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Attribution des greffons hépatiques dans le carcinome hépatocellulaire : impact de l'application des critères AFP dans la vraie vie

Bleuenn Brusset

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ATTRIBUTION DES GREFFONS HEPATIQUES DANS LE CARCINOME
HEPATOCELLULAIRE: IMPACT DE L'APPLICATION DES CRITERES
AFP DANS LA VRAIE VIE

THESE PRESENTEE POUR L'OBTENTION DU DOCTORAT EN
MEDECINE DIPLÔME D'ETAT

Bleuenn BRUSSET

[Données à caractère personnel]

THESE SOUTENUE PUBLIQUEMENT A LA FACULTE DE MEDECINE
DE GRENOBLE*

Le 22 septembre 2017

DEVANT LE JURY COMPOSE DE

Président du jury: Monsieur le Professeur Vincent LEROY

Membres

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Monsieur le Professeur Mircea CHIRICA

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PREAMBULE

Le sujet de cette thèse m'a été proposé par le Pr Thomas Decaens un peu plus d'un an après l'application du modèle AFP (Alpha-foetoprotéine) en France.

Malgré ses avertissements ("tu vas avoir besoin de beaucoup de patients, sans doute aller dans plusieurs centres, mais tu verras, moi j'ai fait ça pendant ma thèse, c'est un super souvenir"), j'ai été rapidement enthousiasmée par ce projet.

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Je souhaite que le travail et la réflexion investis dans cette étude puissent se refléter dans le manuscrit de l'article à suivre.

INTRODUCTION FRANCAISE A L'ARTICLE

Le carcinome hépatocellulaire (CHC) est la tumeur primitive maligne du foie la plus fréquente, et représente le 5ème cancer le plus fréquent chez l'homme, et la deuxième cause de décès lié au cancer dans le monde (1). En France l'incidence du CHC est passée de 1956 nouveaux cas par an en 1980 à 8723 en 2012 (2). Les facteurs favorisant la survenue du CHC sont principalement la cirrhose, quelque soit son étiologie et l'hépatite B, qui doivent faire l'objet d'un dépistage individualisé. Son pronostic, malgré des avancées considérables, reste un des plus sombres (avec une survie à 5 ans évaluée à 9.6% en France (3) et 5.1% aux Etats Unis (4)).

La transplantation hépatique (TH) est considérée comme le traitement théorique idéal du CHC sur cirrhose (5) car elle permet l'ablation de la tumeur diagnostiquée mais aussi des foyers néoplasiques ou pré-néoplasiques non diagnostiqués sur le foie cirrhotique adjacent. Les autres traitements curatifs sont des traitements loco-régionaux (notamment la résection chirurgicale et la radiofréquence), qui ne sont réservés que pour des tumeurs de petite taille et qui exposent les patients à un risque de récurrence plus élevé. La transplantation devient le traitement de sauvetage en cas de récurrence (6).

La limite principale de la TH est le risque de récurrence tumorale après la greffe, qui survient dans 8 à 20% des cas à l'heure actuelle, soit au niveau du greffon soit sous forme de métastases extra-hépatiques (7). La récurrence survient le plus fréquemment dans les deux ans qui suivent la transplantation, et conduit au décès du patient dans la majorité des cas dans l'année suivante dans les séries historiques (8).

Compte tenu de la pénurie actuelle d'organes, il est essentiel de limiter la greffe aux malades ayant un CHC à faible risque de récurrence de façon à utiliser de façon optimale le greffon hépatique (ressource collective rare). On considère actuellement qu'une probabilité de survie après transplantation hépatique pour CHC voisine de celle observée après transplantation pour hépatopathie bénigne doit être atteinte, c'est à dire 65 à 75% de survie globale à 5 ans (9). Il faut prendre en compte le fait que depuis 2014, le CHC est devenu la principale indication de greffe (30% des nouveaux inscrits) selon l'Agence de Biomédecine (10).

Les critères de sélection des malades actuellement retenus dans le monde, et appliqués jusqu'en janvier 2013 en France, sont ceux de l'équipe de Milan (11), ayant permis depuis leur application il y a maintenant 20 ans l'obtention des résultats attendus dans le domaine. Ces critères limitent les indications de greffe pour CHC aux malades n'ayant pas de thrombose portale tumorale et ayant une tumeur de diamètre maximal inférieur ou égal à 5 cm ou 2 ou 3 tumeurs de diamètre maximal inférieur ou égal à 3 cm.

Au cours des années cependant, ces critères ont été remis en cause par les praticiens à qui il est devenu clair qu'ils excluaient une population de malades bien sélectionnée en dehors des critères de Milan qui pouvaient prétendre à de bons résultats (évaluée autour de 30 à 40% (12,13)). Ce décalage a conduit à un mauvais respect en pratique des critères de Milan, et ainsi on estime à environ 25% le nombre des malades transplantés pour CHC en dehors des critères de Milan (14–19). On comprend aisément que l'hétérogénéité des pratiques en découlant peut avoir de lourdes conséquences en terme de résultats, et ne peut être tolérée par les Agences nationales régissant la greffe.

Au niveau international, plusieurs scores qualifiés "d'expansion" ont été proposés pour augmenter le nombre ou la taille des nodules, notamment le score UCSF (University of California, San Francisco), (15,20), et le score Up to Seven (21) explicités plus loin, permettant des résultats similaires aux critères de Milan en terme de survie et récurrence post transplantation. Malgré ces résultats, le score de Milan est resté la référence au niveau international, encore d'après les recommandations de la conférence de consensus internationale de 2010 (22), d'une part en raison de l'absence de données prospectives jugées suffisantes, mais surtout par crainte des répercussions négatives sur la liste d'attente de greffe.

Au delà des critères morphologiques, et comme souligné dans la conférence de consensus internationale de 2010, il semblait nécessaire d'ajouter un marqueur biologique pronostic, tel que l'Alpha-foetoprotéine (AFP) ou la Des-gamma-carboxy-prothrombine (DCP), à la fois marqueurs de différenciation tumorale et d'invasion vasculaire, afin d'affiner la prédiction de la récurrence de CHC (15,23–26).

Encouragée par une exception française tendant à moins respecter les critères de Milan, l'équipe des Pr Duvoux et Decaens a travaillé sur de nouveaux scores d'attribution des greffons avec la constitution d'une base de données de près de 1500 malades et publié un nouveau modèle en 2012, appelé le modèle AFP (16). Dans ce modèle, explicité plus loin, plus que le nombre de nodules, c'est la taille du plus gros nodule et surtout la valeur de l'alpha-foeto-protéine qui est discriminante. L'ambition de ce modèle est donc de récupérer certains patients exclus des critères de Milan grâce à des marqueurs de différenciation de bon pronostic, et à l'inverse d'exclure certains malades à biologie péjorative, comme cela avait pu être montré dans l'étude princeps (14), sans altérer les résultats globaux de la transplantation hépatique.

Ce modèle a été adopté par l'Agence de la Biomédecine pour l'attribution des greffons au 15 janvier 2013. En France, depuis cette date, les malades transplantés pour CHC doivent donc avoir un score AFP inférieur ou égal à 2.

L'objectif principal de cette étude était d'évaluer l'impact de ces modifications sur les résultats de la transplantation hépatique d'une part, mais aussi sur le taux de sortie de liste, les enjeux étant à la fois économiques et déontologiques dans ce domaine.

Il s'agissait donc de comparer, en intention de traiter afin d'évaluer à la fois le pronostic des patients greffés et de ceux sortis de liste, tout d'abord si les pratiques étaient effectivement plus homogènes et raisonnables depuis l'application de ce modèle que sous l'ère des critères de Milan, et ensuite de comparer les résultats en terme de survie et de récurrence de ces patients. Afin de rester objectif, il a été décidé d'évaluer comme critère principal le respect d'un score AFP ≤ 2 sur pièce opératoire pour tous les patients, en comparant une cohorte consécutive de patients greffés peu avant l'implémentation du modèle AFP (inscrits après le 1er mars 2011, greffés avant le 1er juin 2013 afin de prendre en compte le délai de latence alloué aux équipes pour réactualiser le score de chaque patient avant greffe, ou sortis de liste avant le 1er mars 2013 (afin de ne pas imputer un taux de sortie de liste dû au nouveau modèle) et une cohorte de patients greffés ou sortis de liste après ces dates et inscrits sur liste jusqu'au 1er mars 2014.

Impacts of the α -Fetoprotein (AFP) model in real life for patient selection for Liver transplantation (LT) for Hepatocellular Carcinoma (HCC)

B. Brusset^a (Dr), JL. Quesada^a (M.), J. Dumortier^b (Pr), D. Cherqui^c (Pr), GP. Pageaux^d (Pr), S. Dharancy^e (Pr), L. Chapron^a (Mme.), S. Radenne^b (Dr), D. Samuel^c (Pr), F. Navarro^d (Pr), E. Boleslawski^c (Pr), T. Decaens^a (Pr)

^a CHU Grenoble, Grenoble, France ; ^b CHU Lyon, Lyon, France ; ^c Centre Hépato-biliaire Paul Brousse, Villejuif, France ; ^d CHU Montpellier, Montpellier, France ; ^e CHU Lille, Lille, France

Key words

AFP model

Milan criteria

Liver transplantation

Hepatocellular carcinoma

Post-transplant recurrence

Abbreviations

ABM: Agence de Biomédecine corresponding to the French organization for organ sharing; AFP: α -Fetoprotein; AG: AFP group; EASL: European Association for the Study of Liver; HCC: Hepatocellular carcinoma; LT: Liver transplantation; MELD: Model for End-stage Liver Disease; MG Milan group

No conflict of interest regarding this study

ABSTRACT

Introduction: The French organization for organ Sharing (ABM) changed the allocation criteria for Liver transplantation (LT) in Hepatocellular carcinoma (HCC) on January 2013. The AFP Model has replaced Milan criteria. Since then, only patients with an AFP score ≤ 2 access to LT. The aim of this study was to analyze the respect of the criteria and the results of LT with an intention-to-treat design since the adoption of the AFP model, and to compare them to the results of LT before the adoption of the AFP model.

