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EDITORIAL

Selection tool alpha-fetoprotein for patients waiting for liver transplantation: How to easily manage a fractal algorithm

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Abstract

Alpha-fetoprotein (AFP) behavior in patients with hepatocellular carcinoma (HCC) waiting for liver transplant (LT) represents a perfect biological example of a fractal model in which its progressive modification and possible future prediction of its values are very hard to capture. As a consequence, AFP represents a useful but poorly manageable tool to increase the ability to better select HCC patients waiting for LT. Trying to find a "fil-rouge" in the recent literature, no definitive answers can be done to several open questions: (1) the best AFP value to adopt; (2) the best cut-off measurement; and (3) the best way to comfortably capture the effective, time-related, fluctuations of this biological marker. More, structured and prospective, studies using serial determination of AFP values within and without the context of locoregional therapies are needed in order to find the "ideal" (static and dynamic) cut-off values allowing to respond to all the still open questions in this field of transplant oncology.

Key words: Alpha-fetoprotein; Hepatocellular cancer; Milan criteria; Recurrence; Drop-out

Core tip: Alpha-fetoprotein (AFP) behavior in patients with hepatocellular carcinoma waiting for liver transplant (LT) represents a perfect example of a fractal model. Consequently, AFP represents a useful but poorly manageable selection tool for patients waiting for LT. Looking at the recent literature, we can assume that: (1) last AFP value seem to be the best values to adopt; (2) different cut-offs may be adopted in the two different scenarios of Milan Criteria (MC) IN and MC OUT status; (3) AFP cut-off of 1000 ng/mL represent

a good compromise for MC-IN patients; and (4) no definitive conclusion has been reached in relation to MC-OUT patients.

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CHAOS THEORY AND BIOLOGICAL SCIENCES

Chaos is the science of surprise, of nonlinearity and of unpredictability, teaching us to expect the unexpected. Sciences are connected with predictable events such as chemical reactions, electricity, gravity, whilst the chaos theory concerns with non-linear processes such as weather, stock market and biological modifications. These last phenomena are typically described by fractal mathematics, a field of study created with the intent to capture the infinite complexity of nature (Figure 1).

The behavior of alpha-fetoprotein (AFP) in patients having hepatocellular carcinoma (HCC) awaiting for liver transplant (LT) represents a perfect biological example of a fractal model in which its progressive modification and possible future prediction of its values are very hard to capture[1].

AFP AND ITS PREDICTION OF HCC RECURRENCE: ROLE OF STATIC VALUES

During the last years, a growing number of studies has been focused on the predictive role of AFP for the diagnosis of tumor recurrence after LT[2]. AFP has been strongly connected with HCC biological behavior, commonly connecting its values with the grade of differentiation as well as the vascular invasiveness of the tumor[3].

As a confirmation of this renewed interest in relation to the role of AFP, the recently published EASL-EORTC guidelines suggest to investigate AFP modification as a clinical selection parameter of patients waiting for LT[4]. However, several questions still remain unsolved in relation to the clinical use of AFP measurements in daily practice, as clearly stated in a recent focused editorial[5]. Among them: (1) the best static value to adopt; (2) the best cut-off measurement; and (3) the best way to comfortably capture the effective, time-related, fluctuations of this biological marker.

Many authors focused on the last pre-transplant value of AFP as the best predictor of recurrence; the threshold level of 400 ng/mL was most frequently advanced.

A large United States experience including 6817 HCC patients listed for LT showed that patients having AFP values superior to 400 ng/mL at the moment of waiting-list inscription and then downstaged (using locoregional therapies) to AFP values $\leqslant$ 400 ng/mL immediately before LT showed better intent-to-treat survivals respect to the cases in which their values could not be reduced (3-year survivals: 81% *vs* 48%; $P < 0.001$); these downstaged patients had results comparable results to those patients having stable AFP values $\leqslant$ 400 ng/mL (74%; $P = 0.14$). In contrast to AFP at the moment of waiting-list inscription or to modifications of AFP, only last pre-transplant AFP independently predicted survival ($P < 0.001$)[6]. Another United States study proposed the combination total tumor volume inferior to 115 cm^3 and AFP inferior to 400 ng/mL and as a better tool for selecting patients with HCC, showing, 3 years after transplant, survivals inferior to 50% in patients exceeding this cut-off[7]. The Hangzhou group proposed in a study containing 195 patients to combine one of the two following items in order to obtain good tumor free survival rates: total HCC diameter inferior or equal to 8 cm; total HCC diameter superior to 8 cm contemporaneously having pathologic grade Ⅰ-Ⅱ and pre-LT AFP $\leqslant$ 400 ng/mL[8]. An Italian study showed that the combination of morphological and biological parameters (*e.g.*, total tumor diameter > 8 cm and AFP > 400 ng/mL) conferred scarce survivals: patients having the last AFP value > 400 ng/mL had an eight-times incremented risk of tumor recurrence after transplantation[9].

