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# Degradable Starch Microspheres Transcatheter Arterial Chemoembolization (DSM-TACE) in Intrahepatic Cholangiocellular Carcinoma (ICC): Results from a National Multi-Center Study on Safety and Efficacy

**Authors' Contribution:**

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

BCDEF 1 **Andreas Schicho**  
ABCEFG 2 **Philippe L. Pereira**  
BCF 3 **Manfred Pützler**  
BCE 1 **Katharina Michalik**  
BCF 4 **Thomas Albrecht**  
BCF 5 **Claus Nolte-Ernsting**  
ABDEFG 1 **Christian Stroszczyński**  
BCDEFG 1 **Philipp Wiggermann**

1 Department of Radiology, University Medical Center Regensburg, Regensburg, Germany  
2 Department of Radiology, Minimal-invasive Therapies and Nuclear Medicine, SLK Kliniken Heilbronn, Heilbronn, Germany  
3 Department of Radiology and Nuclear Medicine, Raphaelsklinik Münster, Münster, Germany  
4 Department of Radiology, Vivantes Clinic Neukölln, Berlin, Germany  
5 Department of Radiology, Evangelical Hospital Mülheim an der Ruhr, Mülheim an der Ruhr, Germany

**Corresponding Author:** Andreas Schicho, e-mail: andreas.schicho@ukr.de

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**Background:** The aim of this study was to evaluate the safety and efficacy of DSM (degradable starch microspheres) as an embolic agent in transarterial chemoembolization in the treatment of intrahepatic cholangiocellular carcinoma (ICC).

**Material/Methods:** This was a national, multi-center observational cohort study on the safety and efficacy of DSM-TACE using mitomycin, gemcitabine, cisplatin, doxorubicin, and carboplatin in palliative treatment of ICC. Recruitment period for the study was from January 2010 to June 2014. Primary endpoints were toxicity, safety, and response according to mRECIST criteria.





**Results:** Twenty-five DSM-TACE procedures in cases of advanced ICC were performed in seven patients. Nausea and vomiting occurred as adverse event (AE) in eight out of 25 treatments (32%), with seven of eight events (87.5%) associated with the use of gemcitabine. In 11 out of 25 treatments (44%) moderate, transient epigastric pain was registered as an adverse event (AE) within 24 hours of DSM-TACE. One case (1/25) of severe AE (4%) with thrombocytopenia led to discontinuation of the DSM-TACE-treatment.

A total of 25 DSM-TACE procedures with complete clinical and imaging follow-up over a two-year-period were analyzed: objective response (OR) was achieved in three of 25 treatments (12%) Disease control (DC) was achieved in 44% (11/25) of treatments; progress was registered in 4% (1/25).

**Conclusions:** The use of DSM as an embolic agent for TACE is safe in the treatment of ICC. A standardized anti-emetic medication should be established, especially when using gemcitabine. Further prospective studies need to be conducted to find the most suitable, standardized DSM-TACE treatment regime.

**MeSH Keywords:** Chemoembolization, Therapeutic • Cholangiocarcinoma • Clinical Trial • Microspheres

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## Background

In liver malignancies, intrahepatic cholangiocarcinoma (ICC) is the second most common primary cancer, accounting for up to 20% of liver tumors [1]. Both incidence and mortality of ICC recently have been increasing in the Western population, at a rate even greater than that of hepatocellular carcinoma (HCC) [2]. Late onset of symptoms disqualifies up to three-fourths of patients from curative surgical treatment [3]. The median survival of ICC patients in palliative treatment ranges from three to eight months [2]. Promising results have been achieved by radiofrequency ablation in non-resectable ICC [4,5]. It has been shown that transarterial chemotherapy-based treatments for ICC, such as DSM-TACE (degradable starch microspheres – transarterial chemoembolization), yield a survival benefit of up to seven months compared with systemic therapy [6]. As in all palliative treatment settings, reduction of disease-related complications is important while keeping a low level of therapy-related side effects.

