INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Transarterial chemoembolization with drug-eluting beads in patients with hepatocellular carcinoma: response analysis with mRECIST

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PURPOSE
According to the Barcelona Clinic Liver Cancer (BCLC) staging classification, transarterial chemoembolization (TACE) is the treatment of choice for intermediate hepatocellular carcinoma (HCC). Thereby, the use of drug-eluting beads (DEB) as embolic agents has been recently established in clinical practice. The aim of this study was to evaluate tumor response after DEB-TACE.

METHODS
This retrospective study was approved by the institutional ethics committee. Overall, 89 patients with HCC (Child Pugh A or B) receiving DEB-TACE as palliative treatment option or as bridging before liver transplantation were included in the study. Tumor response was assessed by modified response evaluation criteria in solid tumors (mRECIST) and a tumor growth rate. Survival analysis was performed using Kaplan-Meier estimator with log-rank testing and Cox proportional hazards.

RESULTS
A total of 188 TACE procedures were performed between 2006 and 2010. After the last intervention, 18% achieved complete response, 45% achieved partial response, 28% had stable disease and 9% had progressive disease. Using the tumor growth rate, 90% of all patients showed a tumor reduction between first and final response evaluation. The 6-month, 1-, 2- and 3-year overall survival rates were 86.5%, 67.4%, 47.2%, and 33.7%, with a median survival of 45, 24, 15, and 14 months for complete response, partial response, stable disease, and progressive disease, respectively. Tumor reduction showed a positive effect on survival.

CONCLUSION
DEB-TACE offers conclusive response results with mRECIST and proves a strong tendency of tumor reduction on survival benefits. Therefore, tumor growth rate represents a possible parameter to predict survival.

H epatocellular carcinoma (HCC) is the sixth most common cancer and the third deadliest cancer in industrialized countries (1). The relevance for HCC is rising by its increase of incidence which is attributed to a higher occurrence of hepatitis B and C as well as to a growing number of alcohol-associated liver diseases and to the epidemic of metabolic syndrome (2, 3). Taking this into account, as well as late diagnosis and very poor prognosis, prevention and treatment of HCC represents the main focus of research.

The clinical staging system according to the Barcelona Clinic Liver Cancer (BCLC) classification was introduced by Llovet in 1999 and was updated by Forner in 2010, assigning 5 stages according to tumor burden, liver function, and physical condition that are referred to treatment indications (4, 5). With improved surveillance programs nowadays, diagnosis at an initial stage is feasible for 30%–40% of the patients. Still most patients are diagnosed at intermediate and advanced stage and can therefore only be considered for noncurative treatment options (6). Especially patients at intermediate stage (BCLC-B) benefit from transarterial chemoembolization (TACE) which is the only noncurative treatment, combined with systemic chemotherapy of sorafenib, lenvatinib or regorafenib, that shows to improve survival (7–9).

TACE protocols differ widely among centers in regard to technique and chemotherapeutics. In particular the choice of embolic agents is of great scientific interest, as the lipiodol-based conventional TACE (cTACE) is being questioned to release chemotherapeu-

tics in an unregulated high amount to the bloodstream (10). The recent development of drug-eluting beads (DEB) as embolic microspheres, which release high-dose chemotherapeutics in a more controlled way over several weeks, makes them a favorable object of study (11).

To assess therapy success and its connection to survival, the adequate selection of response criteria is crucial. This led us to our current retrospective investigation, analyzing tumor response criteria after DEB-TACE in HCC patients and identifying possible survival benefits among response groups.

Methods

This study was conducted as a retrospective analysis of DEB-TACE procedures of a single center experience and has been approved by our institutional ethics committee (protocol number 3977-01/14). Following clinical protocol, written and informed consent had been given before each intervention.

Patients

A total of 146 patients were registered for treatment with DEB-TACE at the department of surgery and gastroenterology between 2006 and 2010. We excluded 24 patients because of no contrast-enhancing tumor during preinterventional angiography. Due to partial lipiodol use, missing follow-up imaging or no possible accurate lesion measurement, another 33 patients were excluded. Consequently, 89 patients (75 men, 14 women; mean age, 64±8 years; age range, 44–83 years) were included (Fig. 1). According to the European Association for the Study of the Liver (EASL) guidelines, all patients had been diagnosed with HCC via ultrasonography, followed by either biopsy or two independent other imaging modalities such as computed tomography (CT) scan or magnetic resonance imaging (MRI),
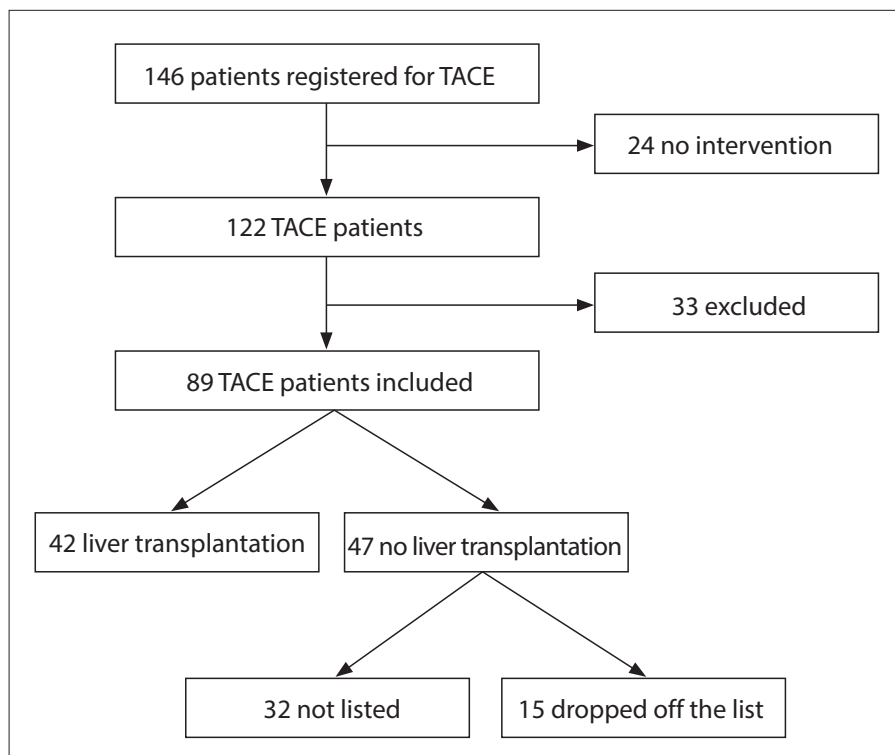