A monocentric Belgian study similarly identified the last AFP determination > 400 ng/mL as the most important independent predictor for tumor recurrence after LT (HR = 4.86; $P = 0.01$)[10]. The United Network for Organ Sharing region 6 experience showed that peak AFP value > 400 and AFP at LT > 400 ng/mL were connected with poor outcomes post-LT in patients previously treated with loco-regional treatment (LRT)[11].

Despite many analyses underlined the role of the last AFP measure > 400 ng/mL before LT as a predictive tool, several, greatly differing, cut-off values (100, 200, 210, 300, 1000 ng/mL) have been put forward in the recent literature. The unfollowing paragraph gives an overview of all these different findings published during the period 2009-2014.

A United States study including 101 patients showed that AFP > 100 ng/mL (OR = 5.0, $P = 0.006$) and tumor size (OR = 4.1, $P = 0.013$) were correlated with microvascular invasion and post-LT recurrence[12]. Another Polish study including 121 HCC patients confirmed the validity of 100 ng/mL as cut-off value in predicting the risk of post-LT recurrence in patients meeting San Francisco criteria or up-to-seven criteria[13]. An Egyptian study identified AFP value > 200 ng/mL as a predictive tool for HCC recurrence in 170 living donor LT (LDLT)[14]. An Italian study reported that a AFP cut-off measure of 210 ng/mL, significantly influenced 5-year survivals (23.3% *vs* 76.2%; $P < 0.0001$)[15]. A Japanese analysis of 167 LDLT patients identified a threshold measure of 300 ng/mL as predictor of HCC recurrence and poor prognosis[16]. Finally some studies identified

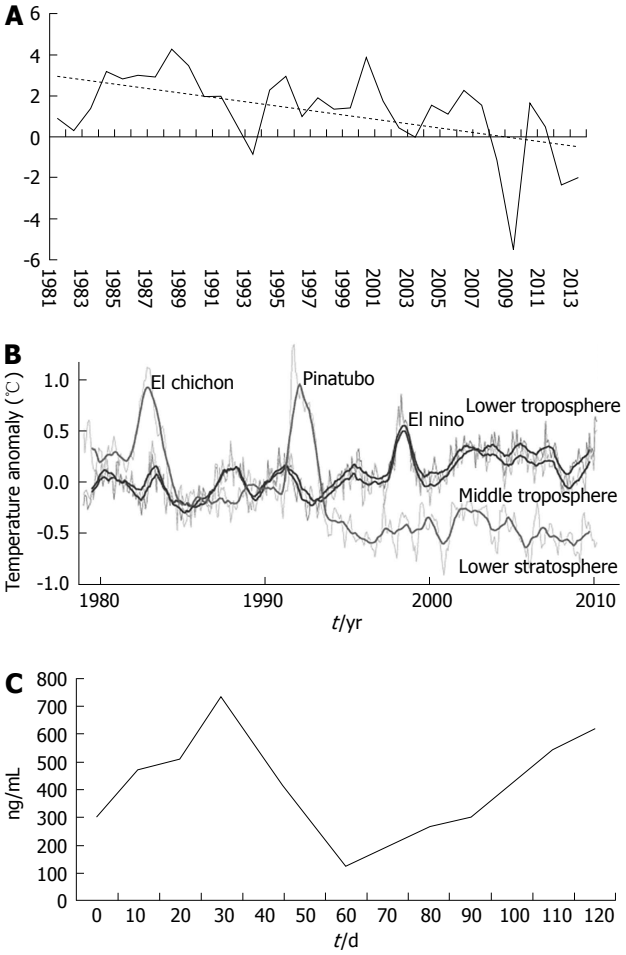

Figure 1 Some examples of systems with chaotic behaviour. A: Annual gross domestic product (GDP) growth of Italy in the last 35 years (%) (from: http://thenextrecession.wordpress.com/2013/08/05/greece-still-bust-spain-depressed-italy-paralysed/); B: Atmospheric temperature from 1979 to 2010, determined by NASA satellites (from: http://earthobservatory.nasa.gov/Features/GlobalWarming/images/msu_1978-2010.png); C: Hypothetical patients' alpha-fetoprotein fluctuation during his waiting list period before liver transplantation.

the value of 1000 ng/mL as significant.

