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Review

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

The place of downstaging for hepatocellular carcinoma☆

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In the treatment of hepatocellular carcinomas, therapies such as trans-arterial chemo-embolisation, trans-arterial radioembolisation, percutaneous ethanol injection and radio-frequency ablation can decrease the size (and overall viability) of the tumours, thus potentially increasing the proportion of patients qualifying for resection and transplantation.

While the use of such downstaging therapies is straightforward when resection is the aim, in a similar way to other neo-adjuvant treatments in the surgery of tumours that are too large or awkwardly placed to be primarily resected the issues related to transplantation are more complex. In the context of transplantation the word "downstaging" designates not only a neo-adjuvant treatment, but also a selection strategy to allow patients who are initially outside accepted listing criteria to benefit from transplantation should the neo-adjuvant therapy be successful in reducing tumour burden. The effectiveness of downstaging as a selection strategy, at first questioned because of methodological bias in the studies that described it, has been recently demonstrated by more solid prospective investigations. Several issues however remain open, such as inclusion criteria before the strategy is implemented (size/number, surrogate markers of differentiation/vascular invasion such as alpha-fetoprotein), the choice of which downstaging therapy, the end-points of treatment, and the need and duration of a period of observation proving disease response or stabilisation before the patient can be listed.

The present review discusses which treatments and strategies are available for downstaging HCC on the basis of the published literature.

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Keywords: Liver; Transplantation; Resection; Downstaging; Neo-adjuvant; Trans-arterial chemo-embolisation.

☆ The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Abbreviations: HCC, hepatocellular carcinoma; TACE, transarterial chemo-embolisation; RFA, radio-frequency ablation; PEI, percutaneous ethanol njection; TARE, transarterial radioembolisation; UCSF, University of California San Francisco; CT, computerised tomography; TTV, Total Tumour Volume; AFP, alpha-fetoprotein; SRTR, Scientific Registry of Transplant Recipients.

Introduction

Curative surgical treatments for patients with hepatocellular carcinoma (HCC) include resection and transplantation. Resection can be performed in patients with good liver function and localised HCCs, while transplantation is favoured in selected patients with decreased liver function and/or multiple nodules. Over the years, the place of these therapies has been well defined, but they can only be attempted in 10–20% of patients with HCC, as in the majority, the disease will be too advanced [1–3]. A broader use of local HCC treatments has the potential to shrink the tumour and allow a curative option in patients for whom tumour size or location next to vital anatomical structures is the limiting factor. These treatments include trans-arterial chemo-embolisation (TACE), radio-frequency ablation (RFA), percutaneous ethanol injection (PEI) and trans-arterial radioembolisation (TARE).

The present review article discusses the use of such local HCC treatment prior to surgery or transplantation, and the place that these treatments have taken in transplant candidates as a selection tool that refines the usual criteria based on number and size.

Neo-adjuvant treatment vs. downstaging: a stricter definition

The word *downstaging* is used loosely to qualify any type of treatment aiming to control tumour growth prior to surgery, with a confusing overlap with the term *neo-adjuvant treatment*. In this review we suggest restricting the use of the word *downstaging* to the aim or the result of a treatment that intends to facilitate or make possible a surgical procedure that would otherwise be too risky or unfeasible. *Neo-adjuvant treatment* can be given to patients in whom the procedure can be done primarily, with aims that may be different from downstaging, such as to improve the long-term results, or to limit the complications during the time waiting for the procedure to be done. While *neo-adjuvant* treatments often refer to the use of systemic drugs, aiming at controlling both the primary lesion and circulating cancer cell, it will here be applied to local HCC therapies.

The aims of neo-adjuvant treatments and of downstaging are different in patients who are candidate for resection or for transplantation (Fig. 1). Before resection, *neo-adjuvant treatment* can be given with the aim to improve the results of surgery, and before transplantation to decrease the risk of drop-out from the transplant waiting list, and to decrease the risks of recurrence in the long-term. *Downstaging* prior to resection is performed to

Neo-adjuvant treatment	Downstaging
Before resection	
To simplify surgery	To render possible a resection that would otherwise be too risky or impossible
To improve long-term results	*(mainly for anatomical reasons)*
Before transplantation	
To decrease tumor progression (and dropout) from the waiting list.	To bring patient whose tumor burden is outside accepted criteria for transplantation to within acceptable criteria
To improve long-term results	To select patients with good long-term outcomes among poor risks *(Response treatment and observation time used as a surrogate markers for favourable biology)*

Fig. 1. Definitions of downstaging and of neo-adjuvant treatments prior to resection or transplantation. In our opinion, the two words should not be used as synonyms.

render non-operable patients operable or to simplify the surgery, mainly for technical reasons. Finally, *downstaging* prior to transplantation is used as a selection tool to detect patients with low rates of recurrence among those that would be excluded according to recognized number-size criteria. While the present article is primarily exploring the place of downstaging, we will also discuss neo-adjuvant options, as they help understanding the expected benefits of the various local HCC treatment modalities.

