

Liver transplantation for hepatocellular carcinoma in clinical practice: the lesson from a 20-year multicentre experience in Italy

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Introduction Hepatocellular carcinoma (HCC) is an established indication for liver transplantation (LT), but the selection criteria and priority are still debated.

Aims To ascertain the number and features of patients with HCC who undergo transplantation in a Western country, the number of patients eligible for LT according to the American Association for the Study of Liver Diseases (AASLD) guidelines, the number of patients who actually undergo transplantation and whether adherence affects survival.

Methods This is a retrospective analysis from a multicentre Italian database of 2042 cases of HCC, recruited prospectively and consecutively. Kaplan–Meier (log rank) and Cox multivariate analysis estimated survival.

Results Patients who had undergone transplantation (50, 2.5%, with no change over time) had a median survival of 133 months, significantly influenced by the number of lesions and alpha-fetoprotein levels, which were found to be independent predictors of survival on multivariate analysis. Milan criteria were fulfilled in 68%, impacting on survival, whereas 48% fulfilled AASLD guidelines, without such an impact. Two hundred and twenty-eight (11%) patients were eligible for LT according to AASLD; in this group, alpha-fetoprotein levels and Child–Pugh class were independent predictors of survival.

Introduction

More than 40 years ago, Thomas Starzl performed the first liver transplantation (LT) [1] and, ever since, hepatocellular carcinoma (HCC) has been a primary indication for LT; however, the selection criteria, neoadjuvant procedures and priority in the waiting list are still under debate [2–4]. The pivotal work by Mazzaferro *et al.* [5] helped establish the most accepted criteria for LT nowadays, since then named the Milan criteria; owing to their efficiency in selecting candidates with an excellent post-LT outcome, these criteria were later adopted by the United Network for Organ Sharing (UNOS) [6]. Currently, the debate is quite intense on whether, how

Conclusion Among patients with HCC, those undergoing LT represent a small minority; even fewer (1%) are those who undergo transplantation according to AASLD guidelines, adherence to which only marginally affects survival. Overall, LT impact on HCC patients' treatment is very limited. *Eur J Gastroenterol Hepatol* 24:195–202 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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and how much these criteria should be broadened, in order to allow more patients to benefit from the only treatment that may cure both HCC and underlying cirrhosis [7], without endangering LT outcome. Indeed, good results were obtained adopting less stringent criteria concerning tumour burden, as in Yao's experience at the UCSF (University of California San Francisco) [8,9] and, more recently, in down-staged cases in three LT centres [10–12]; other authors suggest the application of biological parameters, such as tumour grading, to support the decision on eligibility for LT [13–15]. Recently, this topic has been addressed by Majno and Mazzaferro, who introduced the metro-ticket concept [16], a two-dimensional

graphic system to predict post-LT survival according to tumour size and nodule number [17,18].

The European Association for the Study of the Liver and American Association for the Study of Liver Diseases (AASLD) [19,20] defined the guidelines for the treatment of HCC in 2001 and 2005, respectively. In particular, the latest version has endorsed an articulate HCC staging system where LT is proposed for patients meeting UNOS policy criteria, not eligible for hepatic resection, in Child A or B class and with a good performance status. This therapeutic algorithm, which was updated very recently [21], conflicts with the everyday practice of many transplant centres, where Child C class and a slightly impaired performance status are not considered preclusive conditions.

Despite the past and the present efforts towards defining selection criteria to help identify all patients with HCC who would present excellent overall and disease-free survival after LT, the issue of LT as a treatment for HCC in the everyday clinical practice still raises a number of questions that remain unanswered:

- (1) how many patients actually undergo transplantation among all HCC diagnosed and what are their features, at least in Western countries?
- (2) how many would be eligible for LT according to the AASLD guidelines?
- (3) how many of the eligible patients actually undergo transplantation and how many undergo transplantation despite the lack of a definite indication?
- (4) does adherence to the available (AASLD and UNOS) guidelines have a favourable impact on the survival of patients who are eligible and who undergo transplantation?

The present study aimed at providing answers to the above questions, by analysing a large, multicentric, Italian database on HCC.

