ORIGINAL ARTICLE

Feasibility and safety of liver transplantation or resection after transarterial radioembolization with Yttrium-90 for unresectable hepatocellular carcinoma

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Abstract

Background: The benefit of transarterial radioembolization (TARE) in patients with unresectable hepatocellular carcinoma (HCC) is increasingly evidenced. However, data on outcome of liver transplantation or resection after TARE remain scarce. This study aimed to assess the safety and feasibility of surgery after TARE in patients with unresectable HCC.

Methods: Patients exclusively undergoing TARE followed by either orthotopic liver transplantation (OLT) or liver resection (LR) for HCC between 2012 and 2016 were included. Primary outcomes were postoperative morbidity and mortality. Secondary outcomes were overall survival (OS) and response to TARE.

Results: Among 349 patients with HCC treated with TARE, 32 (9%) underwent either OLT (n = 22) or LR (n = 10), which represent the study cohort. In this group, TARE induced decreased viable nodules ($p < 0.001$), an efficient downsizing ($p < 0.001$) as well as a significant downstaging based on BCLC classification ($p < 0.001$). Overall, major complications and mortality after surgery occurred in 5 (16%) and 1 (3%) patients, respectively. For the whole study cohort, OS was 47 months while survival rates at 1-, 3- and 5-years reached 97%, 86% and 86%, respectively.

Discussion: Liver surgery after TARE is feasible and safe. This strategy allows to offer a curative treatment in a subset of patients with unresectable HCC.

Received 20 September 2018; accepted 13 March 2019

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Introduction

Liver cancer has become the second cause of cancer-related mortality worldwide, with hepatocellular carcinoma (HCC) responsible for 750,000 new cases each year. In the United States (US), the annual incidence of HCC is 33,000, and HCC ranks first in term of increasing cancer-related mortality for the last 2 decades.[1,2] A majority of patients with HCC are diagnosed at advanced stage for which therapeutic options are unfortunately limited.[3] Whenever feasible, surgery with either orthotopic liver transplant (OLT) or liver resection (LR) remains the best long-term curative option. For OLT, the Milan criteria are used to select patients with HCC[4] and remain the benchmark used by both American[5] and European consensus.[6] Access to OLT is also dictated by organ availability; organ shortage has become a tremendous issue, as exemplified in the US.[7] Hence, there is a

This study was presented at the annual conference of Swiss Surgical Society, May 2018, Basel; annual conference of ILCA, September 2018, London and at the annual conference of IHPBA, September 2018, Geneva.

* These authors shared senior supervision of the study.

critical need to identify strategies to increase the proportion of patients with HCC who may benefit from curative treatments. With this aim in mind, transarterial radioembolization with Yttrium-90 (TARE) appears as a pertinent option. It is a locoregional therapy (LRT) approved by the US Food and Drug Administration which has been adopted as primary treatment of unresectable HCC in several leading centers in the US.[8] There is limited evidence on the value of TARE for downstaging/downsizing of HCC as a bridge to surgery.[9] Although TARE is not recommended as first line treatment in HCC guidelines, we followed this approach with the rationale that TARE may offer several advantages in this setting, allowing[1] to control progression of the treated nodules[2] to limit progression of the disease in the untreated lobe[3] to induce volumetric changes, such as hypertrophy[5] to select patients based on biological behavior of the tumor, considering that patients who do not respond to TARE are likely at higher risk of recurrence following OLT or LR and finally[6] to gain time and offer an opportunity to treat HCV-positive patients with anti-viral drugs, while controlling the tumor.

Notwithstanding, data on feasibility and safety of surgery with either OLT or LR after TARE are scarce. This study aims to analyze short- and long-term outcomes of patients undergoing OLT or LR after TARE.

Methods

Patients

We performed a retrospective analysis of a prospectively collected database of patients undergoing TARE for HCC between November 1, 2012 and January 20, 2016, at Icahn School of Medicine at Mount Sinai, New York (US). Inclusion criteria were diagnosis of HCC, age $\geq$18 years, and exclusive treatment of TARE followed by either OLT or LR. Patients with previous treatment other than TARE were excluded. The study protocol was approved by the institutional ethical committee (IRB#17–01723).