Different palliative treatment strategies have been described; within the cluster of interventional transarterial therapies, DSM-TACE is one option; other options include radio-embolization using Yttrium-90 [7] or hepatic arterial infusion (HAI) of chemotherapeutic agents. In TACE, the injection of a chemotherapeutic agent, mixed with Lipiodol or an embolic material such as DSM or DEB (drug eluting beads), aims at reaching a steep drug concentration gradient within the tumor and at the same time a low systemic concentrations [8]. Thus, systemic side effects are limited while higher drug dosages favor local anti-tumor efficacy. As for all transarterial therapies, data on DSM-TACE is sparse since ICCs are a rare malignancy compared to HCC, and treatment regimens are not standardized. TACE-induced complications can be severe and include ascites, acute liver and/or renal failure, hepatic encephalopathy, and gastrointestinal bleedings [9]. Despite the palliative treatment situation, treatment regimens are required which reduce side effects and improve tumor response rates.

This study is the first to report results of a national multi-center observational study on the safety and efficacy of DSM-TACE in ICC as an interventional, locoregional treatment option.

## Material and Methods

### Patients

Patients aged older than 18 years with a confirmed ICC of any stage not suitable for resection or any other curative treatment strategy were eligible for inclusion. Both nodular and infiltrative growth, as well as single-lobar and bilobar disease, were suitable for inclusion. Precluded from study participation were

patients with prior chemoembolization, patients who were enrollment in any other clinical trial and/or other patients with contraindications against DSM-TACE such as lacking a safe arterial access to the intrahepatic malignancy.

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Guideline on Good Clinical Practice, and national laws and regulations where applicable. All patients provided written informed consent for DSM-TACE prior to study inclusion. The IRB was consulted and an official approval was waived because of the observational study design.

### Study design

The study was designed as a national, multi-center observational study on the safety and efficacy of DSM-TACE as palliative treatment of ICC. The recruitment period for the study was from January 2010 to June 2014. Subgroups were formed from the underlying malignancies; we here report on all registered cases of confirmed ICC within our study.

### Embolic agent

EmboCept® S DSM 35/50 (PharmaCept GmbH, Berlin, Germany) is a temporary embolic agent comprised of degradable starch microspheres with an average diameter of 50 micrometers. The microspheres are enzymatically degraded by serum alpha-amylases in the blood yielding a half-life of about 35–40 minutes, both *in vivo* and *in vitro*. Resulting glucose fragments are further degraded by the reticulocyte system. A specific side-effect of transient vascular occlusion strategies such as in TACE is the back-flow of the embolizate to non-target regions, causing ischemia and severe pain. DSM ameliorates the risk of profound organ damage due to its self-limiting degradation; partial resumption of the blood flow will be observed after about 10–15 minutes [10,11].

### Safety

The key aim of our observational study was to evaluate DSM-TACE treatment-emergent side effects. Side effects within 24 hours after a DSM-TACE-procedure and side effects in between single treatment sessions were registered separately, both according to the CTCAE (V4.0) classification of acute and subacute toxic side effects covering both treatment-emergent serious adverse events (TESAEs) and treatment-emergent adverse events (TEAEs).

### Efficacy

DSM-TACE efficacy in ICC treatment was rated according to mRECIST response criteria for the assessment of tumor necrosis

in locoregional therapies six weeks after TACE. Using mRECIST criteria [12,13], complete remission (CR) was defined as no residual malignancy, partial remission as tumor remission greater than 30%. Stable disease (SD) was defined as neither a tumor response greater than 30% nor as a tumor progress greater than 20%. Tumor progress (PD) was defined by a growth of more than 20%. As previously reported, objective response (OR) was defined and calculated as CR + PR and disease control (DC) was defined and calculated as OR + SD.

**DSM-TACE**

After inclusion and imaging (MRI and/or CT), patients received DSM-TACE. Six weeks later, patients were restaged and received another cycle of DSM-TACE when suitable.

The catheter for DSM-TACE was placed via the femoral artery in all patients; selective (*A. hepatica propria*, *A. hepatica sinistra*, *A. hepatica dextra*) or super-selective catheterization was at the discretion of the interventionist in charge, depending on tumor burden, vascular status, and individual patient and case characteristics.