The Seoul National University study including 63 LDLT patients proposed a score based on the following three different variables: (1) tumor size: ⩽ 3, 3.1-5, 5.1-6.5, ⩾ 6.5 cm; (2) tumor number: 1, 2-3, 4-5, ⩾ 6 nodules; and (3) AFP: ⩽ 20, 20.1-200, 200.1-1000, > 1000 ng/mL. According to the proposed score, an excellent stratification in relation to recurrence rates and patient survival could be achieved[17]. Another Chinese study in 303 patients similarly found AFP > 1000 ng/mL together with microvascular invasion and tumor size > 6.5 cm as risk factors for fatal recurrence after LT. Interestingly, dead due to tumor recurrence within one year after LT was 85.7% when all three risk factors were present, 37.8% when two factors, 13.6% when one factor and 6.7% when no risk factor were present[18].

A multicentric analysis from France (n = 435 cases) created a mathematical model based on the number of HCC lesions, tumor size and last AFP value. Interestingly, the authors found two different cut-off values in relation

Table 1 Recent articles focused on alpha-fetoprotein static values

Ref.	Year	*n*	Country	Cut-off value (ng/mL)
McHugh *et al*[12]	2010	101	United States	100
Grąt *et al*[13]	2014	121	Poland	100
Abdel-Wahab *et al*[14]	2013	170 (LDLT)	Egypt	200
Lai *et al*[15]	2011	153	Italy	210
Harimoto *et al*[16]	2013	167 (LDLT)	Japan	300
Merani *et al*[6]	2011	6817	United States	400
Toso *et al*[7]	2009	6478	United States	400
Zheng *et al*[8]	2008	195	China	400
Lai *et al*[9]	2012	158	Italy	400
Ciccarelli *et al*[10]	2012	137	Belgium	400
Wong *et al*[11]	2013	211	United States	400
Yang *et al*[17]	2007	63 (LDLT)	South Korea	1000
Zou *et al*[18]	2008	303	China	1000
Duvoux *et al*[19]	2012	435	France	1000
Hameed *et al*[20]	2014	211	United States	1000

LDLT: Living donor liver transplantation.

to the Milan Criteria (MC) status. When MC status was exceeded, patients experienced high or low 5-year recurrence rates when AFP measures were < 100 or > 1000 ng/mL (47.6% and 14.4%, respectively; P < 0.006). When patients meeting MC had AFP levels > 1000 ng/mL, showed high-risk for recurrence (37.1%; P < 0.001)[19]. An analysis from United States including 211 patients similarly showed that patients meeting MC with last pre-LT AFP > 1000 ng/mL showed a higher number of recurrences 5 years after transplant. An AFP level > 1000 ng/mL strongly predicted vascular invasion (OR = 6.8, P = 0.006), the most important risk factor for recurrence. Five-year recurrence-free survivals were 80.3% and 52.7% for patients meeting or exceeding the AFP threshold measure of 1000 ng/mL (P = 0.026), respectively. Application of the AFP > 1000 ng/mL as a cut-off was connected with the exclusion of 4.7% of cases from the opportunity to be transplanted and with the reduction of 20% of tumor recurrence[20]. All the reported studies are reassumed in Table 1.

FROM STATIC TO DYNAMIC

A fascinating way for trying to better define AFP with the intent to completely capture its selective role in HCC patients is to investigate its dynamic behavior more than its static values. During the waiting list period many conditions can indeed occur, some of them being directly connected to the history of the tumor such as progression or need for LRT. Consequently, these conditions may play an important role in conditioning AFP fluctuations. Starting from this statement, different equations able to define AFP modification have been proposed. The San Francisco transplant center underlined the recent implementation in their inclusion policy for LT to include patients with AFP levels > 1000 ng/mL only if LRT enabled to decrease this level beneath 500 ng/mL[21].

A Canadian study including 48 patients showed by

Table 2 Recent articles focused on alpha-fetoprotein dynamic values

Ref.	Year	*n*	Country	Cut-off value (ng/mL per month)
Han *et al*[22]	2007	48	Canada	50
Vibert *et al*[23]	2010	153	France	15
Dumitra *et al*[24]	2013	92	Canada	0.1[1]
Lai *et al*[25]	2013	422	Europe[2]	15

[1]ng/mL per day; [2]Austria, Belgium, Germany, Italy.

multivariate analysis that preoperative slope of AFP was the unique independent tool able to predict tumor recurrence. Receiver operating characteristic analysis showed that the best discriminant cut-off value was 50 ng/mL per month (sensitivity: 36%; specificity: 97%). Cases having a pre-LT AFP slope > 50 ng/mL per month experienced a much worse one-year recurrence-free survival rate (40% *vs* 90%, $P < 0.001$)[22].

The Paris Paul Brousse experience including 153 patients transplanted during the period 1985-2005 revealed that patients exceeding the cut-off value of 15 ng/mL per month had lower five-year overall (54% *vs* 77%) and recurrence-free survival rates (47% *vs* 74%). At multivariate analysis, progression of AFP > 15 ng/mL per month and presence of more than three nodules at LT were poor prognostic factors[23].