Patients and methods: The ABM's listing identified 523 patients consecutively listed for LT for HCC between March 2011 and March 2014 in five French centers. They have been included, whether they have been transplanted (n=364) or not (n=159). The Milan group (n=199) consisted in patients transplanted before the concrete adoption of the AFP model fixed on 2013, June 1st, or who dropped out of list before 2013, March 1st. The AFP group (n=324) consisted in patients transplanted or who dropped out of list after these dates.

Results: In the AFP group, patients had less advanced cirrhosis and underwent more bridging therapies compared with the Milan group. The median waiting time was 7.7 months in the Milan group vs. 12.3 months in the AFP one (p<0.001), mainly due to the establishing of 'temporary contraindications'.

The non-respect of the AFP score on the explants confirmed to be highly predictive of recurrence (SHR 6.85, p<0.001) and post-transplant death (HR 3.44, p<0.001). There was no difference in the histological AFP score between groups (p=0.838) with a global respect in 88% of patients. Independent factors predicting a non-respect of this score were a downstaging policy and an AFP score exceeding 2 on the last imaging.

Dropout of list, 3-year post-listing survival and 2-year post-transplantation were similar between the groups (respectively 26.3% in Milan vs. 30.6% in AFP, p=0.086; 68.2 vs. 66.7%, p=0.447 and 87.4 vs. 82.7% p=0.100).

Nevertheless, despite no significative difference in the rate of recurrence (9.2% vs. 13.2%, p=0.239), the multivariate analysis clearly showed that belonging to the AFP group, as well as the non-respect of the AFP model, a downstaging policy and a salvage transplantation policy, were predictors of post-LT tumor recurrence.

Conclusion: Implementation of the AFP model in France did not change the histological results of LT but allowed a better respect of the allocation criteria in comparison to Milan criteria, without significative increase in the dropout rate. Nevertheless the affiliation to the AFP group is significantly associated to tumoral recurrence, probably due to the lengthening of the waiting list and the increase of treatments. This study raises the necessity to discuss the principles of temporary contraindications and to develop solutions to cope with the organ shortage.

1. Introduction

Liver transplantation (LT) is considered the best treatment of Hepatocellular carcinoma (HCC) as it would eliminate the tumor and cure the underlying liver disease. But the success of this policy is ruled by the necessity of similar outcomes for HCC and non-HCC recipients, as they directly compete in a large waiting list. Indeed the risk of tumor recurrence has to be the lowest, and HCC candidates for LT should be strictly selected in the context of organ shortage.

That is why in 1996 Mazzaferro et al proposed the Milan Criteria (MC) to limit access to LT for patients with a single tumor $\leq 5\text{cm}$ or ≤ 3 tumors each $\leq 3\text{cm}$ without tumor invasion or metastasis (11). They've been adopted in a large number of LT programs, notably in the USA. Fourteen years later, the 2010 international consensus conference on HCC and LT (22) stated that Milan criteria remained the benchmark for selection of HCC patients for LT, and the basis for comparison with any other suggested criteria.

These other suggested criteria, also called 'expanded criteria', emerged with the idea that Milan criteria were too restrictive, and thus were not respected in about 30% of HCC registrations for LT ((27–31), with an uncontrolled risk of bad outcomes.

Of note, the UCSF criteria (15) extend the allowed tumor burden (a single tumor $\leq 6.5\text{cm}$ or ≤ 3 tumors each $\leq 4.5\text{cm}$ with a total tumor volume $\leq 8\text{cm}$) with a similar survival rate (75% at five years) to the one achieved by the Milan group. The 'up-to-seven' criteria rethink the algorithm (the sum of the number of nodules and the diameter of the largest tumor in cm should not exceed seven, in absence of macro-vascular invasion and metastasis) with a 71.2% 5-year survival rate (21). But studies' limitations and the fear of negatively influencing the non-HCC waiting list blocked the implementation of these 'expanded criteria'.

Subsequently, the French study group for LT reported on a new predictive model for HCC recurrence, namely the AFP model (16) (Table 1) integrating α -Fetoprotein (AFP) values, a pejorative biological marker of both tumor differentiation and vascular invasion (32–34) to the number and size of tumors. It embraces the second recommendation of the international consensus conference (22) underlining that α -fetoprotein concentrations add prognostic information in HCC patients and may be used for making decisions regarding transplantation in combination with imaging criteria. The particularity of this model is that it allows the transplantation of HCC recipients with an infinity of nodules if measuring $\leq 3\text{ cm}$ with AFP levels less than 100ng/mL, but excludes patients with AFP levels greater than 1000ng/mL whatever the size and number of nodules. Indeed the AFP model turned to be superior to Milan criteria in predicting recurrence (16) in a training set of HCC patients, and was then validated prospectively in a large cohort of 435 patients under the control of the French organization for organ sharing (ABM). Based on these facts, the AFP model has been adopted in France in 2013, January 15th and HCC candidates must have an AFP score ≤ 2 to remain on the main list.

Table 2: Simplified, User-friendly Version of the AFP Model

Variables	β coefficient	Hazard ratio	Points	
Largest diameter, cm				
≤ 3		0	1	0
3–6	0.272	1.31		1
> 6	1.347	3.84		4
Number of nodules				
1–3		0	1	0
≥ 4	0.696	2.01		2
AFP level, ng/mL				
≤ 100		0	1	0
100–1000	0.668	1.95		2
> 1000	0.945	2.57		3

The score is calculated by adding the individual points for each obtained variable. A cut-off value of 2 separates between patients at high and low risk of recurrence.. Duvoux et al. Gastroenterology 2012

We have therefore been using in France the AFP model for the last four years with the objective of reducing tumor recurrence, as it was assumed to be a better predictive model and also to be better respected as larger criteria. But neither the use nor the results of this model have yet been verified at the national scale, though discussions started on extending its implementation beyond France (35).

Since 2007 the French allocation system is based, except for emergency grafts, on a common score called 'F score' which essentially takes into account the MELD score and the time spent on waiting list, with a burden for this latter parameter depending on the indication of transplantation. HCC patients obtain a higher F score and get access to LT more quickly than patients with isolated cirrhosis, and compete with them after 12 to 18 months even when they have a low MELD score. Of note, another important change in the French practices occurred approximately during the year 2012 depending on centers, with the generalized use of 'temporary contraindications' patients for LT, which basically mean 'temporary inactivation on waiting list' without losing the allocation points allowed by the time spent on waiting list. Patients with HCC controlled after a curative treatment or exceeding allocation criteria can be 'temporarily contraindicated' until reassessment of the LT indication.

In this French multicentric retrospective study we first aimed at comparing the respect of the AFP score on the explants analysis before and after the adoption of these criteria. The secondary objective is to compare the general results of LT in terms of tumor relapse, dropout, overall survival, and disease free survival before and after the AFP model implementation. Finally, a large cohort and amount of data gives us the opportunity to discuss the impact of downstaging, of waiting time, and of response to bridging therapies.

2. Patients and Methods

2.1 Design of the study and studied population

Based on an expected incidence of the non-respect of MC on the explants analysis around 30% (14,15,18) and on the hypothesis that the AFP model implementation would reduce it to 15%, and taking into account a proportion of patients dropout around 20% we calculated that we would need 397 patients (with a two-sided type 1 error of 5%).

All patients registered consecutively for LT because of an Hepatocellular Carcinoma between March 2011 and March 2014 on the ABM listing in five chosen French centers were included, whether they finally underwent LT or not in order to analyze the overall results of LT in an intention-to-treat design. The hospitals chosen were Centre Hepatobiliaire Paul Brousse (Paris), Montpellier, Lille, Lyon and Grenoble.

A total of 557 patients were screened to participate in this retrospective study.

Exclusion criteria were:

- (i) patients transplanted without any tumor found on the explants without curative pre-LT treatment (n= 24), considering either that the transplantation was not really indicated for HCC but was done for another indication, or that the histological report should not be compared to others,
- (ii) patients transplanted without any tumor on the explants if the tumor had already been treated at the time of registration without any recurrence at the time of LT (n=2),
- (iii) patients whose HCC appeared after registration (n=3),
- (iv) patients whose explants revealed only lymphoma or pure cholangiocarcinoma (n=3), considering thus the initial diagnosis was biased,
- (v) patients who underwent a domino LT with obvious exceeding criteria for conventional LT (n=1).

Neither patients with a laboratory MELD score exceeding some threshold nor patients whose waiting time was influenced because of living donors (n=9), domino grafts (n=11), partial transplantation (n=9), exceptional graft (n=1) or expert component (n=2) were excluded in order to keep the studied population as close to real patients in the daily practice as possible. For the same reason, patients who spent more than one year or are still listed in 'temporary contraindication' because of the absence of tumoral evolution remained in the analysis.

As shown in Figure 1, after exclusion of patients with missing data (n=1) the final study population consisted of 523 patients. 364 patients were eventually transplanted whereas 159 patients were either dropped-out (n=146) or not transplanted because of a non-evolutive tumor currently (n=13).

The study was approved by the Ethics Committee (CECIC of Auvergne Rhone Alpes), and authorized

by CCTIRS and CNIL Committee regarding the use of patients' data (NCT 03156582).