Preparation and dosage of DSM was according to manufacturer’s instructions; choice of chemotherapeutic agent or a combination of up to three drugs was up to the individual patient and case characteristics. The PharmaCept EmboCept® S DSM allows for the use of all different kinds of co-administered contrast agents. As in all TACE-procedures, recommended application of the embolizate and chemotherapeutic agent was as a mixture, but was to the discretion of the interventionist and thus could be as follows: embolizate first, chemotherapeutic(s) first, or as a mixture. The embolic agent was injected intra-arterial via a microcatheter.

**Imaging**

Within this observational study, imaging modality for staging of intrahepatic lesions was chosen according to the institution’s and/or interventionist’s preference. Before and after DSM-TACE, all patients underwent CT scan or MRI using a multiphase liver imaging protocol. All patients underwent the same imaging modalities throughout their participation in the study to enable a reliable rating according to mRECIST.

**Statistical analysis**

For statistical calculations, analysis, and plotting, GraphPad Prism version 5.00a for Mac (GraphPad Software, San Diego California, U.S.A.) was used. Arising from the observational character this study, sole descriptive statistics were used; where appropriate, multivariate analysis with ANOVA with post-hoc Bonferroni comparisons was conducted. Groups were

**Table 1.** Baseline characteristics of patients, pre-treatment, and disease extent.

Age (mean ±SD; min; max)	73.7±6.7; 64; 84 years
Pre-treatment	
Surgery of ICC	2/7 (28.6%)
Chemotherapy	3/7 (42.9%)
No pre-treatment	2/7 (28.6%)
Disease extent	
<3 ICC lesions	1/7 (14.3%)
≥3 ICC lesions	6/7 (85.7%)
Left lobe	1/7 (14.3%)
Right lobe	1/7 (14.3%)
Bilobar; no data	4/7 (57.1%); 1/7 (14.3%)
Infiltrative growth	2/7 (28.6%)
Nodular growth	5/7 (71.4%)

compared using two-sided student’s *t*-test, paired when suitable. Statistical significant differences were assumed at *p*<0.05.

**Results**

In our national, multi-center observational study on safety and efficacy of DSM-TACE in primary and secondary liver malignancies seven patients, all suffering from advanced stage ICC, were included. They received a total of 25 DSM-TACE procedures. Baseline characteristics of patients, pre-treatment and disease extent are summarized in Table 1.

**DSM-TACE**

DSM-TACE was used in a palliative treatment setting in seven out of seven cases (100%). Application of DSM-TACE was conducted selectively via *A. hepatica propria* in four procedures, *A. hepatica dextra* in 16 procedures, *A. hepatica sinistra* in eight procedures, and via super selective catheterization in eight procedures.

A mean of 330.7±117.5 mg of DSM was used per treatment. Application of chemotherapeutic agents spanned over 43.6±28.9 minutes with 55.5±43.0 mL of added contrast agent. DSM was given as a mixture with chemotherapeutic agents in 14 procedures, prior to the chemotherapeutic agents in seven cases and following the chemotherapeutic agents in four cases.

A combination of mitomycin, gemcitabine, and cisplatin was used in four treatments; carboplatin and gemcitabine were

**Table 2.** Relative frequencies of nausea and vomiting in DSM-TACE.

	Absolute	Relative
Mitomycin, gemcitabine, and cisplatin	4/4	100%
Gemcitabine	4/7	57%
Carboplatin	1/14	7.1%

used as sole chemotherapeutic agent in 14 and seven treatments, respectively.

### Safety

Nausea and vomiting as AE occurred in eight out of 25 treatments (32%) within 24 hours of DSM-TACE, most often with the combination of mitomycin, gemcitabine, and cisplatin (four cases), followed by gemcitabine single treatment (three cases), and carboplatin single treatment (one case). Relative frequencies of nausea and vomiting AE are summarized in Table 2. In 11 out of 25 treatments (44%) moderate, transient epigastric pain was registered as AE within 24 hours of DSM-TACE. One TESAE (4%; thrombocytopenia and intracranial, subdural hemorrhage) was registered in between treatments (>24 hours), leading to discontinuation of the DSM-TACE-treatment.