Treatment of HCC prior to resection

When an HCC can be resected primarily, a pre-surgery neo-adjuvant treatment like TACE is usually not recommended [4]. The main limitation is related to the time required to organize and perform TACE, which delays resection by 2–10 weeks and prevents up to 10% of patients from reaching surgery because of tumour progression or liver failure [5,6]. In addition, resection may be more challenging after TACE (requiring longer operative times, often in association with significant inflammatory reaction in the hilum and around the area of parenchymal treatment), TACE does not provide a measurable survival benefit, and has even been associated with increased mortality in two studies [5–10]. This said, some of us do consider that one (and sometimes two) sessions of TACE should always be attempted prior to surgery, giving a chance of achieving tumour necrosis, which has been associated with higher rates of disease-free survival [8].

Some patients with good liver function do not qualify for primary resection because of the size and/or location of one or multiple HCCs, and may be considered for downstaging. Such a strategy has the potential to make surgery possible or easier (away from vascular structures), and potentially with decreased risks. With such a downstaging management, a limited number of non-resectable patients (6–28%) can subsequently undergo surgery [11,12]. Although high rates of recurrence have been observed (up to 40–85%), five-year survivals are between 25% and 60%, which is very reasonable considering the lack of alternative and potentially curative options in these patients [8,11–13]. The place of downstaging as described above is relatively well accepted in the surgical community and does not require, in our opinion, further discussion apart from the best methods to obtain it.

Treatment of HCC prior to transplantation

The issues related to local HCC treatment prior to liver transplantation are more complex than those related to resection. In the setting of transplantation, these treatments will be considered differently whether a patient is within transplant criteria at presentation or not (neo-adjuvant vs. downstaging). The treatments will also be considered differently from a patient or a community point of view, taking into account medical evidence-based data and ethical considerations:

Treatment of HCCs prior to liver transplant: neo-adjuvant vs. downstaging

Currently one third to one half of all HCC patients on the waiting list undergo local HCC treatment prior to transplantation [14,15]. The type of treatment varies from centre to centre, but TACE is the most frequently used, followed by RFA [14–17].

Neo-adjuvant treatments (in contrast to downstaging) are primarily used to decrease the risk of drop-out from the waiting list [16,18–23]. They may be linked to a better post-transplant patient survival, as shown by a large UNOS-based study (78% with treatment vs. 74.8% with surveillance alone at two years, Risk Ratio = 0.785, $p = 0.014$) [17]. This data is also supported by the observation that patients with full HCC necrosis after TACE have better post-transplant survivals than those with partial response [8,24]. Overall, a broader use of local neo-adjuvant HCC treatment in patients within transplant criteria appears justified (without delaying transplantation), as the risk of significant side-effects of these treatments is limited, with potential lower drop-out and higher survival rates.

A further argument in favour of local neo-adjuvant treatments is that they represent the best palliative option for patients who drop-out, avoiding the difficult situation of having delayed a proven effective treatment during the time spent on the waiting list.

When patients have HCCs beyond the accepted transplant criteria, the application of treatments aiming at downstaging tumours appears appropriate, as this is often the only hope of potential cure with a subsequent transplantation. In addition, tumour response to TACE could be used as a selection tool to help identify patients with an outcome that may be superior to that suggested by morphological criteria alone.