Milan Group

The Milan Group (MG) was composed by patients who were either transplanted or dropped-out of list at the time of the Milan criteria implementation (until 2013, June 1st because a mandatory re-evaluation of patients by the various teams in order to respect the criteria at this date. 199 patients were classified in this group.

AFP Group

The AFP Group (AG) was composed by patients who underwent liver transplantation after 2013, June 1st, or were dropped-out list after 2013, March 1st, i.e. after the implementation of the AFP score by ABM (the French organization for organ sharing). 324 patients were classified in this group.

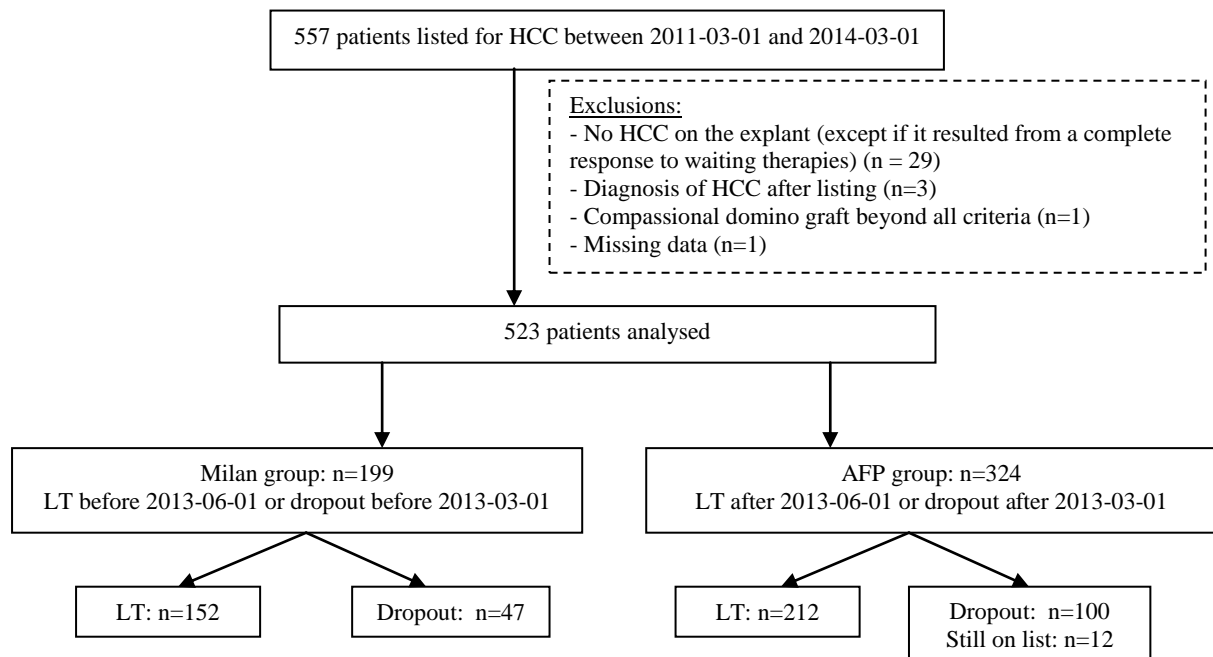


Figure 1: Study flow chart
HCC Hepatocellular carcinoma; LT Liver transplantation

2.2 Collection of data

Two different investigators LC and BB, who visited each centre to consult the files, collected gross data. BB was charged of the analysis and registration of data. The collection began in January 2016 and ended in April 2017.

Pretransplant data included demographics, the cause of cirrhosis, the histological data at time of diagnosis, the imaging tumor features at first diagnosis, the potential treatments realized in order to

avoid transplantation (curative treatments realized more than one year before listing), and the AFP values at the time of diagnosis. Alcohol was considered involved in cirrhosis when the daily consumption was higher than 40 grams per day during more than five years for men and 20 grams per day for women (36). Child Pugh and MELD scores were prospectively calculated and collected by the ABM at the time of listing. We also collected the official registered number and size of nodules and the AFP values declared to ABM, as well as the imaging tumor features collected at the time of the registration. Pre-LT bridging therapies and their results, the last imaging tumor features and the last AFP values (within 3 months before LT) were retrospectively collected. Imaging features of HCC had been collected from imaging reports. 'Total' tumor tissue and 'viable' tumor tissue data were collected, a viable tumor being defined as a contrast-enhanced tumor in the arterial phase of CT or MRI. Response to treatment after loco-regional therapy was assessed according to mRECIST criteria, taking into account the size and number of the residual viable tumor tissue. Downstaging policy was defined as a reduction in the size of tumor using loco-regional therapies specifically to meet acceptable criteria to LT: for the Milan Group we used Milan criteria as a target and for the AFP group we considered an AFP score ≤ 2 as a target.

The collected data allowed the calculations of AFP scores at four steps of the follow-up (Figure 2).

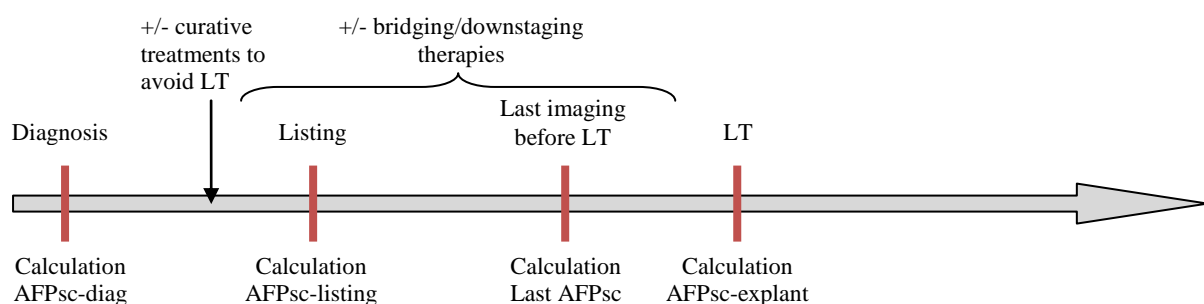


Figure 2: Four distinct end-points in collection data: AFP score from diagnosis to transplantation
 AFPsc: AFP score; LT: Liver transplantation

The pathological features of HCCs, including micro vascular and macro vascular invasion, the presence of satellites nodules, tumor differentiation of the major contingent and the worse contingent, tumor size and number, and necrosis percentage were collected after LT from the explants 'pathological reports. 'Total' tumor tissue and 'viable' tumor tissue were collected, where a nodule was considered as viable when it was not entirely necrosed by a pre-LT treatment.

Post-LT follow-up data included death, cause of death, HCC recurrence and dates of last follow-up visit. The diagnosis of recurrence was established after consulting reports or after histological reports.

2.3 Statistical analysis

Data were expressed as median and interquartile range. The chi-squared test was employed for categorical variables or a Fisher test for small samples. A nonparametric test (Mann-Whitney U) was used for numerical variables. Patient survival rates were estimated with the Kaplan-Meier method and compared with the log-rank test, and a Fine and Gray model was used to take into account the competitive risk due to death. Competitive risk analysis was used to analyze the probabilities of tumor recurrence. Univariate and multivariate analysis were performed as exploratory analyses and only on variables with clinical significance for the outcomes of post-transplant survival and recurrence of HCC after LT. Variables with $p < 0.15$ in univariate analysis were tested in the multivariate Cox proportional hazard model to identify independent prognostic factors.

An independent statistician, not involved in the design of the study, performed statistical analysis. Stata software was used for statistical analysis, version 14.2[®] (StataCorp, College Station, TX) in the Centre d'Investigation Clinique Plurithématique of Centre Hospitalier Universitaire de Grenoble.

3. Results

3.1 Comparison of patients

Main comparative characteristics of the study population are presented in Table 2.

3.2.1 Diagnosis data

The majority of HCC complicated cirrhosis, with a repartition of the causes similar to those reported in the original French validation cohort of the AFP score (10), and similar in the two groups. The initial tumoral characteristics were similar in both groups: at diagnosis, around 87% of patients have an AFP score ≤ 2 vs. 13% >2 . In about one case over four, patients received a curative treatment (surgical resection or radiofrequency) in order to avoid transplantation, over a year before listing.

3.2.1 Listing data

The median MELD score at listing was 10. However it is interesting to note that there were more patients with advanced cirrhosis (Child C, MELD >20) in the MG (Milan Group) than in the AG (AFP group) at the time of listing.

At listing, the AFP score was significantly higher in the AG when considering the total amount of tumor, and thus the AFP model less respected (88% vs. 93.5% in MG, $p=0.041$). Similarly the Milan criteria were less respected in the AG (63% vs. 73.4% in MG, $p=0.014$). These differences disappear when considering 'viable' tumors, i.e. the remaining contrast-enhanced tumor after bridging therapies. Of note, collected data were compared to ABM data regarding the number of nodules, the maximal diameter and the AFP value with a Spearman correlation test. The correlation was better for the total morphological tumor than for the viable tumor data (for the number of nodules $\rho=0.72$ vs. 0.58, for the maximal diameter $\rho=0.57$ vs. 0.52) and was excellent for the AFP value ($\rho=0.94$).

3.2.2 Waiting time before LT

In the AG, 84.3% of patients received waiting therapies to LT (transarterial chemoembolization, surgical resection, thermoablation, ethanol ablation, radiation, sorafenib) versus 75.4% with a median of 2 treatments in both groups but AG patients received more treatments (up to 8) comparatively to MG patients ($p=0.012$). The rate of downstaging intentions remained around 34% of patients, similar in the two periods ($p=0.771$) and its success, around 50%, was also comparable ($p=0.829$).

