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## Transarterial Chemoembolization of Child-A hepatocellular carcinoma: Drug-eluting bead TACE (DEB TACE) vs. TACE with Cisplatin/Lipiodol (cTACE)

### Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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### Background:

This study is an outcome evaluation of the Drug-Eluting-Bead-Chemoembolization (DEB TACE) compared to conventional TACE (cTACE) with Cisplatin and Lipiodol in patients with hepatocellular carcinoma (HCC) and Child-Pugh A Cirrhosis.

### Material/Methods:

A comparison of interventional therapy with either cTACE or DEB-TACE of 22 patients each with unresectable HCC and Child-Pugh A Cirrhosis was carried out. A comparison of therapy-associated complications, tumour response rates and mean survival was performed. Tumour response was evaluated in accordance with the European Association for the Study of the Liver (EASL) response criteria by two radiologists in consensus reading.

### Results:

The choice of TACE procedure (DEB TACE/cTACE) had no significant impact on therapy-associated complications. Objective Response (OR, complete response + partial response) for DEB-TACE was 22.7%; a further 68.2% was stable disease (SD). The respective response rates for the cTACE were OR 22.7 and SD 31.8%. Thus disease control was not significantly increased for DEB TACE (p=0.066). After DEB-TACE mean survival was significantly prolonged with 651±76 days *vs.* 414±43 days for cTACE (p=0.01).

### Conclusions:

Associated with a similar safety profile and an at least comparable tumour response, the DEB-TACE is a method of treatment for HCC that has the potential to improve mean survival compared to cTACE with Cisplatin/Lipiodol.

### key words:

**HCC • TACE • Drug Eluting Bead • Cisplatin • Epirubicin**

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## BACKGROUND

Hepatocellular carcinoma (HCC) is currently the fifth most frequent tumour worldwide. HCC is in third place in the statistics for tumour-associated deaths. The annual incidence of new cases is about 500 000 persons, and about 80% of these patients die in the first year of diagnosis [1,2].

The great majority of HCC patients are not candidates for liver resection because they have advanced disease with extensive tumour growth, greatly impaired functional reserve of the cirrhotic liver and/or existing portal hypertension, possibly with concomitant thrombosis of the portal vein [1,3–6].

Local ablative procedures, such as percutaneous ethanol injection (PEI), radiofrequency ablation (RFA) or laser-induced thermotherapy (LITT), are potentially curative treatment methods that can be employed with a limited form of the disease; diffusely infiltrating or multifocal tumours, which are often present at the initial diagnosis, are not suitable for these treatment methods. There are only a few treatment options for patients who are not suitable for surgery or a local ablative procedure and who are not candidates for liver transplantation because of the advanced tumour stage, age or other comorbidities [7]. Transarterial chemoembolization (TACE) currently represents the standard therapy for patients with advanced unresectable HCC [8]. This procedure is supported by the results of two randomised studies that showed a significant survival advantage for TACE therapy compared with “best supportive care” [9,10]. Despite a number of publications, there is still no agreement on the choice of chemotherapeutic agents and on the TACE treatment regime (treatment intervals, technical equipment) [11–13]. Against this background, this study compared the first clinical results of a new embolization system (DC bead) with the conventional TACE established in our clinic. DC bead (Biocompatibles UK Ltd.) is a new drug delivery and embolization system that enables embolization of vessels supplying hypervascularised malignant tumours with simultaneous administration of a local, controlled, sustained dose of a chemotherapeutic agent to the tumour [14,15]. The aim of this study is evaluation of the outcome of drug-eluting bead chemoembolization (DEB-TACE) with epirubicin of hepatocellular carcinoma (HCC) compared with conventional TACE with cisplatin and lipiodol (cTACE).

