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TOPIC HIGHLIGHT

2016 Hepatocellular Carcinoma: Global view

Contribution of alpha-fetoprotein in liver transplantation for hepatocellular carcinoma

Bérénice Charrière, Charlotte Maulat, Bertrand Suc, Fabrice Muscari

Bérénice Charrière, Charlotte Maulat, Bertrand Suc, Fabrice Muscari, Department of Visceral Surgery, Toulouse-Rangueil University Hospital, 31059 Toulouse, France

Fabrice Muscari, Service de Chirurgie Digestive, CHU Toulouse Rangueil, 31059 Toulouse, France

Author contributions: Charrière B, Maulat C and Muscari F performed the research and wrote the paper; Suc B revised the manuscript for important intellectual content.

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Correspondence to: Fabrice Muscari, Professor, Service de Chirurgie Digestive, CHU Toulouse Rangueil, 1 Avenue du Pr. Jean Poulhès, Cedex 9, 31059 Toulouse, France. muscari.f@chu-toulouse.fr
Telephone: +33-561-322088
Fax: +33-561-322936

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Abstract

Alpha-fetoprotein (AFP) is the main tumor biomarker available for the management of hepatocellular carcinoma (HCC). Although it is neither a good screening test nor an accurate diagnostic tool for HCC, it seems to be a possible prognostic marker. However, its contribution in liver transplantation for HCC has not been fully determined, although its use to predict recurrence after liver transplantation has been underlined by international societies. In an era of organ shortages, it could also have a key role in the selection of patients eligible for liver transplantation. Yet unanswered questions remain. First, the cut-off value of serum AFP above which liver transplantation should not be performed is still a subject of debate. We show that a concentration of 1000 ng/mL could be an exclusion criterion, whereas values of < 15 ng/mL indicate patients with an excellent prognosis whatever the size and number of tumors. Monitoring the dynamics of AFP could also prove useful. However, evidence is lacking regarding the values that should be used. Today, the real input of AFP seems to be its integration into new criteria to select patients eligible for a liver transplantation. These recent tools have associated AFP values with morphological criteria, thus refining pre-existing criteria, such as Milan, University of California, San Francisco, or "up-to-seven". We provide a review of the different criteria submitted within the past years. Finally, AFP can be used to monitor recurrence after transplantation, although there is little evidence to support this claim. Future challenges will be to draft new international guidelines to implement the use of AFP as a selection tool, and to determine a clear cut-off value above which liver transplantation should not be performed.

Key words: Hepatocellular carcinoma; Downstaging; Alpha-fetoprotein; Liver transplantation; Selection criteria

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Core tip: Alpha-fetoprotein (AFP) is the main biomarker available for the management of hepatocellular carcinoma (HCC). Yet, its contribution in liver transplantation for HCC has not been fully determined. We discuss the interest of AFP as a prognostic factor to predict tumor recurrence after liver transplantation, and as a selection tool to assess the best candidates to receive a graft. We also provide an overview of the different ways that AFP could be included in decisional algorithms before liver transplantation, through its static and dynamic values.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the second most common cause of death from cancer worldwide. It is estimated to have caused nearly 745000 deaths in 2012[1]. It represents a frequent indication for liver transplantation (LT). Good results are now achieved by accurate selection of patients. The Milan criteria (MC) are considered as the reference by health systems worldwide and are currently used by the United Network for Organ Sharing[2-4]. The overall survival rates after LT for HCC range from 65% to 80% at 5 years for patients fulfilling these criteria[5-7]. As the incidence of HCC is currently rising, several teams have attempted to extend the selection criteria in order to treat more patients: *i.e.*, University of California, San Francisco (UCSF), "up-to-seven", or "5/5" criteria[8-11]. These criteria are all based on the number and the size of nodules, but other features can influence recurrence rate after LT. Among these, histopathologic findings, poor differentiation, and microvascular invasion are negative prognostic factors[12-14]. However, data on these are difficult to obtain before transplantation. Therefore, we need preoperative prognostic elements to help improve the selection of patients eligible for LT. Today, alpha-fetoprotein (AFP) is the main tumor biomarker available to manage HCC[15]. It has many advantages, as it is simple to use, relatively inexpensive, and is widely available. In this article, we discuss the contribution of AFP in LT in HCC. First we assess its value as a screening and diagnosing tool, then we focus on its prognostic relevance, and finally we analyze its interest for the selection of the best candidates to receive a graft.