Figure 1. Patient acquisition.

or one imaging combined with an elevated alpha fetoprotein (AFP) level >400 ng/mL (12). We included two groups of patients that received TACE. The first group of 47 patients was treated under noncurative indication. The second group of 42 patients received TACE as a bridging modality before liver transplantation to limit tumor progression while being on the waiting list. The diagnosis of cirrhosis was based on blood testing and medical imaging such as ultrasonography or CT scan. If clinical findings left the diagnosis in doubt, a biopsy was performed.

The inclusion criteria contained a confirmed HCC diagnosis with a Child-Pugh score A or B, no vascular invasion, no extrahepatic spread, no hepatic encephalopathy or any severe impaired vital functions. Furthermore, hypervascular lesions in arterial or portal-venous phase, and at least one measurable nodule corresponding to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) was required. Previous treatments such as ablation or sorafenib administration, involving 17 patients, did not represent an exclusion criteria.

TACE procedure

All procedures have been performed by interventional radiologists, each with at least 5-year experience with TACE. Patients were treated every month (4-6 week interval) with up to 6 procedures, depending on accurate devascularization or until liver transplantation. In advance, all patients received a blood clot prevention with heparin (5000 IU), an antibiotic prophylaxis with amoxicillin/clavulanate (2.2 g) and granisetron (1 mg) as antiemetic premedication. An angiography following a standardized protocol was undertaken prior to intervention. A superselective catheterization of the hepatic artery and the artery supplying the tumor via a 2.7 F microcatheter (Progreat, Terumo Corporation) was performed in all patients. DEB-TACE was then applied into the feeding vessel by a combination of DC Bead® (Boston Scientific) loaded with epirubicin (Farmorubicin, Pfizer). The microsphere size (100–300 μm and 300–500 μm) of the beads was chosen depending on the vessel caliber, size and vascularity of the tumor. Epirubicin was applied to a maximum dose of 150 mg per embolization contingent on tumor size. During procedures, Ultravist 300 mg/mL (Bayer Pharmaceuticals) was administered as contrast medium. Intervention ended by interrupting contrast agent drainage into the tumor with a final control image.

Response evaluation

For all patients contrast-enhanced multislice CT or contrast enhanced MRI were used at baseline and every follow-up to evaluate tumor response. As previously reported, CT scan and MRI showed comparable results in tumor necrosis without the use of lipiodol and therefore, were considered as equivalent methods (13, 14). Tumor response was assessed by the mRECIST criteria of the American Association for the Study of Liver Diseases, taking the actual induced tumor necrosis into account by measuring only vital tumor parts (15). Consequently, at baseline all lesions showing an arterial contrast enhancement and being bigger than 1 cm were registered as target lesions and measured in their longest diagonal diameter. Response was reviewed by two experienced radiologists. Considering that measurements can be challenging due to various vascularization and necrosis patterns, Fig. 2 demonstrates the approach performed. All other lesions were considered as nontarget lesions and documented at baseline. We assessed follow-up imaging at least 1 month after each intervention. Fig. 3 shows an example for the stepwise devascularization at follow-up. Response of target lesions, nontarget lesions and detection of new lesions were ascertained after each intervention forming an overall response according to the mRECIST (15). We assessed the final overall response for statistical evaluation, thereby having the objective response (OR) accounting for complete response and partial response.

Furthermore, we established a tumor growth rate with the first and final sum of diagonals to demonstrate the overall amount of tumor reduction.

Primary endpoint was tumor response. Survival was considered as secondary endpoint and was recorded at 6 months, 1-, 2- and 3 years. End of follow-up was reached by March 2013 or death. All patients have been followed up for 3 years.

Technique

Patient scheduling and reporting as well as picture archiving were supplied by iSOFT Radiology Information System (Healthcare Group of CSC). Image display with a resolution of 1600×1200 pixels was supported by Coronis MDCC 2121 Monitor (Barco) and viewing and analyzing by Cerner Provision PACS (Cerner Corporation).

Statistical analysis

Descriptive statistics of the data are presented with the total number in the population n (%), for non-normalized variables are shown as median (25–75 percentiles) and normal distributions are shown as mean ± standard deviation (SD). Spearman's correlation was done to show a possible association for TACE repeats to tumor reduction and to OR. Using Kaplan-Meier estimates, survival functions were generated for overall response groups as well as for bridging and palliative groups. Median survival is indicated by median ± standard error of median. We conducted a log-rank test to compare between those survival functions. Cox regression was utilized for semiparametric time to event analysis. A p value <0.05 was considered significant. Analyses were done using IBM SPSS Statistics 19 (IBM Corporation).