## MATERIAL AND METHODS

### Patient characteristics

In the period 2003 to 2008, 74 consecutive patients with histologically confirmed HCC were treated by TACE in our institution. 44 of these patients were included in this retrospective evaluation. All patients with an advanced stage of liver cirrhosis (Child-Pugh B or C) were excluded, as advanced hepatic failure is the critical prognostic factor for survival in these patients [16,17]. Moreover, patients with embolization alone (TAE), combined therapy (e.g. RFA+TACE), and patients who had partial liver resection or liver transplantation after TACE were not included in this study. Patients who had both cTACE and DEB-TACE were not included either. 37 men and 7 women with HCC at an advanced inoperable stage were included (Table 1). The average age at the time of histological confirmation (first diagnosis) of the

HCC was  $69.02 \pm 8.11$  years (min 45.6/max 84.7). All of the patients had Child-A cirrhosis. 13 cases of cirrhosis were of toxic nutritional aetiology (ethanol) and 5 were due to infection. The remaining 26 patients had cryptogenic cirrhosis. The patients had either one or more administrations of cTACE (n=22), or were given one or more DEB-TACE treatments (n=22); 89 sessions in total (Figure 1).

### Indication

The therapeutic procedure was decided in an interdisciplinary tumour conference together with the visceral surgeons and medical oncologists. Curability by surgical resection or radiological intervention (RFA or PEI) was first ruled out according to the treatment algorithm of the Barcelona Clinic Liver Cancer (BCLC) classification [18].

### TACE exclusion criteria

The exclusion criteria for TACE were tumour involving >75% of the liver, diffuse, non-focal HCC, extrahepatic manifestations, advanced liver cirrhosis of Child-Pugh stage B or C, severe cardiopulmonary comorbidity and known hypersensitivity to lipiodol, epirubicin or cisplatin.

### Chemoembolization protocol

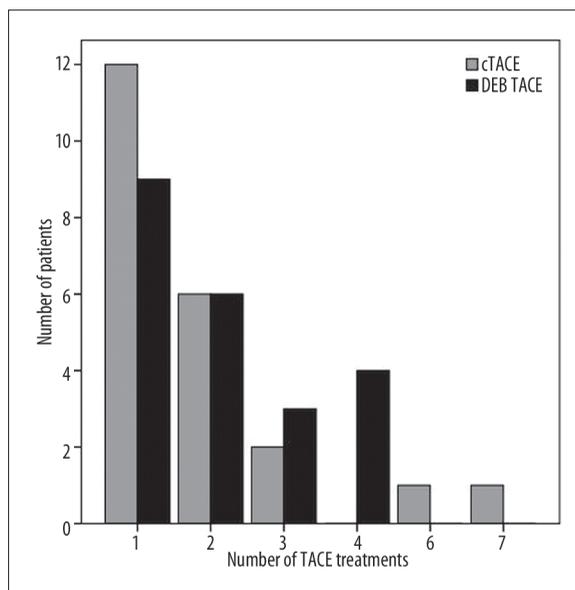
A transfemoral access was chosen in all cases. After local anaesthesia of the skin and subcutaneous tissue (10–20 ml prilocaine hydrochloride), a 5F standard catheter was placed through a 5F introducer in the initial treatment session. Angiography of the upper abdominal vessels was performed first to determine the arterial supply of the liver by means of automated injection of contrast agent. Apart from selective imaging of the coeliac trunk, the superior mesenteric artery was examined separately in order to rule out normal variants of the hepatic blood supply. In the event of a normal supply, the common hepatic artery was cannulated over a hydrophilic guide wire and the catheter was placed in the right or left hepatic artery according to the tumour location. Superselective embolization only of the segmental or subsegmental arteries supplying the tumour was performed by means of a microcatheter (Progreat 2.7 F; Terumo or Tracker 2,4 F; Boston Scientific). In cTACE an emulsion consisting of 20 mg cisplatin and 20 ml lipiodol followed by particle embolization (Contour SE; Boston Scientific) was delivered at each session. In DEB-TACE 50 mg epirubicin coupled with 2 ml DC Beads (1 vial of 300–500  $\mu$ m DC Beads) was given at each session. Particle embolization (Contour SE; Boston Scientific) was performed in addition where necessary. The treatment was concluded after stasis or reflux occurred in the corresponding vascular segment (second- or third-order branches of the right or left hepatic artery) (Figure 2). The patients were admitted to a ward for monitoring and were discharged the next day if asymptomatic. Nausea, pain or fever subsequently were treated symptomatically depending on their severity, e.g. with Navoban 5–15 mg i.v., analgesics (e.g. Metamizole i. v. or drops) and antipyretic agents (e.g. Paracetamol tablets 500–1000 mg).