Only 212 of 364 patients (58.2%) of the AFP group underwent LT, significantly lesser than in the Milan group (76.4%) ($p=0.008$), mainly because of patients remaining 'temporarily contraindicated' at the time of collection data. Median waiting time increased from 7.7 months to 12.3 months ($p\leq 0.001$) mainly because of this phenomenon.

Table 2: Comparative characteristics of the study population

	Milan group (n=199)	AFP group (n=324)	P value
Males (n, %)	179 (89.9%)	280 (86.4%)	0.232
Age at listing (yr, median,)	58.7 [53.7-62.9]	59.4 [52.9-63.2]	0.639
Cirrhosis (n, %)	191 (96.0%)	309 (95.4%)	0.741
Causes of liver cirrhosis (n, %)			
<i>Alcohol</i>	78 (40.8%)	113 (36.6%)	0.340
<i>Viral</i>	50 (26.2%)	90 (29.1%)	0.476
<i>Viral + Alcohol</i>	23 (12%)	47 (15.2%)	0.321
<i>Dysmetabolic</i>	8 (4.2%)	12 (3.9%)	0.866
<i>Alcohol + dysmetabolic</i>	20 (10.5%)	31 (10%)	0.875
<i>Others</i>	12 (6.3%)	16 (5.2%)	0.602
Data at diagnosis			
Pre-treatment biopsy (n, %)	48 (24.1%)	80 (24.7%)	0.883
Number of nodules (median,[IQR])	1 [1-2]	1 [1-2]	0.985
Max diameter (mm, median, [IQR])	25 [20-35]	26 [20-38]	0.367
Total diameter (mm, median,[IQR])	34 [23-48]	34 [25-53]	0.750
AFP value, ng/mL (median, [IQR])	10 [5-24.8]	8.2 [5-21.3]	0.507
AFPsc-diag: ≤2 vs >2	176/23 (88.4% vs 11.6%)	279/45 (86.1% vs 13.9%)	0.441
Preceding treatment to avoid LT	52 (26.1%)	88 (27.2%)	0.796
Number of treatments (median, [IQR])	1 [1-2](1-6)	1 [1-2] (1-4)	0.164
Data at listing			
Lenght diagnosis-listing (d, median, [IQR])	270 [132-521]	238 [130-530]	0.402
Child-Pugh (n, %)			0.024
A	91 (45.7%)	184 (56.8%)	0.017
B	60 (30.2%)	88 (27.2%)	0.591
C	48 (24.1%)	52 (16.1%)	0.016
MELD score (median, [IQR])	10.6 [8.2-15.7]	9.7 [7.6-14]	0.063
MELD >20 (% , n)	13.6% (26)	7.7%(25)	0.045
Number of nodules (median, [IQR])	2 [1-3]	2 [1-3]	0.147
Largest diameter (median, [IQR])	24 [20-33]	26 [19-36]	0.428
Total diameter (mm, median, [IQR])	37 [24-54]	40 [26-61.5]	0.139
AFP value, ng/mL (median, [IQR])	8 [4.1-20.7]	7.4 [4-20]	0.583
Milan criteria 'total': within vs. beyond	146/53 (73.4 vs 26.6%)	204/120 (63% vs 37%)	0.014
Milan criteria 'viable': within vs. beyond	175/24 (87.9 vs 12.1%)	278/46 (85,8 vs 14,2%)	0.486
AFPsc-listing 'total': ≤2 vs >2	186/13 (93.5 vs 6.5%)	285/39 (88% vs 12%)	0.041
AFPsc-listing 'viable': ≤2 vs >2	194/5 (97.5% vs 2.5%)	307/17 (94.8% vs 5.2%)	0.130
Waiting			
Pre-LT bridging treatments (n, %)	150 (75.4%)	273 (84.3%)	0.012
Number of treatments (median, [IQR])	2 [1-2] (1-5)	2 [1-3] (1-8)	≤0.001
Downstaging policy (n, %)	54 (34.8%)	92 (33.4%)	0.771
Unsuccessful downstaging (n, %)	28/54 (52%)	46/92 (50%)	0.829

Dropout of list (n, %, [IQR])	47 (23.6%) [17.9-30.1]	100 (30.9%) [25.9-36.2]	0.073
Dropout for HCC (n, %, [IQR])	35 (17.6%)[12.3-22.9]	67 (18.4%) [14.2-22.6]	0.926

Last imaging n=364	N=152	N=212	
Median time last imaging-LT (days)	42 [18-74]	43.5 [21.5-67.5]	0.9988
Number of nodules (median, [IQR])	2 [1-3]	2 [1-3]	0.340
Largest diameter (median, [IQR])	23.5 [18-31]	27 [20-35]	0.064
Total diameter (mm, median, [IQR])	40 [24-60]	45 [29-76]	0.085
AFP value, ng/mL (median, [IQR], range)	6 [3.6-19.9]	6 [3-13]	0.306
Last Milan criteria 'total': within vs. beyond	101/50 (66.9% vs 33.1%)	125/87 (59% vs 41%)	0.125
Last Milan criteria 'viable': within vs. beyond	130/21 (86.1% vs 13.9%)	186/26 (87.7% vs 12.3%)	0.646
Last-AFPsc 'total': ≤2 vs >2	137/14 (90.7% vs 9.3%)	177/35 (83.5% vs 16.5%)	0.047
Last-AFPsc 'viable': ≤2 vs >2	142/9 (94% vs 6%)	208/8 (96.2% vs 3.8%)	0.331

Transplantation n=364	N=152	N=212	
Number of patients transplanted (%)	152 (76.4)	212 (65.4)	0.008
Median waiting time (months) [IQR]	7.7 [3.7-12] (0.1-56)	12.3 [8.2-16.1] (0.2-50.7)	<0.001
LT consecutive to downstaging policy	36/152 (17.1%)	51/212 (24.1%)	0.949
Number of nodules (median, [IQR])	2 [1-4] (0-20)	2 [1-4] (0-50)	0.775
Largest diameter (mm, median, [IQR])	25 [15.5-35] (0-90)	27.5 [17-37] (0-120)	0.320
Total diameter (median, [IQR])	42 (27-67.5) (0-200)	45 [29-77.5] (0-350)	0.171
Milan criteria explant (total): within vs. beyond	83/69 (54.6 vs 45.4%)	121/91 (57.1% vs 42.9%)	0.639
Milan criteria explant (viable): within vs. beyond	100/52 (65.8% vs 34.2%)	150/62 (70.8% vs 29.2%)	0.314
AFPsc-explant (total): ≤2 vs >2	124/28 (81.6% vs 18.4%)	177/35 (83.5% vs 16.5%)	0.634
AFPsc-explant (viable): ≤2 vs >2	133/19 (87.5% vs 12.5%)	187/25 (88.2% vs 11.8%)	0.838
Cholangiocarcinoma component	8 (5.3%)	12 (5.7%)	0.802
Macrovascular invasion	13 (8.5%)	15 (7.1%)	0.527
Microvascular invasion	35 (23.0%)	50 (23.6%)	0.901
Satellites nodules	33 (21.7%)	43 (20.3%)	0.741
Major differentiation grade			
NA	58 (38.2%)	79 (37.3%)	0.741
1	44 (28.9%)	56 (26.4%)	0.593
2	48 (31.6%)	72 (34%)	0.633
3	2 (1.3%)	5 (2.4%)	0.475
Presence of grade III tumor	12 (7.9%)	13 (6.1%)	0.294
Necrosis Percentage (median)	30.5 [0-82.5] (0-100)	36 [0-75] (0-100)	0.965

Post transplantation (n=364)	N=152	N=212	
Follow up (yr, median, [IQR])	4.13 [1.81-4.81]	2.07 [1.49-2.65]	<0.001
Death (n, %)	26 (17.1%)	39 (18.4%)	0.751
Post-operative related death (n, %)	12 (8.5%)	18 (7.2%)	0.663
Recurrence (% , n, [IQR])	9.2% (14, [5.1 ; 15])	13.2% (28, [9 ; 18.5])	0.239
Cholangiocarcinoma recurrence (n/n recurrence)	1/14	6/28	
2 yr post-transplant survival (% , [IQR])	87.4% [80.9-91.8]	82.7% [76.6-87.4] (% , [IQR])	0.100

In both groups, last imaging occurred within three months before LT. No difference was found neither in the number and size of nodules nor in the AFP value between groups. However, and like at the time of listing, the AFP score was higher in the AG group when considering the total volume of tumor, with only 83.5% of patients with AFP score ≤ 2 compared to 90.7% in the MG (p=0.047). This was not the case considering only viable tumors, or evaluating the respect of Milan criteria. Around 8.2% of patients deceased of post-operative, rejection or sepsis in the weeks after LT, without differences between subgroups.

3.3 Dropout rate

The rate of patients dead or dropped-out of list during the Milan period was 23.6% (95%CI [17.9-30.1]) compared to 30.6% (95%CI [25.6-35.9], p=0.086) during the AFP period and thus no significantly different but showing a trend of more exclusions in the AG. Nevertheless, this trend could be associated to alternative events since HCC progression represented around 18% of listed patients in both groups (p=0.926). Common main causes of 'dropout' were death due to liver failure (around 10% in both groups), anesthetic contraindications (around 4% in both groups), alcohol relapse (2 to 4%), and only in the AG have been reported the secondary refusal from a patient (4%), another cancer (6%) or sustained remission leading to giving-up the LT program (0.9%).

3.4 LT data

Fewer patients in the AG underwent LT (76.4% of the MG vs. 65.4% of the AG, p=0.008). It is partially explained by the fact that 12 patients in the AG (3.3%) were still in 'temporary contraindication' at the last evaluation, because of a remission after a curative bridging therapy. There is no significative difference between groups if we consider these 12 patients as transplanted (p=0.073).