AFP: WHAT IS IT?

AFP is a 67-kDa glycoprotein that is produced in early fetal life by the liver and by a variety of tumors including HCC, hepatoblastoma, and non-seminomatous germ-cell tumors of the ovary and testis (*e.g.,* yolk sac and embryonal carcinoma). Tumor cells synthesize fetal proteins because of the "de-differentiation" of adult hepatocytes[16]. During fetal life, AFP is synthesized at first by the yolk sac, then by the liver. By the end of the first trimester, the fetal liver produces nearly all of the AFP. Although synthesis is reduced markedly shortly after birth, small amounts of AFP continue to be produced during adulthood[17]. Normal concentrations of AFP in adult serum are $\leqslant$ 20 ng/mL. AFP can increase temporarily in cases of liver injury or regeneration, particularly after liver resection, during fulminant viral hepatitis, or chronic viral hepatitis[18,19]. Patients with chronic hepatitis or cirrhosis and persistently elevated AFP levels are at higher risk of developing HCC[20-22]. More than the AFP rate at a given time, it is the increased expression of AFP that suggests the presence of HCC[23].

Up to 20% of cases of HCC do not produce AFP[24]. For others, AFP can raise from normal to $\geqslant$ 100000 μg/L[25]. AFP concentrations do not differ if HCC is developed on a cirrhotic liver or not. Serum AFP levels increase by 20%-80% in patients with HCC and are strongly related to tumor aggressiveness[26-28]. Its concentrations are correlated with tumor size, microvascular invasion and poorly differentiated HCC[15,20,29,30]. However, the utility of AFP is restricted by the existence of non-AFP-secreting tumors[24].

AFP: A POOR MARKER FOR SCREENING AND DIAGNOSING HCC AMONG PATIENTS ON A LT-WAITING LIST

Use of AFP for HCC screening

Literature has shown that serum AFP (> 15 or 20 ng/mL) as a screening test for HCC had a sensitivity of between 39% and 64%, and a specificity of between 76% and 91%. The positive predictive value is estimated at between 9% and 33%[20,31-33].

The association of AFP with ultrasonography only improved the sensitivity by 6%-7% and the specificity by 2% compared to ultrasonography alone[31,34], while also increasing the cost of HCC screening[35].

These results clearly show that AFP is not a useful screening tool for HCC[36]. The first reason is that fluctuating levels of AFP in patients with cirrhosis can reflect flare-ups of HBV or HCV infection, or exacerbation of an underlying liver disease other than HCC development[7,37]. In addition, only a small proportion of tumors at an early stage (10%-20%) present with abnormal AFP serum levels[7].

Current guidelines from the American Association for the Study of Liver Disease and the European Association for the Study of the Liver (EASL) have stopped recommending the use of AFP anymore to screen for HCC in cirrhotic patients. Only ultrasonography must be performed every 6 mo[7,38].

AFP for the diagnosis of HCC

In a case-control study of 340 cirrhotic patients, Trevisani *et al*[39] have shown that AFP levels of > 20 ng/mL had a sensitivity of 60% and a specificity of 91% to diagnose HCC. At this threshold, 40% of all cases of HCC would be missed. An increase in this cut-off value would result in a lower rate of HCC detection whereas a lower cut-off value would increase the false-positive rate. These results demonstrate that AFP should not be used to diagnose HCC. Thus, AFP is no longer part of the diagnostic algorithm for HCC[7,38].

AFP: A PREDICTOR OF RECURRENCE AFTER LT

Although AFP is no longer used to diagnose HCC, several teams have shown that it could be a very interesting tool for prognosis[40,41].