The decision for re-treatment was based on the absence of TACE contraindications and the sequential TACE procedures were performed within 2 weeks after documentation of response. In case of complete response or partial

**Table 1.** Patients demographics: comparison of clinical features of patients: cTACE/DEB TACE.

	cTACE (n=22)	DEB TACE (n=22)	p
Age mean ±SD (min-max)	67.72±9.02 (45.6–84.3)	70.32±7.06 (55.2–84.7)	0.549**
Sex			0.68***
Male	19 (86.4%)	18 (82%)	
Female	3 (13.6%)	4 (18%)	
Aetiology			0.806***
Alcohol alone	7 (32%)	2 (9%)	
Hepatitis	3 (14%)	6 (27%)	
Other and mixed	12 (54%)	14 (64%)	
Clinical features			
Child-Pugh A	22 (100%)	22 (100%)	
BCLC (A/B/C)*	4,15,2	1,17,3	0.547***
Tumour diameter mean ±SD (cm)	6.98±3.81	7.44±3.37	0.496**
Unifocal/Multifocal tumour	9 (41%)/13 (59%)	12 (55%)/10 (44%)	0.365***

\* BCLC classification [15]; \*\* Mann-Whitney-U; \*\*\* Pearson’s chi-square test / Fisher’s exact test.



**Figure 1.** Distribution of TACE procedures per patient: cTACE Mean 1.95±1.62, min 1, max 7, Sum 49; DEB TACE Mean 2.09±1.15, min 1, max 4, Sum 46.

response the patients were first re-evaluated in the interdisciplinary tumour conference to assess curability by surgical resection or radiological intervention (RFA or PEI). Diminishing hepatic functional reserves as well as a marked reduction of general health status were the most common causes to stop sequential TACE procedures.

**CT/MRI documentation protocol**

Pre-treatment CT or MRI scans were used as a basis for documenting the initial findings (maximum of 4 weeks old). The

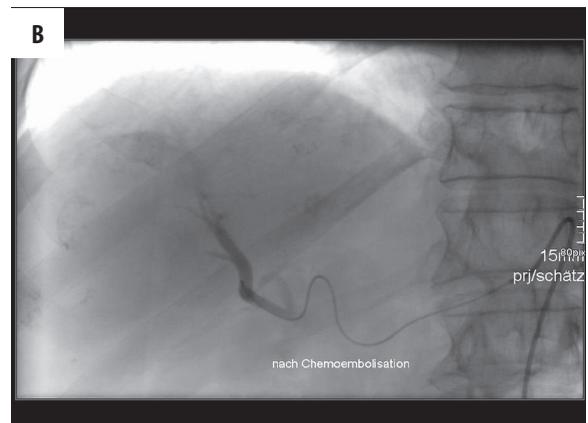
minimum radiological requirement required for discussion in the tumour conference was either a biphasic contrast-enhanced CT or MRI with the specific hepatic contrast agent Gd-EOB-DTPA. In follow-up, the local response to therapy was documented 6–8 weeks after TACE using the same modality (Figures 3, 4). The response to therapy was assessed according to the criteria of the European Association for the Study of the Liver (EASL) by two experienced abdominal radiologists (more than 5 years experience) in consensus. The basis for this was comparison of the initial finding with the last documented examination of the patient. Thus, the therapeutic influence of the two TACE therapies was compared in the long-term course (mean 8.09 months, sd 6.6 months) of the HCC.

