-transplant radiographic findings, despite the potential deviations that may arise³³.

VALENCIA CRITERIA

It was in 2008 that "the baton was handed over" to Silva et al [34] to expand the OLT criteria. Specifically, they proposed the Valencia criteria, which include up to three lesions, each no larger than 5 cm in diameter and a total diameter ≤ 10 cm, based on radiology. The 1-, 3- and 5-year survival rates were 85%, 72% and 67%, respectively, while the 1-, 3- and 5-year recurrence rates were 5%, 9% and 11%, respectively. After histopathological examination of the explanted tumors, those exceeding the Milan criteria, being bilobar and with poor differentiation showed the highest underestimation rates compared to the radiological estimates. The retrospective character, though, of this study highlights the need for larger prospective studies.

SHANGHAI CRITERIA

The Shanghai criteria proposed by Fan et al³⁵ consist of a single lesion ≤ 9 cm in diameter, or no more than three nodules with the largest ≤ 5 cm in diameter, overall tumor diameter ≤ 9 cm without extrahepatic metastasis, lymph node or macrovascular invasion. This study included 1,078 HCC patients with 1- and 5-year overall survival rates of 85.8% and 78.1%, respectively, while the cancer-free survival rates were 59.9% and 52.6%, respectively. It was the largest group of patients with HCC being assessed for OLT criteria in China and notably 45% more patients can benefit by the adoption of these findings with adequate survival outcomes. A major limitation, however, is that most of the patients were HBV-positive and as a result the Shanghai criteria could possibly be generalized only for HCCs of HBV infection origin.

UP-TO-7 CRITERIA

Even Mazzaferro showed an interest in expanding the Milan criteria, therefore publishing with his colleagues the up-to-7 criteria, according to which the sum of tumor number and the size of the largest nodule must be ≤ 7 cm in diameter, without any microvascular invasion[14]. The 5-year overall survival of 283 patients without microscopic invasion of the vessels meeting these criteria was 71.2%. This study provides robust data on adequately and accurately estimating the results of OLT in HCC patients. Nevertheless, the absence of cancer grading, reason of death, etiology behind the origin of cirrhosis and HCC, response rates to preoperative therapeutic modalities and molecular marker testing does not seem to classify these criteria as an excellent patient selection system.

TTV/AFP CRITERIA BY TOSO ET AL

After extracting data from the Scientific Registry of Transplant Recipients (SRTR), Toso et al³⁶ suggested that patient survival is clearly associated with the total tumor volume (TTV) and the pre-transplant serum AFP levels. After validating their suggestion not only retrospectively³⁶, but recently also prospectively³⁷ they proposed their criteria including total tumor volume ≤ 115 cm³ and preoperative serum AFP ≤ 400 ng/mL, which demonstrated a 4-year overall survival rate of 74.6% in their 2015 study. Their contribution was major due to the fact that these expanded criteria could be safely implemented in transplant centers with at least 8-month waiting time.

AFP-TTD CRITERIA BY LAI ET AL

In 2012, Lai et al³⁸ proposed the combination of both biological and morphological characteristics to be

taken into consideration for HCC patient selection for OLT. To elaborate this, they stated that patients with serum AFP ≤ 400 ng/mL and total tumor diameter (TTD) ≤ 8 cm exhibit adequate survival estimates with a 5-year disease-free survival rate of 74.4%. However, this study has the limitations of a retrospective study and its wider application is questionable because of possible selection bias.

WARSAW CRITERIA

One of the recent proposals for expanding the OLT criteria came from Poland by Grat et al³⁹. These are the Warsaw criteria and include HCC patients exceeding the Milan, but meeting the UCSF, or the up-to-7 criteria plus an AFP serum level below 100 ng/mL. The observed 5-year overall survival and recurrence-free survival rates were both 100%, which is a unique finding. Another study from Grat et al⁴⁰ showed similar survival benefits, hence indicating that AFP is a useful marker for patient selection.

NLR-CRP CRITERIA BY NA ET AL

In 2014, Na et al⁴¹ in order to enlarge the LDLT pool evaluated 224 patients by measuring inflammatory markers, such as NLR and C-reactive protein (CRP). Specifically, HCC patients with NLR equal or greater to 6.0 or CRP equal or greater to 1.0 demonstrated significantly lower cancer-free and overall survival rates when compared to patients with NLR < 6.0 or CRP < 1.0 .

NCKK CRITERIA

The efficacy of fluorine-18-fluorodeoxyglucose (18-FDG) positron emission tomography/computed tomography (PET/CT) in detecting extrahepatic metastases and recurrence in HCC patients has been broadly confirmed^{42,43}. In 2015, Lee et al⁴⁴ published a study including 280 patients who received LDLT at the National Cancer Center and reported that HCC patients exceeding the Milan criteria with a negative PET/CT and overall tumor size < 10 cm demonstrated overall survival and recurrence-free survival rates similar to those meeting the Milan criteria. In 2016, they proposed the so-called National Cancer Center Korea (NCKK) criteria, according to which patients selected for LDLT should present with negative PET/CT assessment and a total tumor size < 10 cm⁴⁵.

EXTENDED TORONTO CRITERIA

After reporting the results of a first retrospective cohort study[46], a research group went on with a second validation prospective cohort study⁴⁷ in an effort to prove that tumor size and number are not the only aspects that should be considered in patient selection for OLT, but tumor differentiation and tumor-

related symptoms should be taken into consideration as well. These are named the extended Toronto criteria (after the validation study) and consist of no vascular invasion, no extrahepatic metastasis, no cancer-related symptoms, a percutaneous biopsy result of the largest tumor showing that it is not poorly differentiated and, most significantly, no tumor size or number limitation. An important finding was that the 1-, 3- and 5-year actuarial survival rates in the group exceeding the Milan criteria vs. the group within them were 94%, 76% and 69% vs. 95%, 82% and 78%, respectively ($P=0,3$). They also suggested that $\text{AFP} > 500 \text{ ng/mL}$ was associated with worse outcomes for both groups, and thus the AFP limitations should be included in the criteria for HCC patients meeting or exceeding the Milan criteria.

EMERGING CHALLENGES IN LIVER TRANSPLANTATION

The significant lack of grafts and the subsequent placement of future candidates in the waiting list for a donor organ may be a taxing process for the recipients and thus high "drop-out" rates (10-20%) have been reported^{48,49}. As a result, the rationale of "bridging" therapy has been proposed, according to which another therapeutic method such as surgical resection, radiofrequency ablation (RFA), or transarterial chemoembolization (TACE), is utilized to act as a "bridge" for preventing tumor progression until a suitable graft becomes available. It is also generally accepted that the patient's response to such treatments may be associated with the aggressiveness of the disease and thus could possibly be utilized as a surrogate marker for prognosis. Despite the fact that no firm conclusions can yet be made, data suggest that this process can increase patient survival and decrease tumor recurrence post-OLT⁵⁰.