Thus, it could prove useful when discussing LT. Shetty *et al*[42] in 2004, were among the first to suggest the potential prognostic usefulness of AFP when used specifically for patients who have received a liver graft. In their study, they have shown that elevated serum levels of AFP before LT were significantly associated with poorer recurrence-free survival and overall survival. In the following years, multiple studies have confirmed the prognostic role of AFP to predict outcomes after LT. Most of them are based on small cohorts of patients[28,43-47] and their main drawbacks are their retrospective designs. Yet all of them display the same tendency: Elevated AFP at the time of LT is associated with a worse prognosis after LT. Between 2008 and 2011, three large cohort studies that included thousands of patients, also showed the same pattern[48-50]. As a result, the EASL-EORTC advises on the prognostic relevance of AFP in their Clinical Practice Guidelines for the management of HCC[7]. Nevertheless, AFP alone is not sufficient to predict recurrence. Its interpretation must be associated with other demonstrated prognostic factors such as histopathologic findings, tumor differentiation, and microvascular invasion[12-14].

USE OF AFP TO SELECT LT CANDIDATES

Although the prognostic value of AFP seems well established today, one issue remains: How can we use AFP to improve the selection of LT candidates and ensure acceptable outcomes?

This question raises other issues: What cut-off value must we use to define an "elevated" level of AFP? Is it important to consider the evolution of AFP over time? Can AFP be included in an algorithm to help assess the best candidates for LT?

Defining a cut-off value for AFP

To this day, there is no clear consensus regarding the level of AFP above which a patient should not be a candidate for LT. The international consensus report regarding liver transplantation, published in 2012, mentions that "AFP concentration adds prognostic information in HCC patients and may be used for making decisions regarding transplantation"[4], but with a weak level of evidence. According to these recommendations, whatever the level of AFP, LT can be considered as long as a patient fits within the Milan, UCSF, "up-to-seven" or "5/5" criteria[2,8,11,51].

More than 20 studies have tried to define a cut-off value for pre-LT AFP, above which the prognosis would be too impaired to propose a LT. The main studies are reported Table 1. Several values have been studied, ranging from 15 ng/mL[52,53] to 1000 ng/mL[30,45,54-57]. Three reviews have also focused on the static values of AFP in an attempt to synthesize these various findings[58-60], but none have been designed as a meta-analysis and thus no clear conclusion could be drawn.

However, three values appear repeatedly in the different studies: 15 ng/mL, 400 ng/mL and 1000 ng/mL.

The value of 15 ng/mL is interesting because it could indicate a population with a very good prognosis, even for patients with HCC graded beyond the MC. Lai *et al*[52] and Berry *et al*[53] report almost identical conclusions regarding this 15 ng/mL cut-off point: Patients outside the MC but with AFP < 15 ng/mL and no other adverse prognostic factors have excellent outcomes after a LT. This suggests that, in some cases, AFP could be used to select people with excellent outcomes and who would have been unfairly excluded from receiving a LT because they exceeded the MC.

The value of 1000 ng/mL appears as a value that should exclude patients from receiving a LT, at least in the absence of downstaging. Yao *et al*[8], when defining UCSF criteria in 2001, had already pointed out that an AFP of > 1000 ng/mL was related to a worse outcome, but only in univariate analyses. Later, the same team published a study concluding that AFP > 1000 ng/mL was an independent predictor of vascular invasion and should be an exclusion criterion for LT[30]. According to their study, using this cut-off value could have led to the exclusion of 4.7% of patients from receiving a LT, while decreasing tumor recurrence by 20%. Other publications observed that an AFP > 1000 ng/mL was a predictor of recurrence after a LT[45,55,61]. In 2012, Duvoux *et al*[57] proposed a score that integrated AFP for the selection of patients eligible for LT. The value of 1000 ng/mL automatically led to the exclusion of these patients. In France, Duvoux's algorithm is currently in use and an AFP value of 1000 ng/mL is recognized as a limit over which a LT should not be performed. The UCSF team now applies a similar policy[62].

What about the values in between 15 and 1000 ng/mL? Several cut-off values have been studied over the last few years. The endpoints differ between studies: Some teams have studied the relationships between AFP and recurrence, whereas other have focused on the relationships between AFP and microvascular

Table 1 Main studies suggesting a cut-off value for α-fetoprotein when selecting candidates for liver transplantation

