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# TRANSARTERIAL CHEMOEMBOLIZATION WITH DOXORUBICIN-ELUTING MICROSPHERES: SINGLE-CENTER REVIEW OF SAFETY PROFILE

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**Key words**: DEB-TACE, microspheres, chemoembolization, drug eluting bead.

**Summary**

Background. Since 1977 when TACE was introduced for the first time it became a standard treatment for nonresectable HCC without vascular invasion or extrahepatic disease. TACE is also performed for other indications, such as colorectal metastases, cholangiocarcinoma, neuroendocrine tumors and etc.

Material/methods. the evaluation of interventional therapy with DEB-TACE of 8 patients each with unrespectable HCC, cholangiocarcinoma, neuroendocrine metastatic carcinoma. A comparison of therapy-associated complications performed.

Results. We analyzed results of DEB-TACE performed in our Hospital since 2014. DEB-TACE was technically successful in all patients. A total of 21 DEB-TACE procedure was performed in 8 patients during the 2-year period. Two patients (20%) had five treatments, 1 patient (15%) had four treatments, 4 patients (50%) had two treatments and 1 (15%) had one treatment. Pain, nausea, fever and fatigue were the most common side effects following DEB-TACE, with a frequency of 76%, 33%, 57% and 71% respectively.

Conclusions. The current results show DEB-TACE to produce beneficial tumor response and to have exceptionally low complication rates.

## Introduction

Dr. Yamada introduced transarterial chemoembolization in 1977. Method was used in treatment of hepatocellular carcinoma (HCC). 120 patients were treated and the findings were published in 1983 [1]. During conventional transarterial chemoembolization (cTACE) different chemotherapeutic agents are mixed with viscous carrier (lipidol) and delivered to the feeding artery of the tumor, followed by embolic agent. This causes high concentration of chemo agent in the tumor and ischemic necrosis due to embolization. However, lipidol releases chemo agent quickly and high systemic concentrations of drug are reached [2]. The solution of this problem is the use of drug-eluting microspheres. Procedure is called drug-eluting beads transarterial chemoembolization (DEB-TACE). It prolongs contact tome between cancer cells and chemo agent and prevents systemic drug toxicity. This method is currently used in the treatment of HCC, nonresectable cholangiocarcinoma, colorectal metastases and metastatic neuroendocrine tumors and etc. [3].

**The aim of the study/methods:** the evaluation of interventional therapy with DEB-TACE of 8 patients each with unrespectable HCC, cholangiocarcinoma, neuroendocrine metastatic carcinoma. A comparison of therapy-associated complications performed.

## Materials and methods

**Indications and contraindications for treatment.** TACE is current standard treatment for nonresectable HCC without vascular invasion or extrahepatic disease (Table 1) [4,5]. TACE is also performed for other indications, such as colorectal metastases, cholangiocarcinoma, neuroendocrine tumors and etc.

**Pretreatment imaging.** Contrast material enhanced computer tomography (CT) with triphasic acquisitions or magnetic resonance imaging (MRI) should be performed before every procedure to asses liver lesions (location, number and size). Total body CT should be performed in


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the case of metastases in the liver. Portal vein is better evaluated by CT scan [5].

Periprocedural care. Periprocedural care differs according local clinic practice and experience. All periprocedural medications, including antibiotics, pain medications, intra-arterial lidocaine, corticosteroids and proton-pump inhibitors are administered at the physician's discretion [6]. Hydration with intravenous administration of 150-300 ml/L normal saline solution is essential before all other premedication. Though there is no definitive evidence of benefit, many centers recommend antibiotics prophylaxis to cover Gram-negative enteric pathogens for 3-7 days. In sphincter of Oddi has been disrupted in patients' medical history, antibiotics should be administered for 14 days [7]. Pain relievers, antiemetics should be continued as long as needed.

**HCC.** Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide and the third most common cause of cancer-related deaths [8]. TACE is recommended as standard of care for patients with non-resectable HCC without PV thrombosis or extrahepatic metastases [9]. A recent systematic review had collected sufficient data on the use of DEB-TACE in HCC patients to support its use as a safe and effective chemoembolic treatment in intermediate HCC patients, however, there still needs more strong evidence to support the its superiority over c-TACE [10]. Molecular biology studies have shown that the level of vascular endothelial growth factor (VEGF) usually increases locally and systemically after TACE treatment is performed, whereas sorafenib can inhibit the activity of VEGF receptors [11]. Thus, in recent years a large amount of studies have tried to combine sorafenib with TACE for patients with unresectable HCC, while the results were controversial [12]. Combination therapy may bring benefits for unresectable HCC patients in terms of TTP but not OS. Further well-designed randomized controlled studies are needed to confirm the efficacy of combination therapy [13].