Evaluation and staging

Patient evaluation included history, physical examination, laboratory tests and imaging. HCC diagnosis was based on either biopsy or imaging according to the AASLD guidelines.[5] Liver function, priority for OLT and HCC staging were classified by Child-Pugh, MELD and BCLC classifications, respectively. BCLC classification was based on radiology.

Treatment decision

Each case was discussed at a weekly tumor board involving surgeons, hepatologists, radiologists and oncologists, where therapeutic strategies were decided on a multidisciplinary basis. For patients included in this cohort, the tumor board adopted an initial decision to treat with TARE in order to stabilize the liver disease. Following TARE, repeat evaluation and staging were performed, and based on response to treatment, a second consensus decided to perform LR or OLT. Notably, decisions for TARE and surgery were sequentially taken; in most cases, the tumor board did not make an upfront decision to perform TARE as bridge to OLT or LR. The decision to perform locoregional therapies (LRT *vs.* LR *vs.* OLT) was adopted after consensus according to the institutional guidelines. Briefly, since 2012, TARE was adopted for the treatment of large, unresectable HCC or multiple nodules confined to the liver, and/or patients awaiting OLT. Per our institutional guidelines, cross sectional imaging with Contrast Enhanced MRI or CT scans were obtained 4–6 weeks following each treatment and subsequently at 3 months intervals. We followed the BCLC algorithm for the decision to perform either LR or OLT. The decision to perform LR was validated in the tumor board a minimum of 3 months after TARE treatment, provided that significant response was observed on imaging (according to mRECIST criteria) and liver function was preserved with no portal hypertension (i.e. platelet count over 100′000, no signs of hypersplenism or varices on preoperative imaging). Similarly, OLT was recommended in patients downstaged from United Network for Organ Sharing (UNOS) T3 to T2, making them transplant candidates under the UNOS MELD upgrade for HCC.

TARE procedure

The technique of transarterial radioembolization is standardized at our institution. Board-certified interventional radiologists performed the procedure. Briefly, microcatheter systems (Progreat®, Terumo Interventional, Somerset, New Jersey; Direxion® or Renegade Hi-Flo® Microcatheters, Boston Scientific, Natick, MA) were employed to gain access to hepatic artery branches after radial or femoral access was obtained. Diagnostic digital substraction angiography (DSA) and intra-arterial cone beam computed tomography (CBCT) hepatic angiography was routinely performed in all patients during TARE preparation. A mapping procedure was performed with Technetium-99m macroaggregated albumin (TC99m-MAA) injected at the exact arterial branch/location into which treatment was planned. Radiation doses were calculated according to manufacturer guidelines for hepatic lobar or segmental volume dosing (80–150 Gy). TARE was performed using glass microspheres (TheraSphere®, BTG, United Kingdom).[10] Post- TARE delivery Bremsstrahlung SPET-CT was performed routinely for all patients. Per Institutional protocol, patients were discharged home 2–4 h after the procedure.

Surgery

LR procedure

All resections were performed with low central venous pressure (0–5 mmHg). In brief, after laparotomy and mobilization of the liver, resection was performed according to the tumor location as revealed by preoperative imaging with the help of intraoperative ultrasonography. Selective ipsilateral blood inflow occlusion and/or total inflow occlusion were routinely employed. Parenchymal

transection was performed using CUSA (Integra®, CUSA®) or Metzenbaum-assisted liver resection (MALR) as previously described.[10] Minor structures (<5 mm) were clipped; larger intrahepatic vascular or ductal structures were dissected, exposed and suture ligated preventing devascularization of the surrounding liver tissue. Argon beam coagulation was employed to obtain hemostasis along the cut edge of the liver when needed. Major liver resection was defined as resection of 3 or more Couinaud's segments.