Results

Overall, 89 patients received treatment with TACE and were included for analysis. In the process, 42 patients (47.2%) received a liver transplantation and were therefore bridged to transplantation; 21 of those 42 patients were not within Milan criteria at the time of listing and therefore received a downstaging attempt.

Considering the whole cohort, 52 patients (58.4%) showed a pathologically confirmed HCC by biopsy or explant material,
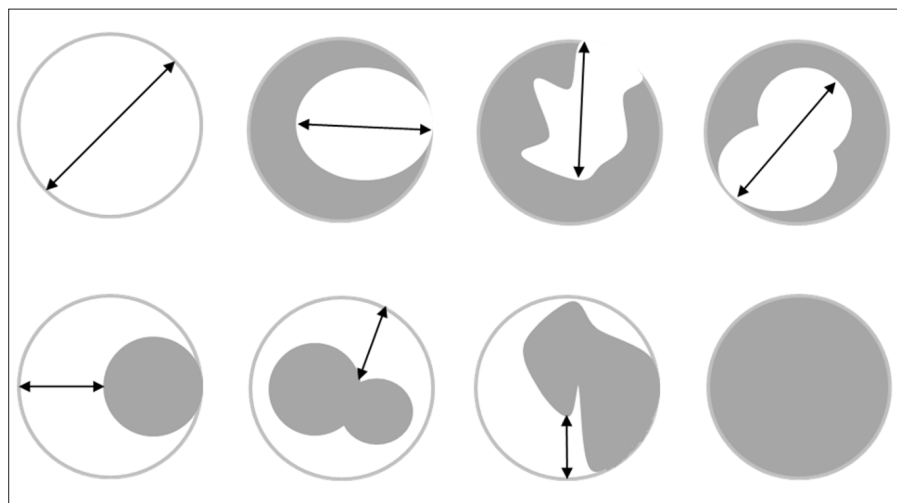
Figure 2. Approaches for measurement of target lesions according to mRECIST: white – viable tumor, gray – necrotic tumor, arrow – longest radial diameter
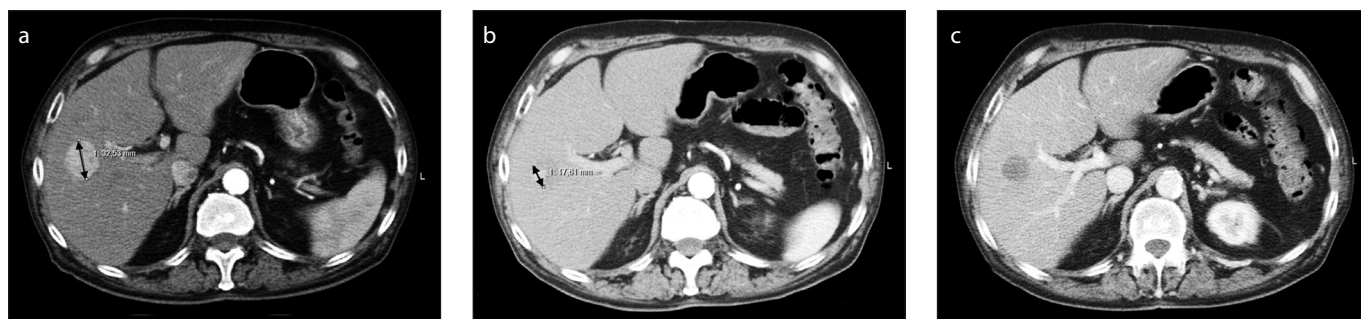
Figure 3. a–c. Contrast-enhanced CT scan with single central HCC lesion: **(a)**, baseline with full arterial contrast enhancing tumor; **(b)**, 2 months follow-up after first intervention with reduction of contrast enhancing tumor; **(c)**, 1 month follow-up after second intervention with disappearance of intratumoral contrast enhancement (complete response).

Table 1. Baseline characteristics

	DEB-TACE (n=89)
Demography	
Age (years), mean±SD	64±8
Male/ female, n (%)	75 (84.3)/ 14 (15.7)
Cause of cirrhosis, n (%)	
Hepatitis C virus	7 (7.9)
Hepatitis B virus	4 (4.5)
Alcohol	53 (59.6)
Cryptogenic	20 (22.5)
Others	6 (6.7)
No cirrhosis	2 (2.2)
Child-Pugh-Score, n (%)	
A	60 (67.4)
B	27 (30.3)
BCLC classification, n (%)	
A	50 (56.2)
B	39 (43.8)
C	0 (0)
Biochemistry	
Serum bilirubin (mmol/L), median (range)	23 (12–31)
Serum albumin (g/L), median (range)	32.50 (29–36)
AFP level (ng/mL), median (range)	16.75 (5.45–184.92)
Distribution of AFP, n (%)	
<10	37 (41.6)
10–400	38 (42.7)
>400	14 (15.7)
Tumor characteristics	
Location, n (%)	
Bilobar	31 (34.8)
Right	48 (53.9)
Left	10 (11.2)
Lesions, n (%)	
1	43 (48.3)
2	25 (28.1)
3	9 (10.1)
>3	12 (13.5)
Largest tumor size (mm), median (range)	52 (38.5–70)
Bridging	42 (29–53.25)
Palliative	61 (49–80)
Milan, n (%)	
In	27 (30.3)
Out	62 (69.7)
Liver transplantation, n (%)	
Yes	42 (47.2)
No	47 (52.8)