**Complications**

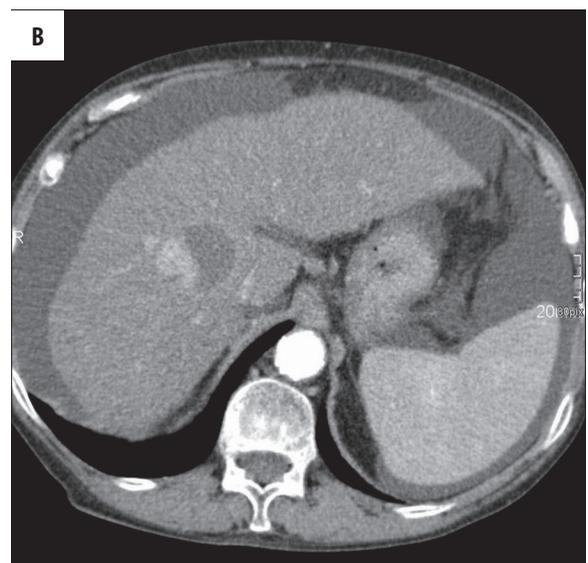
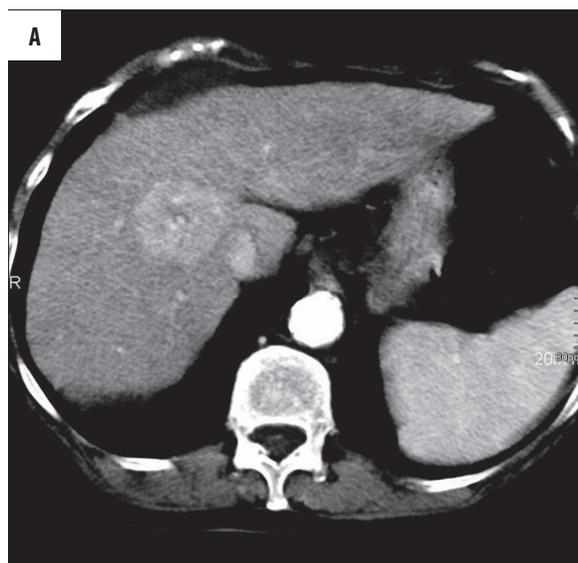
Complications that occurred in association with the TACE treatment were recorded based on the guidelines of the Society for Interventional Radiology [19]. Minor complications correspond to negative effects that are associated with the intervention and either require no consequence and therapy or else result only in nominal therapy without negative consequences including overnight hospitalisation. Major complications are hospitalisation > 24 h, greater therapy and unplanned added costs in treatment, permanent persisting sequelae and death of the patient.

**Data collection and statistics**

The data for our study were recorded by analysis of the radiological databases (reports, images), by viewing the patient’s file and by personal contact with patients, relatives and treating doctors. If necessary, enquiries were made in various institutions (date of death, cause of death). The primary endpoint of the analysis was the interval from the first TACE until the patient’s death. Secondary endpoints were the local response to therapy and the rate of therapy-associated complications.



**Figure 2.** (A) Selective catheterization of feeding arteries of an HCC. The use of a micro catheter facilitates administration of the embolic agent selectively to the tumour, sparing adjacent liver parenchyma. (B) Postembolization image shows complete occlusion of the tumour vessels.



**Figure 3.** (A) Preinterventional abdominal computed tomography (CT) showing an HCC 41 mm in diameter (B) Follow-up CT after 10 weeks post cTACE showing a partial response (PR): in arterial phase tumour reduction (36 mm in diameter) with central necrosis and peripheral persistence of viable enhancing tumour. The patient developed ascites as a sign of the advanced hepatic failure.

Statistical analysis was performed with SPSS (version 15.0 for Windows). The survival rate, calculated from the time of the first intervention until death, was determined according to the Kaplan-Meier method. The univariate log-rank test was used to assess statistically significant differences between the survival curves. The statistical significance of quantitative data was determined using the parameter-free Wilcoxon-Mann-Whitney test. The qualitative variables were tested for significance with the Pearson chi square test and where necessary with Fisher's exact test. A  $p < 0.05$  was regarded as statistically significant.

