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REVIEW

The challenges of liver transplantation for hepatocellular carcinoma on cirrhosis

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Summary

Hepatocellular carcinoma (HCC) is a major cause of cancer mortality worldwide and liver transplantation (LT) has potentials to improve survival for patients with HCC. However, expansion of indications beyond Milan Criteria (MC) and use of bridging/downstaging procedures to convert intermediate-advanced stages of HCC within MC limits are counterbalanced by graft shortage and increasing use of marginal donors, partially limited by the use of donor-division protocols applied to the cadaveric and living-donor settings. Several challenges in technique, indications, pre-LT treatments and prioritization policies of patients on the waiting list have to be precised through prospective investigations that have to include individualization of prognosis, biological variables and pathology surrogates as stratification criteria. Also, liver resection has to be rejuvenated in the general algorithm of HCC treatment in the light of salvage transplantation strategies, while benefit of LT for HCC should be determined through newly designed composite scores that are able to capture both efficiency and equity endpoints. Innovative treatments such as radioembolization for HCC associated with portal vein thrombosis and molecular targeted compounds are likely to influence future strategies. Accepting this challenge has been part of the history of LT and will endure so also for the future.

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and accounts for more than 500 000 deaths annually [1]. The major risk factor for developing HCC is chronic liver disease and cirrhosis, which is present in 70–90% of patients, with a cumulative 5-year incidence ranging between 15% and 20% [2]. The major causes of cirrhosis in patients with HCC include hepatitis B (HBV) and hepatitis C infections (HCV), followed by alcoholic liver disease and nonalcoholic steatohepatitis. Globally, HBV infection is the most frequent cause of HCC, while it is noteworthy that 10–30% of HBV-related HCCs arise in the absence of cirrhosis [3].

Surgical treatment has always been considered as the major curative option for HCC, although eligibility and outcome of patients undergoing resection depend on two variables: the tumour itself and the underlying liver disease at the time of treatment, the latter captured by composite scores such as the Child–Pugh stage [4].

Over the last two decades, the role of surgery has been challenged by nonsurgical options and currently liver resection remains the optimal curative treatment for HCC in noncirrhotic patients, while in the case of overt cirrhosis, candidates to resection have to be carefully selected to diminish the risks of postoperative liver failure and death [5]. Different from resection, liver transplantation (LT) has found an increased application as it offers the perspective of curing at the same time HCC and the underlying cirrhosis, using a single procedure.

The early series of LT for HCC report disappointing results (survival of <40% at 5 years), related to large tumour bulks removed in individuals with several other adverse prognostic factors [6–8]. However, the observation of patients with incidental small HCCs, having similar survival of individuals without cancer, leads to the conclusion that tumour stage at the time of liver removal is a major determinant of prognosis [9]. In particular, the

early stage HCCs defined by the Milan Criteria (MC) (single nodule up to 5 cm or <3 nodules <3 cm) may achieve superior outcome after LT in comparison with any other alternative option [10], and that was recognized by the incorporation of MC in the revisions of the tumour-node-metastasis classification system.

Also, the United Network for Organ Sharing (UNOS) in 1998 incorporated MC into the T1 and T2 categories for enlisting patients with HCC and later on, the T2 stage (T > 2 cm but <5 cm) became a condition worth prioritization in the Model for End Stage Liver Disease (MELD) system [11,12].

In the last two decades, the increasing demand for LT in HCC and the shortage of donors have fostered technical advancements in cadaveric and living donor settings, while challenging procedures such as split-liver and hemiliver donation [13,14] have been paralleled by the use of an increasing number of marginal donors to be assigned to the best matching recipient.

In this review, we will attempt to summarize some of the open issues that LT continues to propose to specialists and general practitioners, both called to accept the challenges of the expanding field of HCC treatment [15].