### Efficacy and tumor response

Therapeutic efficacies of the DSM-TACE procedures are summarized in Table 3. In a total of 18 DSM-TACE procedures with complete clinical and imaging follow-up, three (12%) showed a partial response (PR). Stable disease (SD) was recorded in eight treatments (32%); progress was registered after one treatment (4%). Consistent data was missing in six treatments (28%).

### Drop out

All patients were followed until study drop-out. Two patients (28.5%) decided to discontinue DSM-TACE therapy for no treatment-related reason; three patients (42.8%) changed to radio-embolization. Vascular occlusion due to tumor progress and accompanying inflammatory changes precluded one patient (14.2%) from further DSM-TACE. One patient died from hepatic failure (14.2%).

## Discussion

The median survival of ICC patients in palliative treatment ranges from three to eight months [2]. TACE is one locoregional treatment option; the major components, the chemotherapeutic

**Table 3.** Therapeutic efficacy (mRECIST) of DSM-TACE.

	% (n)	
Objective response (OR)	12%	(3/25)
Disease control (DC)	44%	(11/25)
Progress (PR)	4%	(1/25)

agent as well as the embolization agent, are not standardized yet and are not subject to major clinical investigations since the incidence of ICC is, especially in comparison to HCC, rather low. Nonetheless, degradable starch microspheres (DSM) as an embolization agent shows promising advantages over the traditionally used Lipiodol (iodized poppy seed oil) which has an ill-defined occlusion half-time, and drug eluting beads (DEB) which cause a permanent occlusion [14], thereby eliciting an increased VEGF-response in which itself again favors neoangiogenesis, tumor growth, and even metastatic seeding [15].

Considering treatment options in ICC, our national, multi-center study is the first to observe the safety and efficacy prior to further clinical testing in more advanced therapy set-ups.

As primary observational components, both treatment-emergent adverse events (TEAE) and treatment-emergent severe adverse events (TESAE) occurred rarely in our cohort. The majority of TEAEs were found in the 24-hours following DSM-TACE as reported previously [9]; nausea and vomiting, as well as epigastric pain, were the predominant side effects, and these side effects have been described for other TACE-protocols as well with similar frequencies [9]. These findings are in line with a steep drug concentration gradient being highest in the hepatic tumor mass, leading to ischemia and necrosis-caused moderate locoregional pain. The low systemic chemotherapeutic concentrations still elicit nausea and vomiting, since the area postrema is very susceptible to even the lowest concentrations of toxic agents in the blood stream [16]. Gemcitabine, especially as part of a triple chemotherapy scheme (gemcitabine, mitomycin, and cisplatin), caused nausea and vomiting in 100% of the cases in our cohort. Gemcitabine as a single treatment still elicited nausea and vomiting in 57% of treatments. The use of gemcitabine or its combination should raise special awareness peri-interventionally [17]. A standardized accompanying medication scheme is likely to reduce the onset of TACE-related nausea and vomiting, and should be based on the Multinational Association of Supportive Care in Cancer and European Society of Medical Oncology MASCC-ESMO guidelines on antiemetic therapy in chemotherapy of cancer [18]. Overall, AEs are hardly attributed to the use of DSM instead of Lipiodol or DEB; yet, our observational study was not designed to compare different embolization agents.

As a limitation, our analysis of ICC as primary liver malignancy included a rather low number (seven patients), which was mainly attributable to the low incidence of ICC itself and the non-standardized treatment regimens or approaches, making these patients hard to identify for clinical trial inclusion. As another consequence, lack of standardization of ICC treatment in advanced stages can lead to a diverse spectrum of TACE-regimens: with differences in the type of chemotherapeutic agent, contrast agent, concentration, and order of application, and side medication.

## Conclusions

Our national, multi-center study on the safety and efficacy of DSM-TACE for the treatment of surgically non-resectable ICC

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## Conflict of interest

PLP: in relation with this paper (COI in the last three years including activities as Speaker's honoraria, Symposia, Grants, Advisory Board, Consultant): Bayer Global and Bayer Germany, Biocompatibles and BTG, Celonova (Boston Scientific), Cook Medical, Pharmacept, SIRTEX, Terumo.