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Invited article

Hepatocellular cancer and liver transplantation: necessity to go from chaos to order

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The care for liver-diseased patients presenting with hepatocellular cancer (HCC) is changing rapidly. Many treatment possibilities and caregivers belonging to a multitude of specialities troubled the therapeutic algorithm of the liver cancer patients. HCC in both normal and diseased livers has to be considered firstly as a surgical disease. The possibilities of surgery, including liver resections, as well as liver transplantation, have been underestimated and even been minimalized mainly as a consequence of many studies promoting in an unlimited way all different kinds of locoregional non-surgical and systemic therapies. Locoregional therapies and surgical procedures should not be seen as competing, but as complementary treatment options. Locoregional therapies are of value if surgery is not possible; in the context of transplantation they have an important role as 'downstaging procedures' allowing for bringing of transplantable patients into the required inclusion criteria. Systemic therapies and living donor liver transplantation will without any doubt occupy a more important role in the future therapeutic scheme of HCC.

Key words: hepatocellular cancer, liver transplantation, disease management

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Liver transplantation (LT) has originally been designed by Thomas Starzl to treat *irresectable* primary and secondary hepatobiliary tumours [1, 2]. The first LT was performed on March 1, 1963, whereas the first 'successful' LT on July 23, 1967. This patient was transplanted because of hepatocellular cancer (HCC) developed in the context of biliary atresia. Many re-interventions, done in order to treat both thoracic and abdominal tumour recurrences, 'allowed' the child to survive 400 days. The stage was set, LT became feasible and progressively gained its place in the treatment of many benign and malignant liver diseases. Starzls' original concept became rapidly challenged by the prohibitively high incidence of tumour recurrence and thus dismal patient survival (PS). The explanation for the failing concept was simple. Due to lacking selection criteria, patients were transplanted at a too much advanced tumour stage resulting in a prohibitively high recurrence rate [3]. As a consequence, LT developed over a period of three decades towards the standard treatment of end-stage benign liver diseases. As it is frequently the case, the pendulum came back beginning of the 1990s, when the LT community renewed its interest in LT as a possible treatment of HCC by introducing more strict selection criteria. The Paris and Milan groups were the first to show that excellent results and even cure could be obtained by restricting the indication to *resectable* tumours [4, 5]. A tumour load restricted to not more than 3 tumours having a diameter ≤ 3 cm or to 1 tumour having a diameter ≤ 5 cm allowed to obtain five- and even ten-years disease free survival (DFS) rates reaching 80 to 90%. Many, especially Western, groups worked at a cautious extension of these inclusion criteria; many, especially Eastern, groups adopted a more aggressive attitude essentially based on the explosive development of living donor liver transplantation (LDLT) [6]. The Milan criteria, introduced in 1996 and accepted thereafter by the international community as the gold standard to select HCC patients for LT, became rapidly challenged [7–9]. These criteria were proven to be too restrictive thereby denying the access of many patients to a potentially curative LT. The 'kick off' for the 'score rush' had been given… up to now at least 40 have been reported in literature!

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In parallel to the development of LT, many surgical and non-surgical locoregional therapies (LRT) as well as systemic treatments, have been developed to treat HCC [10]. Without any doubt, surgery in form of partial or total hepatectomy (or LT) is still the only therapy that can provide definitive cure [11, 12]. Unfortunately, partial resection is only possible in a minority (10 to 20%) of patients due to the frequently present insufficient functional reserve caused by the underlying liver disease [13]. Several, less aggressive, interventional radiologic procedures (such as percutaneous alcoolisation, radiofrequency [RF]), transarterial[chemo-]embolisation [TA[C]E]) and external radiotherapy ('CyberKnife') have all been developed to overcome this problem [10]. In the beginning of the 21st century systemic therapy using multi-kinase-inhibitors (e.g. the target drugs sorafenib and derivatives) and immunotherapy (e.g. the PD1-inhibitor nivolumab and derivatives) were added to the therapeutic algorithm of HCC in liver diseased patients [14, 15]. The 'kick off' for the search towards the best possible treatment had been given, and up to now at least 30 treatment modalities have been reported! Unfortunately, these developments lead to a reduced impact of liver resection and transplantation in the therapeutic algorithm of HCC developed in a diseased liver!