Another main difference is the median waiting time which was 12.3 months in the AG vs. 7.7 months in the MG (p<0.001), also as a consequence of 'temporary contraindication' generalization.

No difference was found in the number, size, tumor differentiation and pejorative histological criteria between the two groups. No statistical difference was found in the frequency of the respect of Milan criteria (considering total tumor 54.6% in MG and 57.1% in AG, and considering viable tumor 65.8% in MG and 70.8% in AG).

3.5 Non-respect of the histological AFP score

No statistical difference in the frequency of non-respect of the histological was found between the MG and the AG: 18.4 % (95%CI [12.6-25.5]) and 16.5% (95%CI [11.8-22.2]), p=0.634. Likewise, when

eliminating completely necrosed nodules to consider only viable tumor, 12.5% in the MG and 11.8% in the AG were above AFP criteria (p=0.838).

However, results of univariate but mostly multivariate analyses differ depending on the 'viable' histological AFP score and data, or the 'total tumor' histological AFP score and data (Table 3).

Indeed, considering the 'total tumor tissue' for AFP score calculation, the univariate analysis showed a correlation between the non-respect of the AFP model on the explant and 6 criteria: a high risk AFP score at diagnosis, listing, and last-evaluation, being outside Milan criteria on last-evaluation, a downstaging policy and a high number of bridging therapies. Among them the multivariate analysis retained only the fact of exceeding Milan criteria or the AFP model on last imaging as significant predictors but identified a long waiting time (using the threshold of 14.5 months corresponding to the last quartile of our population) as well as the fact of being in the Milan group as predictors of a bad respect of the AFP model on the explant. This analysis suggests a better respect of the AFP model in the AG.

Table 3: Risks factors for non-respect of the histological AFP score: Univariate and Multivariate analyses (n=364)

A- Total tumor tissue and imaging data

Risk factors	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
AFP group/Milan group	0.88	0.51-1.51	0.635	0.42	0.18-0.96	0.041
AFPsc-diag > 2	2.03	1.02-4.03	0.043	NS		
Treatment to avoid transplantation	1.46	0.82-2.60	0.201			
Child B	1.26	0.68-2.32	0.463			
Meld score > 20	0.47	0.14-1.59	0.224			
AFPsc-listing 'total'>2	9.1	3.86-21.41	<0.001	3.31	0.94-11.7	0.062
Pre-LT bridging treatments	2.08	0.90-4.78	0.086	NS		
Number of bridging treatments	1.33	1.04-1.69	0.022	0.75	0.51-1.10	0.140
Downstaging policy	3.01	1.70-5.35	<0.001	NS		
Waiting time > 14.5 months	1.68	0.93-3.03	0.084	2.98	1.24-7.14	0.015
Beyond Milan on last imaging	10.6	5.37-20.8	<0.001	7.20	2.89-17.9	<0.001
Last AFPsc 'total' >2	22.3	10.9-45.7	<0.001	10.8	4.23-27.4	<0.001

B- Viable tumor tissue and imaging data

Risk factors	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
AFP group/Milan group	0.94	0.50-1.77	0.838	1.07	0.51-2.23	0.865
AFPsc-diag > 2	1.99	0.92-4.34	0.082	NS		
Treatment to avoid transplantation	0.83	0.40-1.70	0.605			
Child B	1.58	0.79-3.15	0.192			
Meld score > 20	0.46	0.11-2.00	0.300			
AFPsc-listing 'viable'>2	1.86	0.38-9.04	0.443			
Pre-LT bridging treatments	2.55	0.88-9.04	0.085	NS		
Number of bridging treatments	1.43	1.09-1.86	0.009	NS		
Downstaging policy	4.38	2.28-8.41	<0.001	5.13	2.45-10.8	<0.001
Waiting time > 14.5 months	1.69	0.86-3.32	0.128			
Beyond Milan on last imaging	5.31	2.59-10.9	<0.001	NS		
Last AFPsc 'viable' >2	33.0	10.2-108	<0.001	40.4	11.5-142	<0.001

However this result is no longer valid when analyzing the 'viable tumor tissue'. In the univariate analysis, being outside Milan criteria or an AFP score exceeding 2 on last imaging, a high number of bridging therapies and a downstaging policy were predictive factors of non-respect of the histological AFP model. Cox regression analysis identified only 2 independent predictors: last-evaluation AFP score exceeding 2 and a downstaging policy. No influence of the group was found.

It is thus difficult to conclude on a better respect of the histological AFP model after its implementation by the French Organization for organ sharing because it seems that it would mostly take into account histological 'non viable' tumor, with no consensus on its pertinence in post-transplant outcomes.

Of note the correlation between the last imaging AFP score and the histological AFP score was moderate (Spearman's rho 0.39). Considering 'viable' data, when the AFP model was respected on the last imaging, 9% of patients had an AFP score > 2 on the explants (underestimation of 9%). When the AFP model was not respected on the last imaging, 76.5% of patients had a histological AFP score > 2 (being a radiological overestimation of 23.5% of patients) ($p < 0.001$) (Table 4).

Table : Comparison of explants findings and last-imaging findings regarding the AFP score, assessed on viable tumors (n=364)

		Explant findings		
		AFP score \leq 2	AFP score > 2	Total
Last-imaging findings	AFP score \leq 2	315	31	346
	AFP score > 2	4	13	17
	Total	316	46	364

As expected, whatever the period (before or after the implementation of the AFP model), the AFP model was significantly better respected than Milan criteria on the explant analyses of viable tumors ($p < 0.001$ in both groups).

3.6 Recurrence

42 patients presented a tumor relapse during the follow-up: 14 (9.2%) in MG and 28 (13.2%) in AG ($p=0.239$) with an obvious difference of follow-up between the groups. Of note, in an intention-to-treat design, we included the cholangiocarcinoma apparitions as tumor recurrence. Among 7 patients concerned, 6 were in the AG and 1 in the MG.

2-year recurrence-free survival rates, as assessed by Kaplan-Meier estimates were of 92.1% (95%CI [86.1-95.5]) in MG vs. 85.8% (95%CI [79.8-90.1]) in AG ($p=0.054$, HR 1.9 [0.98-3.69]). Risks of

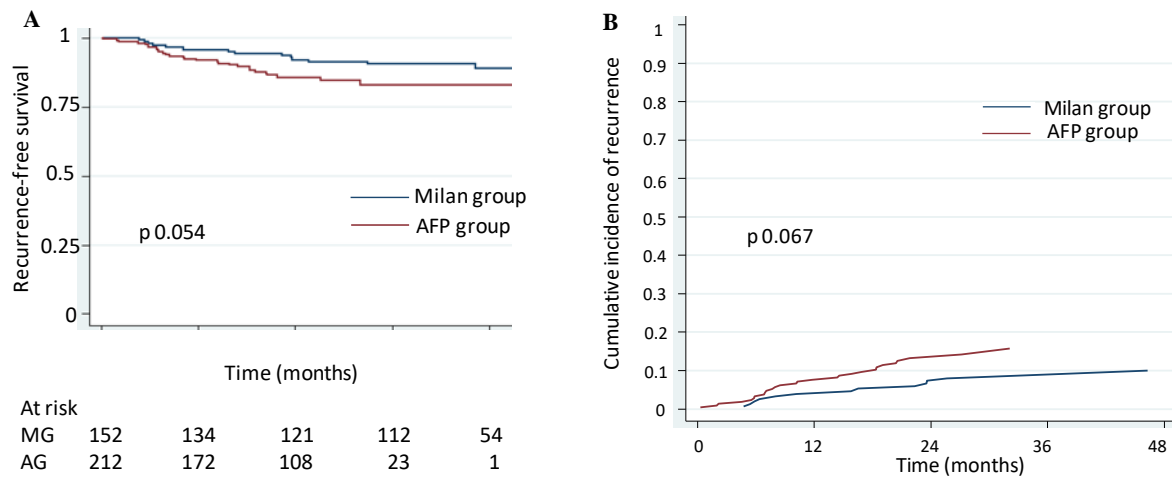


Figure 3: Risk of recurrence. Probabilities of recurrence-free survival according to Kaplan Meyer estimates (A) and cumulative incidence of recurrence on competing analysis (B) (Fine and Gray model (37))

recurrence as assessed by competing risk analysis, taking into account the competing risk of non-HCC related death, were estimated by the Fine and Gray model and showed similar results with a Sub hazard ratio of 1.83 (95% IC [0.96-3.48]), $p=0.067$ and thus a trend to a higher risk in the AG group (Figure 3).

The univariate analysis showed a strong correlation of recurrence with expected histological pejorative criteria (Table 5), but also with the realization of a preceding treatment in order to avoid transplantation (SHR 2.01, 95% CI [1.09-3.71], $p=0.025$), with the realization of bridging therapies and especially if there was a downstaging policy (SHR 3.54, 95% CI [1.94-6.48], $p<0.001$). As well, using the threshold of 14.5 months corresponding to the last quartile of our population, a longer waiting time was associated to recurrence (SHR 2.02, 95% CI [1.06-3.84] $p=0.032$). The histological AFP score, on total as on viable tumor, was a strong predictor (SHR 5.72 and 6.85 respectively, 95%CI [3.11-10.51] and [3.69-12.71], $p<0.001$ and $p=0.001$), as well as the hepatocholangiocarcinoma component (SHR 6.98, 95% CI [3.46-14.10], $p<0.001$). The multivariate analysis confirmed that the AFP group was correlated to HCC recurrence, independently to six other factors: treatments to avoid transplantation, a downstaging policy, a high risk AFP score on last evaluation and on the explants, microvascular invasion and hepatocholangiocarcinoma on the explants.