Ref.	Year	No. of patients	Country	Study design	AFP cut-off value	Endpoint
Yamashiki *et al*[43]	2004	93	United States	Prospective	100 ng/mL	Drop-out from list
Shetty *et al*[42]	2004	109	United States	Retrospective	300 ng/mL	Recurrence, death
Todo *et al*[54]	2007	653	Japan	Retrospective	200 ng/mL 1000 ng/mL	Recurrence
Parfitt *et al*[61]	2007	75	Canada	Retrospective	1000 ng/mL	Recurrence
Pérez-Saborido *et al*[44]	2007	95	Spain	Retrospective	200 ng/mL	Recurrence
Onaca *et al*[10]	2007	902	United States	Retrospective	200 ng/mL	Recurrence
Adler *et al*[86]	2008	226	Belgium	Retrospective	100 ng/mL	Recurrence
Zou *et al*[45]	2008	303	China	Retrospective	1000 ng/mL	Fatal recurrence
Ioannou *et al*[50]	2008	5028	United States	Retrospective	455 ng/mL	Death
Xu *et al*[46]	2009	97	China	Retrospective	400 ng/mL	Recurrence
Toso *et al*[49]	2009	6478	Canada	Retrospective	400 ng/mL	Death
Lao *et al*[55]	2009	124	United States	Prospective	1000 ng/mL	Recurrence
Xiao *et al*[87]	2009	224	China	Retrospective	800 ng/mL	Death
McHugh *et al*[47]	2010	101	United States	Retrospective	100 ng/mL	Recurrence, death
Levi *et al*[88]	2010	244	United States	Retrospective	100 ng/mL	Recurrence
Merani *et al*[66]	2011	6817	United States	Retrospective	400 ng/mL	Death
Lai *et al*[89]	2011	153	Italy	Retrospective	210 ng/mL	Recurrence
Mailey *et al*[48]	2011	2253	United States	Retrospective	400 ng/mL	Death
Muscari *et al*[28]	2012	122	France	Retrospective	500 ng/mL	Recurrence, death
Ciccarelli *et al*[65]	2012	137	Belgium	Retrospective	400 ng/mL	Recurrence
Wong *et al*[59]	2013	211	United States	Retrospective	400 ng/mL	Recurrence
Harimoto *et al*[90]	2013	167	Japan	Retrospective	300 ng/mL	Recurrence
Abdel-Wahab *et al*[68]	2013	170	Egypt	Retrospective	200 ng/mL	Recurrence, death
Grąt *et al*[67]	2014	121	Poland	Retrospective	100 ng/mL	Recurrence
Hameed *et al*[30]	2014	211	United States	Retrospective	1000 ng/mL	Microvascular invasion
Lee *et al*[91]	2014	69	South Korea	Retrospective	200 ng/mL	Recurrence
Grąt *et al*[92]	2016	146	Poland	Retrospective	100 ng/mL	Recurrence

AFP: Alpha-fetoprotein.

invasion, or AFP and drop-out rates from waiting lists. The most frequent cut-off value reported in the literature is 400 ng/mL. This has been reported by authors from various countries in Asia[63], Europe[64,65] and the United States[49,59,66]. It appears to be linked to recurrence but also to the risk of dropout while on a waiting list. However, it seems difficult to use the cut-off value of 400 ng/mL to directly exclude patients from a waiting list, because this value has been mostly studied as part of algorithms that include tumor volume, tumor size, the MC, and/or the UCSF-criteria. Moreover, many other cut-off values have been suggested, such as 100 ng/mL[47,57,67] and 200 ng/mL[10,68]. The level of evidence to define an optimal value is very weak and thus calls for further studies.

As to which AFP value should be considered, Merani *et al*[66] showed that only the last pre-transplant value of AFP independently predicted survival, unlike the AFP at the time of listing. Most of the studies cited above also used the last pre-transplant value of AFP to perform their analyses.

Evolution of AFP over time: A critical marker

Studies have tried to assess the impact of the dynamic behavior of AFP. They are presented Table 2. The first team to address this issue was Han *et al*[69] in 2007. Although focusing on only 47 patients, this Canadian study found out that the preoperative AFP slope was an independent prognostic factor for recurrence, with a cut-off at 50 ng per month. Later, Vibert *et al*[70] studied the outcomes of 153 patients in a monocentric French cohort, and concluded that a progression of AFP of > 15 ng per month was associated with decreased overall survival. Lai *et al*[52] in 2013, in a multicentric European study, obtained the same results. A fourth study proposed the cut-off value of 0.1 ng per day[71]. The main drawback of these four studies was the small number of data points used to determine the slope of AFP: Only two values were used by Vibert *et al*[70] (lowest and highest) and by Lai *et al*[52] (time of listing and time of LT). Han *et al*[69] used a median of 4 values (ranging from 2 to 11).