OLT procedure

Several techniques were used for the OLT surgery, specifically in regard to the hepatic outflow reconstruction. Bicaval and piggyback techniques were used based upon surgical preference. After the reconstruction of hepatic veins and portal vein, the transplanted liver was re-perfused, followed by the hepatic artery reconstruction. Donor livers were flushed with University of Wisconsin (UW) solution (Bridge to Life solutions LLC, Columbia, SC).

Follow-up

Based on institutional guidelines, patients with HCC are followed at 3-, 4- and 6-months intervals during the 1st-, 2nd- and >2nd year following treatment, respectively. Follow-up includes history, physical examination, laboratory and imaging studies.

Outcomes

Postoperative complications were graded according to the Dindo-Clavien[11] and to the International Study Group of Liver Surgery (ISGLS)[12,13] classifications. Potential treatment-induced toxicity was monitored with laboratory tests including liver enzymes (Alanine transaminase (ALT) and Aspartate transaminase (AST)), kidney function (creatinine) and coagulation (international normalized ratio (INR)).

Recurrence and overall survival (OS) were calculated from the time of (first) TARE.

Response to therapy was assessed by radiology and pathology. Radiology included mRECIST criteria.[14] Liver volume was assessed by dedicated triple phase volumetric CT scan and MRI (after Eovist® injection). Analyses of pathology were performed by liver pathologists assessing the amount of necrosis within each specimen.

Statistical analyses

Categorical variables are displayed as frequency with corresponding percentages, whereas continuous variables are presented as mean with SE or median value with IQR, depending on normality of the distribution. Paired samples were compared with paired-t or McNemar-Bowker tests for continuous and categorical variables, respectively.

Kaplan-Meier method was utilized to estimate survival and recurrence.

A p-value of<0.05 was considered significant. Analyses were performed using SPSS v22 statistical software, Chicago, IL (US).

Results

Cohort

During the study period, a total of 349 patients were exclusively treated with TARE for unresectable HCC. Among them, 32 patients (9%) subsequently became candidates for surgery, with 22 and 10 patients undergoing OLT and LR, respectively (Supplementary Fig. 1). These 32 patients were included in final analysis and constitute the study cohort.

Demographics and baseline characteristics (before TARE) of the patients are summarized in Table 1.

Table 1 Demographics and baseline tumors characteristics

	OLT (n = 22)	LR (n = 10)	Total (n = 32)
Age (years)	61 (56–64)	59 (50–65)	60 (55–65)
Age ≥ 60 years	13 (59)	5 (50)	18 (56)
Gender (male)	15 (68)	7 (70)	22 (69)
BMI (kg/m^2)	27.6 (25–30.8)	24.9 (22.1–28.4)	26.6 (24.4–30.5)
Cirrhosis (Child-Pugh)	21 (95)	6 (60)	27 (84)
Grade A	0 (0)	6 (100)	6 (22)
Grade B	8 (38)	0 (0)	8 (30)
Grade C	13 (62)	0 (0)	13 (48)
MELD score	31 (25–33)	8 (7–10)	26 (10–33)
Underlying liver disease	22 (100)	8 (80)	30 (94)
HBV	2 (9)	0 (0)	2 (6)
HCV	15 (68)	7 (70)	22 (69)
EtOH	2 (9)	0 (0)	2 (6)
Other	3 (14)	1 (10)	4 (13)
HIV	0	2 (20)	2 (6)
Portal hypertension	21 (96)	0	21 (66)
Multiple lesions	14 (64)	5 (50)	19 (59)
Bilobar Disease	4 (18)	1 (10)	5 (16)
Size of tumor (cm)[a]	4.2 (2.6–5)	5.2 (2.6–11.5)	4.5 (2.7–5.7)
Staging (BCLC)			
BCLC-A A1/A2/A3/A4	0/7/2/10 (0/32/9/46)	3/1/0/0 (30/10/0/0)	3/8/2/10 (9/25/6/31)
BCLC-B	3 (14)	4 (40)	7 (22)
BCLC-C	0 (0)	2 (20)	2 (6)
Beyond Milan criteria	3 (14)	NA	NA

OLT: orthotopic liver transplantation; LR: liver resection; BMI: body mass index; MELD: Model End Stage Liver Disease; HBV: Hepatitis B virus; HCV: hepatitis C virus; EtOH: ethyl alcohol; HIV: human immunodeficiency virus.
[a] Combined size of each nodules.