It is of note that if we had not classified the seven post-LT cholangiocarcinomas as recurrences, we would have found similar outcomes in terms of recurrences in the MG and AG groups ($p=0.138$).

Table 5: Risks factors for tumor recurrence: Univariate and Multivariate Analyses (n=364)

Risk factors	Univariate Analysis			Multivariate Analysis		
	SHR	95% CI	p	SHR	95% CI	p
AFP group/Milan group	1.82	0.96-3.48	0.067	2.34	1.16-4.73	0.017
AFPsc-diag > 2	2.56	1.32-4.95	0.005	NS		
αFP value diag > 100ng/mL	1.74	0.74-4.09	0.202			
Treatment to avoid transplantation	2.01	1.09-3.71	0.025	2.24	1.20-4.17	0.011
Number of preemptive treatments	1,33	2.11	0.222			
Child B	0.90	0.45-1.80	0.760			
Meld>20	0.69	0.22-2.15	0.520			
AFPsc-listing 'total' >2	2.03	0.81-5.08	0.130			
AFPsc-listing 'viable'>2	1.87	0.50-7.00	0.354			
αFP value listing> 100ng/mL	0.68	0.10-4.56	0.689			
Pre-LT bridging treatments	3.43	1.08-10.87	0.036	NS		
Number of bridging treatments	1.37	1.13-1.65	0.001			
Downstaging policy	3.54	1.94-6.48	< 0.001	2.50	1.30-4.81	0.006
Waiting time	1.02	0.99-1.05	0.274			
Waiting time > 14.5 months	2.02	1.06-3.84	0.032	NS		
Last AFPsc 'total'>2	3.79	1.99-7.21	<0.001			
Last AFPsc 'viable'>2	5.97	2.74-13.02	<0.001	2.58	1.06-6.30	0.038
Last αFP value> 100ng/mL	5.26	2.59-10.68	<0.001			
Macrovascular invasion	5.98	3.07-11.67	<0.001			
Microvascular invasion	5.58	3.02-10.33	p<0.001	2.61	1.17-5.81	0.018
Satellites nodules	2.59	1.38-4.84	0.003			
Presence of intermediate differentiation	3.13	1.10-8.94	0.033			
Presence of poor differentiation	7.55	2.28-25.0	0.001			
Necrosis (for 10%)	0.97	0.91-1.05	p 0.472			
AFPsc-explant (total) >2	5.72	3.11-10.51	<0.001			
AFPsc-explant (viable) >2	6.85	3.69-12.71	<0.001	2.82	1.14-6.99	0.025
Cholangiocarcinoma component	6.98	3.46-14.10	<0.001	5.22	2.65-10.30	≤0.001

3.7 Influence of downstaging on histological AFP score and tumor recurrence

Among 54 patients included in a downstaging policy in the MG, 26 patients (48%) were successfully reintegrated in Milan criteria and were transplanted, and 10 patients (18%) were transplanted despite a failure of downstaging according to Milan. Out of 26 patients successfully downstaged, 5 patients had a non-respect of the histological AFP score (19.2%) (Figure 4A) and 4 patients had a recurrence (15.4%) (Figure 4B). Out of 10 patients transplanted despite a failure to downstaging, 5 patients had a non-respect of the histological AFP score (50%) (Figure 4A) and 3 had a recurrence (30%) (Figure 4B).

Among 92 patients included in a downstaging policy in the AG, 46 patients (50%) successfully obtained an AFP score < 2 and were transplanted, and only 5 patients (5%) were transplanted despite a failure of downstaging according to AFP score. Out of 46 patients successfully downstaged 13 patients had a non-respect of the histological AFP score (29.3%) (Figure 4A) and 10 patients had a recurrence (21.7%) (Figure 4B). Out of 5 patients transplanted despite a failure to downstaging, 4 patients had a non-respect of the histological AFP score (80%) (Figure 4A) and 4 had a recurrence (80%) (Figure

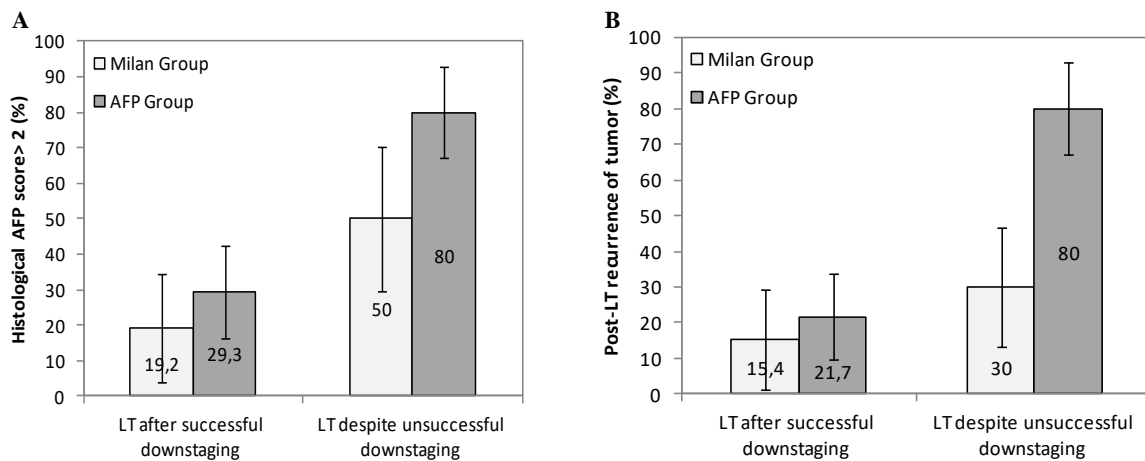


Figure 4: Post-transplant results after a downstaging policy: Non-respect of the AFP model on the explants (A) and rates of recurrence of HCC (B). Values are given as % of the corresponding population.

4B). HCC recurrence was significantly higher in the AG subgroup of patients transplanted despite unsuccessful downstaging (80%) than in the subgroup of patients with successful downstaging (21.7%) (OR 13.5, 95% CI [1.2-724.6] $p=0.017$) or than in the global population of the AG group (OR 25.6, 95% CI [2.4-1290.3], $p<0.001$). In the MG, despite a trend of higher tumor recurrence, there was no significant difference (15.4% versus 30%), probably due to a lack of power.

3.8 Survival analysis

Post-listing survival and post-transplantation overall survival assessed by Kaplan-Meier were similar in the subgroups (Figure 5). Three-year post-listing survival rates were 68.2% (95% CI [61.2-74.2]) vs. 66.7% (95% CI [61.2-71.6]), $p=0.447$. Two-year post-transplantation survival was 87.4% (95% IC [80.9-91.8]) vs. 82.7% (95% IC [76.6-87,4]), $p=0.100$.

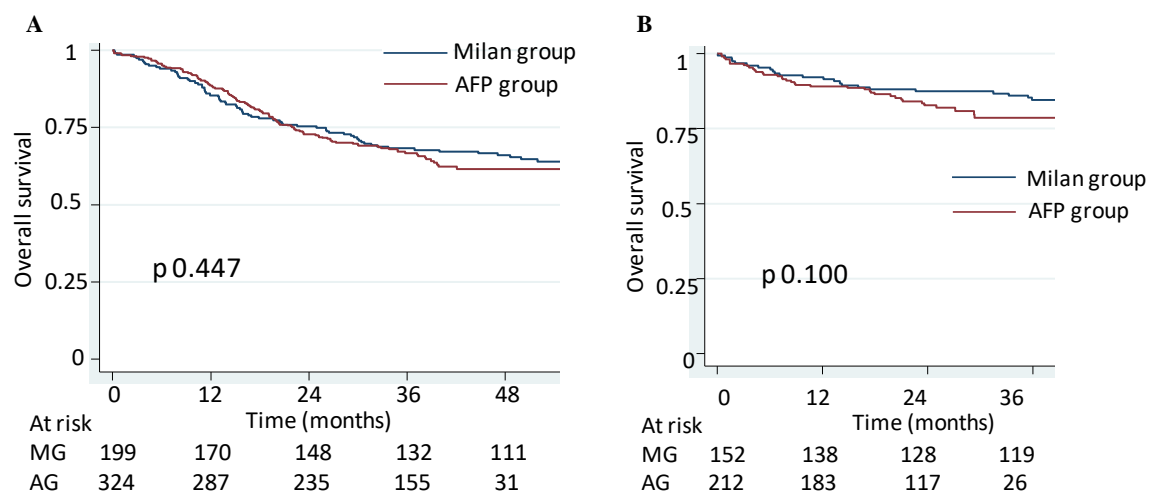


Figure 5: Overall probabilities of survival. Post-listing survival in Milan and AFP group (A) and Post-transplantation survival in Milan and AFP group (B).

Complementary analyses were performed for post-transplantation survival. The univariate analysis (Table 6) identified recurrence, preceding treatments to avoid transplantation, Child B status at listing, a downstaging policy, a last-evaluation AFP score > 2, a histological AFP score > 2, a macrovascular invasion or the presence of poor differentiation or a cholangiocarcinoma on the explants as risk factors of post-LT death.

The multivariate analysis identified two distinct models depending on the occurrence of a tumor recurrence, because it was too influential as predictor of death in univariate analysis (HR 5.51, 95%CI [3.34-9.13], p<0.001). In the absence of recurrence (causes of death being vascular or septic post-LT complications, other cancers, strokes, myocardial infarction, rejection, suicide or viral recurrences under cholestatic forms), the only significant factor was status Child B at listing (HR 2.20, 95%CI [1.18-4.12], p=0.013). For patients who underwent a recurrence, only the histological AFP score beyond 2 was a significant risk factor of death (HR 3.84, 95%CI [1.52-9.74] p=0.005), but belonging to the AFP group tended to be a pejorative factor (HR 2.86, 95%CI [1.00-8.18] p=0.051).