The challenge of technique

Since the first operation performed in 1963 and up to the introduction of cyclosporine as the cornerstone immunosuppressant agent about 20 years later [16], liver transplantation represented an exclusive technical challenge. In the late 1980s, the field rapidly developed and since then surgical techniques have contributed to the worldwide practice of LT, through continuous refinements aimed at two main end-points:

1 Make the procedure easier (i.e. through reconstruction of the venous outflow of the graft with no need of extracorporeal circulation [17,18]) and/or prevail over recipient-related obstacles, such as portal thrombosis or arterial anatomic variations [19].

2 Overcome the shortage of donors by means of innovative procedures such as split-liver division of a deceased-donor organ for two recipients of different sizes [13,20], domino liver transplantation [21] and living-donor liver transplantation (LDLT): the ultimate figure of technical expertise originally applied in children [22] and then in adult living donor liver transplantation (ALDLT), mainly through the use of a donated right-lobe graft (segments V to VIII) [23] or through the implantation of two left lobes harvested from two different living donors [24].

The number of such procurements based on parenchimal division of the graft either from cadaveric or living donors seems to have reached a plateau, at least in the Western world. However, the technical challenge offered by demanding donor-recipient characteristics has become routine and this has provided realistic hope of new life for thousand of recipients with HCC, who otherwise would have no access to transplantation.

Although further improvements in technical management of the donor-recipient couple can be expected, some anatomical limitations are likely to represent a permanent limit for the universal application of LT. Therefore, pre- and post-transplant combined strategies against HCC and allocation of resources according to precise individualization of prognosis will be crucial areas of clinical research. Particularly, in the field of organ allocation, the 'sickest-first' strategy, derived from the application of the MELD principle to cirrhotic patients, still needs to find a reliable counterpart in the subgroup of patients with HCC, whose transplantation benefit cannot be completely captured with the currently available instruments.

Close to the operating theatre, pharmacological interventions may have also a role in promoting experimental perspectives currently excluded from standard criteria for LT such as the routine use of non heart-beating donors [25], the management of small-for-size syndrome [26,27] and the development of dedicated immunosuppression protocols for patients with cancer [28].

The challenge of indication: expansion of selection criteria for LT in HCC

Although excellent post-transplant survival can be achieved when MC [10] are applied (<10% recurrence rate at 5 years), several experiences suggest that such restrictive criteria may exclude from LT patients with HCC at various stages of advancement, who could potentially benefit from transplantation.

Unfortunately, with the partial exception of the University of California San Francisco (UCSF) criteria (single HCC up to 6.5 cm in diameter or up to three nodules, none larger than 4.5 cm, a cumulative diameter up to 8 cm) [29] all the proposals of criteria extensions are derived from retrospective monocentric cohort studies. The lack of robust data and the low scientific evidence (Table 1) derived from most of these studies have caused significant heterogeneities among Centres with respect to listing policies, with particular reference to patients with HCC exceeding MC [30].

In a recent retrospective cohort study [31] collecting the largest sample ever of transplant patients exceeding MC, it has been shown that an excellent outcome exists outside the conventional restrictive criteria, with the upper limits defined by the 'up-to-seven' rule in the absence of vascular invasion. This proposal emphasizes the worth of transplanting HCCs presenting with a sum of the combination of size-and-number covariates equal

Table 1. Classification of evidence according to the strength of study design and of endpoints (adapted from National Cancer Institute: http://www.cancer.gov).

Study design	
Randomized controlled trial, meta-analysis	1
Double blinded	1i
Nonblinded treatment delivery	1ii
Nonrandomized controlled trials	2
Case series	3
Population-based	3i
Non population-based, consecutive	3ii
Non population-based, nonconsecutive	3iii
Endpoint	
Survival	A
Cause-specific mortality	B
Quality of life	C
Indirect surrogates	D
Disease-free survival	Di
Progression-free survival	Dii
Tumour response	Diii

The various types of study design and the commonly measured endpoints for cancer treatment studies are described in descending order of strength.

to 7 or less [i.e. five nodules up to 2 cm (5 + 2 = 7) or four nodules up to 3 cm (4 + 3 = 7) or three nodules up to 4 cm or two nodules up to 5 cm or a single nodule of 6 cm]. The 'up-to-7' limits, although based on post-transplant pathology assessment of tumour stage rather than on preoperative radiology, capture most of the alternative proposals of expansion of conventional criteria originated both in the East and the West (Table 2) [29,31–42] and it is likely to represent an important aid for medical and surgical prospective investigations.