This strategy was initially suggested by the group in Hopital Paul Brousse, Paris, who retrospectively observed higher rates of survival in TACE responders than in non-responders in an analysis of patients with more than three nodules or nodules larger than 3 cm [8]. The wider recognition and adoption of this strategy has been slow because of poor agreement on definition, lack of selection criteria, absence of long-term outcome data and, until recently, the overall inability to construct prospective studies (exceptions listed in Table 1). As an example, the original report

Table 1. Selected publications on downstaging prior to transplant.*

Author	Journal, year	Evidence level**	Criteria to enter downstaging	Downstaging treatment (nb of patients)	Transplant criteria	Time stable prior to transplant	Downstaging success rate	Intent-to treat post-HCC treatment survival	Post-transplant survival
Graziadei et al.	Liver Transplant, 2003	13	Outside Milan, no vascular invasion, no extrahepatic disease	TACE	50% decrease in size	no limit	73%	31% (at 5 years)	41% (at 4 years survival)
Otto et al.	Liver Transplant, 2006	15	Beyond Milan, no extra-hepatic disease	TACE (62)	30% decrease in the diameter of 5 target lesions	no limit	55%	?	74.5% (at 5 years)
Yao et al.	Hepatology, 2008	16	1 lesion >5 cm and ⩽8 cm or 2 or 3 lesions at least 1 >3 cm but ⩽5 cm with total tumor diameter of ⩽8 cm or 4 or 5 nodules all ⩽3 cm with total tumor diameter ⩽8 cm	TACE, RFA and/or resection (30)	Milan	minimum 3 months (mean: 6 months)	70%	69% (at 4 years)	92% (at 4 years DFS)
Ravaioli et al.	AJT, 2008	19	1 lesion >5 cm and ⩽6 cm or 2 lesions at least 1 >3 cm but ⩽5 cm with total tumor diameter of ⩽8 cm or 4 or 5 nodules all ⩽4 cm with total tumor diameter ⩽12 cm	TACE, RFA, PEI and/or resection (48)	Milan and AFP ⩽400 ng/ml	minimum 3 months (mean: 6 months)	90%	62% (at 3 years)	71% (at 3 years DFS)
Chapman et al.	Ann Surg, 2008	15	Beyond Milan, no lobar major vessel involvement or metastasis	TACE (76)	Milan	usually minimum 4 months (mean: 6 months)	23.7%	?	100% (at 3 years) 50% (at 5 years)
Lewandowski et al.	AJT, 2009	18	T3	TACE (43)	Milan	no limit	31%	19% (at 3 years)	73% (at 1 year DFS)
				TARE-Y90 (43)			58%	59% (at 3 years)	89% (at 1 year DFS)
De Luna et al.	AJT, 2009	16	Beyond Milan	TACI (27)	Milan	no limit (mean: 11 months)	63%	84% (at 3 years)	78.8% (survival at 3 years)
Jang et al.	Aliment Pharmacol Ther, 2009	11	Beyond Milan, no lobar major vessel involvement or metastasis	TACE (386)	Milan	no limit (median: 2 months)	41.5%	25% (at 5 years)	66.3% (at 5 years DFS)
Proposed strategy			TTV ⩽250 cm^3	open***	TTV⩽115 cm^3 and AFP ⩽400 ng/ml	minimum 6 months			

RFA: radio-frequency ablation, TACE: transarterial chemo-embolisation, TACI: transcatheter arterial chemoinfusion, TARE-Y90: transarterial radioembolization with Yttrium-90 microspheres.
T 2: T 3: 1 nodule >5 cm or up to 3 nodules with one >3 cm
* Referenced in Medline until Oct. 25, 2009 under "liver transplant, hepatocellular carcinoma, downstaging".
** Assessed according to the Downs and Black checklist (51).
*** Treatment is guided by tumor and patient characteristics.

from UCSF on downstaging included only 16 months of median follow-up, too short to convincingly rule out the risk of HCC recurrence (this has been corrected in new studies from the same group) [25].

More recent reports have demonstrated that downstaging can be successful in 24 to 90% of patients (Table 1). This wide range of observed rates is primarily related to the use of different criteria to include patients in downstaging protocols and different criteria to subsequently decide on listing for transplantation. Some groups consider patients for listing as soon as HCCs have decreased in size by 30 or 50%, while others will require full necrosis (absence of any uptake on CT) prior to doing so [22,26–28]. In addition, some centres follow Milan transplant criteria, while others use expanded ones [22,26–29].

Despite these limitations, recent prospective studies have demonstrated that downstaging is a valid strategy prior to transplant [27,28,30]: following successful downstaging, post-transplant disease-free survivals have been reported at over 70% at 3 years, and intention-to-treat post-HCC treatment survivals between 60 and 70% at 3 years [22,27,28,30]. Such outcomes have been substantially better than anticipated in a group of patients with such an advanced cancer, in some series not just beyond Milan criteria, but beyond UCSF criteria as well [2,31]. In addition, they appear to compare favourably with the generally accepted minimal

long-term post-transplant survival of 50% at 5 years, an unrefined and arbitrary target that holds consensus [32,33].