DEB-TACE, drug-eluting beads transarterial chemoembolization; BCLC, Barcelona Clinic Liver cancer.

whereas for 37 patients (41.6%) diagnosis was validated by radiological imaging with combination of AFP levels. Liver cirrhosis was found in 87 patients (97.8%), mainly caused by alcohol abuse (n=53, 59.6%), followed by hepatitis C virus (n=7, 7.9%) and hepatitis B virus (n=4, 4.5%) (Table 1). Other etiologies of cirrhosis were identified as primary biliary cirrhosis (n=4), hemochromatosis (n=1) and autoimmune hepatitis (n=1) or combined entities (n=3). Overall, 20 patients (22.5%) presented with unknown cause and 2 (2.2%) had no cirrhosis. Child-Pugh classification for liver cirrhosis resulted in 60 patients (60.4%) with score A and 27 (30.3%) with score B.

Median AFP levels were 16.75 ng/mL (5.45–184.92 ng/mL) with only 14 patients (15.7%) being over 400 ng/mL. Concerning tumor spread and appearance, 1 lesion (48.3%) and 2 lesions (28.1%) presented the most while 3 lesions (10.1%) or more (13.5%) were rarely found within the collective. Of the nodules, 34.8% (n=31) were located bilobar, 53.9% (n=48) were in the right liver lobe, and 11.2% (n=10) in the left liver lobe. Median tumor size at baseline according to mRECIST (sum of diagonals) was 52 mm (38.5–70 mm) (Table 1).

Altogether, 188 TACE procedures in 89 patients were performed. Patients received up to 6 treatments each, although 1- and 2-courses of TACE were represented the most (n=34, 38.2% and n=27, 30.43%) (Table 2). Mean time between interventions was 85±65 days. Only few complications occurred during the procedure with 3 patients (3.4%) having spasms of liver supplying arteries and 2 patients (2.2%) with a cardiac event such as bradyarrhythmia and hypertensive crisis. Additional procedures were performed: 5 patients (5.6%) had radiofrequency ablation, 6 (6.7%) had sorafenib administered, 3 (3.4%) were treated with selective internal radiotherapy, 2 (2.2%) also received chemoembolization in external hospitals and 2 (2.2%) had a partial hepatectomy.

All lesions used for the study showed initial hypervascularity. Evaluation of overall response following mRECIST criteria yielded complete response in 16 cases (18%), partial response in 40 (44.9%), stable disease in 25 (28.1%) and progressive disease in 8 (9%). Considering the whole sample, 56 patients (62.9%) achieved OR; comparing bridging versus palliative treatment 30 (71.4%) vs. 26 (55.3%) patients achieved OR. Most of the bridging patients showed complete and partial response (n=11,

Table 2. Procedure and results	
	DEB-TACE (n=89)
TACE procedures	
Absolute count	188
Number of repetition, n (%)	
1	34 (38.2)
2	27 (30.3)
3	18 (20.2)
> 4	10 (11.2)
Responses overall, n (%)	
CR	16 (18)
PR	40 (44.9)
SD	25 (28.1)
PD	8 (9)
Event, n (%)	
None	28 (31.5)
Death	61 (68.5)
CR	8 (50)
PR	29 (72.5)
SD	19 (76)
PD	5 (62.5)
Kaplan Meier	
Median survival (months), median (± standard error of median)	
CR	45 (±16.71)
PR	24 (±7.08)
SD	15 (±2.50)
PD	14 (±4.24)
Liver transplantation	45 (- *)
No liver transplantation	14 (±1.71)
Log-Rank (p)	
CR/ PR	0.021
CR/ SD	0.012
CR/ PD	0.186
PR/ SD	0.535
PR/ PD	0.688
SD/ PD	0.477
Liver transplantation yes/no	<0.001

DEB-TACE, drug-eluting beads transarterial chemoembolization; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
* No event after median survival of 45 months.

26.2% and n=19, 45.2%) and for the palliative group partial response and stable disease (n=21, 44.7% and n=17, 36.2%) represented the majority. Using the tumor growth rate, an absolute tumor reduction for 80 patients (89.9%) was achieved (Table 3). Fig. 4 shows the distribution of tumor reduction among patients. Both OR and absolute tumor reduction showed no correlation to TACE repeats (Spearman's correlation coefficient r= 0.046, p = 0.671 and r = -0.182, p = 0.087).

At the end of follow-up, 28 patients (31.5%) were alive and 61 (68.5%) had died. The 6-month, 1-, 2- and 3-year survival rates were 86.5%, 68.5%, 48.3% and 33.7% for the whole patient collective from the date of diagnosis. Kaplan-Meier curves displayed a median survival of 45±16.7 months for complete response, 24±7.1 months for partial response, 15±2.5 months for stable disease, and 14±4.2 months for progressive disease (Fig. 5). Log-rank evaluation demonstrated superiority of complete response over partial response and stable disease (p = 0.021 and p = 0.012). Concerning progressive disease no significant difference to complete response, partial response or stable disease (p = 0.186, p = 0.688 and p = 0.477) could be found (Table 2). Of 8 patients with progressive disease, 7 developed new lesions and only 4 showed an actual tumor growth. Comparing survival for bridging and palliative groups, overall survival at 6 months, 1, 2 and 3 years were 92.9%, 83.3%, 71.4% and 47.6% for bridging patients and 80.8%, 55.3%, 25.5%, and 21.3% for palliative patients. Kaplan-Meier estimates resulted in significantly longer survival for patients with transplantation (p < 0.001). Median survival was 14±1.7 months for the palliative group and 45 months (no standard error of median) for the bridging group (Fig. 6).