The use of a prognostication software derived from the analyses of this experience (http://www.hcc-olt-metroticket.org/calculator/) will allow the adherence to an inclusive investigational attitude focused on HCC exceeding MC, through a more objective pretransplant determination of prognosis and through a better subgroup stratification.

Within the results of the Metroticket project is the fact that different morphological combinations of HCC (size-and-number) are associated with similar post-transplant survival. This is part of the common practice and confirms the paradigma of a progressively decreased post-transplant survival as the tumour bulk increases at the time of first diagnosis [30].

A possibly different approach has been advocated for living donation where rules are not dictated by graft shortage and by long waiting lists [34–38,40]. Nevertheless, the origin of liver graft *per se*, either from deceased or living-related donors, is likely to exert a small influence on post-transplant outcome of patients with HCC, although cancer growth and viral reactivation have been related to graft regeneration in recipients of living donations or small-for-size-grafts [43].

Conversely, the virtual zeroing of the waiting time for advanced HCC undergoing LDLT can be associated with a 'fast-track effect': a higher recurrence rate in patients

Table 2. Proposals of expansion of conventional criteria in deceased and living donor liver transplantation for HCC.

Author (year), centre	Expanded criteria	Five-year specific survival for exceeding MC
Yao *et al.* (2001), San Francisco [29]	1 HCC ≤ 6.5 cm or ≤3 HCC ≤ 4.5 cm with cumulated diameter ≤ 8 cm	73%
Herrero *et al.* (2001), Pamplona [32]	1 HCC ≤ 6 cm or ≤3 HCC ≤ 5 cm	73%
Onaca *et al.* (2007), Dallas [33]	1 HCC ≤ 6 cm or ≤4 HCC ≤ 5 cm	N/A
*Kwon (2007), Seoul [34]	HCC ≤ 5 cm, no number restriction AFP ≤ 400 ng/ml	80% (including Milan)
*Jonas *et al.* (2007), Berlin [35]	Any number, each ≤6 cm with cumulated diameter ≤ 15 cm	62% at 3 years
*Takada *et al.* (2007), Kyoto [36]	≤10 HCC, each ≤5 cm PIVKA-II < 400 mAU/ml	67%
*Soejima *et al.* (2007), Fukuoka [37]	Any number, each ≤5 cm	74%
*Sugawara *et al.* (2007), Tokyo [38]	≤5 HCC ≤ 5 cm	70% (at 3 years)
Zheng *et al.* (2008), Hangzhou [39]	Total tumour diameter ≤8 cm or HCC grade I/II and AFP ≤ 400 ng/ml	72.3%
*Lee *et al.* (2008), Asan [40]	≤6 HCC ≤ 5 cm	76.3%
Silva *et al.* (2008), Valencia [41]	≤3 HCC ≤ 5 cm with cumulated diameter ≤ 10 cm	67%
Toso *et al.* (2008), Edmonton [42]	TTV ≤ 115 cm^3	72%
Mazzaferro *et al.* (2009), Milan [31]	Number of HCC nodules + maximum diameter (cm) ≤ 7	71% (if mVI absent)

N/A, not available; MC, Milan Criteria; HCC, hepatocellular carcinoma; mVI, microvascular invasion.
*LDLT, living donor liver transplantation.

with a biologically aggressive tumour, whose drop-out on list because of tumour progression may be prevented by the prompt availability of the graft [44].

Based on such an experience and considering the time factor as a surrogate of tumour aggressiveness, reconsideration of lengthening of the waiting time in recipients largely exceeding MC and receiving a living donation should be taken into account, especially when reliable prognostic factors or effective downstaging procedures are not available.