However, a fair percentage of HCC patients do not even get close to being placed in the waiting list due to their advanced stage disease. Therefore, downstaging of HCC by liver-directed therapies, such as RFA, TACE, transarterial radioembolization (TARE), stereotactic body radiation (SBRT) or a combination of them, to within the Milan criteria has been proposed as the process of expanding the criteria has not yet reached a definitive conclusion. A recent study compared the survival outcomes between patients presenting initially within the Milan criteria and patients receiving locoregional treatments in order to be downstaged to within the Milan criteria⁵¹. It was reported that survival rates were similar between the two study arms. Interestingly, a percentage of the patients beyond the Milan criteria after downstaging received resection

after being downstaged, and were able to avoid OLT. On the other hand, a systematic review showed that almost half of the patients outside the Milan criteria can be successfully downstaged, but it seems that they exhibit higher recurrence rates, when compared to those meeting the Milan criteria⁵². Due to the vast heterogeneity of the studies, larger prospective ones with standardized reporting criteria need to be carried out in order to achieve robust and trustworthy results.

Also, living donor liver transplantation (LDLT) represents an alternative to the lengthy period on the waiting list for a donor organ and may pose acceptable threat to the donor's health if performed in qualified and specialized centers. Specifically, donor mortality has been estimated around 0.1-0.3% for right lobe grafts^{53,54}, while the reported risk of donor fatal complication is around 2-10%⁵⁵⁻⁵⁷. LDLT comprises the majority of liver transplantations performed in Asian countries in contrast to Western countries⁵⁸. This however does not mean that we should take lightly this type of donation, as we are referring to donors who are healthy and enter a surgery where there will be no benefit to their health, a truly altruistic act. This type of OLT does not impose further on the lack of grafts, because it is personal issue between patients and their relatives or close contacts (according to the existing legal system in each country) and as such selection criteria should be set based on the tumor's characteristics and each case should be managed uniquely. That is partly the reason why so many Asian centers proposed their own criteria for LDLT, as discussed above. A systematic review and meta-analysis comparing LDLT vs. DDLT reported a hazard ratio (HR) of 0.97 for overall survival (95% CI 0.73-1.27, $P=0.8$) and a HR of 1.59 for disease-free survival (95% CI 1.02-2.49, $P=0.041$), indicating a possible superiority of DDLT over LDLT in terms of disease-free survival⁵⁹.

The use of marginal or extended-criteria organs is another way to enlarge the liver donor pool (Table 2)⁶⁰. These are organs with high risk of complications, for instance primary dysfunction, delayed graft function or biliary complications⁶¹. This category incorporates organs from split livers, non-heart beating donors, elderly donors and HCV-infected donors⁶²⁻⁶⁶.

In split liver transplantation (SLT) the liver from a deceased donor is divided: a) between a pediatric and an adult recipient or b) between a small adult or big child and a medium-sized adult. A fact that should be mentioned is that these grafts need to undergo a regeneration process, which may trigger the proliferation and growth of a tumor⁶⁷. In spite of

the disbelief lurking behind the split livers, a recently published study indicates that when compared to whole-grafts, split livers demonstrated similar survival rates, as well as prevalence and severity of complications, as long as donors were carefully selected and matched to recipients and the surgical skills were of high expertise⁶⁸.

The utilization of donor organs from non-heart beating donors (NHBD), or otherwise known as donation after circulatory death (DCD), currently corresponds to around 20% of the grafts used for transplantation in Europe⁶⁹. One version of this is the controlled DCD, when the heart stops after removal of the life support⁷⁰ and another is the uncontrolled DCD, in which unexpected heart arrest occurs and organ recovery takes place after failure of resuscitation⁷¹. Regardless of the case, in contrast to the conventional DDLT after brain death, CDC is accompanied by ischemia reperfusion injury, which is thought of having pro-oncogenic and tumor proliferation promoting effects, thus predisposing to poorer oncological outcomes⁷². Additionally, the incidence of biliary adverse events is thought to increase as well⁷³.

HCV-infected donors could also be accepted for OLT under certain circumstances. Even though only 5% of the donors seem to be HCV-positive, such a utilization can decrease mortality on the waiting list and limit organ shortage, while studies have shown similar graft and patient survival rates when compared to HCV-negative donors, except for HCV-HIV co infected recipients⁶⁶. A new age of OLT is upon us with the introduction of direct-acting antivirals (DAA) either pre- or post-OLT, which have shown to be efficacious and safe and to decrease the number of HCV-infected donors with positive HCV-RNA, thus reducing transmission rates, as well as the number of HCV-related HCC patients on the waiting list^{66,74}. Nevertheless, before proceeding with the acceptance of HCV-positive donors for OLT in HCC patients, issues regarding viral extirpation and HCC recurrence need to be resolved⁷⁵.

The use of grafts from elderly donors or the use of steatotic organs is also an alternative way to increase the liver donor pool. Unfortunately, this method can result in a high risk of HCC recurrence, if by reducing the waiting time, the biological evolution of the tumor's behavior is underestimated^{76,77}. Also, criteria regarding this strategy have been evolving over time, with some organs being acceptable grafts in some geographical regions yet unacceptable in others,

hence highlighting the steps needed to be made in this field of research. Currently, although age may affect certain parameters, there is no limitation in terms of age⁷⁸, whereas steatosis up to a certain degree (usually macrosteatosis of 40%) is considered acceptable⁶³.

TUMOR BIOLOGY: ANASPECT TO BE INCLUDED IN THE CRITERIA

The overreaching aim of OLT is to prevent HCC from recurring. Consequently, what we should aim for is how to predict tumor biologic behavior and recurrence prior to transplantation, so that HCC patients with optimal characteristics can benefit the most and demonstrate increased survival rates. This has become widely acceptable, hence the latest tendency to include biological tumor markers in the different criteria suggested.

The histopathological examination of the explant reveals the biology of the tumor by assessing microvascular invasion and tumor grade. However, it would be preferable to evaluate these findings prior to transplantation, as they correlate with recurrent disease prognosis¹³. DuBay et al^[46] included percutaneous biopsy in their criteria (Toronto), which did not impose any limitation to tumor number or size, in order to avoid OLT in patients with poorly differentiated HCC. Although, as previously discussed, these were further validated (extended Toronto criteria) by Sapisochin et al⁴⁷, the vast heterogeneity of HCC, the low sensitivity of biopsy and the potential for bleeding or even needle track seeding, render routine biopsy not an easily recommended action⁷⁹. Additionally, patients with decompensated cirrhosis may not be able to undergo biopsy owing to retention of ascites. As a result, noninvasive methods, such as markers and PET, should be preferred.