Patients and methods

This study is based on a retrospective analysis of data, inclusive of 2042 patients with HCC, recruited consecutively and prospectively from January 1987 to December 2006 at 10 clinical institutions forming the ITA.LI.CA (Italian Liver Cancer) group. Five of the nine centres belonging to the ITA.LI.CA group have a transplant centre at their institution, and the remaining centres are located in cities or in the hinterland of cities where a transplant centre is available. The diagnosis of HCC was histologically confirmed in 33% of the cases. In the rest of the patients, it was based on the guidelines on HCC, for lesions showing arterial enhancement and typical wash out in two imaging evaluations or combining a diagnostic increase in alpha-fetoprotein (AFP) (> 200 ng/ml) with typical features detected by one imaging technique. The modality of cancer diagnosis was defined as 'surveillance'

when HCC was detected during routine follow-up (6-monthly or yearly clinical examination and imaging), 'incidental' when an asymptomatic neoplasm was discovered outside a surveillance programme and 'symptomatic' when HCC was diagnosed because of the onset of symptoms.

Tumour size and number of lesions were determined on the basis of the imaging procedures performed, considering the diameter of the largest lesion in the case of multiple nodules. Tumour stage was determined according to the tumour–node–metastasis [22] and Cancer of the Liver Italian Program [23] staging systems, as in previous ITA.LI.CA reports [24–26]. Tumour stage was also retrospectively evaluated using the BCLC system [20], given the availability of reliable data on symptoms and performance status in the original database.

Virological status with respect to hepatitis B virus and hepatitis C virus infection was determined on the basis of routine virological tests. Alcohol abuse was considered as the regular consumption of more than 80 g of alcohol/day in men and 40 g of alcohol/day in women. The Child–Pugh class [27], the presence of relevant symptoms such as ascites, jaundice and 'constitutional syndrome' (fever, weight loss and pain), portal thrombosis, extrahepatic metastases or associated extrahepatic disease were recorded.

First treatment after diagnosis, that is, (a) transplantation (LT), (b) surgical resection, (c) radiofrequency-mediated thermal ablation (RFA) and percutaneous ethanol injection (PEI), (d) transcatheter arterial chemoembolization (TACE) or a combination of TACE and percutaneous treatments and (e) best supportive care (BSC) were recorded.

Survival was calculated from the time of HCC diagnosis to death or to December 2006 (end of the survey). Cases lost at the follow-up were censored at the time of the last clinical examination.

The data are reported as absolute numbers and median and range. The Kaplan–Meier method was used to estimate the overall survival (median and 95% confidence interval), defined as the interval between HCC diagnosis and death or the last follow-up visit. The forward conditional Cox model was utilized to identify the independent predictors of survival among the variables significantly associated with the survival on log-rank analysis. A *P* value less than 0.05 was considered statistically significant. The software utilized was SPSS 15.0 for Windows (International Business Machines Corp., Armonk, New York, USA).

Results

Patients who underwent liver transplantation

Overall, only 50 patients out of 2042 (2.5%) underwent transplantation. No increasing trend was observed on comparing the first decade (1987–1996) with the second

Table 1 Distribution of the patients who underwent transplantation according to the different variables

Variables	N (%)	Comments
Sex		
Males	43 (86)	M:F 6:1
Females	7 (14)	
Aetiology		
Viral	40 (80)	HBV = 14 HCV = 20, HCV + HBV = 6
Alcohol	3 (6)	
Viral + alcohol	7 (14)	
Child–Pugh		
A	19 (39)	Data available in 48 patients
B	22 (44)	
C	7 (17)	
TNM		
I	16 (33)	Data available in 48 patients
II	28 (59)	
III	2 (4)	
IV	2 (4)	
CLIP		
0	9 (20)	Data available in 47 patients
1	17 (36)	
2	15 (31)	
3	5 (10)	
4	1 (3)	
MELD	16 (median)	(range 6–27)
UNOS criteria		
In	34 (68)	–
Out	16 (32)	–
UCSF criteria		
In	41 (82)	–
Out	9 (18)	–
AASLD guidelines		
Indication for LT	24 (48)	–
Other indications	26 (52)	17: tumour burden beyond the limits; 5: Child C; 4: indication for resection