Even though some experiences from the East show survival rates of 70% at 5 years after LDLT in patients with HCC exceeding MC (Table 1), the upper limits in tumour stage allowing listing or delisting policies remain to be determined *a priori*, to avoid dreadful outcomes or to transform pre-LT drop-outs into post-LT recurrences [30]. It also has to be considered that when the technical challenges offered by some transplant procedures are so demanding, learning curves are slow and insufficient [15].

A further development of investigations dealing with tumour characteristics affecting post-LT survival is the total tumour volume (TTV) determination as a surrogate of the conventional morphological covariates: size and number [42]. A TTV of ≤115 cm^3 associated with an alpha-fetoprotein (AFP) serum level of ≤400 ng/ml may select HCC patients with a 3-year post-transplant survival similar to those within MC [45]. The main advantage of TTV with respect to Milan and UCSF criteria is that the number of nodules does not represent a limitation and this, as for the 'up-to-7' criteria, may increase the number of transplant procedures for HCC without a significant deterioration of outcome [46].

Further contribution to the disputed field of expanded criteria will be given by composite scores that are able to include both morphological and biological/pathological covariates. While reliable markers of HCC behaviour are still in the pipe-line of genomic and epigenomic search of a molecular classification of liver cancer, pathology surrogates such as microvascular invasion (mVI) [47], grade (G) of tumour differentiation [48] and microsatellites close to the main tumour nodule [49] remain significantly associated with post-LT outcome in most studies [50]. Open questions remain on how pathology covariates can be determined with high specificity and sensitivity ahead of transplantation, avoiding mismatched pathology–radiology staging. There is evidence that the relative importance of pathology surrogates in determining post-transplant prognosis appears to be more important in patients exceeding conventional criteria. In that respect, pretransplant biopsy of HCCs exceeding conventional limits could be an option, [51] even though the positive and negative predictive value of an HCC biopsy in cirrhosis has been questioned, particularly in multifocal tumours [52,53].

Besides differences among centres in staging and listing policies for patients with HCC, a reliable expansion of MC remains a major issue to be solved only through prospective multicentric investigations; these cannot disregard morphology parameters, reliable molecular predictors of tumour behaviour (i.e. the probability of vascular invasion) and effect of pretransplant strategies as main determinants of trials with survival as a primary end-point [54].

The challenge of pretransplant therapies: role of bridging and downstaging

Two possible roles can be assigned to pretransplant therapies against HCC according to tumour stage.

The role of bridging

The aim of what is called a bridging therapy for someone carrying an HCC within Milan or UCSF Criteria, namely a favourable condition for transplant candidacy, is the avoidance of drop-out due to tumour progression while on waiting list.

In any transplant list, the drop-out risk increases as waiting time progresses and it has been shown that in case of HCC enlisted for more than 3 months, the drop-out rate is superior to that observed for nonmalignant diseases [55]. A large variability in waiting list time, prioritization policies and criteria for de-listing patients with tumour progression is observed across Europe and US; therefore, a true evidence of the usefulness of bridging therapies for HCC is very difficult to obtain [56]. In detail, the role of bridging therapies for patients enlisted for HCC remains controversial as the results we can refer to originate mainly from retrospective studies. With such limitations, some questions can be answered:

What is the length of waiting time that recommends bridging?

The initial estimates of tumour progression beyond MC at 3 months, based mainly on tumour doubling time range between 15% and 30% for T1 (one nodule <2 cm) and T2 (one nodule 2–5 cm or one to three nodules <3 cm) respectively. Further data from single centre experiences and Markov model analyses [57,58] found these perspectives to be overestimated, while successive analysis set the risk of tumour progression at 3 months at 8% and 15% for T1 and T2 respectively. These results were used for further refining allocation criteria under the MELD policy and for discarding the increased priorities for T1 HCCs.

Based on these estimates, in Centres where progression to beyond MC equates with drop-out, it would seem reasonable to use bridging therapies for T2 patients even if the estimated waiting time is inferior to 3 months to prevent an expected 15% drop-out rate. The Barcelona group has reported a Markov simulation demonstrating that nonsurgical HCC treatments using percutaneous ethanol injection are cost-effective in increasing intention-to-treat survival if the expected waiting list time is superior to 6 months [59]. This is particularly common after 3 months on list and leads to the indication to treat any HCC with proven progression.