The utility of 18-FDG-PET in determining tumor biology has been shown by Kornberg et al⁸⁰. They reported that pre-OLT factors with high predictive value for recurrence-free survival were: negative PET uptake, AFP < 400 IU/mL and total tumor diameter < 10 cm. Significantly, PET-positive findings were the only independent factor predictive of cancer-related patient drop-out from the waiting list. On this basis, Lee et al⁴⁵ proposed the aforementioned NCCK criteria.

Regarding the remaining surrogate tumor markers, AFP and DCP are the most commonly implemented. AFP is included as a parameter of several criteria around the world, such as Hangzhou, TTV/AFP, TTD-AFP and Warsaw as mentioned in Table 1. Besides, the international consensus highlighted that AFP

resembles a marker with high prognostic value⁷⁹. In Japan, DCP predominates as a tumor marker. This has become apparent by its inclusion in several Japanese criteria, such as Kyoto and Kyushu (Table 1). It has been associated with histopathological findings, i.e. invasion of portal vein^{81,82} or high grade HCC differentiation⁸³. In addition, Fujiki et al⁸⁴ showed that DCP levels are superior to pre-OLT tumor size or number regarding prognosis and recurrence, as well as that it correlates with histopathological characteristics and thus patient selection should depend on DCP levels. Besides, Todo et al⁸⁵ used both AFP and DCP as serological markers and both correlated with the biological behavior of HCC, while patients with AFP ≤ 200 ng/mL and DCP ≤ 100 mAU/mL exhibited better prognosis. Interestingly, a study published by Feng et al⁸⁶ in March 2017, proposed a novel model for predicting early recurrence of HCC within the Milan criteria after OLT. This included the combination of AFP levels (cut-off value: 321 ng/mL) and cytokeratin-19 (CK19)/glypican-3 (GPC3) subtyping within the Milan criteria. It could potentially be found to be helpful in patient selection based on pre-OLT needle core biopsy.

Angiogenesis and tumor invasion are partially mediated by inflammation-induced upregulation of cytokines⁸⁷. Angiogenesis plays an important

role in HCC, thus inflammatory mediators could not be omitted from the search of surrogate markers. Specifically, pre-transplant NLR has been shown to correlate with HCC recurrence post-OLT^{88,89}. An et al also reported that CRP levels equal to or above 1 mg/dL were related to tumor recurrence⁹⁰, while this could not be proven by others⁸⁹. Both NLR and CRP are included in the criteria proposed by Na et al⁴¹. However, their implementation is still controversial, as they reflect the tumor's microenvironment, which may be altered by several irrelevant factors, i.e. infection, hence further research is needed on this field.

We previously mentioned that response to pre-OLT treatments, either in terms of bridging therapy or downstaging, may also serve as a surrogate marker for HCC recurrence. Response to such locoregional treatments, according to the EASL-EORTC guidelines, should be evaluated by modifications in serum AFP levels or radiological changes based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST)⁹. Additionally, according to a European multicenter study assessing 306 HCC patients meeting the Milan criteria and 116 exceeding them after locoregional therapies (for bridging or downstaging purpose) and OLT, those two factors were indeed the most useful in the prognosis of HCC recurrence after OLT.

Tabla 2. Advantages and disadvantages of different liver donor sources for liver transplantation in HCC by Sapisochin et al⁶⁰.

SOURCE	ADVANTAGES	DISADVANTAGES
Living donor liver transplantation	<ul style="list-style-type: none"> • Reduced drop-out rates (if donor graft available) • Unlimited donor source • Immunological benefits 	<ul style="list-style-type: none"> • Reduced waiting time (if donor graft available) • Donor's health risk • Elevated HCC recurrence risk owing to liver regeneration?
Split liver transplantation	<ul style="list-style-type: none"> • Reduced waiting time 	<ul style="list-style-type: none"> • Elevated HCC recurrence risk owing to liver regeneration? • Elevated risk of biliary adverse events
Non-heart beating donors	<ul style="list-style-type: none"> • Reduced waiting time • Low MELD score patients may demonstrate fewer adverse events 	<ul style="list-style-type: none"> • Elevated rates of adverse events • Elevated risk of graft loss • Biliary strictures