Other studies have focused on AFP dynamics, but with a different goal. They have evaluated the prognostic value of AFP evolution after loco-regional therapy. One of the first teams to address this question was Riaz *et al*[72] in 2009. They showed that a drop in AFP following loco-regional therapy was associated with better outcomes after LT. Bhat *et al*[73] used a logistic regression model to show that a decrease in AFP value after trans-arterial chemoembolization was significantly associated with better overall survival[73]. Wong *et al*[59] also obtained similar results. These studies enabled AFP to be part of the definition of a successful downstaging, along with radiological features. In fact, Yao *et al*[62] in California require that patients with an initial AFP > 1000 ng/mL have AFP decreased to < 500 ng/mL after loco-regional therapy, before undergoing LT. Similarly, in

Table 2 Studies focusing on dynamic values of α-fetoprotein before liver transplantation

Ref.	Year	No. of patients	AFP slope
Han *et al*[69]	2007	47	50 ng/mo
Vibert *et al*[70]	2010	153	15 ng/mo
Lai *et al*[52]	2013	422	15 ng/mo
Dumitra *et al*[71]	2013	92	0.1 ng/d

AFP: Alpha-fetoprotein.

France, the use of the Duvoux algorithm enables a patient with an AFP of > 1000 ng/mL to be back on the waiting list if AFP drops below this value[57]. Yet, to this day, the international recommendations only mention the number and size of viable tumors as criteria for successful downstaging[4]. The AFP concentrations before and after downstaging are just considered as giving "additional information" because evidence is not strong enough to enforce the wider use of AFP dynamics in the management of LT candidates. These recommendations date back from 2012 and they may evolve based on the recent studies mentioned above.

Designing new scores that integrate AFP: The end of the MC?

If AFP can be used to obtain additional information to select LT candidates, then it appears logical to integrate it into an algorithm, along with other prognostic factors. Since Mazzaferro's study in 1996[2], attempts have been made to improve the MC. Including AFP to create a new selection tool could be a key.

This idea arose as early as 2007, when a Korean team designed a score based on tumor size, number of tumors, and value of AFP in order to select the best candidates for living donor LT[56]. For each feature, the patient was awarded between 1 and 4 points. In this small study (n = 63), the different values of AFP used were < 20 ng/mL, 200 ng/mL, and 1000 ng/mL. According to the authors, this score allowed a slight expansion of the MC with comparable outcomes. Five years later, Duvoux *et al*[57] developed a very similar score. Their multicentric French study was based on a much larger cohort of patients (n = 492), and used the same three characteristics for the selection of patients: *i.e.*, tumor size, number, and AFP. However, the number of points awarded for each feature was different; as were the cut-off values for AFP: *i.e.,* 100 ng/mL and 1000 ng/mL. It is interesting to note that in this latter score, an AFP > 1000 ng/mL provided enough points for patients to be excluded directly from LT, whatever the size and number of tumors. This means that, according to this score, AFP overpowers the MC. In France, Duvoux *et al*[51]'s study precluded to a radical change in the allocation policy for LT: This score is now used to select candidates for LT. Patients exceeding the criteria are classed as having a temporary contra-indication as long as a downstaging is not successfully performed. A recent study by Varona *et al*[74] has confirmed the accuracy of this model for the prediction of recurrence and survival after a LT.

Other teams have come up with different scoring systems that include AFP when selecting LT candidates. The main ones are presented in Table 3. In 2008, a Chinese team designed the Hangzhou criteria[63], based on total tumor diameter, AFP, and histopathologic grade. The main issue with this score was the necessity for histopathologic evaluation prior to LT, which is not easy to obtain and may be inaccurate as it is based on a biopsy. Nevertheless, this work raised the idea of total tumor size, rather than maximum size of tumor, or number of tumors. Lai's team simplified the Hangzhou score and suggested using a score that featured only AFP and total tumor diameter (TTD), with a cut-off value at 400 ng/mL for AFP and 8 cm for TTD[64]. Various teams have developed slightly different scores, still using an AFP cut-off value of 400 ng/mL but replacing TTD with total tumor volume[49,75] or actual tumor volume[76]. More recently, a Korean team suggested that a combination of AFP and F-FDG PET data could be a very interesting selection tool[77]: A positive PET (cut-off at 1.10) and an AFP of > 200 ng/mL defined a group of patients with a high risk of recurrence and who should not be selected for LT. The main drawback of this study is the cost of F-FDG PET, but the authors point out the usefulness of PET to predict tumor aggressiveness, rather than sheer size and number.