Multivariate analysis identified transplantation to be a distinct significant and independent determinant for survival (p = 0.002). Tumor growth rate could not show significance (p = 0.089) (Table 4).

Discussion

In 2002, the randomized controlled trial of Llovet et al. (16) detected survival benefits for TACE compared with conservative treatment for the first time, making it an important therapy option for unresectable hepatocellular carcinoma. But throughout the years the mainly applied embolisat lipiodol in combination with doxorubicin as an emulsion used for example in Llovet`s study, did not allow a controlled release of chemotherapeutic agents. Thus, lipid-based cTACE was more and more replaced by DEB to improve patients' response and tolerability facilitating the standardization of the chemoembolization procedure. Previous studies already focused on the comparison of DEB-TACE with cTACE. The multicenter phase II randomized-controlled trial of Lammer et al. (17) in 2010 showed, though superiority could not be met, higher rates of
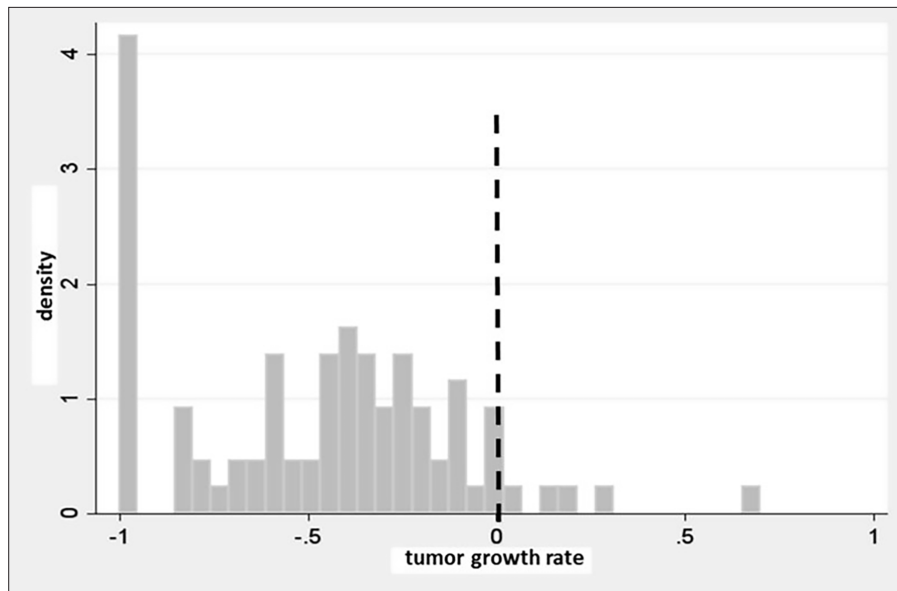
Figure 4. Graph shows the quantitative distribution for tumor growth, displaying most patients (90%) with a negative growth rate (= tumor reduction):

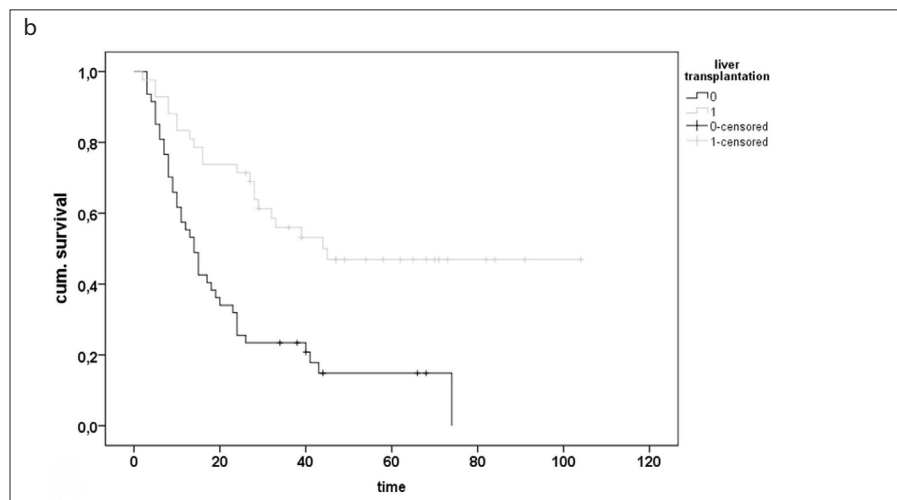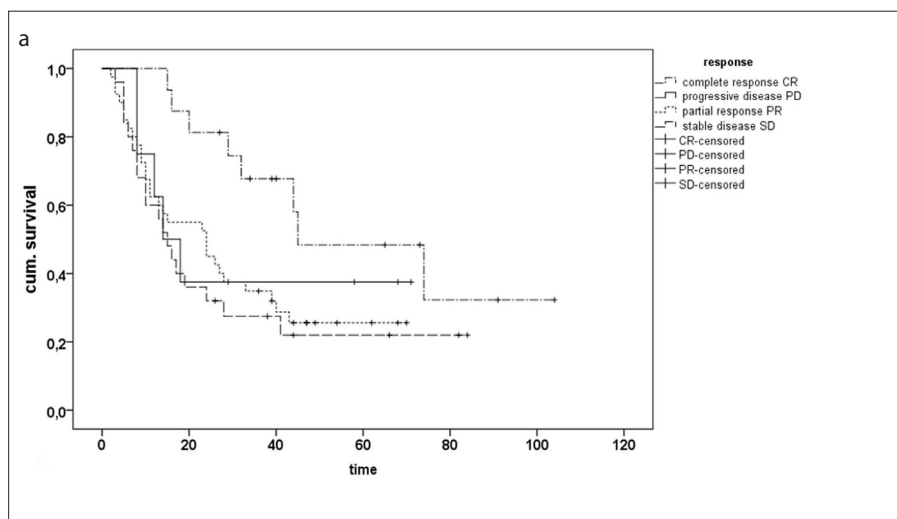$$tumor\ growth\ rate = \frac{tumor\ size\ (end) - tumor\ size\ (start)}{tumor\ size\ (start)}$$