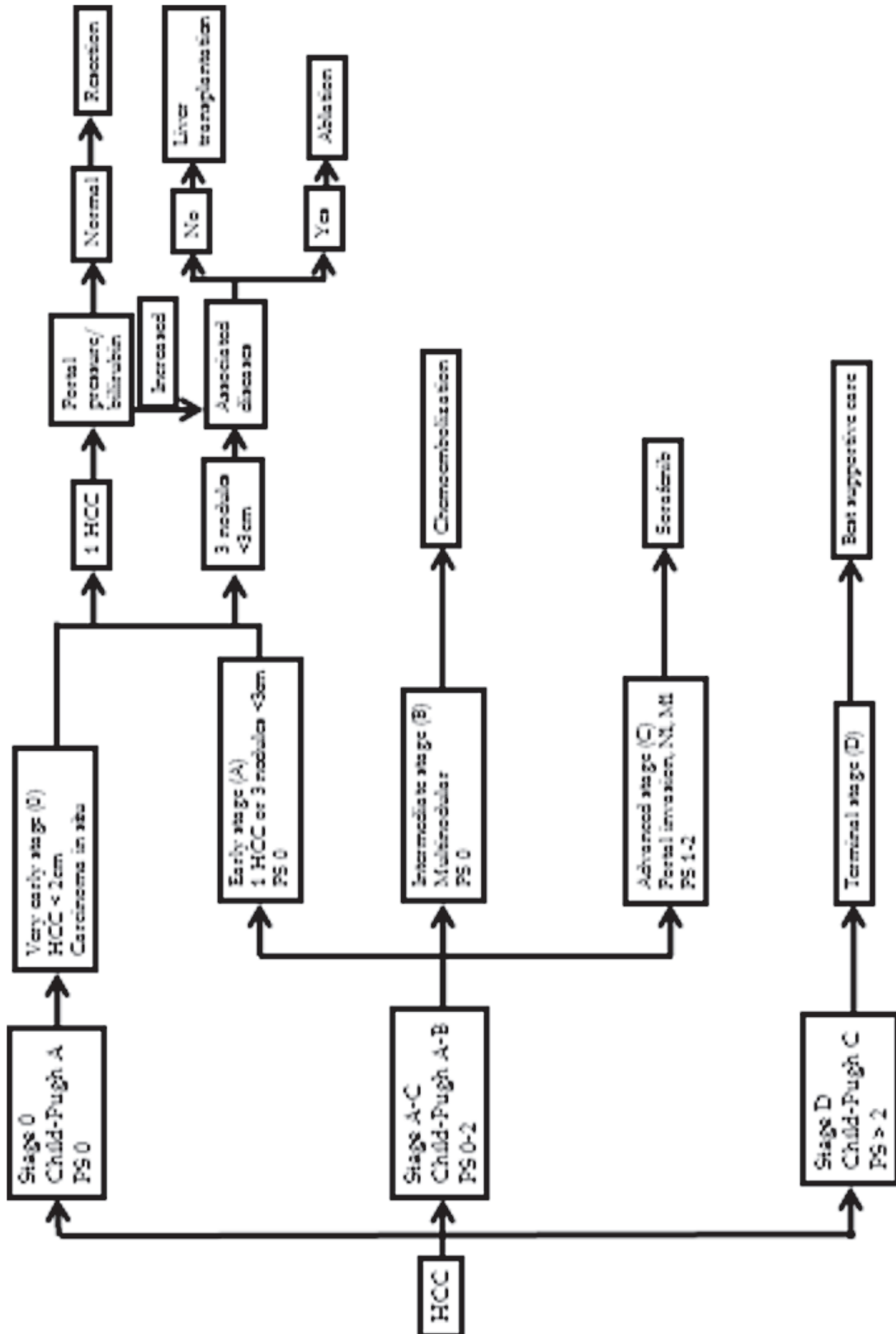


Figure 1. Legend: Barcelona Clinic Liver Cancer staging system and treatment algorithm, PS: performance status, N: nodules, M: metastases

Tabla 1. Liver transplantation selection criteria for patients with hepatocellular carcinoma in different centers.

ARTÍCULO DE REVISIÓN

CRITERIA	YEAR	COUNTRY	SAMPLE SIZE		CONTENTS OF CRITERIA	SURVIVAL (5-YEAR)	
			DDLTL	LDLTL		OS	RFS
Milan ¹⁰	1996	Italy	48	0	one ≤ 5 cm or no more than three ≤ 3 cm in diameter	85% (4-year)	92% (4-year)
UCSF ¹⁵	2001	USA	70	0	one ≤ 6,5 cm or ≤ three with the largest one ≤ 4,5 cm in diameter and an overall tumor diameter ≤ 8 cm	75,2%	--
CUN ¹⁹	2001	Spain	47	0	one ≤ 6 cm, or up to three ≤ 5 cm	79%	70% (3-year)
Mount-Sinai ²⁰	2002	USA	43	0	any number of lesions, each 5-7 cm in diameter	--	55%
Edmonton ²¹	2004	Canada	40	0	one < 7,5 cm or any number < 5 cm in diameter	82,9% (4-year)	76,8% (4-year)
Dallas ²²	2007	USA	1206	0	one ≤ 6 cm, or two to four each ≤ 5 cm in diameter	--	63,9%-64,6%
Tokyo ²³	2007	Japan	0	78	≤ five tumors not exceeding 5cm in diameter	75%	90%
Kyoto ²⁷	2007	Japan	0	125	≤ ten tumors all of which ≤ 5 cm in diameter and serum DCP ≤ 400 mAU/mL	86,7%	--
Kyushu University ²⁹	2007	Japan	0	60	≤ 5 cm in diameter and serum DCP ≤ 300 mAU/mL	68,6% (3-year)	--
Hangzhou ³⁰	2008	China	195	0	a) ≤ 8 cm in diameter, or b) >8 cm in diameter, histopathologic grade I or II and preoperative AFP ≤ 400 ng/mL	70,7%	62,4%
Asan ³²	2008	South Korea	0	221	≤ 5cm in diameter, ≤ six nodules and no gross vascular invasion	76,3%	--
Valencia ³⁴	2008	Spain	257	0	≤ three lesions, each ≤ 5 cm in diameter, total diameter ≤ 10 cm	67%	--
Shanghai ³⁵	2009	China	1074	4	one ≤ 9 cm in diameter, or no more than three nodules with the largest ≤ 5 cm in diameter, overall tumor diameter ≤ 9 cm without extrahepatic metastasis, lymph node or macrovascular invasion	78,1%	52,6%
Up-to-7 ¹⁴	2009	Italy	1404	121	sum of tumor number and size of the largest nodule ≤ 7 cm in diameter, without microvascular invasion	71,2%	--
TTV/AFP ³⁶	2009	Canada	6478	0	total tumor volume ≤ 115 cm ³ and AFP ≤ 400 ng/mL	--	--
AFP-TTD ³⁸	2012	Italy	158	0	total tumor diameter ≤ 8 cm and AFP ≤ 400 ng/mL	--	74,4%
Warsaw ³⁹	2014	Poland	121	0	beyond Milan, but within UCSF or up-to-7 criteria with AFP < 100 ng/mL	100%	100%
NLR-CRP ⁴¹	2014	South Korea	0	224	NLR < 6,0 or CRP < 1,0	--	--
NCKK ⁴⁵	2016	South Korea	0	280	negative PET/CT findings and total tumor size < 10 cm	85,2%	84%
Extended Toronto ⁴⁷	2016	Canada	210	0	no size-number limitation, no vascular invasion nor extrahepatic disease, no cancer-related symptoms, biopsy of the largest tumor not poorly differentiated	68%	30% (cumulative risk of re-currence)

Abbreviations: DDLT: deceased donor liver transplantation; LDLT: living donor liver transplantation; OS: overall survival; RFS: recurrence-free survival; UCSF: University of California, San Francisco; CUN: University Clinic of Navarra; DCP: des-Gamma-carboxy prothrombin; AFP: a-fetoprotein; TTV: total tumor volume; TTD: total tumor diameter; NLR: neutrophil-lymphocyte ratio; CRP: C-reactive protein; PET/CT: positron emission tomography/computed tomography.

Abbreviations: MELD: model for end-stage liver disease

CONCLUSIÓN

Liver transplantation has witnessed great progress over the past few decades. The Milan criteria, although proposed more than 20 years ago, still remain the gold-standard for patient selection. Nevertheless, many HCC patients that could possibly benefit from OLT with acceptable survival rates do not have access to the waiting list due to the restrictive character of those criteria. Scientists, researchers and surgeons from all over the world attempted to expand them with acceptable oncologic and survival outcomes, but it soon became apparent that the effort of expanding the OLT criteria further and further resembles the price of a metro ticket. Just as the longer distance you travel, the more you must pay for the ticket, similarly the

higher the acceptable tumor diameter, the higher the recurrence rates. On the other hand, expanding the donor liver pool has been tried out by implementing grafts from living, non-heart beating, steatotic, elderly, HCV-infected donors or even split livers, but more research is needed so as to achieve optimal outcomes, as with the conventional brain dead donors. As in many aspects of medicine, the future of OLT relies on molecular markers, which could be utilized in an effort to effectively predict HCC recurrence after liver transplantation.