For these reasons, it appears legitimate to attempt downstaging in any patient beyond transplant criteria and without distant metastasis, even more so as downstaging treatments are identical to palliative ones. The downside of a too liberal access to downstaging strategies (and subsequent transplant) could be an enhanced competition for donor livers with patients within standard transplant criteria (with or without HCC) and should be countered by defining reasonable inclusion criteria.

Which criteria should be used to include patients in a downstaging protocol?

While any patient with HCC beyond transplant criteria, but without distant metastasis, may benefit from a local HCC treatment (palliative or downstaging), we believe that only clearly selected candidates should enter downstaging protocols. The two main reasons for a strict attitude are: (a) the need to gather robust data on this topic, and (b) the implicit obligation to treat all patients on the waiting list equitably, including those with HCC or benign disease. This even if from a patient's point of view, transplantation may represent the best option for cure. The individual's perspective that a small chance of successful transplantation is better than the certainty of HCC progressing on palliative treatment has to be balanced with the societal demand – and transplant program commitment – for the responsible use of a scarce resource.

To establish a reliable selection policy, three points have to be taken into account

(a) defined entry criteria
- size/number or total tumour volume of HCC
- biological/pathological and molecular markers

(b) defined end-points of successful downstaging
- radiological
  i. degree of necrosis
  ii. decrease in size
- biological: alpha-fetoprotein (AFP)

(c) defined time between downstaging and listing for transplant

Defined entry criteria

The criteria to enter a downstaging program should include patients who have well defined and acceptable chances of good outcomes after transplantation if the downstaging goal is reached. Such a strict attitude would maintain the expansion of transplant criteria within reasonable limits, and allow gathering of robust and comparable data for progress. For this reason, patients with metastasis or with large vessel thrombosis seen on radiology should be excluded. Several groups have prospectively assessed various scores (Table 1), including UNOS T3 (one nodule >5 cm or up to three nodules with one >3 cm) or combinations of size and number with up to five nodules and a total tumour diameter of 8 or 12 cm [27,28,30]. While these scores have not been validated externally, they appear reasonable as they can lead to post-transplant disease-free survival rates over 70% at 3 years [27,28,30]. We would however advocate that the UNOS T3 is too restrictive regarding tumour number, as patients with more than three lesions (even of small size) cannot be considered for downstaging. Following our previous work on Total Tumour Volume (TTV) [14,15], the group in Edmonton has decided to include for downstaging all patients with TTV $\leqslant$250 cm^3. This corresponds to a single HCC of 7.8 cm in diameter or three HCCs of 5.4 cm, but any size and number combination can be considered as long as the cumulated tumour volume remains within the limit. TTV does not include any number restriction and has better expected radiological accuracy (larger HCCs have more weight in the score and can be better defined by radiology), but downstaging results are still pending [14].

Evidence is accumulating that biological markers such as alpha-fetoprotein (AFP) or PIVKA-II add additional predictive accuracy if used in addition to morphological characteristics [15,28,34,35]. We can speculate that AFP and PIVKA-II provide a good assessment of tumour biology, including microvascular invasion, grade and tumour aggressiveness in general. In a Scientific Registry for Transplant Recipients (SRTR)-based study, we have shown that tumour volume and AFP are independent predictors of post-transplant survival, and that morphological criteria alone will miss many patients with expected poor outcomes [15]. Even within Milan criteria, AFP values >400 ng/ml were able to select patients at high risk of tumour recurrence.

Defined end-points of successful downstaging

While it is clear that patients not responding to downstaging should not be considered for transplantation [22,29], transplant criteria after successful downstaging remain to be defined more precisely. We believe the most useful parameters for this are radiological response in terms of viability and size of the tumours, and probably biological response measured as a decrease in AFP.

While some investigators have accepted for transplantation patients with HCCs demonstrating partial response (decrease in size of 30–50%), the most recent studies have considered only patients whose tumours have demonstrated complete ablation/no augmentation on imaging [22,26–28]. Intuitively, this attitude makes sense as extinction of vascularisation after treatment can be taken as a surrogate marker for a favourable biology, while on the contrary the probabilities of a distant spread associated with a large tumour size will likely not change if a lesion is still partially viable.

Lesions that are fully inactive on radiology are no longer counted as a nodule in the final score in most studies [27,28].