**Hepatic colorectal metastases.** Colorectal cancer (CRC) remains one of the leading causes of cancer-related deaths worldwide. Synchronous or metachronous liver metastases can be present in almost half of all individuals diagnosed with CRC [14]. TACE has a long history and has led to better patient survival while permitting a good quality of life, and as a result has been introduced into the guidelines for primary liver cancer and is considered, and used worldwide, in the treatment of metastatic disease from neuroendocrine tumors and CRC [15]. TACE and DEBIRI have been proven safe and effective in salvage treatment of non-responsive liver metastases (LM) from CRC, and are more frequently used than in the past. The phase III trial provided evidence that infusion of DEBIRI offers superior survival with better quality of life when compared with the same chemotherapy administered intravenously [16].

Case report

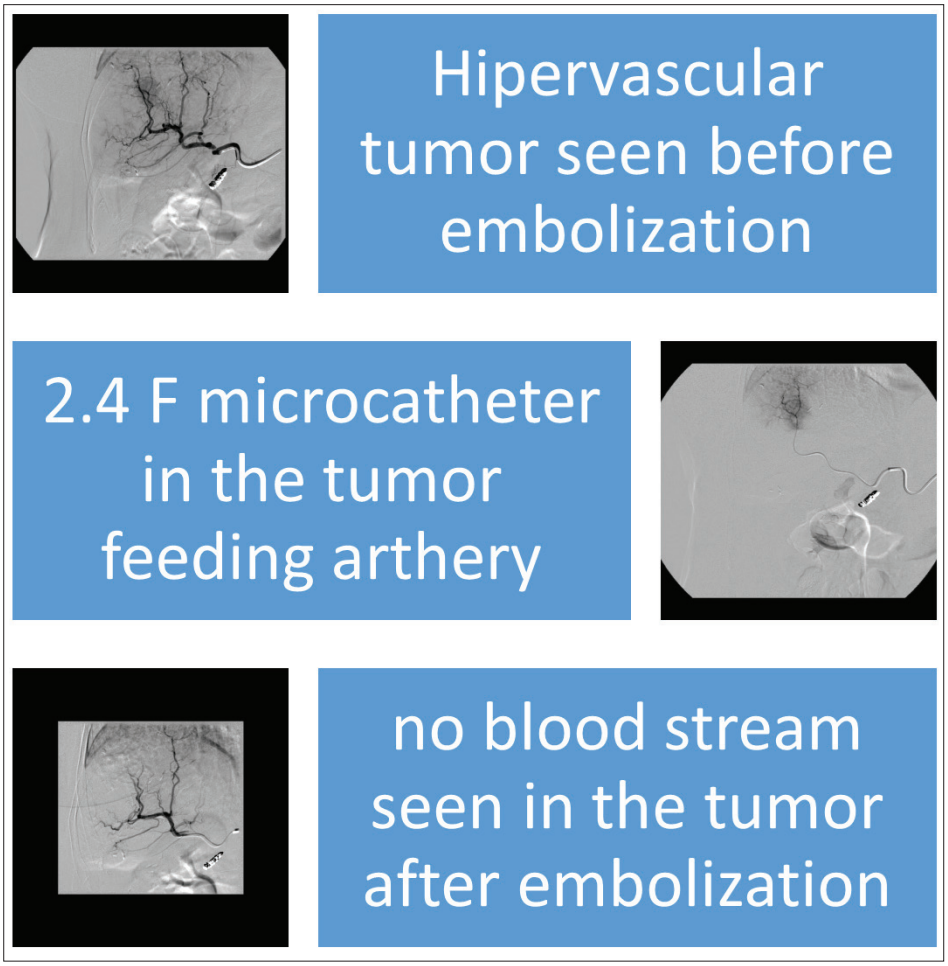

**Table 1.** Indications and contraindications for TACE in HCC patients

| Indications | Absolute contraindications | Relative contraindications |
|---|---|---|
| Patients with confirmed diagnosis of HCC | Decompensated cirrhosis (Child-Pugh score >8), jaundice, encephalopathy or hepatorenal syndrome | Untreated esophageal varices at high risk of bleeding |
| No extrahepatic lesions | Main PV thrombosis | Large tumor (>10 cm) |
| No main PV thrombosis | Extensive tumor involving both lobes of liver | Severe comorbidities |
| Tumor involvement >50% of the liver parenchyma | Technical contraindications, e.g. untreatable arteriovenous fistula | Incompetent papilla with aerobilia |
| Patients with HCC are not suitable for curative treatments | Creatinine clearance <30 ml/min | Biliary dilatation |
| Disease recurrence after curative treatment | | |
| ECOG <3 | | |
| Good liver function (Child-Pugh class A/B) | | |
| Serum creatinine < 177umol/L | | |
| Platelet count > 50.00 cells/mm3 | | |
| Prothrombin activity >50% | | |
| WBC[3,000 cells/mm3; neutrophils[1,500 cells/mm3; left-ventricular ejection fraction <50 % | | |