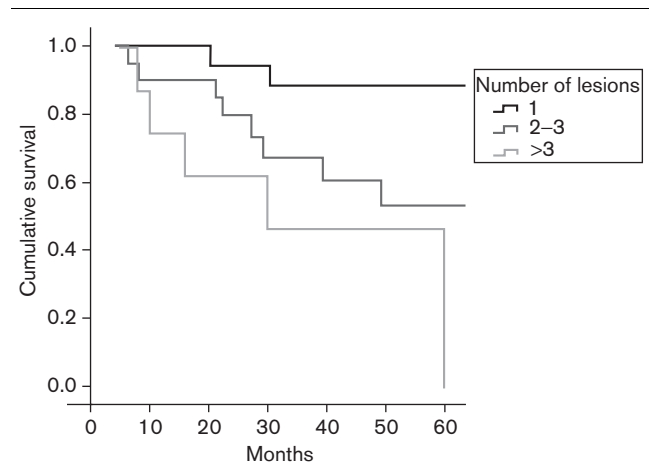
AASLD, American Association for the Study of Liver Diseases; CLIP, Cancer of the Liver Italian Program; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, model for end stage liver disease (available in 35 cases); TNM, tumour–node–metastasis; UCSF, University California San Francisco; UNOS, United Network for Organ Sharing.

decade (1997–2006) (2.5 vs. 2.4%). The series included 43 men and seven women, with a male to female ratio of 6.1:1. Their median age was 54.5 years. In the vast majority of patients, the aetiology of liver disease was viral. The Child–Pugh class was A or B in most cases, but 17% of patients were in class C. The MELD score was available in 35 out of 50 patients and its median value at the time of HCC detection was 16 (no information available for the MELD score at LT). The demographic and clinical characteristics of these patients are detailed in Table 1.

Of these 50 patients, 34 underwent transplantation according to UNOS criteria (68%) and 16 did not; among these, seven met the UCSF criteria, whereas nine did not meet the expanded criteria.

In terms of the number of nodules, 20 (40%) patients with a single HCC underwent transplantation, 21 (42%) with up to three nodules and nine (18%) with more than three nodules. Tumour size in patients with a single HCC was over 5 cm only in one case, whereas in those with multinodular disease, the size exceeded 3 cm in 10 cases (33%).

Fig. 1



Survival curves of patients who underwent transplantation according to the number of lesions ($P=0.009$).

Overall survival of patients who underwent transplantation at 1, 3 and 5 years was 85, 75 and 62%, respectively.

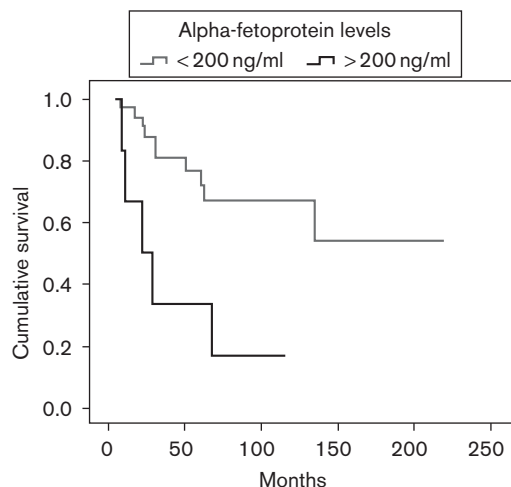
Survival was significantly better in patients with a single lesion than in those with up to three nodules or more than three nodules ($P=0.009$) (Fig. 1). There was no statistically significant difference in survival according to the size of lesions.

Twenty-one patients had AFP levels less than 20 ng/ml (42%), 15 had levels above this limit, but lower than 200 ng/ml, and 16 had levels above 200 ng/ml. The difference in survival among those with normal or slightly elevated AFP levels versus those with AFP higher than 200 ng/ml was highly significant ($P=0.003$) (Fig. 2). AFP levels and number of lesions were independent predictors of survival in the Cox multivariate analysis ($P=0.0001$ for both).

The survival was significantly better in patients who underwent transplantation according to UNOS criteria than those who did not meet the UNOS criteria ($P<0.0001$) (Fig. 3); the survival of patients who underwent transplantation according to the UCSF criteria, instead, was dismal and not significantly different from that of patients who did not meet the criteria. All the patients who met the UNOS criteria and had undergone transplantation were younger than 65 years; four of these patients were in Child–Pugh C class.