As for the final radiological end-point to define successful downstaging, most published studies have been using the goal of Milan criteria after treatment (with or without AFP $\leqslant$400 ng/ml) to select patients eligible for transplantation (Table 1) [27–30,36,37]. Results have been similar to those achieved in patients within Milan from the beginning [36].

As for biological markers, a persistently high AFP after treatment should raise the suspicion of distant spread or vascular invasion and may represent a useful marker of unsuccessful downstaging.

Defining a time between downstaging and listing for transplant

The time interval between downstaging and transplantation can be considered an additional tool to help in the selection of HCCs with a favourable biology. This "test of time", will disclose rapidly recurring lesions, vascular invasion and distant metastases. Some

published reports have not pre-defined a minimal surveillance time, but this was achieved in fact naturally, by a mean waiting time of at least 6 months between activation on the waiting list after downstaging and the date of transplantation (Table 1). The commonest surveillance time in published reports was 3 months, and appears as the minimum required. In contrast, centres allowing transplantation early after downstaging may face a shift from progression on the waiting list to recurrence in the post-transplant period, and thereby experience poor overall results [38].

In general, the criteria for inclusion in downstaging protocols used to date (with an upper limit at 8 cm, or 250 cm^3), while still needing external validation within formal protocols, appear reasonable, and have proven to be working. As a measure of achievement of successful downstaging we would recommend the endpoint of Milan criteria, counting fully inactive nodules as nonexistent and partially inactive nodules at their original size. We would also suggest excluding patients with an AFP remaining above 400 ng/ml after treatment, and a minimum observation time of 6 months between entry into the downstaging program and activation on the waiting list for transplantation. Additional data forthcoming in future may validate more expanded criteria, or a shorter surveillance period.

Which local HCC downstaging treatment should be used?

The choice of a downstaging treatment should be based both on the morphological characteristics of the HCC and on the patient condition, balancing the risks and benefits of each technique. The efficiency of some treatments (including TACE and TARE) is linked to HCC biology, with a better response in HCCs with higher blood supply and uptake. Others are physico-mechanical treatments, like RFA, where an HCC can be destroyed whether well differentiated or not.

Radio-frequency ablation (RFA)

RFA uses radiofrequency energy for hyperthermic ablation. It can be performed by interventional radiology or at laparoscopy. Over time, it has replaced ethanol injection in the treatment of small HCCs in most centres, as RFA ablation results in a higher rate of complete necrosis (usually over 90%) and requires fewer treatment sessions [39–43]. RFA is safe in terms of liver function and can be performed even in cases of advanced liver failure [44,45]. It is most effective for the treatment of HCCs $\leqslant$3 cm in diameter (Table 2). RFA should be avoided for lesions located close to the surface of the liver and neighbouring organs due to the risk of rupture of the liver capsule and seeding of malignant cells in the peritoneal cavity. Another potential complication of RFA (again shared with ethanol ablation or biopsy) is the seeding of cancer along the needle tract, which has been estimated to occur in 1–2% [16]. In addition, the use of RFA can be hampered by the presence of ascites, which should first be drained. In the absence of transplantation, 5-year survivals up to 30–40% can be expected after RFA [39,41], limited mainly by liver failure and the development of new primaries.

Trans-arterial embolisation (TACE)

TACE is currently the most popular neo-adjuvant treatment option for patients with HCCs [8,22,27,46]. Treatment is usually performed using a combination of mitomycin, adriamycin or cisplatinum mixed with lipiodol as the drug carrier and an embolisation using permanent or re-absorbable occlusive particles (gelatine). Post-procedure the patients are hospitalised for observation (usually for 24 h).

Several randomized studies have compared TACE to conservative management in HCC patients not candidate to curative options, and when analysed together in a meta-analysis, TACE demonstrated a significant superiority in terms of survival [47]. TACE also allows treatment of larger tumours than RFA and may simplify treatment of patients with multiple tumours. On the basis of the studies quoted above, we suggest TACE may merit consideration as the first line neo-adjuvant option prior to resection or transplantation in the majority of patients (see Table 3).

The main risks of TACE are linked to the ischemic insults of the embolisation. Patients with large lesions may develop a postembolisation syndrome due to tumour necrosis, with fever and abdominal pain. When a large area of liver parenchyma has been embolised, patients are also exposed to the risk of liver failure, and TACE should as a rule not be attempted in patients with decreased liver function (Child–Pugh C), except when an hyperselective TACE can be offered by expert hands. Finally, this procedure includes a small risk of arterial injury, estimated at 2% [48]. Another limitation is linked to the poor uptake of dye by hypovascular HCCs, and these lesions may be better treated with RFA.