Table 6: Risks factors for post-transplantation death: Univariate and Multivariate Analysis (n=364)

Risk factors	Univariate Analysis			Multivariate Analysis					
	OR	95% CI	p	If no recurrence			If recurrence		
				OR	95% CI	p	OR	95% CI	p
AFP group/Milan group	1.55	0.92-2.63	0.103	NS			1.95	1.00-8.17	0.051
AFPsc-diag > 2	1.54	0.84-2.83	0.165						
αFP value diag > 100ng/mL	1.44	0.69-3.02	0.336						
Treatment to avoid transplantation	2.02	1.24-3.31	0.005	1.93	0.99-3.64	0.054	NS		
Number of preemptive treatments	1.30	0.84-2.01	0.231						
Child B	1.88	1.10-3.18	0.020	2.50	1.19-4.16	0.012	1.77	0.85-4.47	0.077
Meld>20	1.12	0.51-2.46	0.778						
AFPsc-listing 'total'>2	1.48	0.64-3.44	0.358						
AFPsc-listing 'viable'>2	0.53	0.07-3.85	0.534						
αFP value listing > 100ng/mL	1.46	0.46-4.66	0.520						
Pre-LT bridging treatments	1.11	0.59-2.09	0.737						
Number of bridging treatments	1.18	0.94-1.46	0.154						
Downstaging policy	1.70	1.02-2.84	0.043	NS			NS		
Waiting time	1.02	0.98-1.05	0.337						
Waiting time > 14.5 months	1.55	0.89-2.70	0.119						
Last AFPsc 'total' >2	2.37	1.35-4.17	0.003						
Last AFPsc 'viable' >2	3.06	1.46-6.43	0.003	NS			NS		
Last αFP value > 100ng/mL	1.75	0.84-3.67	0.138						
Macrovascular invasion	2.75	1.47-5.15	0.002	NS			NS		
Microvascular invasion	1.35	0.79-2.30	0.277						
Satellites nodules	1.13	0.649-2.02	0.669						
Presence of intermediate differentiation	1.30	0.67-2.51	0.443						
Presence of poor differentiation	3.11	1.34-7.21	0.008	NS			NS		
Necrosis	0.94	0.88-1.01	0.075						
AFPsc-explant 'total'>2	3.12	1.88-5.16	<0.001						
AFPsc-explant 'viable'>2	3.44	2.01-5.87	<0.001	NS			2.84	1.52-9.74	0.005
Cholangiocarcinoma form	3.49	1.78-6.85	<0.001	NS			NS		
Recurrence	5.51	3.34-9.13	<0.001						
Secondary other tumors	2.08	0.99-4.35	0.053						

4. Discussion

The aim of this study was to assess whether the implementation of the AFP model in France had led to an improvement of the practices and LT outcomes in comparison to Milan criteria. We chose to assess the respect of an AFP score ≤ 2 on explant analysis in order to limit the bias resulting from imaging doubts or interpretations but also because we assumed it would be a solid predictor of outcomes.

No clear changes in explant findings

The first result is that we did not find a better respect of the AFP criteria on the explant since the adoption of the AFP model, which is approximately 88% of transplanted patients for HCC (considering viable tumor). Consistently, pejorative histopathological findings were no different in the two populations analyzed. We found around 56% of respect of Milan criteria on explants, which is similar rate to the one reported in literature between 47% and 66% (18,19,27,38–40).

This result thus traduces the fact that the medical teams did not respect Milan criteria (since in the Milan group only 54.6% of patients were in the MC on the explant, or 65.8% considering viable tumor) but intuitively took similar decisions regarding transplanting HCC patients than after knowing and applying the AFP model.

However it is worth noting the discordance of results between 'total tumor tissue' and 'viable tissue' analyses regarding the fact that being in the AFP group was a predictive factor for respecting the AFP model on the explant for 'total tumor' but not for 'viable tumor' in the multivariate analyses. It could reflect the transplant community's dubious assessment of the real impact of 'non viable' tumor on outcomes and an increased carefulness and compliance to rules, that our study did not find possibly due to a lack of power.

We can deplore that 12% of patients are still transplanted over the AFP score, explained by the fact that 4 to 6% patients have been transplanted despite an AFP score > 2 on last-imaging, and by underestimation of tumor burden on last imaging. One can however note that we found a relative low rate of underestimation (9%) of tumor burden on last imaging according to the AFP model in comparison to recent data of 37.4% of underestimation of tumor burden with Milan criteria (18), finding which is reassuring for the daily practice in LT.

Moreover, it is of interest to note an improvement in the respect of downstaging rules since only 5% patients were transplanted despite unsuccessful downstaging in the AFP group whereas 18% were transplanted in the Milan group. This could be linked to the fact that AFP criteria are to a certain extent larger than MC, and maybe reflect an awareness of the pejorative outcomes of failures to downstaging.

The AFP model confirmed as a good predictor of outcome.

In our study, the non-respect of the AFP model on the explants was highly predictive of tumor recurrence (in univariate as in the multivariate analysis), and was also a predictor of post-transplant death (which correlates with the fact that recurrence was the most influential factor of 2-year post-transplant survival, in agreement with the optimization of surgical outcomes).

Moreover our analysis of risks factors of tumor recurrence showed, as described in the founding publication of Duvoux et al. (16), that exceeding the AFP score was dynamic since whatever the time since diagnosis (except surprisingly at listing) it was predictive of recurrence, speaking of 'total' as 'viable' tumor. Our ambition to improve the model would be to build a prognostic algorithm taking into account the three main times of examination of patients' data before transplantation (diagnosis, listing and last-evaluation as shown in Fig. 2) in order to create an optimized prevision of the risk of recurrence.

Not an 'expansion' model

There is a general concern regarding the consequences of the AFP model implementation on the burden of HCC patients it would cause on waiting list. It has to be underlined it is a central reason why Milan criteria have never been replaced by any of the 'expanded criteria' by fear of their negative influence on the non-HCC waiting list (5). However our study did not identify any argument supporting this concern. Indeed we observed a higher rate of transplantation during the Milan period than during the AFP period, taking into account that the proportion of new patients listed for HCC did not significantly increase (between 27 and 30%) during this time according to ABM data (10). This is explained in one hand by an overall higher rate of dropout in the AFP group (though not significative and not related to HCC progression), and on the other hand by the fact that a significant amount of patients were inactivated on list (12 patients in the AFP group in our analysis) because of the 'temporary contraindication' policy.

Worrying results

Despite the absence of difference in the respect of transplantation criteria, we observed a higher rate of recurrence in the AFP group, as well as a shorter post-transplant survival when recurrence occurred compared to the Milan group. We formulate several hypotheses to explain these bad outcomes. The first consideration is that the Milan group had a low recurrence rate in our study (9.2% with a median follow-up superior to 4 years). The second one is that we observed a surprising number of 6 post-transplant tumor recurrences as cholangiocarcinomas in the AFP group (21%) (vs. 1 in the Milan group (7%)), counted as recurrence in an intention-to-treat design. In 5 of the 6 patients, at least one nodule was noted as a cholangiocarcinoma on the explants analysis. It is impossible to presume whether this distinct amount between groups is unforeseen or an indirect consequence of our practice. Looking closer at those, it is noteworthy that one major variable between the two periods is the fact

that patients in the AFP group underwent significantly more waiting therapies than those in the Milan's one. Though we certainly don't have neither the design nor a sufficient amount of patients to corroborate it, we raise the hypothesis of a modification of tumoral contingents because of the additional waiting therapies undergone by patients in the AFP group. It is contradictory with the actual belief that characteristics of tumor response to transarterial chemoembolization allow identification of suitable patients for transplantation (40,41). Many other environmental modifications could participate to this result though. Only time and case-reports will tell if this clinical impression of an increased amount of hepatocholangiocarcinoma forms is valid or not. As a fourth consideration we would like to emphasize that another main change between the two populations is the practice of a curative treatment with consecutive listing in 'temporary contraindication' until a recurrence occurs and thus a reactivation in waiting list is triggered. Though no such recommendation has been officially made, it became a habit during the year 2012. It is worth noting that of 2016, January 1st, 50% of the patients waiting for LT in France were 'temporarily contraindicated', and nearly half of them were listed for HCC (10). One consequence is the longer waiting time on list, which interestingly is a risk factor of recurrence in the univariate analysis when it exceeded 14.5 months (what is highly probable to correspond to patients cumulating 'temporary contraindication' since the actual system in France favors time for HCC patients waiting for LT). We are thus concerned by our data, as it suggests we may delay transplantation because of the absence of evident active tumor on imaging, at the expense of a non-visible or predictable progression with post-transplant recurrence. Further explorations according to the cumulative time on 'temporary contraindication' are ongoing with the ABM collaboration.

The downstaging influence on the AFP model

The downstaging intention was found as a pejorative risk factor in the univariate analysis of non-respect of the AFP model, of recurrence and post-transplant death, and in the multivariate analysis of non-respect of the AFP model and recurrence. The time-out of observational period was not collected, and our small amount of patients does not allow us to draw firm conclusions. We observed that the results of downstaging were similar for patients with successful downstaging (though with a trend to a higher probability of recurrence) and for patients without downstaging policy. However they were catastrophic when the last-imaging criteria (Milan or AFP depending on the period) were overstepped, the recurrence occurring as often as the histological AFP criteria were not respected. It should be mentioned no clear inclusion criteria for downstaging were applied (UCSF criteria notably) as recommended (22,42). These data speak in favor of a more careful attention to downstaging in our practice, with an established and respected frame, where the accession of a pre-transplant AFP score < 2 seems a good target.

