Review

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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.

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

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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

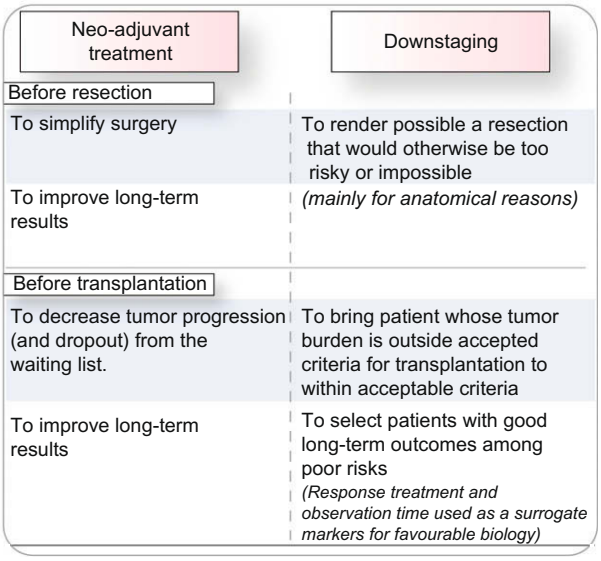

Fig. 1. Definitions of downstaging and of neo-adjuvant treatments prior to resection or transplantation. In our opinion, the two words should not be used as synonyms.

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