Transarterial Chemoembolization – Status Quo in Germany

Die transarterielle Chemoembolisation – Status quo in Deutschland

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Key words
● HCC
● chemoembolization
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Abstract

Purpose: Against the background of the current preparation of the national disease management guideline for the diagnosis and treatment of hepatocellular carcinoma (HCC), the German Society for Interventional Radiology (DEGIR) launched a statewide survey in order to evaluate the current status of transarterial chemoembolization (TACE) in Germany.

Materials and Methods: In April 2012 an e-mail questionnaire relating to TACE practices in patients with intermediate-stage HCC was sent to all chief physicians of interventional radiology departments in Germany that were members of DEGIR.

Results: 96 questionnaires were completed and evaluated statistically. The most frequent combinations of embolic agents and cytotoxic drugs are drug-eluting beads combined with doxorubicin or epirubicin as well as lipiodol plus doxorubicin, epirubicin or cisplatin. 60 % of the interventionalists prefer superselective chemoembolization. In most cases more than one chemoembolization per patient is performed (95.5 %). The most common (77 %) time interval between two interventions ranges between one and two months.

Conclusion: The results of this survey show the often stated criticism in Germany regarding the substantial differences in TACE protocols and highlight the importance of standards of practice for TACE in HCC patients.

Key Points:

▶ For determining the suitable treatment regime for hepatocellular carcinoma, the BCLC classification has become established. TACE currently represents standard therapy for intermediate stage of HCC.
▶ Drug-eluting beads TACE (DEB-TACE) and conventional TACE with Lipiodol (cTACE) currently represent the most favoured TACE protocols with a trend toward preferably selective application of embolic and chemotherapeutic agent.

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Hepatocelluläre Karzinome (HCC) machen etwa 7% aller malignen Tumoren und sind das fünfthäufigste Malignom weltweit mit etwa 749.000 neuen Fällen pro Jahr [1, 2]. Die höchste Inzidenzrate liegt in Asien, in Europa sind derzeit mehr Fälle als in Asien zu verzeichnen [3, 4]. Der Ddeployment von Intervention und gleichzeitiger Embolisation spielt bei HCC eine wichtige Rolle im intermediären HCC. Daher, Llovet et al. und Lo et al. war able to show a survival advantage for TACE compared to symptomatic treatment in 2 randomized controlled studies [3, 4].


4. Bland embolization of the tumor-feeding artery (TAE) via closely calibrated microparticles with a variable size between 40 and 100 μm. The selection of the particle diameter to be used depends on the size of the vessel to be embolized. In a small cohort of 53 patients, Orsi et al. were able to achieve satisfactory results for TAE with respect to local tumor control and patient survival [5].

In a special type of embolization called radioembolization or selective internal radiotherapy (SIRT), yttrium-loaded microspheres are applied as beta-emitters with a penetration depth of a few millimeters instead of a chemotherapeutic agent. SIRT requires the interdisciplinary collaboration of nuclear medicine physicians and interventional radiologists. Due to the continuously growing instrumentarium for interventional radiologists using different embolization materials, the German Society for Interventional Radiology (DEGIR) in coordination with the German X-Ray Society (DRG) conducted a national survey. The goal was to obtain an overview of the embolic agents and chemotherapeutic agents currently used in Germany, the intervention protocols being used, and the number of TACE procedures being performed.

Materials and Methods

As part of an online survey, questionnaires were sent in April 2012 to all chief physicians of interventional radiology departments who were members of DEGIR at the time of the survey. A response period of 3 months was specified. The questionnaires first posed questions regarding epidemiological data. Four categories (0–10, 10–30, 30–70, and more than 70 patients per year) were to be used to indicate how many patients with HCC are treated on average per year via a transarterial procedure (excluding transarterial radioembolization) at the indicated site. Moreover, the general experience with available alternative methods, e.g. local thermoablation methods (radiofrequency ablation, microwave ablation, laser-induced thermoablation, cryoablation), percutaneous ethanol injection, or radioembolization, was to be specified. This was followed by data regarding the available materials, e.g. conventional TACE with lipiodol in combination with doxorubicin, epirubicin, or cisplatin, TACE with drug-eluting beads or degradable starch microspheres, bland embolization, or other intraarterial treatments, and the size of the used embolization particles. The selectivity of the artery
probing could be classified as bilobar, lobar, segmental, or superselective. With respect to treatment regimens, information regarding the number of repeat interventions, the amount of time between interventions, and the time point of restaging after a completed intervention was recorded. Finally questions regarding the willingness to participate in a multicenter study and the preferred intervention protocol were posed.