**Table 2.** Complications post DEB-TACE (21 procedure)

| Complication | 7 days after procedure | 14 days after procedure |
|---|---|---|
| Pain | 16 | 1 |
| Fatigue | 15 | 0 |
| Nausea and vomiting | 12 | 0 |
| Fever | 7 | 5 |
| Cholangitis | 5 | 2 |
| Elevation of hepatic transaminases | 10 | 3 |
| pulmonary embolism | 0 | 1 |

**Neuroendocrine Hepatic Metastases.** According to the 2010 WHO classification, NENs are divided into: well differentiated neuroendocrine neoplasm (NEN) G1 (mitotic count <2 per 10 high power fields (HPF) and/or ≤2% Ki67 index), NEN G2 (mitotic count 2–20 per 10 HPF and/or 3–20% Ki67 index), and poorly differentiated high grade malignant neoplasm (NEC) G3 (mitotic count >20 per 10 116 HPF and/or >20% Ki67 index) [17]. Metastatic involvement of the liver typically develops in about 46–93% of NEN patients. In 12.9% of these patients, metastases are already detectable at the time of initial tumor diagnosis and 5-10% of them present with metastases and primary of unknown origin [18]. c-TACE has been proven to be effective in symptom relief in ≤90 % of patients, with long-term palliation being achieved with repeated c-TACE sessions, and a reported 5-year survival of ≤83 % [19]. There has been only one study on patients with liver metastases from these gastroenteropancreatic tumors. At 3-month follow-up, 80 % of the 20 patients enrolled in the study had partial response, 15 % had stable disease, and 5 % had progressive disease [20]. TAE appears to be an optimal treatment approach for inoperable liver metastases from NENs, for higher metastatic load, for management of symptoms alone and in association with interferon or somatostatin analogues, suggesting a prolonged 5-yr survival and local tumor control and for survival improvement [21].

**Treatment complications.** As usually, all complications can be divided into the groups of immediate, periprocedural, long term complications. It also can be divided to minor and major complications. Postembolization syndrome does not count as complication by itself. It includes fever, pain, and increased white blood cell count [22]. Major complication are liver failure, postembolization syndrome requiring readmission or prolonged hospitalization, intrahepatic abscess, biloma requiring percutaneous drainage, gastrointestinal bleeding, iatrogenic dissection, death within 30 days [6,22].

Intraprocedural hepatic artery injury can be considered as immediate complication. It may only lead to reversible events, as artery spasm or inflammatory constriction. In severe cases it can cause dissection, thrombosis or formation of aneurism. However hepatic artery damage is more likely to occur in cirrhotic patients [23]. Periprocedural and long-term complications are probably related to metabolic impairment. Findings from liver function tests often worsen slightly after c-TACE, but the majority of studies have showed a return to baseline function within 1 week. However, a significant number of cases of hepatic failure have been reported. It was found that the dosage of chemotherapeutic agent, the basal bilirubin level, the basal prothrombin time, the basal AST level, and the stage of cirrhosis (Child's score) are significantly associated with the post-TACE increase in bilirubin. Patients with irreversible post-TACE hepatic decompensation present with significantly higher pre-TACE bilirubin levels and longer prothrombin time in the dorsal and lateral surfaces of the left lobe, receive larger doses of drug, and have a more advanced stage of cirrhosis [24].

Reported complications of DEB-TACE include cholecystitis, liver abscess formation, tumor rupture, pancreatitis, pleural effusion, gastric ulcer bleeding, esophageal variceal bleeding, and spontaneous bacterial peritonitis. The list of complications of DEB-TACE is relatively shorter than that for c-TACE. This is mainly because the former technique is a relatively new procedure and is not practiced as widely as the latter one, but it could also be due to the lack of lipidol [25].

**Our experience.** In the period 2014 to 2016, 8 patients were treated by DEB-TACE in our institution. 5 patients had confirmed HCC, 2 patients – metastatic neuroendocrine tumors and 1 patient – hepatic sarcoma. The therapeutic procedure was decided in an interdisciplinary tumor conference together with the visceral surgeons, interventional radiologists and medical oncologists. Median age of the patients at first TACE was 69 years (range, 38–79 years).