Trans-arterial radioembolisation (TARE)

TARE is a trans-arterial procedure, which is performed by embolising 20–30 μm insoluble glass microspheres impregnated with yttrium-90 (a β emitter) (TheraSphere, MDS Nordion, Ottawa, Canada; SIR-Spheres, Sirtex Medical Limited, Australia) [49]. The treatment induces a local necrosis of the tumour, due to the β emission.

Table 2. Benefits and limitation of local HCC treatments.

	Indications	Risks	Benefits
Radiofrequency ablation	small HCC (usually $\leqslant$3 cm) away from the liver surface away from major vessels	HCC seeding (1-2%) liver rupture (small)	ok even in case of decreased liver function only one session usually required complete necrosis in >90% of cases
Transarterial chemoembolisation	any HCC size preserved liver function (Child A-B) uptake of contrast	liver failure arterial injury (2%)	ok even for large HCCs
Transarterial radioembolisation	any HCC preserved liver function (Child A-B) absence of intra-hepatic shunt uptake of contrast	off-target embolisation arterial injury	ok even for large HCCs (up to 10 cm?) ok even in case of portal vein thrombosis more efficient than TACE (to be confirmed) shorter time to response (to be confirmed)

Table 3. Key messages.

• Downstaging = make a surgery or a transplant feasible
• Post-transplant outcomes can be similar to those of patients within Milan
• Transplant criteria should combine morphological (size/number or total tumour volume) and biological (AFP) data
• Minimum observation time = 3-6 months

This type of local HCC treatment has gained more interest in recent years. It represents an interesting alternative to TACE, as it appears to induce a more efficient decrease in tumour size, with a shorter time to response (4.2 vs. 10.9 months) [30]. In addition, TARE can be performed in cases of portal vein thrombosis, a contraindication to TACE. Finally, TARE induces a regeneration of the contra-lateral liver, which may prove to be useful in case of planned resection with a small liver remnant [50].

TARE is well tolerated in most patients leading to a discharge within 2–6 h (without inpatient surveillance like TACE). The most common side-effects include fatigue and flu-like symptoms [30]. Several complications of TARE are similar to those of TACE, including the risk of arterial injury [51]. The presence of excessive intrahepatic shunting should be excluded by 99Tc-macroaggregated albumin scanning and mesenteric angiogram to minimize the risk of nontarget embolisation, especially radiation injury to the lungs [30]. While TARE has several advantages over TACE, its place remains to be fully defined (together with its cost-efficiency) [30].

Altogether, the choice of a local HCC treatment should be guided by the tumour and patient characteristics, as well as the local expertise. In consideration of the relative advantages and risks of ablative and trans-arterial approaches, we would suggest primary application of RFA for more centrally placed tumours when <3 cm diameter and in candidates with poor liver function who may not tolerate trans-arterial therapies well. TACE or TARE should receive primary consideration in candidates with satisfactory liver function when tumours are above optimal size for RFA (>3 cm), when multiple tumours are present or when tumours are in a subcapsular position or adjacent to major vessels or bile ducts. Incomplete control should lead to re-evaluation and consideration of the alternative approaches.

Final considerations

While further validations to refine the application of downstaging strategies are required, most of them appear reasonable, and can be used advantageously in patients with primarily unresectable tumours before partial hepatectomy, or to identify patients with a high likelihood of a good outcome despite being outside current transplantation criteria. Current evidence suggests that patients with solitary HCCs up to 8 cm in diameter and with up to five tumours (all $\leqslant$4 cm with total tumour diameter $\leqslant$12 cm) can be considered for downstaging. We would favour combining these cut-offs within the Total Tumour Volume score (250 cm^3), or with the up to seven criteria recently published by the Metroticket collaborative study group [15,52]. Patients who reach traditional Milan criteria (inactive tumours counting as zero), with no contraindication to transplantation appearing during a waiting time of at least 3 months (ideally 6 months) have a more favourable biology, as shown by a low recurrence rate. These criteria may be further refined by adding AFP as a selection marker, and should be confirmed in further prospective investigations that are organised in the present collaborative spirit.

Conflicts of interest

The Authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Acknowledgements

C.T. was supported by the Swiss National Science Foundation. N.M.K was supported by a CIHR/Wyeth Research Chair in Transplantation, and was a Senior Scholar of the AHFMR.

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