Today, when facing liver diseased patients harbouring HCC, the clinician is confronted with two 'towers of Babel': one of scores and one of therapeutic modalities [13, 16]. Needless to say that this leads to lots of confusion resulting in very heterogeneous approaches to the same disease. It's time to bring order in the chaos…

The 'treatment tower of Babel' or how to integrate at the best all possible systemic and (surgical as well as non-surgical) locoregional treatments? (Fig. 1)

In the widely accepted EASL-AASLD criteria, surgery only plays a minor role. The Barcelona (or AASLD-EASL) 'HCC in cirrhotic liver' scheme deals with five stages: very early (A), early (B), intermediate (C), advanced (D) and terminal (E). Even in the April 2018 revision of this algorithm, the role of surgery and even transplantation is (still) reduced to the very early (single tumour < 2 cm with preserved liver function) and early (single or 2–3 nodules with preserved liver function) stages [13]. In case of intermediate (meaning multiple, unresectable tumours with preserved liver function) or advanced stage (meaning macrovascular [portal] invasion or extrahepatic in the presence of preserved liver function) surgery is eliminated from the treatment, despite the fact that recent East-West experiences showed that in these two stages (C and D) the results can be obtained which are much better than those obtained by chemo-embolization and systemic therapy [12, 17]. Indeed five-year PS rates ranging from 30 to 50% and five-year DFS rates of 20 to 25% can be obtained if surgical and peri-operative care expertise is on board [11]. In case of portal vein thrombosis five-year PS can reach 20 to 50%, depending on the extension of the tumour thrombus; similar results have been reported after resection in the presence of hepatic vein thrombosis [12, 17].

The Hong Kong group, disagreeing firmly with the Barcelona scheme, proposed a new therapeutic scheme, in which surgery is implemented in nearly all stages of the disease. By doing so, results were generated which were far superior to those obtained when applying the Barcelona criteria [18].

The feasibility of minor (tumorectomy or ≤ 3 segmentectomies) or major (> 3 segmentectomies) liver resection depends on the functional liver reserve. Different tests have been developed to determine this. The Indocyanine green retention rate at 15 minutes (ICG R15) and the absence of ascites and jaundice remain good indicators of an adequate functional reserve [19]. Indeed, complying with these 'Makuuchi criteria' allows for liver resections in cirrhotic patients with a very low mortality (< 5%). More recently the regenerative capacity of the cirrhotic liver after portal vein embolization (PVE) has been added to these criteria to further improve the selection criteria