Does bridging prevent progression and therefore drop-outs?
Patients at increased risk for drop-out have been identified in previous studies demonstrating that those with more than one HCC or with a single lesion >3 cm have a drop-out risk at 1 year of over 50% in comparison with a 10% risk for patients with a lower tumour burden [60].

The efficacy of radiofrequency ablation (RFA) as a bridging procedure has been demonstrated in many studies [61–64]: patients enlisted within MC and treated with RFA while on waiting list showed drop-out rates ranging from 0% to 21% and these results compare favourably with historical nontreated controls, in which drop-out rates at 1 year are reported to be nearly 30% [55,65].

In absence of prospective comparative studies based on intention-to-treat analysis, the effectiveness of RFA in preventing drop-outs is still uncertain. Even if RFA is a safe and effective treatment of small HCCs in cirrhotics awaiting LT, tumour size (>3 cm) and time from treatment (>1 year) are the strongest predictors of tumour persistence in the targeted nodule after a single session of RFA [63]: a timeframe and a perspective of possible failure that have to be considered when performing RFA as a bridge therapy for LT.

While the ability of trans-arterial chemoembolization (TACE) to achieve objective tumour response has been confirmed in a randomized controlled trial [66], its effectiveness in preventing drop-outs from waiting list is still unclear. The most complete metanalysis performed on this topic concludes that there is insufficient evidence that TACE, prior to LT for HCC, decreases drop-out rates on the waiting list [67] (low quality grade C recommendation [68]).

Does bridging ameliorate prognosis after LT?
Defining whether there is a survival benefit related to any pre-LT therapy in patients with good prognosis (within MC) remains hard to demonstrate, because the impact on survival of bridging therapies is not clearly established.

Similarly, response to pretransplant therapies as a positive prognostic indicator in favour of a higher chance of post-transplant survival has not been proven yet. In a recent study, there was a marked survival benefit according to pretransplant response to TACE even though subgroup analysis showed that these benefits were only seen in patients whose tumours met the MC (true bridging) [69]. As the study was not comparing treated patients versus nontreated patients, it could not be stated if TACE had a real efficacy on post-transplant survival or if response to TACE was a surrogate marker of tumour behaviour. On the contrary, post-TACE tumour necrosis has been suggested to be related to higher chances of tumour post-transplant recurrence [70].

A recent meta-analysis of TACE as a bridge to transplantation highlighted that there is insufficient evidence to support the use of TACE prior to LT, as it did not seem to improve long-term survival [67]. Again, a clear answer on the possible benefit of pretransplant treatment of HCC will only be assessed through prospective trials, in which the existing differences among Centres with respect to on-list waiting-time for patients with HCC will have to be routed within accepted limits [56].

The prognostic effect of RFA as a bridge to transplantation has not been clearly defined, as only observational cohort studies have been reported [61–64]. However, effectiveness of RFA in obtaining a complete tumour necrosis for T2 nodules with a diameter of <3 cm has been confirmed in many studies [71], and there is a high level of clinical evidence supporting RFA as a safe and promising bridge to liver transplantation for patients in which waiting time is expected to exceed 6 months.

Which therapy should be used for bridging?
The most promising therapy for bridging patients to transplantation is RFA, with several studies demonstrating a decrease in drop-out rates for patients with a single nodule of HCC pretreated with RFA when compared with historical nontreated controls [63,64,72,73]. Conversely, TACE should be preferred in patients presenting with HCC larger than 3 cm or with a multinodular pattern, although there is still no clear evidence of its benefit in the bridging setting when compared with no treatment.