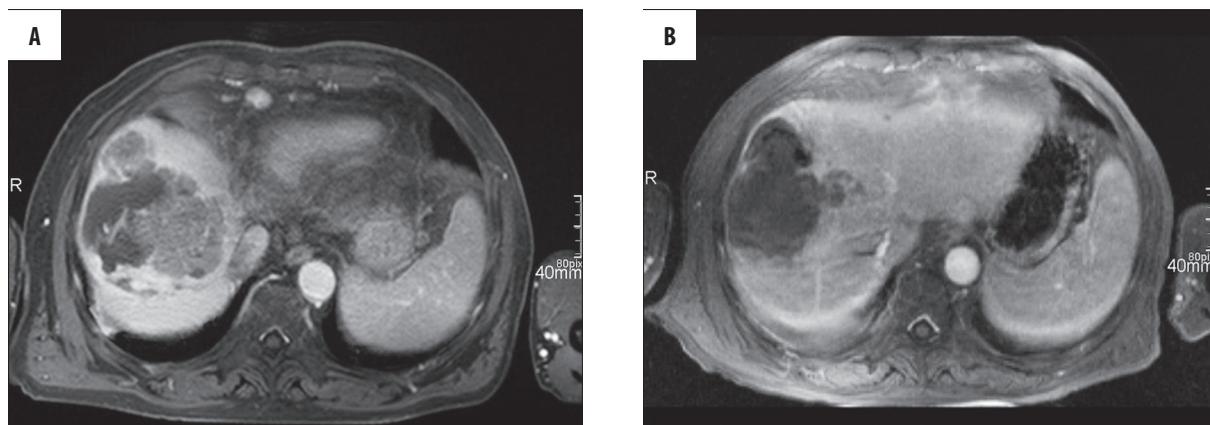
## RESULTS

A total of 44 patients with HCC at an advanced inoperable disease stage were included. There were no significant

differences between the two treatment groups with regard to demographic data, tumour burden and health status (Table 1). The average lesion diameter was  $6.98 \pm 3.81$  cm (2.3 to 16.0) in the cTACE group and  $7.44 \pm 3.37$  cm (3.9 to 16.2) in the DEB-TACE group. 13 of 22 patients in the cTACE group had multifocal HCC and the proportion in the DEB-TACE group was 10 out of 22.

## Therapy-induced side effects

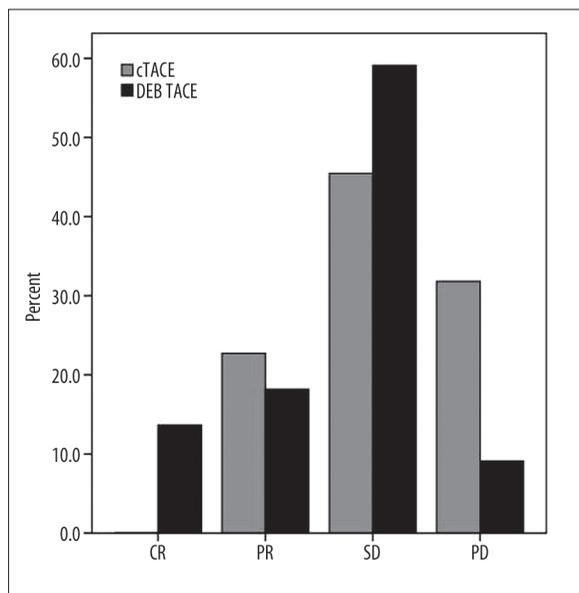
7 major complications and 17 minor complications occurred in total with 89 TACE treatments (Table 2). Minor complications belonged to the „post-embolization syndrome“, which is expressed by fever, fatigue, abdominal pain and nausea. 7 (16%) cases of minor complications were recorded for cTACE



**Figure 4.** (A) Contrast-enhanced MR image before DEB TACE with viable enhancing neoplastic tissue. (B) Contrast-enhanced MR image after two DEB-TACE procedures showing a partial response (PR).