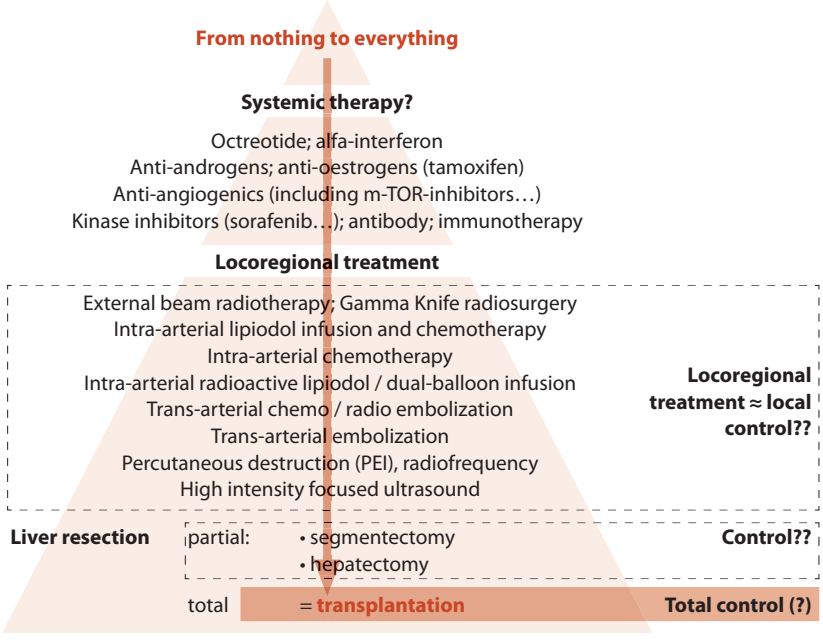

Fig. 1. The hepatocellular cancer therapeutic tower of Babel: from nothing (therapeutic abstention) to everything (liver transplantation)

for resection. It is clear that such results can only be obtained by combining thorough investigation, good knowledge of intra-operative ultrasound and excellent surgical skills. The introduction of PVE, sequential TACE-PVE, and even the ALPPS procedure (Associating [partial] Liver Partition and Portal vein ligation for Staged hepatectomy) have been added to the armamentarium of the surgeon in order to extend the possibilities of safe liver resection [20].

Based on all these knowledge, it is clear that HCC, especially in a diseased liver, has firstly to be considered as a surgical disease. The first question to put forward in the multidisciplinary team discussion should be if the patient has to be considered as a candidate for locoregional surgical (this means partial resection) treatment or for total hepatectomy (this means LT). If not, one should take into consideration all other non-surgical LRTs and authorized systemic therapies. RF and TACE are the most frequently used non-surgical LRT [10, 13, 21]. RF is an excellent treatment for the very early / early tumour, generating results equal to resection. Evidently, if such LRTs are applied, tight follow-up schemes are necessary in order to detect early recurrence.

The 'score tower of Babel' or how to expand inclusion criteria for liver transplantation in a justified way? (Fig. 2)

In 1996, V. Mazzaferro et al. published in the New England Journal of Medicine a retrospective study in 48 HCC liver recipients [5]. When the tumour load was restricted to not more than 3 tumours having a diameter up to 3 cm or to 1 tumour having a diameter ≤ 5 cm, it was possible to obtain four-year DFS rates of 92%. Bismuth's group had already published 3 years before similar results in a series of 60 liver recipients: tumour load of less than 2 tumours of < 3 cm resulted in 92% DFS at 3 years [4]. In 2001, the UCSF group was the first to challenge the restricted Milan criteria… by extending the tumour load by 1.5 cm (1 nodule ≤ 6.5 cm, or 2–3 nodules ≤ 4.5 cm and total tumour diameter ≤ 8 cm) [8]. Similar PS and DFS rates could be obtained. Many more criteria were developed since then, reaching the number of 20. The majority (16) of them were proposed by Western centers. Only a minority of them includes tumour biopsy [22]. All of them allowed in a certain way to extend inclusion criteria without significant compromising of the results, if the tumour load remained within their extended 'newly proposed' criteria (75 to 85% five-year PS). Basically all these criteria can be grouped under the common denominator 'Metroticket', meaning that the more extended are the criteria, the higher is the price to pay, this means the higher is the recurrence rate after transplantation [9]. It is of great importance to underline that all these extensions were based on *morphologic criteria only*, namely, tumour *number and diameter*. Such concept should nowadays be overruled by the principles of modern oncologic treatment which combines both tumour morphology and biology [23–25]. Twenty scores combining both tumour characteristics have been reported; the majority (13) of them originated from Eastern centers. Compared to the Milan criteria, combination of tumour morphology and biology allowed to extend inclusion criteria up to 66% (!) without heavily compromising the outcomes [6, 25]. The Kyoto group was the first one to add to tumour number and diameter the level of des-carboxy-prothrombin (DCP or Protein Induced by Vitamin K Absence [PIVKA II]) [26] followed by the Hangzhou group who added alfa-foetoprotein (AFP) level [27]. The Japanese LT Society and Seoul National University scores added a combination of both tumour markers, AFP and DCP [28, 29]. All these scores merely vary in relation to cut off values of tumour number (from 1 to 10), diameter of the largest tumour (from 3 to 10 cm), AFP and DCP cut off values (from 100 to more than 1000 ng/ml and from 300 to 450 mAU/ml, respectively). Further refinements were made by adding inflammatory markers, such as neutrophil-lymphocyte (NLR) and/or platelet to lymphocyte (PLR) ratios [30].