An emerging loco-regional treatment against HCC is trans-arterial radioembolization (TARE) with Yttrium-90: an interventional procedure similar to TACE, using intra-arterial injection of glass microspheres loaded with ^{90}Y. This techinique is able to deliver a selective brachytherapy up to 120 Gy into the affected lobe, with minimal toxicity on the nontumoural surrounding liver tissue. Safety and efficacy of TARE in the treatment of advanced HCC have been demonstrated in various studies [74,75] and recently a tumour response rate of 58% has been reported after TARE also in intermediate (T3) HCC [76]. If results, collected in retrospective experiences, will be confirmed

in prospective studies, TARE could provide a longer time-to-progression with respect to TACE in intermediate HCC. This could be crucial in choosing the best treatment for HCC on the waiting list, especially in patients with tumour exceeding MC, in which the attainment of a sustained response is instrumental in avoiding early drop-outs because of tumour progression.

Finally, the emerging molecular targeted therapies [77] could contribute to the strategy of bridging patients with HCC to liver transplantation. In particular, a study based on a Markov model simulation concluded that sorafenib could be cost-effective in comparison with no therapy for T2-HCC patients waiting for transplant, particularly for a median time to transplant of <6 months [78]. This model, aimed at quantifying the cost/benefit ratio of targeted therapies in neoadjuvant regimens, does not promote targeted therapies as the first-line bridging treatment, even though it opens a debate on the effect of sorafenib in prolonging time-to-tumour-progression in intermediate/advanced HCC, therefore reducing their risk of drop-out.

The role of downstaging

The term 'downstaging' applies to a treatment aimed at converting patients with tumour burdens beyond conventional criteria (for number, size, AFP and viable tissue at imaging) within limits established *a priori* (generally Milan or UCSF Criteria) to make patients originally excluded suitable for transplant candidacy. Through downstaging protocols, HCC patients affected by advanced tumours may become transplantable, although with a final outcome that is still difficult to predict.

There are few specific studies investigating the benefit of downstaging procedures before transplantation, while most of the literature is focused on tumour response and stage migration after treatment. The most recent downstaging proposals are summarized in Fig. 1 [61,79–88], with indication of their efficacy on post-transplant outcome from cadaveric donors; according to the observed trends of results, tumour bulk at the time of treatment implementation seems to be more important than the treatment itself. It should be noted that in living-related LT, the short waiting time and the absence of defined upper limits for HCC are confounding factors for evaluating the true benefit of downstaging protocols.

The role of downstaging: selection tool or beneficial strategy per se?

Response to downstaging treatments and maintenance of sustained tumour response over a sufficient period of time are frequently used as a reliable selection tool and a surrogate of tumour aggressiveness in patients exceeding MC. However, downstaging of HCC could represent a beneficial strategy *per se*, aimed at prolonging survival of HCC regardless of allocation to transplant list or non-transplant alternatives.