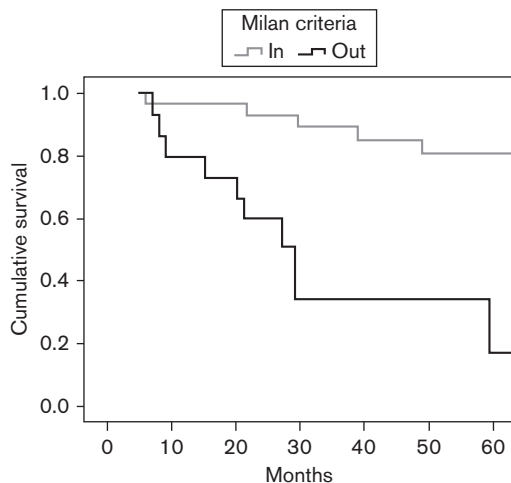
Overall, only 24 out of 50 patients (48%) underwent transplantation according to the AASLD guidelines. Of those who were not eligible for the procedure, nine had more than three nodules, one had a single lesion larger than 5 cm, seven had multiple nodules, one or more of whom larger than 3 cm, five were in Child–Pugh C class and four should have been referred for tumour resection

Fig. 2



Survival curves of patients who underwent transplantation according to alpha-fetoprotein levels ($P=0.003$).

Fig. 3



Survival curves for patients who underwent transplantation according to Milan criteria or beyond ($P<0.0001$).

since they had normal bilirubin levels and no oesophageal varices.

There was no statistically significant difference in survival between patients who met the AASLD criteria and underwent transplantation versus those who did not meet these criteria ($P=0.120$), even though the median survivals were 86 and 59 months, respectively (confidence intervals were 8–164 and 50–97 months, respectively).

Patients with indications to liver transplantation

According to the AASLD guidelines, patients eligible for LT should present the following features:

- (1) Child–Pugh class A–B, single lesion of 5 cm or less or up to three nodules, each of 3 cm or less, no indication for hepatic resection, no extrahepatic disease precluding LT and age lower than 65 years.

Considering the entire group of 2042 patients, 1038 (51%) had a tumour burden (number and size of lesions, absence of extrahepatic disease) that met the above criteria. Among these patients, 412 were not eligible for LT because they had very early HCC (123 patients) or early HCC (289 patients) with indication for resection, 73 only because they were in Child–Pugh C class and 325 because they were older than 65 years. As a result, 228 patients were eventually eligible for LT according to the AASLD criteria, that is, 11% of the entire series of patients with HCC. Comparing the two decades, the percentage was 15.8% in the first one and 9.8% in the second, with no significant difference. The main features of these patients were as follows:

- (1) 177 were men and 51 were women (M/F ratio of 3.5:1);
- (2) 142 had a single lesion and 86 had up to three nodules;
- (3) 119 were in Child–Pugh class A and 109 in class B.

Of the patients eligible for LT according to the above criteria, only 25 (11%) actually underwent transplantation, whereas the remaining patients underwent the following treatments:

- (1) 27 hepatic resections;
- (2) 55 percutaneous ablations (33 PEI and 22 RFA);
- (3) 68 TACE;
- (4) 12 TACE + PEI;
- (5) 41 received other medical therapy or BSC.

Among the 228 patients potentially amenable to LT, this treatment offered the best survival, followed by hepatic resection, RFA, PEI, TACE and BSC ($P=0.001$) (Table 2).

The relevance of the therapeutic choice was confirmed by the multivariate Cox analysis, which retained the following variables as independent predictors of survival: type of treatment, tumour size, AFP levels and Child–Pugh class, in that order (Table 3).

Finally, even if Child–Pugh C class patients with age below 65 years (41 patients) had been included among those eligible for LT, as is the rule in Italy, the overall number of patients eligible would have increased from 228 to 269 (from 11 to 13% of the initial population).

Discussion

The available data on the eligibility for LT and its outcome derive from the clinical activity of highly experienced transplantation units. Because of this selec-

Table 2 Survival of patients eligible for transplantation (228 patients), according to the treatment performed

Treatment	Survival		Confidence interval (95%)	
	Median value (months)		Inferior	Superior
Liver transplantation	143.7 (mean value) (median not reached)		104.115	183.253
Resection (27 patients)	56		39.306	72.294
RFA (22 patients)	44		32.897	55.103
PEI + TACE (12 patients)	41		32.664	49.336
PEI (33 patients)	36		27.586	44.414
TACE (68 patients)	34		28.330	39.670
Medical treatment	27		15.746	38.254
Best supportive care	23		15.043	30.957
Whole population	37		33.464	40.536

PEI, percutaneous ethanol injection; RFA, radiofrequency-mediated thermal ablation; TACE, transcatheter arterial chemoembolization.