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BIBLIOGRAPHIC REFERENCES

1. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 2007;132:2557–76 [PMID: 17570226 DOI: 10.1053/j.gastro.2007.04.061]
2. Tejada-Maldonado J, Garcia-Juarez I, Aguirre-Valadez J, Gonzalez-Aguirre A, Vilatoba-Chapa M, Armengol-Alonso A, Escobar-Penagos F, Torre A, Sanchez-Avila JF, Carrillo-Perez DL. Diagnosis and treatment of hepatocellular carcinoma: An update. *World J Hepatol* 2015;7:362–76 [PMID: 25848464 DOI: 10.4254/wjh.v7.i3.362]
3. Sherman M. Epidemiology of hepatocellular carcinoma. *Oncology* 2010;78 Suppl 1:7–10 [PMID: 20616577 DOI: 10.1159/000315223]
4. Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, Liang DC, Shau WY, Chen DS. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med* 1997;336:1855–9 [PMID: 9197213 DOI: 10.1056/NEJM199706263362602]
5. El-Serag HB, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go? *Hepatology* 2014;60:1767–75 [PMID: 24839253 DOI: 10.1002/hep.27222]
6. Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, Nakajima Y, Ohnishi K. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer* 1985;56:918–28 [PMID: 2990661]
7. Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso M del C, Sala M, Bru C, Rodes J, Bruix J. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 1999;29:62–7 [PMID: 9862851 DOI: 10.1002/hep.510290145]
8. Cabibbo G, Enea M, Attanasio M, Bruix J, Craxi A, Camma C. A meta-analysis of survival rates of untreated patients in randomized clinical trials of hepatocellular carcinoma. *Hepatology* 2010;51:1274–83 [PMID: 20112254 DOI: 10.1002/hep.23485]
9. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012;56:908–43 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]
10. 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;334:693–9 [PMID: 8594428 DOI: 10.1056/NEJM199603143341104]
11. Bismuth H, Chiche L, Adam R, Castaing D, Diamond T, Dennison A. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. *Ann Surg* 1993;218:145–51 [PMID: 8393649]
12. Bismuth H, Majno PE, Adam R. Liver transplantation for hepatocellular carcinoma. *Semin Liver Dis* 1999;19:311–22 [PMID: 10518310 DOI: 10.1055/s-2007-1007120]
13. Mazzaferro V, Bhoori S, Sposito C, Bongini M, Langer M, Miceli R, Mariani L. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2011;17 Suppl 2:S44–57 [PMID: 21695773 DOI: 10.1002/lt.22365]
14. 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]
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;33:1394–403 [PMID: 11391528 DOI: 10.1053/jhep.2001.24563]
16. Yao FY, Xiao L, Bass NM, Kerlan R, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging. *Am J Transplant* 2007;7:2587–96 [PMID: 17868066 DOI: 10.1111/j.1600-6143.2007.01965.x]
17. Xu X, Lu D, Ling Q, Wei X, Wu J, Zhou L, Yan S, Wu L, Geng L, Ke Q, Gao F, Tu Z, Wang W, Zhang M, Shen Y, Xie H, Jiang W, Wang H, Zheng S. Liver transplantation for hepatocellular carcinoma beyond the Milan criteria. *Gut* 2016;65:1035–41 [PMID: 25804634 DOI: 10.1136/gutjnl-2014-308513]
18. Marsh JW, Dvorchik I, Bonham CA, Iwatsuki S. Is the pathologic TNM staging system for patients with hepatoma predictive of outcome? *Cancer* 2000;88:538–43 [PMID: 10649244]
19. Herrero JI, Sangro B, Quiroga J, Pardo F, Herraiz M, Cienfuegos JA, Prieto J. Influence of tumor characteristics on the outcome of liver transplantation among patients with liver cirrhosis and hepatocellular carcinoma. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2001;7:631–6 [PMID: 11460231 DOI: 10.1053/jlts.2001.25458]
20. Roayaie S, Frischer JS, Emre SH, Fishbein TM, Sheiner PA, Sung M, Miller CM, Schwartz ME. Long-term results with multimodal adjuvant therapy and liver transplantation for the treatment of hepatocellular carcinomas larger than 5 centimeters. *Ann Surg* 2002;235:533–9 [PMID: 11923610]
21. Kneteman NM, Oberholzer J, Al Saghier M, Meeberg GA, Blitz M, Ma MM, Wong WWS, Gutfreund K, Mason AL, Jewell LD, Shapiro AMJ, Bain VG, Bigam DL. Sirolimus-based immunosuppression for liver transplantation in the presence of extended criteria for hepatocellular carcinoma. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2004;10:1301–11 [PMID: 15376305 DOI: 10.1002/lt.20237]
22. Onaca N, Davis GL, Goldstein RM, Jennings LW, Klintmalm GB. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma: a report from the International Registry of Hepatic Tumors in Liver Transplantation. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2007;13:391–9 [PMID: 17318865 DOI: 10.1002/lt.21095]
23. Sugawara Y, Tamura S, Makuuchi M. Living donor liver transplantation for hepatocellular carcinoma: Tokyo University series. *Dig Dis* 2007;25:310–2 [PMID: 17960065 DOI: 10.1159/000106910]
24. Togashi J, Akamastu N, Kokudo N. Living donor liver transplantation for hepatocellular carcinoma at the University of Tokyo Hospital. *Hepatobiliary Surg Nutr* 2016;5:399–407 [PMID: 27826554 DOI: 10.21037/hbsn.2016.08.05]
25. Shindoh J, Sugawara Y, Nagata R, Kaneko J, Tamura S, Aoki T, Sakamoto Y, Hasegawa K, Tanaka T, Kokudo N. Evaluation methods for pretransplant oncologic markers and their prognostic impacts in patient undergoing living donor liver transplantation for hepatocellular carcinoma. *Transpl Int* 2014;27:391–8 [PMID: 24472068 DOI: 10.1111/tri.12274]
26. Liebman HA, Furie BC, Tong MJ, Blanchard RA, Lo KJ, Lee SD, Coleman MS, Furie B. Des-gamma-carboxy (abnormal) prothrombin as a serum marker of primary hepatocellular carcinoma. *N Engl J Med* 1984;310:1427–31 [PMID: 6201741 DOI: 10.1056/NEJM198405313102204]
27. Ito T, Takada Y, Ueda M, Haga H, Maetani Y, Oike F, Ogawa K, Sakamoto S, Ogura Y, Egawa H, Tanaka K, Uemoto S. Expansion of selection criteria for patients with hepatocellular carcinoma in living donor liver transplantation. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2007;13:1637–44 [PMID: 18044766 DOI: 10.1002/lt.21281]
28. Kaido T, Ogawa K, Mori A, Fujimoto Y, Ito T, Tomiyama K, Takada Y, Uemoto S. Usefulness of the Kyoto criteria as expanded selection criteria for liver transplantation for hepatocellular carcinoma. *Surgery* 2013;154:1053–60 [PMID: 24074704 DOI: 10.1016/j.surg.2013.04.056]
29. Soejima Y, Taketomi A, Yoshizumi T, Uchiyama H, Aishima S, Terashi T, Shimada M, Maehara Y. Extended indication for living donor liver transplantation in patients with hepatocellular carcinoma. *Transplantation* 2007;83:893–9 [PMID: 17460559 DOI: 10.1097/01.tp.0000259015.46798.ec]
30. Zheng S-S, Xu X, Wu J, Chen J, Wang W-L, Zhang M, Liang T-B, Wu L-M. Liver transplantation for hepatocellular carcinoma: Hangzhou experiences. *Transplantation* 2008;85:1726–32 [PMID: 18580463 DOI: 10.1097/TP.0b013e31816b67e4]
31. Xiao G-Q, Yang J-Y, Yan L-N. Combined Hangzhou criteria with neutrophil-lymphocyte ratio is superior to other criteria in selecting liver transplantation candidates with HBV-related hepatocellular carcinoma. *Hepatobiliary Pancreat Dis Int* 2015;14:588–95 [PMID: 26663006]
32. Lee S-G, Hwang S, Moon D-B, Ahn C-S, Kim K-H, Sung K-B, Ko G-Y, Park K-M, Ha T-Y, Song G-W. Expanded indication criteria of living donor liver transplantation for hepatocellular carcinoma at one large-volume center. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2008;14:935–45 [PMID: 18581465 DOI: 10.1002/lt.21445]
33. Mejia GA, Gomez MA, Serrano J, Garcia I, Tamayo MJ, Pareja F, Sousa JM, Pascacio JM, Gavilan F, Castell J, Vargas B, Bernardos A. Correlation between the radiologic and histologic size of hepatocellular carcinoma in patients eligible for liver transplantation. *Transplant Proc* 2006;38:1394–5 [PMID: 16797313 DOI: 10.1016/j.transproceed.2006.02.064]
34. Silva M, Moya A, Berenguer M, Sanjuan F, Lopez-Andujar R, Pareja E, Torres-Quevedo R, Aguilera V, Montalva E, De Juan M, Mattos A, Prieto M, Mir J. Expanded criteria for liver transplantation in patients with cirrhosis and hepatocellular carcinoma. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2008;14:1449–60 [PMID: 18825681 DOI: 10.1002/lt.21576]
35. Fan J, Yang G-S, Fu Z-R, Peng Z-H, Xia Q, Peng C-H, Qian J-M, Zhou J, Xu Y, Qiu S-J, Zhong L, Zhou G-W, Zhang J-J. Liver transplantation outcomes in 1,078 hepatocellular carcinoma patients: a multi-center experience in Shanghai, China. *J Cancer Res Clin Oncol* 2009;135:1403–12 [PMID: 19381688 DOI: 10.1007/s00432-009-0584-6]
36. Toso C, Asthana S, Bigam DL, Shapiro AMJ, Kneteman NM. Reassessing selection criteria prior to liver transplantation for hepatocellular carcinoma utilizing the Scientific Registry of Transplant Recipients database. *Hepatology* 2009;49:832–8 [PMID: 19152426 DOI: 10.1002/hep.22693]
37. Toso C, Meeberg G, Hernandez-Alejandro R, Dufour J-F, Marotta P, Majno P, Kneteman NM. Total tumor volume and alpha-fetoprotein for selection of transplant candidates with hepatocellular carcinoma: A prospective validation. *Hepatology* 2015;62:158–65 [PMID: 25777590 DOI: 10.1002/hep.27787]
38. Lai Q, Avolio AW, Manzia TM, Sorge R, Agnes S, Tisone G, Berloco PB, Rossi M. Combination of biological and morphological parameters for the selection of patients with hepatocellular carcinoma waiting for liver transplantation. *Clin Transplant* 2012;26:E125-31 [PMID: 22192083 DOI: 10.1111/j.1399-0012.2011.01572.x]
39. Grat M, Kornasiewicz O, Lewandowski Z, Holowko W, Grat K, Kobryn K, Patkowski W, Zieniewicz K, Krawczyk M. Combination of morphologic criteria and alpha-fetoprotein in selection of patients with hepatocellular carcinoma for liver transplantation minimizes the problem of posttransplant tumor recurrence. *World J Surg* 2014;38:2698–707 [PMID: 24858191 DOI: 10.1007/s00268-014-2647-3]
40. Grat M, Wronka KM, Stypulkowski J, Bik E, Krasnodebski M, Masior L, Lewandowski Z, Grat K, Patkowski W, Krawczyk M. The Warsaw Proposal for the Use of Extended Selection Criteria in Liver Transplantation for Hepatocellular Cancer. *Ann Surg Oncol* 2017;24:526–34 [PMID: 27531306 DOI: 10.1245/s10434-016-5500-0]
41. Na GH, Kim DG, Han JH, Kim EY, Lee SH, Hong TH, You YK. Inflammatory markers as selection criteria of hepatocellular carcinoma in living-donor liver transplantation. *World J Gastroenterol* 2014;20:6594–601 [PMID: 24914382 DOI: 10.3748/wjg.v20.i21.6594]
42. Hatano E, Ikai I, Higashi T, Teramukai S, Torizuka T, Saga T, Fujii H, Shimahara Y. Preoperative positron emission tomography with fluorine-18-fluorodeoxyglucose is predictive of prognosis in patients with hepatocellular carcinoma after resection. *World J Surg* 2006;30:1736–41 [PMID: 16850145 DOI: 10.1007/s00268-005-0791-5]
43. Lin C-Y, Chen J-H, Liang J-A, Lin C-C, Jeng L-B, Kao C-H. 18F-FDG PET or PET/CT for detecting extrahepatic metastases or recurrent hepatocellular carcinoma: a systematic review and meta-analysis. *Eur J Radiol* 2012;81:2417–22 [PMID: 21899970 DOI: 10.1016/j.ejrad.2011.08.004]
44. Lee SD, Kim SH, Kim S-K, Kim Y-K, Park S-J. Clinical Impact of 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Living Donor Liver Transplantation for Advanced Hepatocellular Carcinoma. *Transplantation* 2015;99:2142–9 [PMID: 25905981 DOI: 10.1097/TP.0000000000000719]
45. Lee SD, Lee B, Kim SH, Joo J, Kim S-K, Kim Y-K, Park S-J. Proposal of new expanded selection criteria using total tumor size and (18F)-fluorodeoxyglucose - positron emission tomography/computed tomography for living donor liver transplantation in patients with hepatocellular carcinoma: The National Cancer Center Korea criteria. *World J Transplant* 2016;6:411–22 [PMID: 27358787 DOI: 10.5500/wjt.v6.i2.411]