Treatments details

Details on sequential treatments are provided in Table 2. Each of the 32 patients exclusively underwent TARE, with more than one session performed in 9 cases (28%). After a median of 9 and 5 months following TARE, OLT and LR were performed in 22 and 10 patients, respectively. For the latter, 9 patients (90%) underwent major resection.

Outcomes

Short-term outcomes

Table 3 provides detailed short-term outcomes. Overall, major complications according to Clavien classification were observed in 5 (16%) patients with one death (3%) reported in the LR group.

Table 2 Treatments details

	OLT (n = 22)	LR (n = 10)	Total (n = 32)
TARE			
Repeated TARE	8 (36)	1 (10)	9 (28)
Number of treated segments	2 (1–4)	4 (3.75–4)	3 (1–4)
≥3 treated segments	14 (64)	9 (90)	23 (72)
Radioactivity (GBq)	2.17 (1.33–2.83)	2.73 (2.33–4.2)	2.49 (1.48–3.03)
Dose absorption (Gy)	150 (120–209)	140 (123–150)	150 (121–181)
Time to surgery (months)	9.0 (6.0–15.3)	4.5 (2.8–5.9)	6.5 (3.6–14.6)
Surgery			
Extension of resection			
Minor (<3 segments)	NA	1 (10)	NA
Major (≥3 segments)	NA	9 (90)	NA
Intraoperative blood loss (mL)	NA	250 (100–875)	250 (100–875)
Transfusion			
PRBC (units)	3 (0–8.5)	0 (0–0.5)	2 (0–6)
PLT (units)	0 (0–2)	0 (0)	0 (0)
Clamping			
Pringle maneuver	NA	5 (50)	NA
Total Pringle time (min)	NA	3 (0–16)	0 (0)
TVI	21 (100)	1 (10)	22 (71)
Total TVI time (min)	31 (26–33)	0 (0)	26 (0–32)

OLT: orthotopic liver transplantation; LR: liver resection; TARE: transarterial radioembolization with yttrium-90; GBq: giga-becquerel; Gy: gray; PRBC: packed red blood cells; PLT: platelets; TVI: total vascular isolation; NA: not applicable.

Table 3 Outcomes

	OLT (n = 22)	LR (n = 10)	Total (n = 32)
Short-term outcomes			
Complications (Clavien)			
Minor (I–II)	20 (91)	4 (40)	24 (75)
Major (III–IV)	4 (18)	1 (10)	5 (16)
Mortality (V)	0	1 (10)	1 (3)
Complications (ISGLS)			
Liver failure	0	1 (10)	1 (3)
Grade A	0	0	0
Grade B	0	0	0
Grade C	0	1 (10)	1 (3)
Bile leak	1 (5)	0	1 (3)
Grade A	0	0	0
Grade B	1 (5)	0	1 (3)
Grade C	0	0	0
Long-term outcomes			
Recurrence			
Any location	0	4 (40)	4 (13)
Intra-hepatic	0	2 (20)	2 (6)
Extra-hepatic	0	2 (20)	2 (6)
Time to recurrence (months)	NA[a]	10 (4–21)	10 (4–21)

OLT: orthotopic liver transplantation; LT: liver resection; ISGLS: international study group of liver surgery; AST: Aspartate transaminase; ALT: Alanine transaminase; INR: international normalized ratio; NA: not applicable.
[a] No reported recurrence.

Long-term outcomes

Median follow up was 30 (19–41) months. No recurrence was observed in transplanted patients whereas 4 patients recurred following LR (40%). Survival and recurrence curves after LR or OLT are shown in Fig. 1.

Response to TARE

We performed a comprehensive analysis of response to therapy integrating pathology and radiology studies (Table 4) as well as downstaging/downsizing induced by TARE (Fig. 2).