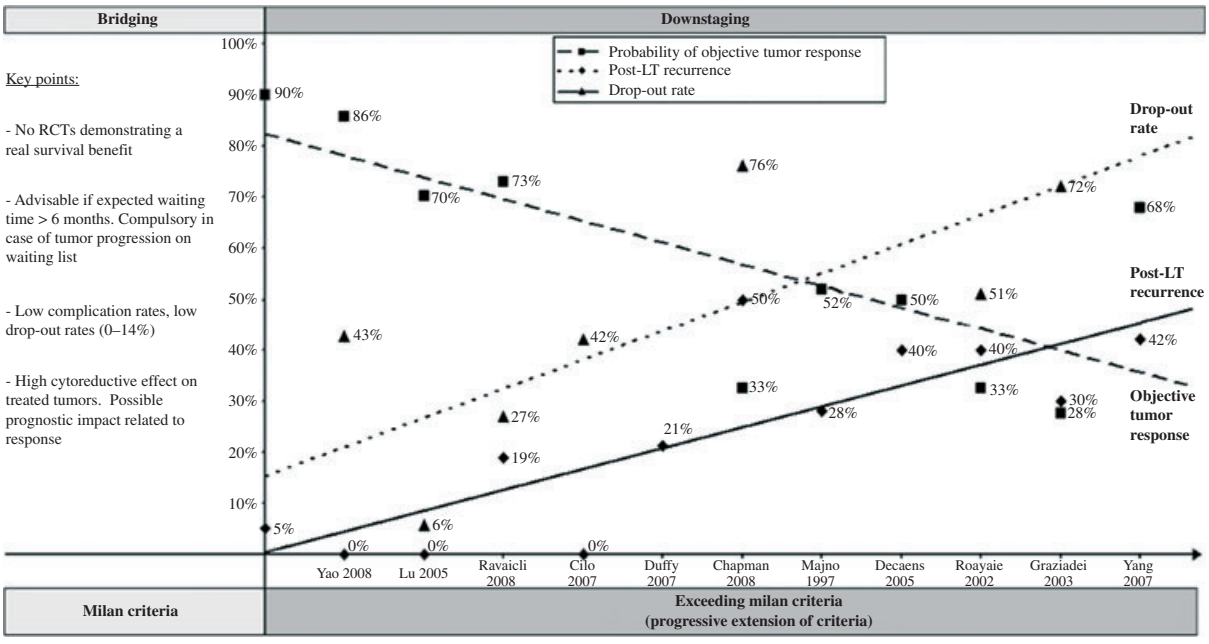

Figure 1 Trends of results of downstaging in relation to pretreatment tumour bulk (size-and-number). Efficacy of downstaging in patients exceeding Milan Criteria (MC) is strictly related to tumour size-and-number at presentation. The bigger the tumour bulk, the lower the efficacy of downstaging in terms of tumour response, risk of drop-out from waiting list and tumour recurrence after liver transplantation (LT).

The ultimate use of downstaging protocols for selecting HCCs likely to behave better after LT is debatable, even though a good outcome can be observed in responding patients [79]. Future investigations should rather address the crucial questions related to survival benefit of the partially controlled HCCs at intermediate/advanced stage in the light of transplant candidacy versus other options that may be continued until complete tumour response or progression.

In fact, the possible gain in life expectancy obtained by downstaging treatments applied at various stages of HCC should be objectively measured and used for less arbitrary choices in treatment-planning of patients largely exceeding MC, in which transplantation should be an option, although not the exclusive one.

Which therapy should be used for downstaging?

Trans-arterial chemoembolization is the preferred single treatment modality in downstaging protocols, especially for multifocal tumours. In most instances, a pre-determined disease stability, from 3 to 6 months after treatment and before patients' listing is mandatory to select patients with a less aggressive tumour behaviour and less chances of post-transplant recurrence [79,80].

Combined modalities of TACE, RFA, percutaneous ethanol injection and resection seem to downstage patients more effectively than TACE alone (about 70% success rate vs. 40% respectively [76,83]), and TARE [76,89] may be in the near future, an interesting perspective as an alternative to conventional TACE.

The particular role of pretransplant liver resection

Approximately 25% of patients with HCC in which surgery may be pursued, is hypothetically eligible for both transplantation and resection: in general, patients eligible to both indications (overlapping population) should be evaluated for liver resection first, being the final choice decided after balancing the risk of drop-out, recurrence [90,91], life expectancy with either option, age, quality of the donor organ, aetiology of cirrhosis etc.

Liver resection, with a close to zero mortality and no waiting time, can be considered a competitive option with transplantation, especially in patients over 65 years of age. In patients within MC, 5-year survival rates after resection are comparable to those after transplantation, although recurrence rates significantly favour the latter [92].

In the daily practice, time to recurrence and pattern of recurrence after liver resection may bring to reconsider patients for LT as candidates of a 'salvage' procedure in case of postresection recurrence, or as recipients of a 'pre-emptive' transplantation in the particular case of patients showing unfavourable histology (high grade of differentiation, microsatellitosis, mVI) of the removed HCC [93].

Assuming that outcomes after primary-transplantation may be comparable to secondary-transplantation, as suggested by previous experiences [94], salvage transplantation may be offered to patients as a second option at the onset of recurrence with the limitations of age, inclusion in the MC, and time to recurrence >12 months.