Figure 5. a, b. Kaplan-Meier survival estimates for response groups.

tumor response in the DEB group as well as significant reduction of serious liver toxicity and doxorubicin side-effects compared to cTACE. Other retrospective studies verified a significantly higher treatment response and survival benefits for the DEB-TACE group (18, 19). A recent meta-analysis by Chen et al. (20) included 16 cohort studies comparing cTACE with DEB-TACE. It revealed a significantly improved 1-, 2-, and 3-year overall survival rate for the DEB-TACE group. Taking this into account, no cTACE with lipiodol has been performed in our institution since 2006, as we did not believe it to be the standard therapy anymore. Therefore, this retrospective analysis recorded all DEB treatments undertaken in our tertiary university hospital as a single center, single arm study with the purpose of evaluating tumor response and their impact on survival for each response group. Nonetheless, a randomized-controlled trial of Golfieri et al. (21) found equally effective outcomes for DEB-TACE and cTACE, suggesting a reconsideration of the cTACE regimen in our center to make further comparative studies possible.

Taking the importance of response criteria for treatment evaluation into account, an expert panel by the American Association for the Study of Liver Diseases provided a framework for the design of clinical trials dealing with HCC, updating the standard RECIST criteria that focused on tumor shrinkage to the mRECIST criteria (22). With respect to tumor directed therapy, the major advantage of mRECIST was the consideration of induced necrosis by only measuring contrast-enhanced viable tumor parts. After a similar proposal by the 2000 EASL guidelines, mRECIST was even more detailed regarding target lesions, non-target lesions and new lesions (12, 15). Several studies demonstrated superiorty of mRECIST for response evaluation suggesting it as a predictor of survival (23–26). In our study, 1 month after treatment, OR evaluated with mRECIST, was 63% for the whole cohort, putting it in line with previously reported ORs for DEB-TACE ranging from 52.5% to 89.9%, with follow-up from 1 to 3 months (18, 21, 24). Other studies such as Lammer et al. (17) with an OR of 51.6%, Malagari et al. (27) with an OR of 80.7%, and Varela et al. (10) with an OR of 66.6% were analyzed by EASL. A comparative study of mRECIST vs. EASL, with an OR of 52.5% vs. 39.2% respectively, underlines the wide range of the tumor response criteria ap-

Table 3. Tumor response depending on TACE repeats

	Spearman's rho (p) for TACE repeats	All patients with TACE (n=89)	Number of TACE =1 (n=34)	Number of TACE =2 (n=27)	Number of TACE ≥3 (n=28)
Absolute tumor reduction	-0.182 (p = 0.087)	80 (89.9%)	31 (91.2%)	23 (85.2%)	26 (92.9%)
OR mRECIST	0.046 (p = 0.671)	56 (62.9%)	20 (58.8%)	18 (66.7%)	18 (64.3%)

TACE, transarterial chemoembolization; OR, objective response; mRECIST, modified response evaluation criteria in solid tumors.

Table 4. Mortality risks controlled for various variables

	Hazard ratio	p	95% CI
Tumor growth rate	1.918	0.089	0.905; 4.065
Liver transplantation (yes/no)	2.610	0.002	1.424; 4.784
Age (per year)	0.995	0.817	0.957; 1.035
Tumor size at baseline in mm	1.003	0.280	0.997; 1.009
New lesion (yes/no)	1.160	0.718	0.519; 2.595
Tumor count (per number)	1.017	0.910	0.760; 1.362

Model p = 0.001.
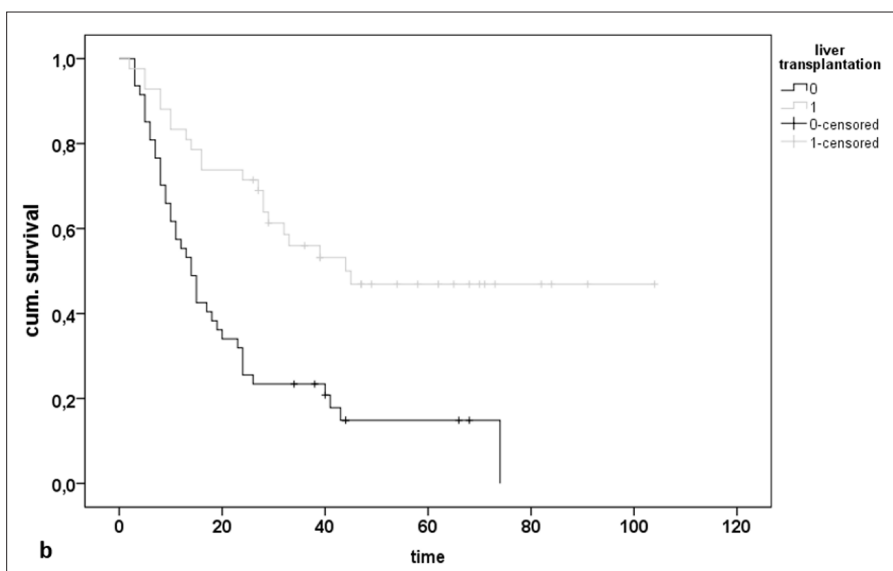
Figure 6. Kaplan-Meier survival estimates for bridging versus palliative groups.

plied, requiring further investigation to standardize response criteria (24).