We also explored the capacity of TARE to downstage/downsize HCC. Overall, TARE was associated with a decrease in the number viable nodules ($p < 0.001$), the size of nodules ($p < 0.001$), and a successful downstaging according to BCLC classification ($p < 0.001$) (Fig. 2).

Discussion

This study is one of the largest series of patients with initially unresectable HCC treated exclusively with TARE, followed by LR or OLT. It demonstrated a significant response to therapy, in a

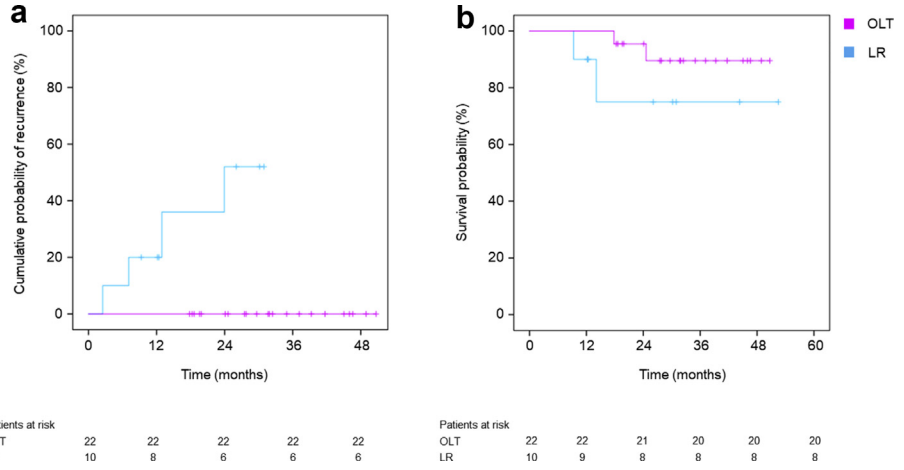

Figure 1 **Long-term Outcomes.** (a) Kaplan-Meier curves for recurrence in patients undergoing OLT (pink) or LR (blue).(b) Kaplan-Meier curves illustrating survival in patients undergoing OLT (pink) or LR (blue). OLT: orthotopic liver transplantation; LR: liver resection

subset of patients (32/349), allowing subsequent definitive therapy with OLT or LR.

Short- and long-term postoperative outcomes did not indicate any deleterious effect of TARE treatment, supporting the feasibility and safety of surgery after TARE.

Previous trials have failed to demonstrate any superiority of TARE compared to standard systemic therapies in advanced HCC.[15] Hence, TARE is not recommended by current HCC guidelines.[16] On the other hand, there is observational data indicating the value of TARE a group of patients with HCC, particularly those with borderline or unresectable tumors, in term of tumor control and downstaging or downsizing.[8] Data are particularly scant examining the role of TARE as bridge to OLT or LR. In a recent review on OLT after TARE, the authors identified 187 cases, from 20 reports.[16] Among the 12 studies reporting more than 3 cases, 7 were conducted in two centers. Vouche *et al.* reported their experience of OLT after TARE in 33 patients, showing a median survival of 53 months; their results are concordant with our study but their cohort included patients with HCC with solitary tumors $\leq$ 5 cm, corresponding to BCLC A stage.[17] TARE was used in BCLC A patients with large tumor (>5 cm) to allow downsizing rather than downstaging. In addition, the use of TARE in this setting allowed to treat hepatitis C in newly diagnosed patients while awaiting surgery. Finally, it offers a good control of the tumor burden, while patients with low MELD score are on the waiting list for OLT, in the current context of organ shortage. There are limited reported cases of LR following TARE and reports include multiple tumor types (colorectal metastases (CRM), neuroendocrine tumors and HCC), making direct comparison difficult. Two studies analyzed their experience of patients undergoing LR after TARE, reporting 4 cases of HCC in each study. In comparison to our results, adverse outcomes were higher in both studies with mortality and major complications rates reaching 33% and 78%, respectively, as opposed to 3% and 16% in our study. Overall survival also appeared prolonged in our cohort with 42 months, compared to 19–25 months in these series.[18,19]