46. DuBay D, Sandroussi C, Sandhu L, Cleary S, Guba M, Cattral MS, McGilvray I, Ghanekar A, Selzner M, Greig PD, Grant DR. Liver transplantation for advanced hepatocellular carcinoma using poor tumor differentiation on biopsy as an exclusion criterion. *Ann Surg* 2011;253:166–72 [PMID: 21294289]
47. Sapisochin G, Goldaracena N, Laurence JM, Dib M, Barbas A, Ghanekar A, Cleary SP, Lilly L, Cattral MS, Marquez M, Selzner M, Renner E, Selzner N, McGilvray ID, Greig PD, Grant DR. The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: A prospective validation study. *Hepatology* 2016;64:2077–88 [PMID: 27178646 DOI: 10.1002/hep.28643]
48. Yao FY, Bass NM, Nikolai B, Merriman R, Davern TJ, Kerlan R, Ascher NL, Roberts JP. A follow-up analysis of the pattern and predictors of dropout from the waiting list for liver transplantation in patients with hepatocellular carcinoma: implications for the current organ allocation policy. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2003;9:684–92 [PMID: 12827553 DOI: 10.1053/jlts.2003.50147]
49. Majno P, Lencioni R, Mornex F, Girard N, Poon RT, Cherqui D. Is the treatment of hepatocellular carcinoma on the waiting list necessary? *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2011;17 Suppl 2:S98–108 [PMID: 21954097 DOI: 10.1002/lt.22391]
50. 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;19:7515–30 [PMID: 24282343 DOI: 10.3748/wjg.v19.i43.7515]
51. Chapman WC, Garcia-Aroz S, Vachharajani N, Fowler K, Saad N, Lin Y, Wellen J, Tan B, Khan AS, Majella Doyle MB. Liver Transplantation for Advanced Hepatocellular Carcinoma after Downstaging Without Up-Front Stage Restrictions. *J Am Coll Surg* 2017; [PMID: 28069527 DOI: 10.1016/j.jamcollsurg.2016.12.020]
52. Parikh ND, Waljee AK, Singal AG. Downstaging hepatocellular carcinoma: A systematic review and pooled analysis. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2015;21:1142–52 [PMID: 25981135 DOI: 10.1002/lt.24169]
53. Barr ML, Belghiti J, Villamil FG, Pomfret EA, Sutherland DS, Gruessner RW, Langnas AN, Delmonico FL. A report of the Vancouver Forum on the care of the live organ donor: lung, liver, pancreas, and intestine data and medical guidelines. *Transplantation* 2006;81:1373–85 [PMID: 16732172 DOI: 10.1097/01.tp.0000216825.56841.cd]
54. Cheah YL, Simpson MA, Pomposelli JJ, Pomfret EA. Incidence of death and potentially life-threatening near-miss events in living donor hepatic lobectomy: a world-wide survey. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2013;19:499–506 [PMID: 23172840 DOI: 10.1002/lt.23575]
55. Ghobrial RM, Freise CE, Trotter JF, Tong L, Ojo AO, Fair JH, Fisher RA, Emond JC, Koffron AJ, Pruett TL, Olthoff KM. Donor morbidity after living donation for liver transplantation. *Gastroenterology* 2008;135:468–76 [PMID: 18505689 DOI: 10.1053/j.gastro.2008.04.018]
56. Abecassis MM, Fisher RA, Olthoff KM, Freise CE, Rodrigo DR, Samstein B, Kam I, Merion RM. Complications of living donor hepatic lobectomy—a comprehensive report. *Am J Transplant* 2012;12:1208–17 [PMID: 22335782 DOI: 10.1111/j.1600-6143.2011.03972.x]
57. Sapisochin G, Goldaracena N, Laurence JM, Levy GA, Grant DR, Cattral MS. Right lobe living-donor hepatectomy—the Toronto approach, tips and tricks. *Hepatobiliary Surg Nutr* 2016;5:118–26 [PMID: 27115005 DOI: 10.3978/j.issn.2304-3881.2015.07.03]
58. de Villa V, Lo CM. Liver transplantation for hepatocellular carcinoma in Asia. *Oncologist* 2007;12:1321–31 [PMID: 18055852 DOI: 10.1634/theoncologist.12-11-1321]
59. Grant RC, Sandhu L, Dixon PR, Greig PD, Grant DR, McGilvray ID. Living vs. deceased donor liver transplantation for hepatocellular carcinoma: a systematic review and meta-analysis. *Clin Transplant* 2013;27:140–7 [PMID: 23157398 DOI: 10.1111/ctr.12031]
60. Sapisochin G, Bruix J. Liver transplantation for hepatocellular carcinoma: outcomes and novel surgical approaches. *Nat Rev Gastroenterol Hepatol* 2017; [PMID: 28053342 DOI: 10.1038/nrgastro.2016.193]
61. Busuttil RW, Tanaka K. The utility of marginal donors in liver transplantation. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2003;9:651–63 [PMID: 12827549 DOI: 10.1053/jlts.2003.50105]
62. Emre S, Schwartz ME, Altaca G, Sethi P, Fiel MI, Guy SR, Kelly DM, Sebastian A, Fisher A, Eickmeyer D, Sheiner PA, Miller CM. Safe use of hepatic allografts from donors older than 70 years. *Transplantation* 1996;62:62–5 [PMID: 8693547]
63. McCormack L, Dutkowski P, El-Badry AM, Clavien P-A. Liver transplantation using fatty livers: always feasible? *J Hepatol* 2011;54:1055–62 [PMID: 21145846 DOI: 10.1016/j.jhep.2010.11.004]
64. Renz JF, Yersiz H, Reichert PR, Hisatake GM, Farmer DG, Emond JC, Busuttil RW. Split-liver transplantation: a review. *Am J Transplant* 2003;3:1323–35 [PMID: 14525591]
65. Fondevila C. A bridge too far: We have not overstepped the line for extended deceased donors. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2014;20 Suppl 2:S9–13 [PMID: 25220866 DOI: 10.1002/lt.24000]
66. Coilly A, Samuel D. Pros and Cons: Usage of organs from donors infected with hepatitis C virus - Revision in the direct-acting antiviral era. *J Hepatol* 2016;64:226–31 [PMID: 26375245 DOI: 10.1016/j.jhep.2015.09.002]
67. Shi J-H, Huitfeldt HS, Suo Z-H, Line P-D. Growth of hepatocellular carcinoma in the regenerating liver. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2011;17:866–74 [PMID: 21542129 DOI: 10.1002/lt.22325]
68. Moussaoui D, Toso C, Nowacka A, McLin VA, Bednarkiewicz M, Andres A, Berney T, Majno P, Wildhaber BE. Early complications after liver transplantation in children and adults: Are split grafts equal to each other and equal to whole livers? *Pediatr Transplant* 2017; [PMID: 28261944 DOI: 10.1111/petr.12908]
69. Monbaliu D, Pirenne J, Talbot D. Liver transplantation using Donation after Cardiac Death donors. *J Hepatol* 2012;56:474–85 [PMID: 21782762 DOI: 10.1016/j.jhep.2011.07.004]
70. Kootstra G, Daemen JH, Oomen AP. Categories of non-heart-beating donors. *Transplant Proc* 1995;27:2893–4 [PMID: 7482956]
71. Fondevila C, Hessheimer AJ, Ruiz A, Calatayud D, Ferrer J, Charco R, Fuster J, Navasa M, Rimola A, Taura P, Gines P, Manyalich M, Garcia-Valdecasas JC. Liver transplant using donors after unexpected cardiac death: novel preservation protocol and acceptance criteria. *Am J Transplant* 2007;7:1849–55 [PMID: 17564639 DOI: 10.1111/j.1600-6143.2007.01846.x]
72. Man K, Ng KT, Lo CM, Ho JW, Sun BS, Sun CK, Lee TK, Poon RTP, Fan ST. Ischemia-reperfusion of small liver remnant promotes liver tumor growth and metastases—activation of cell invasion and migration pathways. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2007;13:1669–77 [PMID: 18044786 DOI: 10.1002/lt.21193]
73. Mathur AK, Heimbach J, Steffek DE, Sonnenday CJ, Goodrich NP, Merion RM. Donation after cardiac death liver transplantation: predictors of outcome. *Am J Transplant* 2010;10:2512–9 [PMID: 20977642 DOI: 10.1111/j.1600-6143.2010.03293.x]
74. Righi E, Londero A, Carnelutti A, Baccarani U, Bassetti M. Impact of new treatment options for hepatitis C virus infection in liver transplantation. *World J Gastroenterol* 2015;21:10760–75 [PMID: 26478668 DOI: 10.3748/wjg.v21.i38.10760]
75. Reig M, Marino Z, Perello C, Inarrairaegui M, Ribeiro A, Lens S, Diaz A, Vilana R, Darnell A, Varela M, Sangro B, Calleja JL, Forns X, Bruix J. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. *J Hepatol* 2016;65:719–26 [PMID: 27084592 DOI: 10.1016/j.jhep.2016.04.008]
76. Kulik L, Abecassis M. Living donor liver transplantation for hepatocellular carcinoma. *Gastroenterology* 2004;127:S277–82 [PMID: 15508095]
77. Pang TC, Lam VW. Surgical management of hepatocellular carcinoma. *World J Hepatol* 2015;7:245–52 [PMID: 25729479 DOI: 10.4254/wjh.v7.i2.245]
78. Lue A, Solanas E, Baptista P, Lorente S, Araiz JJ, Garcia-Gil A, Serrano MT. How important is donor age in liver transplantation? *World J Gastroenterol* 2016;22:4966–76 [PMID: 27275089 DOI: 10.3748/wjg.v22.i21.4966]
79. Clavien P-A, Lesurtel M, Bossuyt PMM, Gores GJ, Langer B, Perrier A. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol* 2012;13:e11–22 [PMID: 22047762 DOI: 10.1016/S1470-2045(11)70175-9]
80. Kornberg A, Kupper B, Tannapfel A, Buchler P, Krause B, Witt U, Gottschild D, Friess H. Patients with non-¹⁸F-fluorodeoxyglucose-avid advanced hepatocellular carcinoma on clinical staging may achieve long-term recurrence-free survival after liver transplantation. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2012;18:53–61 [PMID: 21850692 DOI: 10.1002/lt.22416]
81. Koike Y, Shiratori Y, Sato S, Obi S, Teratani T, Imamura M, Yoshida H, Shiina S, Omata M. Des-gamma-carboxy prothrombin as a useful predisposing factor for the development of portal venous invasion in patients with hepatocellular carcinoma: a prospective analysis of 227 patients. *Cancer* 2001;91:561–9 [PMID: 11169939]