Complication and survival rates may be negatively affected after salvage transplantation [90]; however, in the era of graft shortage, this procedure has been increasingly implemented without apparent detrimental effects, as confirmed on large series [95]. On the other hand, the pre-emptive approach selects patients at high risk of tumour recurrence; although fascinating, it requires good procurement rates within a prioritization policy that is difficult to reproduce. For reasons of such limitations and according to recent experiences, salvage transplantation with respect to the pre-emptive approach should be preferred as a more efficient procedure in terms of graft-sparing rates [94,96].

The challenge of prioritization: how can the benefit of transplantation for HCC be assessed?

While the MELD algorithm *per se* represents a major achievement because of the ability to identify the sickest patient on the list to receive the first available graft, the MELD score modifications applied to HCC seem insufficient to capture the complexity of those patients carrying cancer on top of cirrhosis.

Over the last 7 years, the system has been re-modelled through three subsequent adjustments using arbitrary extra points aimed at offering transplantation to patients within the T2 HCC stage, without prolonging on-list waiting time for noncancer patients.

In the light of the lack of consensus for patients exceeding conventional criteria, the consideration of downstaging efficacy only if tumours are converted to T2 stage (within MC) and the elimination of extra-point assignment to T1 HCC (favouring futile transplantations) should be considered consistent steps to regulate the increasing flow of requests for the limited resource of donor organs.

However, different from pure advanced cirrhosis, in many instances, HCC can be routed to alternative non-transplant strategies without detrimental effects on survival, in particular subsets of patients (i.e. >65 years of age, HCV infection, sever co-morbidities etc.).

This justifies studies focused on the assessment of benefit of transplantation in the specific category of HCC in cirrhosis, using standardized instruments that are able to capture in composite scores what is part of the daily

practice of treating individuals with HCC at various stages of presentation: namely, the allocation to the best available treatment according to the patients' needs and expectations.

A standardized and validated system to determine benefit of LT in HCC is instrumental for the advancement of our field. In such respect, equity principles and efficiency measures determined by QALY models (quality of adjusted life years) should be included in the equation determining the benefit of LT in HCC, together with gain in life expectancy offered by transplantation in comparison with alternative treatment options.

Priorities may be different depending on whether patients are ranked according to efficiency (net cost per QALY) or equity consideration, based on individualized patient-specific indexes [97,98]. In fact, the particular model of LT for HCC should be a good benchmark to quantify the extent of efficiency loss (in terms of lost QALY and increased costs) when equity concerns are routed to prevail over efficiency end-points to comply and capture public preferences in the allocation of the donated livers.

Such investigations are worth the effort for those in the transplant community who feel trapped into the current prioritization policy based on questionable points' assignment. A new generation of decision making scores for HCC eligible to LT should be more individualized and should consider the complex reality of cirrhotic patients with cancer.

Conclusions

Liver transplantation represents the best curative option for HCC on cirrhosis as it is able to remove both the tumoural bulk and the underlying liver disease. During the last two decades, the definition of restrictive criteria (MC) has brought to identify patients who benefit the most from this procedure.

A plethora of proposals of expansion of MC have been forwarded, mostly with limited evidence. The 'up-to-seven' criteria and the TTV emphasize the need of including biological parameters (AFP and mVI) in the definition of modern transplantability criteria.

The expansion of the recipient pool may alternatively be pursued trying to limit on-list drop-out through bridging or downstaging, depending on tumour stage at the time of transplant consideration. HCC management may markedly differ in the transplant Centres and this may jeopardize results.

In this respect, downstaging and bridging procedures should not be reduced only to selection tools for transplant candidates, rather the assessment of their therapeutic potential at whatever tumour stage, should be part of prospective investigations. In general, combined treatment modalities seem to downstage patients more effectively than TACE/RFA alone, and TARE with ^{90}Y-loaded microspheres may be promising.

Most of the surgical issues regarding liver transplantation have been solved, but challenges on techniques, indications and prioritization still remain, while molecular classification of HCC is likely to influence any future strategies designed for patients with liver cancer. Acceptance of challenges has been part of the history of LT and, for the sake of our patients, such an attitude should endure in the future years.

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