Table 3 Independent predictors of survival, identified by Cox analysis, in patients eligible for transplantation

	Significance	Hazard ratio	Confidence Interval 95%	
Step 1				
Treatment	0.000	1.320	1.192	1.461
Step 2				
Treatment	0.000	1.339	1.204	1.490
Tumour size	0.000	1.426	1.194	1.703
Step 3				
Treatment	0.000	1.346	1.208	1.500
Tumour size	0.000	1.401	1.174	1.672
AFP	0.016	1.335	1.056	1.689
Step 4				
Treatment	0.000	1.319	1.185	1.469
Child–Pugh class	0.033	1.497	1.034	2.166
Tumour size	0.000	1.402	1.174	1.676
AFP	0.010	1.370	1.079	1.740

Tumour size and AFP were stratified. Treatments were as follows: (a) liver transplantation (LT), (b) surgical resection, (c) radiofrequency-mediated thermal ablation (RFA) and percutaneous ethanol injection (PEI), (d) transcatheter arterial chemoembolization (TACE) or a combination of TACE and percutaneous treatments and (e) best supportive care (BSC).

AFP, alpha-fetoprotein.

tion bias, our knowledge of the actual applicability of LT for HCC in an unselected population of patients, and consequently the real impact of this treatment, remains unclear. For an answer to this simple but important question, we analysed the data, collected prospectively, generated by the everyday clinical practice of 10 centres spread all over Italy where HCC is diagnosed and treated.

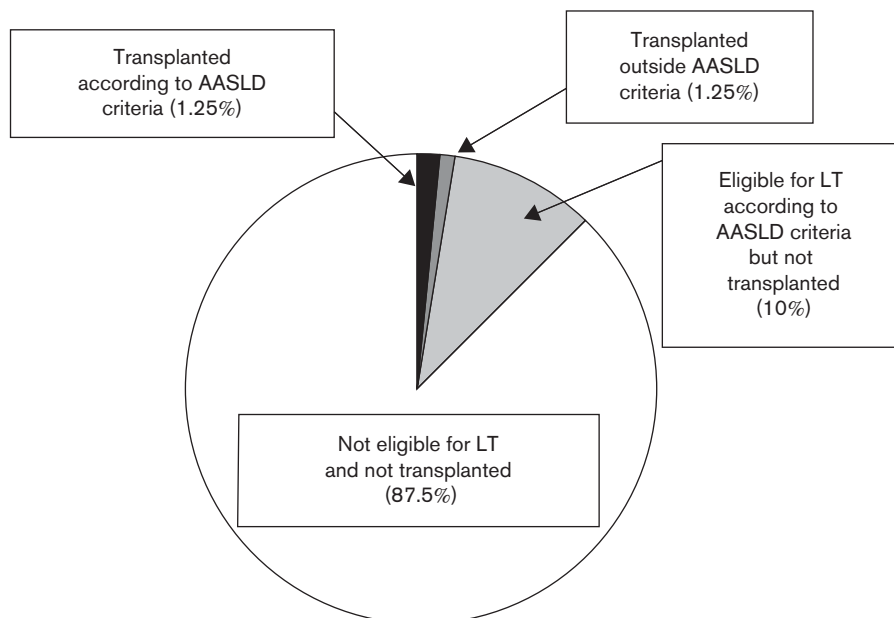
Our study showed that, in the clinical practice of the last 20 years in Italy, the percentage of patients among those who had been diagnosed with HCC who underwent transplantation is very small (2.5%). This figure was confirmed by the fact that, of over about 12 000–15 000 new cases of HCC diagnosed every year in Italy, 250–300 actually underwent transplantation, at least in the last 3 years (North Italian Transplant data), which is about 2%, a number that reinforces our conclusions. This occurred despite a definitely higher percentage of patients presenting indications of LT (11 or 13% if Child–Pugh C cases are also included). The same results have been reported by Braillon for France [28], where only 2% of patients with HCC undergo LT. Therefore, our study