**Table 2.** Therapy induced side effects after TACE; in 89 TACE procedures 17 minor-Complications and 7 Major-Complications were recorded, Comparison of cTACE vs. DEB TACE using the Mann-Whitney-U-test.

	cTACE	DEB TACE	Mann-Whitney U (p)
Patients	n=22	n=22	
TACE-procedures	n=43	n=46	
No therapy-induced side effects	35 (81.4%)	30 (65.2%)	
Complications total	8 (18.6%)	16 (34.8%)	0.09
Minor-Complications	7 (16.3%)	10 (21.7%)	0.52
Major-Complications	1 (2.3%)	6 (13.0%)	0.06



**Figure 5.** Comparison of overall response at the end of study ([%] of patients): CR, complete response, PR, partial response, SD, stable disease, PD progressive disease.

and 10 (21%) for DEB-TACE. In the DEB-TACE group, 6 major complications occurred (including 2 liver abscesses) compared with 1 major complication in the cTACE group

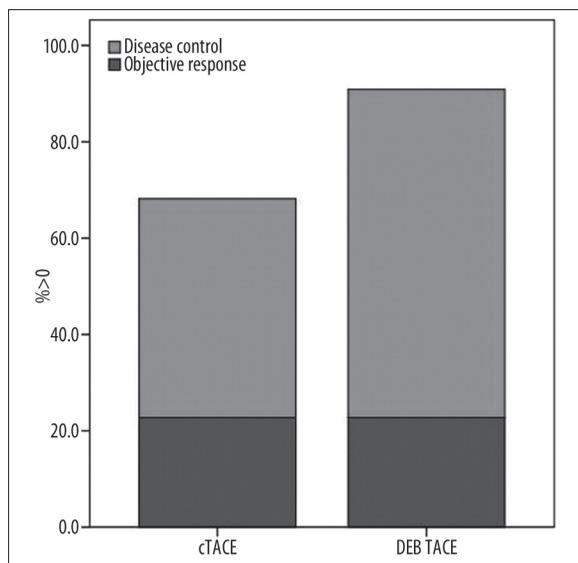
(Table 2). A statistically significant difference with regard to therapy-associated complications was not found although the p-value of 0.06 for the major complications is indicative of a possibly increased risk with DEB-TACE treatment.

**Tumour response rates according to EASL**

After an average of 8 months, complete remission was achieved in 13.6% vs. 0% of patients, partial remission in 9.1% vs. 22.7% of patients and stable disease in 68.2% vs. 45.5 of patients in the DEB-TACE and cTACE arms respectively. Progression of the HCC was seen in 9.1% vs. 31.8% of patients (Figure 5). This results in an objective response to therapy (OR; complete remission + partial remission) of 22.7% vs. 22.7% (DEB-TACE vs. cTACE); this difference is not significant. Disease control (DC; objective response + stable disease) was achieved in 90.9% and 68.2% respectively (Figure 6). While there were no differences with regard to OR, there was a trend to better results in the DEB-TACE group on average with regard to DC (p=0.066).

**Survival rates**

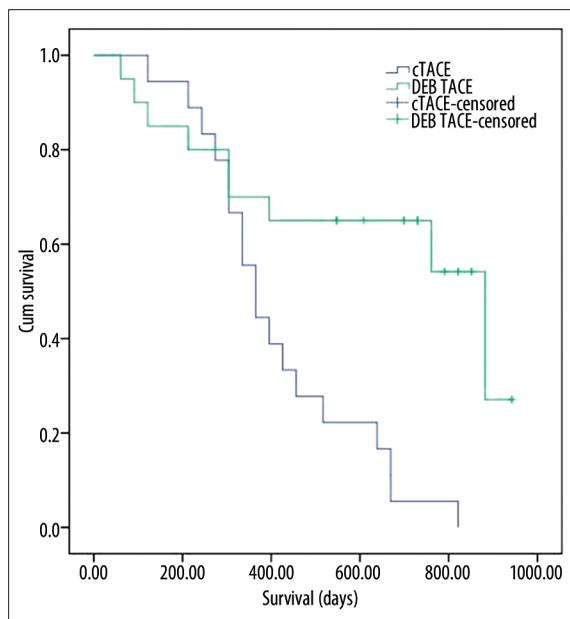
The survival in the cTACE group was 414±43 days on average (95% CI; 329–499) and 651±76 days (95% CI; 502–800) in the DEB-TACE group. The influence of the form of therapy on the survival rate was significant in the log-rank test (p=0.01). The corresponding one-year survival probability was 55% in the cTACE group and 70% in the DEB-TACE group (Figure 7).