The next progress in refinement of inclusion criteria was the change from *static to dynamic tumour behaviour*, this mostly as a corollary of pre-transplant neo-adjuvant LRTs, which are applied in daily clinical practice in around 70% of potential recipients [31]. It has indeed been shown in several studies without and (merely) with LRTs that tumour dynamics as documented by the slope of AFP and/or DCP and m-RECIST (modified-Response Evaluation Criteria In Solid Tumours) criteria are able to erase the differences in outcome between Milan criteria-in and Milan criteria-out recipients [32]. AFP slope of < 14 ng/ml / 14 days and a morphologic response on imaging using m-RECIST criteria are favourable prognostic factors [33, 34]. The larger SRTR (Scientific Registry of Transplant Recipients) study by S. Merani et al. even showed that patients reducing their original AFP levels from above to beneath 400 ng/ml after LRT generate the best results after LT [35]. More recently, the introduction of positron emission tomography allowed to further extention of the inclusion criteria to HCC presenting macrovascular tumour invasion [29, 36]. The first results are encouraging… a story to follow carefully!

Morphology	Morphology and biology	
• MILAN = GOLD STANDARD (?)	• SEOUL	+ AFP
• UCSF	• HANGZHOU*	+ AFP
• BARCELONA	• CHENGDU*	+ AFP + NLR
• BOLOGNA	• NEW YORK MORAL	+ AFP
• BERLIN	• SRTR TTV	+ AFP
• ITALIAN SCORE	• FRENCH	+ AFP
• MILAN UP TO SEVEN	• METROTICKET 2.0	+ AFP
• PARIS	• MEDANTA	+ AFP + PET SCAN
• NAVARRA	• KYOTO	+ DCP
• VALENCIA	• KIYUSHU	+ DCP
• DALLAS	• JAPANESE AP	+ AFP × DCP
• EDMONTON	• SNUH MoRal	+ AFP × DCP
• NEW YORK MOUNT SINAI	• SEOUL	+ PET SCAN
• PITTSBURGH*	• MUNCHEN	+ PET SCAN
• TORONTO*	• TRAIN	AFP + NLR
• UCSF-RETREAT		
• FUKUOKA		
• SHANGAI FUDAN		
• TOKYO		
• TUMOR BURDEN SCORE		

Fig. 2. The hepatocellular cancer – Liver transplantation prognostic tower of Babel: scores developed by different centers based on either morphologic (number and diameter of tumours) and biologic tumour behaviour (tumour markers, response to locoregional therapies, positron-emission tomography scanning); *UCSF* University of California, San Francisco; *SRTR* Scientific Registry of Transplant Recipients; *TTV* total tumour volume; *SNUH* Seoul National University Hospital; *AFP* alfa-foetoprotein; *NLR* neutrophil lymphocyte ratio; *PET SCAN* positron-emission tomography; *DCP* des-carboxy-prothrombin; *TRAIN* Time on waiting list, Response to locoregional treatment, AFP slope and INflammatory marker NLR; * tumor biopsy

LRTs are frequently used as 'downstage' procedures allowing for bringing the patient to comply with the inclusion criteria for transplantation.

The implementation of immunosuppressive minimization protocols will undoubtedly be of importance when enlarging the inclusion criteria for transplantation [37, 38].

The rather aggressive extension of inclusion criteria in the Eastern world is largely explained by the extensive experience in the field of LDLT [39]. This condition indeed allows for approach the HCC patient in a planned way, which by definition allows to 'dominate' both the factors 'time and tumour'.