82. Suehiro T, Matsumata T, Itasaka H, Taketomi A, Yamamoto K, Sugimachi K. Des-gamma-carboxy prothrombin and proliferative activity of hepatocellular carcinoma. *Surgery* 1995;117:682-91 [PMID: 7539944]
83. Okuda H, Nakanishi T, Takatsu K, Saito A, Hayashi N, Takasaki K, Takenami K, Yamamoto M, Nakano M. Serum levels of des-gamma-carboxy prothrombin measured using the revised enzyme immunoassay kit with increased sensitivity in relation to clinicopathologic features of solitary hepatocellular carcinoma. *Cancer* 2000;88:544-9 [PMID: 10649245]
84. Fujiki M, Takada Y, Ogura Y, Oike F, Kaido T, Teramukai S, Uemoto S. Significance of des-gamma-carboxy prothrombin in selection criteria for living donor liver transplantation for hepatocellular carcinoma. *Am J Transplant* 2009;9:2362-71 [PMID: 19656125 DOI: 10.1111/j.1600-6143.2009.02783.x]
85. Todo S, Furukawa H, Tada M. Extending indication: role of living donor liver transplantation for hepatocellular carcinoma. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2007;13:548-54 [PMID: 17969069 DOI: 10.1002/lt.21334]
86. Feng J, Wu J, Zhu R, Feng D, Yu L, Zhang Y, Bu D, Li C, Zhou Y, Si L, Liu Y, Liang Z, Xu J, Wu T. Simple Risk Score for Prediction of Early Recurrence of Hepatocellular Carcinoma within the Milan Criteria after Orthotopic Liver