**Figure 6.** Comparison of tumour response rates according to EASL: OR, objective response, DC disease control rate ([%] of patients).

## DISCUSSION

TACE currently represents the first-line therapy of inoperable HCC [8]. Although this is an established therapy, there is still disagreement on the best combination of the anti-tumour drug to be administered, the embolic agents, the doses to be given and the frequency of treatment. The local response rates published in the literature and survival rates vary markedly. This study presents the results in patients of a single university centre with inoperable HCC and Child-Pugh stage A hepatic cirrhosis, who were treated with palliative intent with cTACE or DEB-TACE. DC beads (Biocompatibles UK Ltd.) are a new drug delivery and embolization system for embolization of vessels supplying hypervascularised malignant tumours enabling simultaneous administration of a local, controlled, sustained dose of a chemotherapeutic agent to the tumour [14,15]. In preclinical and clinical studies, prolonged and greater persistence of the chemotherapeutic agent in the tumour was confirmed [14,15,20,21]. At the same time, the systemic effect of the administered drugs is less because of lower plasma levels [22]. Lammer et al. showed a trend to higher response rates with DEB-TACE compared with cTACE with doxorubicin and lipiodol in the only prospective multicentre study so far. In the majority of published studies on DEB-TACE, doxorubicin was used as chemotherapeutic agent. In this study, the DC beads were loaded with epirubicin. The objective of this study was to compare the clinical results of this new embolization method with the results of conventional TACE with cisplatin and lipiodol. Even though this study was a comparison of historical groups, there was still clear evidence of a prolongation of the average survival; with a difference of 237 days in favour of DEB-TACE, a significant survival advantage was shown for the first time in this study for DEB-TACE compared with cTACE ( $p=0.01$ ). This might be due to the markedly lower rate of progression in the DEB group (9.1% for DEB-TACE vs. 31.8% for cTACE,  $p=0.064$ ). The objective response rates for DEB-TACE published hitherto are between 44 and 82% [20,21,23,24]. It must be borne in mind that the previous data refer to the 6-month OR. In contrast, the time of follow-up



**Figure 7.** Survival: Kaplan-Meier curves for all patients in both groups, censored data come from patients who were still alive at the end of the study.

evaluation of the therapy in this study was 8.1 months on average (sd 6.6 months). This might partially explain the lower OR of 22.7% after DEB-TACE for palliation, when follow-up was prolonged by one third. There is another important methodological difference compared to previous publications, the use of epirubicin instead of doxorubicin as the agent to load the drug-eluting beads. Thus the efficacy of epirubicin in DEB-TACE might be lower than the one of doxorubicin leading to a lower OR. As previously in the PRECISION V study [25], which evaluated the success of therapy after 6 months, a significantly higher OR in the DEB-TACE group compared with cTACE was not confirmed in this study with the longer follow-up. However, a trend to better disease control was apparent (90.9% vs. 68.2% DEB-TACE vs. CTACE,  $p=0.065$ ). Analysis of the side effect profiles did not result in any statistically significant differences, but our data appear to indicate an increased side effect risk with DEB-TACE, particularly with regard to serious complications such as liver abscess. This might be due to the greater embolic effect of DEB-TACE in hepatic tissue. The limitations of the present study are its retrospective character and the limited number of patients. Because of the historical patient groups and retrospective study, it is likely that the framework conditions differed so that, for example, technical progress and increasing operator experience led to more frequent achievement of superselective catheter positioning, which might have favourably influenced the results in the DEB-TACE group. Since other factors might have influenced patient survival besides the selected treatment options, the results of this study must be appraised with caution. However, we believe that it would be useful to investigate transarterial drug-eluting bead chemoembolization in larger groups of patients in further studies.

## CONCLUSIONS

In conclusion, the DEB TACE of inoperable HCC represents an effective new treatment option. It is associated with

a similar safety profile and at least comparable tumour response rates compared to the cTACE. At the same time it does seem that DEB TACE has the potential to prolong the patients' average survival compared to cTACE.

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