French Editorial Commentary from the ACHBPT

Resection post-radio-embolization in patients with single large hepatocellular carcinoma

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We read with interest this article evaluating the results of transarterial radioembolization (TARE) in the management of large (≥5 cm) initially unresectable hepatocellular carcinoma (HCC) (1). The aim of this retrospective study was to compare the results of upfront resection (single, resectable large HCC) with resection preceded by TARE (single, initially unresectable large HCC).

The authors retrospectively analyzed the 216 patients managed with a single HCC larger than 5 cm, between 2015 and 2020 in their center. Patients were divided into two groups: upfront surgery (n=144, 66.7%) or TARE if considered unresectable (n=72, 33.3%). Then, among those who had undergone TARE, a further dichotomy was made between those who had undergone surgery ("TARE-surgery", n=20, 9%) and those who had not ("TARE-only", n=52, 24%).

TARE enabled resection of 27.8% of initially unresectable patients (20/72). After a median follow-up of 41 months, the TARE-surgery group had an overall and recurrence-free survivals comparable to patients who underwent upfront surgery, while the TARE-only group (without surgery) had a significantly lower overall survival. There was no difference in the complication rate between the two resected groups. No patient in the TARE-surgery group required preoperative portal vein embolization; this group had greater tumor necrosis.

A propensity score was then performed between the Upfront-surgery and TARE-surgery groups with a ratio of 2:1 (30 Upfront-resected patients *vs.* 15 TARE-surgery). This matching resulted in a better 5-year overall survival in the TARE-surgery group compared with the Upfront-surgery group (40% *vs.* 33%, P=0.021), with identical recurrence-free survival (P=0.29).

This study concludes that radioembolization could have an important place in the management of initially unresectable single large HCC, and would make it possible to offer surgery in a second stage to patients otherwise candidates for exclusive palliative treatment.

Comments

Interpretation of main findings

HCC curative management comprises two therapeutic options, resection and transplantation, reserved for a minority of patients at diagnosis. Every effort must therefore be made to steer patients with HCC towards one of these treatments. This Rennes study comes from a team with extensive experience in hepatobiliary surgery, which pioneered the use of TARE.

This study highlights the value of TARE as induction treatment, with the aim of rendering a single large HCC resectable. Certain weaknesses, usual in the evaluation of

innovative strategies, limit the scope of the study: limited number of patients, monocentric and retrospective study, control groups and inhomogeneous treatments in terms of medical or radiological co-treatment administered.

Several notable features of the populations reported here merit specific comment:

- The Upfront-surgery group presented significantly more favorable general and oncological characteristics than the TARE group: fewer cirrhotics, better preserved liver function, lower alpha-fetoprotein (AFP) rate and less vascular invasion (portal/hepatic veins) justifying the TARE group's primary non-resectability.
- More interestingly, comparison of the Upfront-surgery and TARE-surgery groups showed more advanced hepatological and oncological data for the TARE-first group, particularly more cirrhotics, higher AFP and more macro-vascular invasion. Despite these pejorative features, the TARE-surgery group achieved the same overall and recurrence-free survival as the primary surgery group, suggesting the positive impact of combined radiosurgical treatment in (rare) responder patients. The authors suggest that TARE-induced downstaging brings initially unresectable patients back to the same prognosis as those who are resectable straightaway. The rate of tumour necrosis >50%, 12 times more frequent in the TARE-surgery group, may explain these good results, combined with the 20-week delay (before surgery) enabling better selection of candidates.
- After propensity scoring to obtain comparable Upfront-surgery and TARE-surgery groups, the benefit of TARE was confirmed, since overall survival at 5 years was superior (40% *vs.* 33%, P=0.02). However, it is difficult to formally conclude on the explanation of this improved survival insofar as (I) recurrence-free survival did not differ between the two groups (P=0.29), and (II) overall survival of HCC patients is the result of multiple successive therapies, and not only of the first line received.

A bias not fully explained by the authors is the use of other perioperative treatments associated with surgery and/or TARE. Indeed, 15% of patients in the TARE-surgery group had received another neoadjuvant treatment [intra-arterial chemoembolization or tyrosine kinase inhibitor (TKI)], compared with less than 1% in the Upfront-surgery group (P=0.2). Conversely, only patients in the Upfront-surgery group had received adjuvant treatment (immunotherapy or TKI, 13.8% *vs.* 0%, P=0.08). This inhomogeneity in the distribution of associated systemic or regional treatments complicates interpretation of the specific role of TARE.