Salvage transplantation

Our study did not properly study the influence of 'salvage transplantation', since it separated curative treatments realized more than one year before listing in order to avoid transplantation, but it did not identify patients directly listed, then resected and put in 'temporary contraindication' until an hypothetical 'salvage transplantation'. Salvage transplantation is an ongoing debate: despite the fact that LT is considered the best oncological option even for small HCC (43), organ shortage and potential good outcomes of resected patients lead to a salvage transplantation strategy (44). Solitary tumor nodules with limited resection could be the best targets to achieve good results (45) but the lack of accurate markers to preoperatively or postoperatively prognosticate the outcomes accounts for intention-to-treat and post-transplant disappointing results (6). In our study, the amount of patients with preceding treatment to avoid LT was the same in the two subgroups (26-27%), but it is of note that it was a pejorative risk factor of recurrence in univariate and multivariate analysis, as well as a pejorative factor for post-transplant survival in univariate analysis. It is a confirmation of the necessity of an improvement in guidelines in this topic: should not be transplanted cured patients (we excluded 2 patients for that reason) but this guideline could not be as beneficial and cost-effective as it is thought (46).

Limitations of the study

The main limitations of the study are the retrospective design, subject to the calculation of the AFP score from imaging or histological reports without central revision, and the absence of long-term data. We did not take into account immunosuppressive therapies since the interpretation would have been too complex on a retrospective design.

Interest of the study and consequences on our practice

This is the first study, to our knowledge, to have compared a consecutive population of patients and their outcomes depending on whether they had been transplanted before or after the implementation of the AFP model in France. Under the same allocation system, we observed a change in practice, which complicates the interpretation of our results. Indeed we found a similar respect of the AFP model before or after its implementation, and we confirmed its value in predicting recurrence, but we observed a higher rate of recurrence during the recent period we can only partly explain.

The first message concerns the French practices. Downstaging policy, as it is applied for now, should be better framed, using for example USCF criteria for downstaging. Moreover, since there is a willingness to change the grafts allocation system for HCC (47) by introducing utility and favoring patients with no therapeutic alternatives, or patients with recurrence after a curative treatment (salvage transplantation), it is primordial to take into account the data of our findings: the 'temporary contraindication' policy and the multiplication of waiting therapies may have altered our results but the

study shows preceding treatments to LT caused an increased risk of recurrence. This has to be taken into account notably to decide at what moment the patients should be listed in this new system.

The second message concerns the external validity of the AFP model since recently, it has been evaluated in Italy (17), in Latin America (19) while the UK LT program discussed these criteria in the National Consensus Meeting. Our study emphasizes that the influence of many parameters on recurrence (compliance of teams, criteria for downstaging, median waiting time, salvage transplantation policy or subtleties such as 'temporary contraindication', maybe viral or immunosuppressive therapies) interfere and prospective studies would be necessary for each different system to assess the outcomes (35). Nevertheless, proofs that the AFP model has a better accuracy than Milan criteria for selection of HCC candidates are accumulating (16,17,19) and our study showed that the implementation of the AFP model did not cause a significant burden on our waiting list.

In conclusion, our study demonstrated that the implementation of the AFP model did not clearly change our practice at the time of LT, but rather helped to formalize the intuitive behavior of LT teams. The AFP score > 2 on the explants as on last imaging is well correlated to recurrence and survival and has to be more strictly respected. Finally, this study alerts on pejorative results in our recent cohort, with the necessity to initiate further and larger studies for a better understanding of the consequences of the recent changes in our practices.

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THESE SOUTENUE PAR : Bleuenn BRUSSET

TITRE : Impacts de l'application du modèle AFP pour l'attribution des greffons hépatiques dans le carcinome hépatocellulaire dans la vraie vie

CONCLUSION

Le modèle AFP conditionne en France depuis le 1er mars 2013 l'accès à la transplantation hépatique (TH) des patients atteints d'un carcinome hépatocellulaire (CHC). Cette étude rétrospective multicentrique en intention de traiter est la première à évaluer l'impact de ce changement de pratiques en comparaison avec les critères de Milan utilisés jusqu'alors. Elle montre d'une part que l'adoption du modèle n'a pas entraîné de modification notable sur les résultats histologiques de la greffe, puisque le taux de respect du score AFP était identique dans les deux populations étudiées, avant et après l'implémentation. La modification des critères n'a pas non-plus augmenté de manière significative le taux de sortie de liste de greffe pour CHC. D'autre part cette étude confirme qu'un score AFP supérieur à 2 est associé à un taux de récurrence élevé en post transplantation et donc à de moins bons résultats en survie post-greffe. Par ailleurs elle met en avant des résultats préoccupants en terme de récurrences tumorales au cours des dernières années. Cette discordance doit faire l'objet d'investigations complémentaires, car les hypothèses soulevées par l'étude observationnelle de notre cohorte sont la forte incidence de formes cholangiocarcinomeuses, mais également peut-être l'impact de nouvelles pratiques en transplantation hépatique comme la mise en contre-indication temporaire associée à la multiplication de traitements néo-adjuvants.

VU ET PERMIS D'IMPRIMER

Grenoble, le 25/08/2017

LE DOYEN

J.P. ROMANET

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et par délégation
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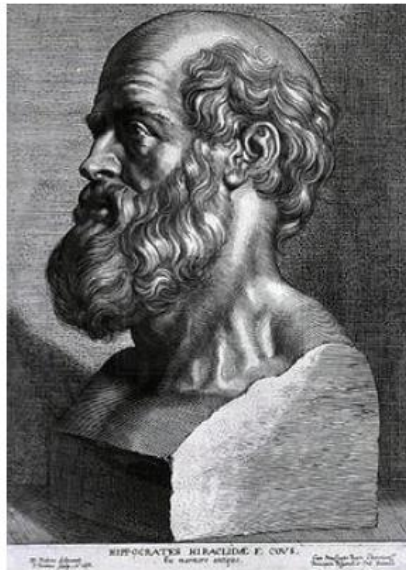
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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerais mes soins gratuitement à l'indigent et n'exigerais jamais un salaire au dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.

RESUME

Contexte: Au 1er mars 2013, l'Agence de Biomédecine a changé les critères d'attribution de greffon hépatique pour les patients atteints de carcinome hépatocellulaire (CHC). Les critères de Milan ont été remplacés par le modèle Alpha-Foeto-Protéine (AFP). Depuis cette date, seuls les malades avec un score $AFP \leq 2$ ont accès à la greffe. Le but de cette étude était d'analyser les résultats de la transplantation hépatique (TH) en intention de traiter depuis l'adoption du modèle AFP, et de les comparer aux résultats de la TH avant l'adoption du score AFP.

Patients et méthodes: La liste d'inscription de l'Agence de la Biomédecine a permis d'identifier 523 patients inscrits consécutivement sur liste de TH pour CHC entre mars 2011 et mars 2014 dans 5 centres français (Villejuif, Lyon, Lille, Montpellier et Grenoble). Ces 523 patients ont été inclus, qu'ils aient été transplantés ($n=364$) ou non ($n=159$). Le groupe Milan ($n=199$) était constitué des patients transplantés sous l'ère d'application des critères de Milan, fixée jusqu'au 1er juin 2013 pour prendre en compte la réévaluation trimestrielle, ou sortis de liste avant le 1er mars 2013. Le groupe AFP ($n=324$) était constitué des patients transplantés ou sortis de liste après.

Résultats:

Les caractéristiques des populations différaient dès l'inscription avec notamment des patients aux cirrhoses moins évoluées dans le groupe AFP, puis qui recevaient plus de traitements d'attente. Le temps d'attente médian était de 7,7 mois dans le groupe Milan vs 12,3 mois ($p < 0,001$) dans le groupe AFP, en grande partie du fait de l'instauration des mises en contre-indication temporaire.

En population globale le non-respect du modèle AFP sur l'explant était un facteur hautement prédictif de récurrence (SHR 6,85, $p < 0,001$) et de décès post-transplantation (HR 3,44, $p < 0,001$). Le taux de non-respect des critères AFP sur l'explant était similaire entre les deux populations (12,5% dans Milan vs 11,8% dans AFP, $p = 0,838$). Les facteurs indépendants prédictifs d'un non-respect du score étaient une politique de downstaging et un score $AFP > 2$ sur la dernière imagerie pré-greffe.

Le taux de sortie de liste, la survie globale post-inscription et la survie post-transplantation étaient similaires entre les groupes (respectivement 23,6 chez Milan vs 30,6% dans AFP, $p = 0,086$; 68,2 vs 66,7% de survie globale à 3 ans, $p = 0,447$ et 87,4 vs 82,7% de survie post-TH à 2 ans, $p = 0,100$).

Cependant, malgré l'absence de différence brute du taux de récurrence (9,2 vs 13,2%, $p = 0,239$), on retrouve dans les facteurs prédictifs de récurrence en analyse multivariée, l'appartenance au groupe AFP, ainsi que les traitements avant inscription, une politique de downstaging, et le fait d'être hors-critères AFP sur l'explant.

Conclusion:

L'implémentation du score AFP en France n'a pas changé les résultats histologiques de la greffe, mais permet le respect des critères d'allocation par les équipes, sans augmentation significative du taux de sortie de liste. Cependant l'appartenance au groupe AFP est significativement associée à la récurrence tumorale probablement du fait de l'allongement du temps d'attente et de l'augmentation des traitements. Cette étude soulève la nécessité de rediscuter la mise en CIT et de développer des solutions pour palier à la pénurie de greffons.