Concerning response groups, survival showed superiority of complete response over partial response and stable disease indicating a reasonable use of mRECIST predicting survival. Whereas progressive disease failed to show a significant difference to other response groups. A very likely reason was the small sample of 8 patients, with 5 of them showing an event in this group. Furthermore, 7 out of 8 patients showed new lesions qualifying for progressive disease despite no actual tumor growth. This indicates that new lesions themselves might be less important in predicting survival than actual tumor growth.

As OR only takes account of at least 30% of reduction in tumor size, we introduced a tumor growth rate to demonstrate the absolute tumor reduction displaying a response of 90%. We also tested it to see if it could be a possible surrogate to predict survival. The Cox regression model did not show significance. Data indicated a positive tendency. So far, no comparable studies have been undertaken. Therefore, we suggest the tumor growth rate as a favorable future object of study also given that statistical analysis is more accurate compared to

response groups. However, the appearance of multiple new lesions, usually indicating progressive disease, complicates exact measurement. A possible combination of response groups and growth rates needs further discussion. In another approach, Lin et al. (28) performed a 3D voxel by voxel volumetric assessment (vRECIST) of tumor response in a time efficient manner, such that an exact idea of tumor size could be computed in 4 minutes. Despite this study having a small sample size and only descriptive character, a correlation with established response criteria and survival would be interesting.

In our study, overall survival was worse than the rates previously reported for DEB-TACE interventions. With liver transplantation having a signicant influence on survival, we only took the palliative group to evaluate overall survival compared to other studies. In our study, 6 months, 1-, 2-, and 3-year survival rates were 80.8%, 55.3%, 25.5%, and 21.3%, while other studies showed 93%–100%, 86%–94%, 56%–88%, and 62%–66%, respectively (10, 18, 21, 29–31). Focusing on patient selection, a major difference compared to the other studies was the high percentage of cirrhosis due to alcohol abuse, with 60% vs. 6%–26%, raising the question of an influence of etiology on survival (10, 18, 21, 29–31). Few studies have been performed to compare prognosis for different etiologies of cirrhosis. We could not demonstrate a significant impact of alcohol on survival. However, a recent study by Schutte et al. (32) showed prolonged survival in alcohol-related disease compared to viral infections in early stage (BCLC-A) patients, suggesting further attention to etiology regarding prognosis. With selected patients having fulfilled inclusion criteria for TACE, such as preserved liver function (Child-Pugh A/B), intermediate tumor stage or no impaired other organ dysfunctions, recruitment has been performed as restrictive as possible. The results of previous studies could not be confirmed by our data analysis because of inadequate documentation due to the retrospective

character. This is stating the importance of selective recruitment with respect to future prospective studies. An important study by Sieghart et al. (33) developed the ART score helping to identify patients that might not benefit from further TACE sessions. Though not focusing on the initial TACE indication, this score for the retreatment with TACE gives an excellent example for reasonable patient selection.

Nevertheless, Cox regression analysis did not identify tumor size at baseline and tumor count as independent prognostic factors for survival evening out the groups to have the same conditions from first TACE to imaging follow-up before transplantation. But taking a focus on the post-transplantation process, liver transplantation had, as very well known, a significant influence on survival. Of the included patients, 50% were outside MILAN and could successfully be downstaged by chemoembolization. Thus, they were given the opportunity to be registered on the transplant waiting list and to receive a liver transplant.

Data suggested a strong effect of tumor reduction on survival as well. The whole collective achieved prolonged survival by tumor reduction independent from the transplant patients. Though we did not have a cTACE comparative group, we assume tumor reduction to be achieved by DEB-TACE. We therefore encourage further performance of DEB-TACE in palliative as well as in bridging patients.

The retrospective design is surely the biggest limitation of our study, which inevitably led to patient selection bias that effected the response groups. Another drawback was the particle sizes. Two different sizes of beads were applied, depending on the interventionalists' preference. Therefore, our analysis was based on a range of sizes from 100 to 500 μm rather than on a specific size, even though only one product was used.

In conclusion, mRECIST showed good tumor responses to DEB-TACE supporting recent studies, although progressive disease group needs reevaluation concerning new lesions. We introduce the tumor growth rate as a possible future predictor for survival and suggest incorporating it into established tumor response criteria. The outcome for 1-, 2- and 3- year overall survival was less favorable in comparison with previous studies, but tumor reduction after DEB-TACE treatment showed a positive effect on survival. Our study contributes to

the experience with DEBs, with reasonable response evaluation by mRECIST and survival benefit by tumor reduction. To verify the superiority of DEB-TACE, multicenter comparative studies with cTACE in a larger patient collective are necessary.