Interpretation with regard to literature

It is worth recalling the context of this therapeutic strategy. Indeed, downstaging of HCC, notably using TARE, has been reported for several years, and Franco-American recommendations have even been reported recently (2). However, the detractors of TARE have been numerous since the publication of three trials showing no superiority of this treatment *vs.* sorafenib. Importantly, these trials used resin microspheres without personalized dosimetry (3), in contrast to the work analyzed here (glass microspheres + personalized dosimetry). The Chicago team, another expert, also showed that glass microspheres were effective, notably more effective than chemoembolization (4), and this was recently confirmed in a prospective randomized study (5).

The article by Tzedakis *et al.* (1) included patients classified as BCLC-A for whom TARE is currently only a downstaging therapeutic option for HCCs ≤8 cm (6), based on the Legacy study that included single unresectable HCCs ≤8 cm (7). The work commented on here therefore broadens the candidates for TARE since 50% of patients in the TARE-surgery group had tumors ≥10 cm. With a greater experience (n=72 *vs.* n=21), this series from Rennes confirms the data published over 10 years ago by Iñarrairaegui *et al.* who showed a conversion rate to surgery of 28.5% after TARE (*vs.* 27.8% for Tzedakis *et al.*) (8). They also demonstrate the feasibility of hepatectomy after TARE, without any notable excess morbidity.

Another aspect raised by this Rennes series is the place of surgery in the context of tumoral portal vein thrombosis (PVT). It has been well reported that surgery does not achieve satisfactory oncological results in cases of PVT grade 3 (portal trunk) or 4 (superior mesenteric vein). While Tzedakis *et al.* reported only grade 1 or 2 PVTs in the Upfront-surgery group, 20% of grade 3 PVTs were reported in the TARE-surgery group, with no apparent negative impact on survival. While it is not possible to determine here, retrospectively, certain prognostic scores in cases of resected or unresected PVT, it seems clear that TARE presents a definite efficacy in cases of PVT, and this will merit confirmation on a larger scale.

But TARE is not the only approach to tumor control with a view to downstaging for secondary resectability. For several years now, immunotherapy (9) has played an increasingly important role in the therapeutic arsenal, both as a palliative treatment (proven superiority over sorafenib) and as an adjuvant therapy, with the recent report of superiority of atezolizumab plus bevacizumab *vs.* active surveillance after resection of HCC at high risk of recurrence (10). With regard to immunotherapy with neoadjuvant (or induction) indication, successful conversion to surgical treatment has been described at between 5% and 35%, varying according to the clinical situation (11,12). The rate reported here by Tzedakis *et al.* of 27.8% for TARE is therefore comparable, although the indications are not strictly superimposable (1). In particular, the Rennes team included Child B patients, whereas the results of immunotherapy in the literature concerned almost exclusively Child A patients. Clearly, immunotherapy and TARE appear to be truly effective induction treatments, in complete contrast to the results previously obtained with TKIs, conventional chemotherapy or chemoembolization reported to date, with very low conversion rates. The role of neoadjuvant external radiotherapy remains marginal, mainly in the case of initially resectable lesions, and it should be compared with TARE in the same indications.

Rather than opposing treatments, we are currently moving towards a personalized combination of locoregional and systemic therapies to achieve better tumor control and additive anti-tumor effects. The patients reported by Tzedakis *et al.* are gradually falling into line with this multimodal strategy, with 14% of resected patients having received a treatment (other than TARE). Several recent trials have demonstrated the superiority of combinations such as immunotherapy + TKI + chemoembolization (13), immunotherapy + TKI (14) or double immunotherapy (15). These encouraging results remain to be confirmed, as does the TARE + immunotherapy combination currently being tested in several ongoing trials.

Conclusions

First and foremost, the excellent oncological results presented here should be emphasized, irrespective of the group resected (with or without TARE), in patients with large HCC. Despite its low level of evidence (level 4), this study provides additional evidence for proposing TARE (glass sphere + personalized dosimetry) to patients with large unresectable HCC. These results are in line with modern literature on the subject, and need to be confirmed in larger cohorts. The role of immunotherapy in induction, alone or in combination with TARE, needs to be clarified, even if there is evidence to suggest that multimodal therapies would further improve oncological outcomes and secondary resection rates.

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