One may hypothesize that tissue changes induced by TARE, such as fibrosis, may render surgical procedures more complex and more difficult. In our experience, LR or OLT after TARE were not associated with increased clamping time, blood transfusion, or postoperative complications as opposed to upfront LR or OLT.[11,21]

In this group of patients with initially unresectable HCC, the use of TARE allowed (i) to control the tumor burden in the diseased lobe (ii) to prevent extension of the tumor in the naïve nontumoral lobe, and (iii) significant future remnant liver hypertrophy to perform safe major liver resections. The capacity of TARE to control disease progression in both treated and

Table 4 Response to TARE

	OLT (n = 22)	LR (n = 10)	Total (n = 32)
Histology			
No necrosis	2 (9)	0	2 (6)
Necrosis <30%	2 (9)	0	2 (6)
Necrosis 30–50%	4 (18)	1 (10)	5 (16)
Necrosis >50%	8 (36)	4 (40)	12 (38)
Necrosis 100%	6 (27)	5 (50)	11 (34)
Radiology (mRECIST)			
Progression of the disease	0	1 (10)	1 (6)
Stable disease	3 (14)	0	3 (9)
Partial response	7 (32)	3 (30)	10 (31)
Complete response	12 (55)	6 (60)	18 (56)

TARE: transarterial radioembolization with Yttrium-90; OLT: orthotopic liver transplantation; LR: liver resection; FLR: future liver remnant; TELV: total estimated liver volume; mRECIST: modified response evaluation criteria in solid tumors; NA: not applicable.