Despite the important progresses made in relation to the extension of inclusion criteria for LT by integrating tumour morphology and biology, two important problems remain to be solved. How to integrate in a reliable way microvascular invasion, a feature which reduces in every setting the results of LT for HCC by around 20% and how to provide an easy and reliable score consisting of easily obtainable parameters before LT. Microvascular invasion, as well as the degree of tumour differentiation, are difficult to capture even with a biopsy. This is explained by the morphologic and immunohistochemical heterogeneity of the tumour, as well as by the differences in 'tumour drive' [40]. DCP could serve as a surrogate marker for microvascular invasion; the higher the DCP level, the higher the probability of microvascular invasion [41, 42].

Q. Lai et al. developed a score based on *easily obtainable pre-LT parameters* able to predict drop out in case of long and a recurrence in case of short waiting times. This TRAIN score looks at intention-to-treat mortality of HCC patients by combining the following, both dynamic, morphologic and biologic parameters: **T**ime on waiting list, tumour number and diameter (Milan criteria), **R**esponse to LRT, **A**FP slope and the **IN**flammatory marker NLR. Recently the original study patient cohort of 289 patients has been extended up to 2200 patients by including five Eastern (Dehli Medanta, Hangzhou, Kaoshiung, Kyoto, and Kyushu) and five Western (Brussels, Innsbruck, Mainz, New York Columbia and Rome) centers [43]. The involvement of the Eastern centers allowed to include LDLT as a fifth (protective) parameter. Based on this most recent analysis, a score has been made with the range of 6 to 40, similarly to the MELD (Model for End-stage Liver Disease) score. Different categories could be created allowing for an accurate prediction of mortality and tumour recurrence after LT [Q. Lai et al. in press].

Recently, more and more attention has been given to transplant benefit and intention-to-treat transplant benefit, thereby highlighting that to offer the best possible treatment to the patient, all treatments for HCC have to be seen as complementary and not as competing ones [44, 45]. Transplant survival benefit corresponds to the number of years gained by LT minus the number of years offered by alternate

treatments from the moment of LT in an 'time horizon' of 10 years. This time span allows for making the difference between the principles of urgency and utility of LT [44]. Transplant intention-to-treat survival benefit adheres to a same concept, but now by considering the gain in life expectancy from the moment of registration in the waiting list, taking thereby thus into consideration any therapeutic possibility from the moment of diagnosis of the HCC. Four variables, namely, Milan criteria in status, low MELD score, radiological progression or complete response (measured by m-RECIST criteria) and biological progression (measured by AFP level) allow for identification of groups with no, small, moderate and high benefit. Low and high benefit means that LT confers a median survival gain ranging from 0 to 60 months [46]. It is important in this context to develop an allograft allocation process guaranteeing an equal access to the organ pool for patients with and without HCC [47–49].

Conclusions

The care for liver diseased patients presenting HCC is changing rapidly. Too much treatment possibilities and too many caregivers belonging to a multitude of specialities troubled the therapeutic algorithm of the liver cancer patients. Multidisciplinary care is evidently at stake when dealing with these patients, the decision maker in the team should however (again) be(come) the surgeon. HCC in both normal and diseased livers has to be considered firstly as a surgical disease. The possibilities of surgery, including partial, as well as total hepatectomy (this means LT), have been underestimated and even been minimalized mainly as a consequence of many industry-driven studies promoting in an unlimited way all different kinds of locoregional non-surgical and systemic therapies. LRTs and surgical procedures should not be seen as competing, but as complementary treatment options. LRTs are of value if surgery is not possible; in the context of transplantation they have an important role as 'downstaging procedures' allowing for bringing of transplantable patients into the required inclusion criteria. Systemic therapies and LDLT will without any doubt occupy a more important role in the future therapeutic scheme of HCC. Putting together both Western and Eastern experiences in this important field of oncology will be the way to go forward and so bring order in the chaos… a necessity to improve the long-term outcome of these patients!

Conflict of interests

No conflicts have to be declared in relation to the presented work. S.I. is recipient of the Hepatotransplant and Euroliver Foundation grants, attributed for research in hepatocellular cancer and liver transplantation.

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