Despite a few discrepancies, these studies share many common points: All of them agree that an AFP value of > 1000 ng/mL should lead to exclusion of these patients from receiving a LT; most suggest an association between AFP and morphological characteristics (size, number, and/or volume of tumors); and a few of these studies suggest the probable need for another marker for aggressiveness, such as histopathologic findings or PET.

MONITORING AFP AFTER LIVER TRANSPLANTATION: A WISE POLICY OR A WASTE OF TIME (AND MONEY)?

In the absence of HCC recurrence, AFP levels decrease to < 20 ng/mL within 2 mo post-transplantation[78]. Hepatocellular carcinoma recurs in 10%-20% of transplant recipients, despite careful patient selection[2,7,78-80]. There is no evidence-based recommendation to be applied after transplantation in order to promptly detect and treat HCC recurrence.

Because few recurrences after LT can benefit from curative treatment, this raises questions about the usefulness of active surveillance after LT[81,82]. Roberts[82] suggest that screening all patients for HCC recurrence after transplantation, using both imaging and serum biomarkers, is probably not cost effective. However, AFP monitoring, in itself, is not very costly and may be appropriate at regular intervals[83]. Yamashiki *et al*[78] proposed to measure AFP at monthly periods for the first two years after LT, to detect any HCC recurrence. When a cut-off level of 20 ng/mL was used, the sensitivity and

Table 3 Suggestions for new selection criteria for liver transplantation that integrate α-fetoprotein

Ref.	Year	No. of patients	Study design	Criteria	AFP cut-off values
Yang *et al*[56]	2007	63	Retrospective	AFP Tumor size Number of tumors	20 ng/mL, 200 ng/mL, 1000 ng/mL
Zheng *et al*[63]	2008	195	Retrospective	AFP Total tumor diameter Histopathologic grade	400 ng/mL
Lai *et al*[64]	2012	158	Retrospective	AFP Total tumor diameter	400 ng/mL
Duvoux *et al*[57]	2012	435	Prospective	AFP Tumor size Number of tumors	100 ng/mL, 1000 ng/mL
Kashkoush *et al*[76]	2014	115	Retrospective	AFP Actual tumor volume	400 ng/mL
Toso *et al*[75]	2015	233	Prospective	AFP Total tumor volume	400 ng/mL
Hong *et al*[77]	2015	123	Retrospective	AFP F-FDG PET positivity	200 ng/mL

AFP: Alpha-fetoprotein; F-FDG PET: F-fluorodeoxyglucose positron emission tomography.

specificity of AFP to detect HCC recurrence after liver transplantation were 67% and 100%, respectively[78]. Several other studies suggest that active surveillance with AFP should be performed, but the optimal frequency is not clear[83-85]. Since 2010, international guidelines state that post-transplant monitoring may be performed every 6 to 12 mo, using contrast-enhanced computed tomography or magnetic resonance imaging imaging in addition to AFP measurements[4].

CONCLUSION

Today, AFP is a key element to consider in the management of patients with HCC and who are eligible for LT. Although it does not contribute to screening or obtaining a diagnosis of HCC among patients on a LT waiting list, it can help predict the aggressiveness of the tumor and its risk of recurrence after LT.

The main usefulness of AFP regarding LT for HCC is its ability to assess the best LT candidates. It can be considered as an excellent selection criterion in association with the size and number of HCC nodules. This enables a reasonable enlargement of the MC while also guaranteeing satisfactory outcomes. Integrating an upper limit of 1000 ng/mL to the selection criteria would also allow exclusion of the few patients within the MC but who have a high risk of recurrence after LT. Furthermore, AFP can be used to monitor the evolution of HCC while on a waiting list, particularly in cases where there is downstaging.

Future challenges lie in the drafting of new international guidelines to implement the use of AFP as a selection tool, and to clarify the exact values that must be considered when using this biomarker in LT for HCC.

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