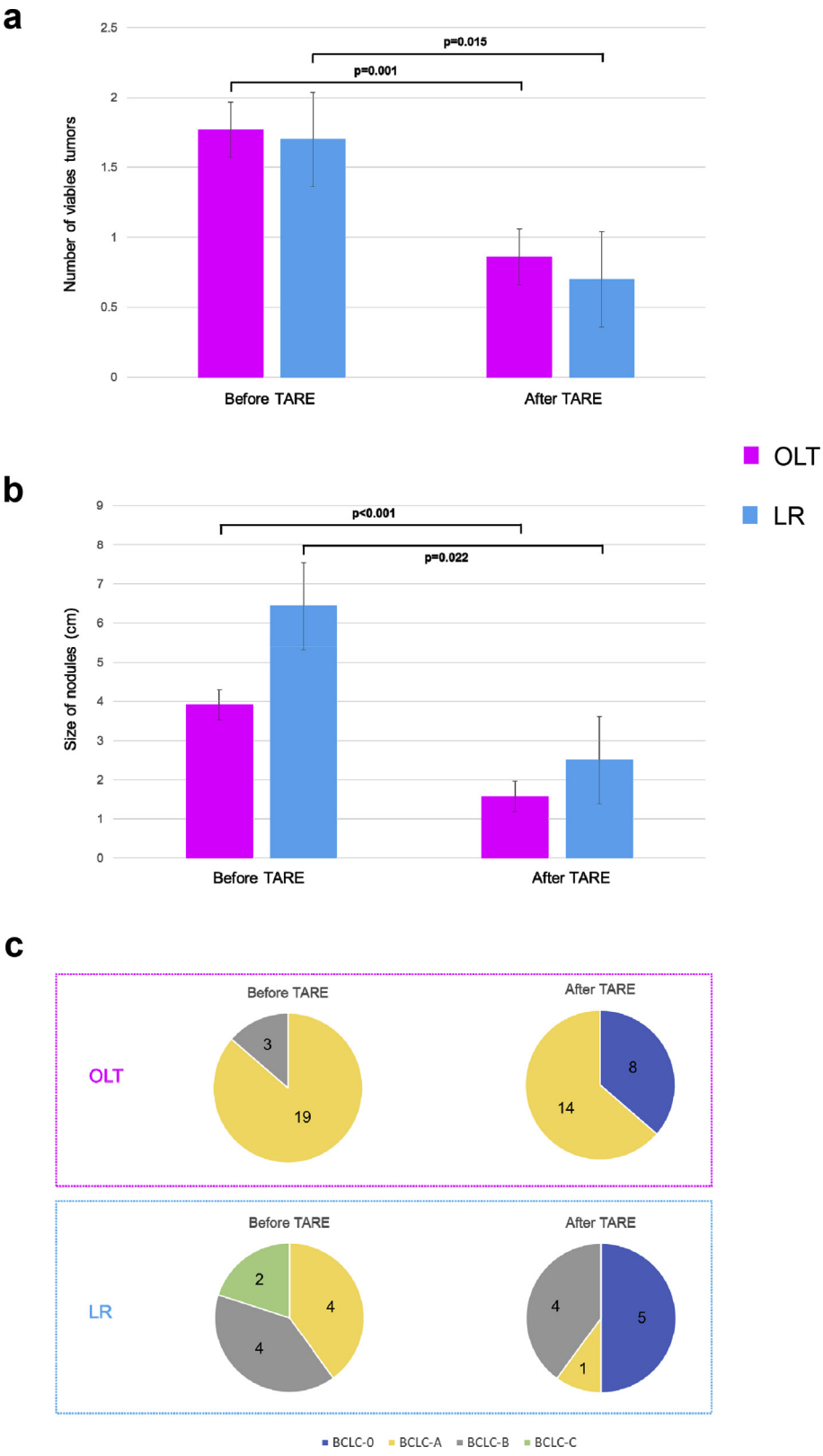

Figure 2 **Response to TARE.** Bar plots illustrating mean values before and after TARE for (a) number of viable tumors (b) combined size of tumor nodules and (c) BCLC staging. TARE: transarterial radioembolization with Yttrium-90; OLT: orthotopic liver transplantation; LR: liver resection

untreated lobes is well established.[8,20,21] In addition, as previously analyzed, significant hypertrophy of the non-treated lobe is achieved after TARE in patients with HCC. Interestingly, no sign of major portal hypertension was observed.[22] The same research group also explored the underlying physiological mechanisms, identifying activation of pathways such as inflammation, endothelial stress, coagulation as well as liver regeneration.[23]

We believe that TARE allows assessment of tumor the biology while preparing the future liver remnant for major resection. Although this hypothesis needs to be confirmed by dedicated studies on TARE in patients with HCC, a comparable strategy has been adopted in patients undergoing LR for CRM after neoadjuvant therapies.[24]

In patients with HCC, multiple treatment options exist and selecting the best therapy is paramount to obtain long-term survival. Contraindications to LR due to large tumor burden precluding major hepatectomy and long waiting list with organ shortage for OLT are limitations that frequently preclude a curative approach. Therefore, there is a clear need to identify new strategies to improve resectability or enable access to OLT which remains the best curative treatment.

In the group treated with TARE followed by OLT, a subset of patients may have undergone a theoretical upfront OLT, but as previously mentioned, organ shortage has become a major hurdle worldwide. Hence, TARE offers a precious opportunity to control HCC for the patients in waiting list. Our results support the use of TARE as bridge to surgery, with no increased risk of adverse outcomes in a subset of patients with HCC.

Some limitations need to be addressed. The study is limited by its retrospective design. Although sample size is not very large, it is one of the largest series of patients with HCC undergoing major liver resection after TARE. Finally, the study was conducted in a single center, as were most other comparable studies. Multicenter studies or studies integrating both training and validation cohorts would be valuable and are needed in the future.

Conclusions

This study provides the proof-of-concept to use TARE as a downstaging/downsizing strategy, which allows to subsequently offer curative treatments with OLT or LR in a subset of patients with unresectable HCC, without increasing the risk of postoperative adverse outcomes. Further prospective studies are needed to confirm these data. In addition, there is a need to create multicenter collaboration to compile the data on TARE as neoadjuvant treatment of patients with HCC.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2019.03.360.