primarily shows that, despite a relatively high proportion of patients with HCC amenable to LT and with a clear indication according to the current guidelines [20], only one-quarter to one-fifth actually undergo transplantation (Fig. 4). Because of the retrospective nature of our analysis, however, we cannot exclude that the impressive LT underutilization we observed was improperly increased by residual unreported comorbidities and/or a rather high rate of tumour progression among listed patients precluding LT; considering the observational model of the study of a multicentre Italian database, no further information is available on the dropout rate, time in the waiting list or bridging therapies that the patients had. Moreover, the criteria for LT eligibility in patients with HCC may vary among different transplantation units: in some, tumour grading is a relevant variable and in others, the up-to-seven updated Mazzaferro's criteria are used; in some cases, aggressive down-staging is performed. In fact, 97.5% of patients with HCC underwent alternative management, whether they had an indication for LT or not. This is a rather disappointing finding, particularly when considering that it indicates what actually happens in a developed country with a widespread application of surveillance programmes for the early diagnosis of HCC and with a good national network of transplantation centres. These figures would indeed be even more remarkable in countries with very high mortality rates for HCC, such as China, or sub-Saharan Africa, where tumours are most often diagnosed in an advanced stage and LT is not a therapeutic option.

In any case, it should be pointed out that, even in a country with a public and developed national health system, the probability of detecting a HCC at a stage theoretically amenable to LT is about 10%. Even though some of these patients can be efficiently treated by other methods, our data clearly show that their survival is lower than patients treated with LT.

Conversely, this study also shows that, if the therapeutic algorithm proposed by the AASLD guidelines had been followed, less than 50% of the patients who had under-

Fig. 4



Impact of liver transplantation on the entire population of patients with HCC. AASLD, American Association for the Study of Liver Diseases; LT, liver transplantation.

gone transplantation should have been treated by LT, the other half having tumour staging and/or liver function that should have precluded LT or indicated resection. As a result, overall, only 1% of the patients undergo transplantation in Italy according to the AASLD indications. Braillon [28] reports the same gap between indications and transplantation for France. In addition, the survival of transplanted patients is not significantly different whether they undergo transplantation according to the AASLD guidelines or not. This suggests that the recommended algorithm needs to be improved.

In our patients who underwent transplantation, the number of lesions was the most important prognostic predictor, followed by AFP levels. These data are in clear agreement with those recently published by Toso *et al.* [29], who suggest a composite selection score combining tumour burden and AFP for patients with HCC evaluated for LT.

In this experience, the overall survival, which is comparable to that reported in several other series, was influenced by adherence to the UNOS guidelines. Indeed, LT carried out according to the UCSF criteria indicated a marked decrease in survival, with figures that are not better than those of patients who did not meet the same criteria and had undergone transplantation. This result conflicts with what was recently reported by the centre that proposed these criteria [30], but needs to be confirmed, as it is based on a limited number of patients.

What happened to the patients who had an indication for LT but did not actually undergo transplantation? They underwent other types of treatment, radical or not, with over one-third being treated with TACE, one-quarter with percutaneous ablation and about 10% with tumour resection. As expected, on the basis of the available literature [31], those who underwent transplantation survived longer than those who had alternative treatment, with resection and RFA showing a better performance than PEI or TACE.

These data cannot be generalized to a worldwide scenario, but may help to shed light on the actual role of LT as a therapeutic option for HCC. If the figures we report from Italy were to be applied to approximately 600 000 new HCCs diagnosed per year worldwide, only about 15 000 patients would undergo transplantation, while all the debate on LT in HCC would not concern 585 000 patients. Moreover, as stated already, the proportion of patients undergoing LT is probably much lower worldwide, as in most countries where HCC incidence is high, LT is not a real therapeutic option, thus leaving it as a mirage to an even higher share of patients. Finally, adopting the AASLD therapeutic algorithm or not does not appear to be of paramount importance, given that most of the patients who undergo transplantation do not fulfil these indications for LT and, furthermore, whether or not they do, their survival is similar. More reliable prognostic staging systems are needed to optimize allocation to the different therapeutic

alternatives. To improve the prognostic accuracy of the selection criteria, we should probably take into account new molecular biomarkers and the response to neoadjuvant treatments aimed at downstaging and at avoiding tumour progression [32].

Is the debate on LT for HCC excessive? Is LT, as is commonly considered, a 'virtual' option for HCC? Should our efforts be more concentrated on improving surveillance, early diagnosis and alternative treatments? Obviously, the answer to these questions cannot be provided by our study, whose main goal is to consider the problem of an overstressed role of LT in the management of HCC.

Ethics: this epidemiological analysis did not involve studies on humans and thus did not need ethic committee approval; no details that may disclose the identity of the subjects were included.

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uted towards the collection and interpretation of the data. All authors have approved the final draft.

Conflicts of interest

There are no conflicts of interest.

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