Preprocedure evaluation included review of medical history, physical examination, and laboratory studies for hematologic, hepatic, and renal functions. The imaging workup consisted of a baseline contrast-material enhanced CT or MRI within 1 month preceding the DEB-TACE procedure. Following the procedure, patients were followed at 4–8 weeks interval through clinical, laboratory, and imaging evaluation. Informed consent was obtained from all patients. All procedures were performed according to a standard protocol.

All patients were premedicated antacids (ranitidine) and pain relievers. Drug eluting microspheres were prepared using 100 μm-sized microspheres with doxorubicin dosage ranging from 75 to 150 mg per session. Femoral arterial access was used in all patients. Celiac and/or superior mesenteric arteriography was performed to assess the arterial anatomy, vascular supply to the tumor, and patency of the portal vein. The lobar/segmental hepatic artery supplying the tumor was selectively cannulated with a microcatheter and embolized with drug-eluting microspheres. The end point for embolization was stasis of blood flow in the arterial feeders to the tumor. The decision for re-treatment was based on the absence of DEB-TACE contraindications and the sequential DEB-TACE procedures were performed within 2 weeks after documentation of response.

Patients were admitted for observation for 24-48 hours following the procedure. Prophylactic medications -against nausea (ondansetron IV), pain (hydromorphone) and intravascular hydration were administered during hospitalization.

DEB-TACE was technically successful in all patients. A total of 21 DEB-TACE procedure was performed in 8 patients during the 2-year period. Two patients (20%) had five treatments, 1 patient (15%) had four treatments, 4 patients (50%) had two treatments and 1 (15%) had one treatment. Mean hospital stay after the procedure was 1.5 days (range 1–4 days).

Pain, nausea, fever and fatigue were the most common side effects following DEB-TACE, with a frequency of 76%, 33%, 57% and 71% respectively (Table 2). At 24 hours post-DEB-TACE, total bilirubin remained unchanged, whereas AST, ALT, and alkaline phosphatase showed significant increase. The values were classified according to the NCI-CTC version 3.0. At 1 month post DEB-TACE, six patients had normal liver function tests, 1 patients were in grade 1 and 1 patient in grade 2 of NCI v3 toxicity grading criteria. One patient had pulmonary embolism within 10 days after procedure. Cholangitis, requiring hospitalization, was observed in two patients within two weeks after procedure. No deaths within 30 days were observed.

## Conclusions

The current results show DEB-TACE to produce beneficial tumor response and to have exceptionally low complication rates. The technique has the potential to become an effective alternative therapy or palliative measure in the treatment of hepatic malignancy.

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## TRANSARTERINĖ CHEMOEMBOLIZACIJA NAUDOJANT DOKSORUBICINU IMPREGNUOTAS MIKROSFERAS: VIENOS GYDYMO ĮSTAIGOS PROCEDŪROS SAUGUMO ANALIZĖ

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Raktažodžiai: DEB-TACE, mikrosferos, chemoembolizacija, vaistais impregnuotos dalelės.

Santrauka

Įvadas. Transarterinės chemoembolizacijos (TACE) procedūra

pirmą kartą buvo aprašyta ir pradėta naudoti 1977 metais. Ji tapo standartu gydant pacientus, kuriems diagnozuota neoperabili kepenų ląstelių karcinoma (HCC). Ši procedūra taip pat taikoma gydant neoperabilius pakitimus kepenyse sergant cholangiokarcinoma, neuroendokrininiais navikais ir kt.

Tyrimo tikslas ir metodai. Įvertinti procedūros saugumą gydant HCC, cholangiokarcinomą ir neuroendokrininius navikus taikant DEB-TACE. Apžvelgtos pagrindinės periprocedūrinės komplikacijos, jų dažnis.

Rezultatai. Atlikta duomenų apie DEB-TACE procedūrų, atliktų Klaipėdos universitetinėje ligoninėje nuo 2014 metų, analizė. Šiuo periodu gydymo įstaigoje gydymo metodas buva taikomas 8 pacientams ir iš viso atlikta 21 procedūra. Dviem pacientams (20%) buvo atliktos keturios procedūros, vienam pacientui (15%) atliktos keturios procedūros, keturiems pacientams (50%) atliktos dvi procedūros ir vienam pacientui (15%) atlikta viena procedūra. Pagrindinės komplikacijos buvo skausmas (76%), pykinimas (33%), karščiavimas (57%) ir nuovargis (71%).

Išvados. Tyrimo metu nustatyta, kad DEB-TACE yra saugi procedūra, kurios metu pasiekiami geri gydymo rezultatai.

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