Another study from Canada based on 92 patients transplanted during the period 1992-2010 showed that patients with an AFP slope exceeding 0.1 ng/mL per day had an increased risk of recurrence. Such slope was able to strongly predict post-LT recurrence, and microvascular invasion[24].

Finally, the European multicenter experience (EURHECALT study) performed on 306 patients meeting and 116 exceeding MC showed that mRECIST progression during waiting time and AFP slope > 15 ng/mL per month were the sole predictors of tumor recurrence and post-LT death[25]. All the reported studies are reassumed in Table 2.

It should be underlined that in all these mentioned studies, AFP slope was calculated using only two data points. Vibert *et al*[23] adopted the value obtained from the difference between the lowest and highest measured divided by the lapse of time passed between the two measurements; our group (Lai *et al*[25]) adopted the measures at the moment of waiting-list inscription and at moment of LT. Both methods insufficiently show the real behavior of AFP changes overtime because they are not able to completely capture the AFP oscillations during the time.

Until now, neither "dynamic" *vs* "static" values nor the proposed cut-off value of AFP slope (15 or 50 ng/mL per month, 0.1 ng/mL per day) have been validated.

CONSIDERATION FOR AN INTEGRATED MODEL

Several questions are thus still open in relation to the possible adoption of AFP as a refinement selector of patients with HCC awaiting for transplant. The, growing, recent literature focused on the prognostic role of AFP in relation to tumoral features, recurrence and overall patient survival, did not yet identify the best way to integrating this marker into the morphologic tumor behavior. It is however clear that besides the fundamental starting point, namely tumor morphology (based on MC), biologic tumor behaviour must obtain a valid place within the construction of every LT selection model. In a fascinating editorial, Marsh stressed that biological features, typically considered the "king" among all prognostic variables in oncology, have not enough space in the "Metroticket" paradigm (the longer the distance the higher the price; the more the tumor is advanced, the higher is the risk of recurrence) proposed by Marsh *et al*[3] and Mazzaferro *et al*[26]. Lai *et al*[27] reported that biology is like a dwarf on the shoulder of a giant (the MC), but thanks to this "privileged position", the dwarf is able to see further, this means to identify risk factors and so to refine selection criteria for LT[27]. Despite these "visionary" statements, AFP appears not to be a manageable variable. Firstly, AFP may increase due to tumor-unrelated events such as viral- and toxic- (due to LRT or medication) related events; secondly, this marker frequently is not secreted by the tumor, explaining its poor sensitivity and specificity in the diagnostic process of HCC. As a consequence, all high AFP values are not equal to aggressive tumors and not all the low-value are equal to good-prognosis HCC. Moreover, the chaotic fluctuations of AFP make it difficult to find the best variable/equation able to capture them and finally, no definitive answer has been found to identify the best cut-off value to adopt.

Trying to find a "fil-rouge" in the recent literature, we assume that: (1) last AFP value or AFP slope seem to be the best values to adopt; (2) different cut-offs may be adopted in the two different scenarios of MC-IN and MC-OUT, adopting lower values in this latter context; (3) the possible use of 1000 ng/mL as cut-off for MC-IN patients seems to represent a good compromise between the necessity to exclude high-risk patients from LT and the desire to give the transplant opportunity to the highest number of patients; (4) the latter considerations can be potentially extended also to University California San Francisco criteria, eventually adopting a more stringent AFP parameter (necessity of post-LRT AFP reduction from 1000 to 500 ng/mL? eventually a lower value?); (5) no definitive conclusion has been reached in relation to the best cut-off value to adopt in case of MC-OUT patients (400 ng/mL or less?) and finally (6), no definitive cut-off has been investigated in relation to AFP slope in the two different published scenarios, so more studies are required (Table 3).

CONCLUSION

AFP represents a useful but poorly manageable tool to

Table 3 Proposal for the integration of alpha-fetoprotein values and morphological tumor criteria into the selection process for liver transplantation in hepatocellular carcinoma cirrhotic patients

Criteria	No. of lesions	Maximum diameter (cm)	Last AFP value (ng/mL)	AFP slope (ng/mL per month)
MC	1	5	1000	15, 50, higher?
	2-3	3	1000	15, 50, higher?
UCSFC	1	5.1-6.5	1000?	50 or higher?
			1000 → 500? lower?	
	2-3	3.1-4.5 (total sum 8)	1000?	50 or higher?
			1000 → 500? lower?	
Out of conventional criteria			400? lower?	50 or higher?

AFP: Alpha-fetoprotein; MC: Milan Criteria; UCSFC: University of California San Francisco Criteria.

increase the ability to better select HCC patients waiting for LT. More, structured and prospective, studies using serial determination of AFP values within and without the context of locoregional therapies are needed in order to find the "ideal" (static and dynamic) cut-off values allowing to respond to all the still open questions in this field of transplant oncology.

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