- Transplantation. *Sci. Rep.* 2017;7 [PMID: 28276470 DOI: 10.1038/srep44036]
87. Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002;420:860-7 [PMID: 12490959 DOI: 10.1038/nature01322]
88. Halazun KJ, Hardy MA, Rana AA, Woodland DC 4th, Luyten EJ, Mahadev S, Witkowski P, Siegel AB, Brown RSJ, Emond JC. Negative impact of neutrophil-lymphocyte ratio on outcome after liver transplantation for hepatocellular carcinoma. *Ann Surg* 2009;250:141-51 [PMID: 19561458 DOI: 10.1097/SLA.0b013e3181a77e59]
89. Bertuzzo VR, Cescon M, Ravaoli M, Grazi GL, Ercolani G, Del Gaudio M, Cucchetti A, D'Errico-Grigioni A, Golfieri R, Pinna AD. Analysis of factors affecting recurrence of hepatocellular carcinoma after liver transplantation with a special focus on inflammation markers. *Transplantation* 2011;91:1279-85 [PMID: 21617590 DOI: 10.1097/TP.0b013e3182187cf0]
90. An HJ, Jang JW, Bae SH, Choi JY, Yoon SK, Lee MA, You YK, Kim DG, Jung ES. Serum C-reactive protein is a useful biomarker for predicting outcomes after liver transplantation in patients with hepatocellular carcinoma. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc* 2012;18:1406-14 [PMID: 22821639 DOI: 10.1002/lt.23512]

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