Acknowledgement

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet 2012; 379:1245–1255. [Crossref]
2. Malek NP, Schmidt S, Huber P, Manns MP, Greten TF. The diagnosis and treatment of hepatocellular carcinoma. Deutsches Arzteblatt Int 2014; 111:101–106. [Crossref]
3. Degasperi E, Colombo M. Distinctive features of hepatocellular carcinoma in non-alcoholic fatty liver disease. Lancet Gastroenterol Hepatol 2016; 1:156–164. [Crossref]
4. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Sem Liver Dis 1999; 19:329–338. [Crossref]
5. Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. Sem Liver Dis 2010; 30:61–74. [Crossref]
6. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003; 362:1907–1917. [Crossref]
7. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 2003; 37:429–442. [Crossref]
8. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. New Engl J Med 2008; 359:378–390. [Crossref]
9. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018; 391:1301–1314. [Crossref]
10. Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol 2007; 46:474–481. [Crossref]
11. Lewis AL, Gonzalez MV, Lloyd AW, et al. DC bead: in vitro characterization of a drug-delivery device for transarterial chemoembolization. J Vasc Interv Radiol 2006; 17:335–342. [Crossref]
12. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001; 35:421–430. [Crossref]
13. Kloeckner R, Otto G, Biesterfeld S, Oberholzer K, Dueber C, Pitton MB. MDCT versus MRI assessment of tumor response after transarterial chemoembolization for the treatment of hepatocellular carcinoma. Cardiovasc Intervent Radiol 2010; 33:532–540. [Crossref]

14. Syha R, Ketelsen D, Heller S, et al. Hepatocellular carcinoma: initial tumour response after short-term and long-interval chemoembolization with drug-eluting beads using modified RECIST. Eur J Gastroenterol Hepatol 2012; 24:1325–1332. [Crossref]
15. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010; 30:52–60. [Crossref]
16. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002; 359:1734–1739. [Crossref]
17. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010; 33:41–52. [Crossref]
18. Song MJ, Chun HJ, Song do S, et al. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. J Hepatol 2012; 57:1244–1250. [Crossref]
19. Dhanasekaran R, Kooby DA, Staley CA, Kauh JS, Khanna V, Kim HS. Comparison of conventional transarterial chemoembolization (TACE) and chemoembolization with doxorubicin drug eluting beads (DEB) for unresectable hepatocellular carcinoma (HCC). J Surg Oncol 2010; 101:476–480. [Crossref]
20. Chen P, Yuan P, Chen B, Sun J, Shen H, Qian Y. Evaluation of drug-eluting beads versus conventional transcatheter arterial chemoembolization in patients with unresectable hepatocellular carcinoma: A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2017; 41:75–85. [Crossref]
21. Golfieri R, Giampalma E, Renzulli M, et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer 2014; 111:255–264. [Crossref]
22. Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008; 100:698–711. [Crossref]
23. Gillmore R, Stuart S, Kirkwood A, et al. EASL and mRECIST responses are independent prognostic factors for survival in hepatocellular cancer patients treated with transarterial embolization. J Hepatol 2011; 55:1309–1316. [Crossref]
24. Prajapati HJ, Spivey JR, Hanish SI, et al. mRECIST and EASL responses at early time point by contrast-enhanced dynamic MRI predict survival in patients with unresectable hepatocellular carcinoma (HCC) treated by doxorubicin drug-eluting beads transarterial chemoembolization (DEB TACE). Ann Oncol 2013; 24:965–973. [Crossref]
25. Yeo DM, Choi JI, Lee YJ, Park MY, Chun HJ, Lee HG. Comparison of RECIST, mRECIST, and Choi Criteria for early response evaluation of hepatocellular carcinoma after transarterial chemoembolization using drug-eluting beads. J Comput Assist Tomogr 2014; 38:391–397. [Crossref]
26. Shim JH, Lee HC, Kim SO, et al. Which response criteria best help predict survival of patients with hepatocellular carcinoma following chemoembolization? A validation study of old and new models. Radiology 2012; 262:708–718. [Crossref]

27. Malagari K, Chatzimichael K, Alexopoulou E, et al. Transarterial chemoembolization of unresectable hepatocellular carcinoma with drug eluting beads: results of an open-label study of 62 patients. Cardiovasc Intervent Radiol 2008; 31:269–280. [Crossref]

28. Lin M, Pellerin O, Bhagat N, et al. Quantitative and volumetric European Association for the Study of the Liver and Response Evaluation Criteria in Solid Tumors measurements: feasibility of a semiautomated software method to assess tumor response after transcatheter arterial chemoembolization. J Vasc Interv Radiol 2012; 23:1629–1637. [Crossref]

29. Burrel M, Reig M, Forner A, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. J Hepatol 2012; 56:1330–1335. [Crossref]

30. Malagari K, Pomoni M, Kelekis A, et al. Prospective randomized comparison of chemoembolization with doxorubicin-eluting beads and bland embolization with BeadBlock for hepatocellular carcinoma. Cardiovasc Intervent Radiol 2010; 33:541–551. [Crossref]

31. Malagari K, Pomoni M, Moschouris H, et al. Chemoembolization with doxorubicin-eluting beads for unresectable hepatocellular carcinoma: five-year survival analysis. Cardiovasc Intervent Radiol 2012; 35:1119–1128. [Crossref]

32. Schutte K, Bornschein J, Kahl S, et al. Delayed diagnosis of HCC with chronic alcoholic liver disease. Liver Cancer 2012; 1:257–266. [Crossref]

33. Sieghart W, Hucke F, Pinter M, et al. The ART of decision making: retreatment with transarterial chemoembolization in patients with hepatocellular carcinoma. Hepatology 2013; 57:2261–2273. [Crossref]