Results

TACE epidemiology

In total, 96 interventional radiology departments in Germany participated with the majority of the departments being part of a municipal entity (42%). With respect to the relevant target group of departments participating in the quality assurance system of the German Society of Interventional Radiology, i.e., 158 departments in 2011, this corresponds to a response rate of approximately 61% [14]. The percentage of university hospitals and church-run institutions was almost equal with 23% and 26%, respectively (Fig. 1). 36% of the surveyed departments treat 10–30 patients per year, and 32% treat less than 10 patients with TACE annually. 19% of the hospitals treat 30–70 patients each year, while 13% of the hospitals treat more than 70 patients annually (Fig. 2).

With 87.5%, most departments perform transarterial chemoembolization as well as percutaneous thermoablation. In addition, percutaneous alcohol instillation (PAI) is performed in less than one-third of the participating departments (27%). In 36 of the 96 participating hospitals (37.5%), selective internal radiotherapy in cooperation with nuclear medicine is also offered (Fig. 3).

TACE modalities

With 43.5% and 42%, respectively, DEB-TACE and cTACE with doxorubicin or epirubicin are the most frequently used methods. DSM-TACE in combination with doxorubicin or epirubicin is performed as frequently as bland embolization with microparticles without the addition of a chemotherapeutic agent in 5% of the participating departments. 2.5% of the participating departments use individual combinations. 2% of the departments use the combination of lipiodol as an embolic agent and cisplatin as a chemotherapeutic agent as the standard procedure. Only 31.3% of the departments use a single TACE protocol. 34.4% use two different TACE protocols and 34.4% of the departments use more than two different TACE protocols.

TACE protocol

In 60% of the participating department, superselective chemoembolization is performed as a function of the tumor location and growth pattern, while segmental, lobar, and bilobar chemoembolization is preferred in 25%, 12%, and 3% of the departments, respectively (Fig. 4).

Preferred particle size:

Particle sizes of 100–300 μm are used in 56% of cases. In 22.5% of cases, larger particles with a diameter of greater than 300 μm are used, while smaller diameters of less than 100 μm are used in 14% of cases.

In most departments (77%), the period of time between two interventions in the case of persistent evidence of a tumor is in the range of one to two months. In 15.5% of the departments, chemoembolization is repeated after only two to four weeks, while the procedure is only repeated...
after more than two months in 7.5 % of the departments (\textit{Fig. 5}).

The number of treatments per patient is 2 – 5 interventions at 48 % of the participating departments and is more than 5 interventions per patient depending on the stage of the disease at 47 % of the departments. TACE is only performed once per patient at 1.5 % of the departments. 3 % of those surveyed did not provide an answer to this question.

**TACE follow-up**

At 40 of the 96 participating departments, intermediate staging is not performed at fixed time intervals but rather as a function of the number of interventions. Intermediate staging is performed after every TACE at 25 departments, after every second TACE at 5 departments, after every third TACE at 7 departments, and after every fourth TACE at 3 departments.

Intermediate staging follows a fixed schedule at 56 departments. Restaging is performed after one month at 21 departments, after two months at 14 departments, and after three months at another 21 departments.

**Willingness to participate in a TACE study**

A recurring criticism regarding TACE studies is the significant variability in TACE protocols. 99 % of the participating departments stated that they would be willing to take part in a multicenter study involving one standardized TACE protocol to be used to treat at least 75 % of the patients. 84 % of those surveyed would accept TACE with medication-loaded particles as the standard protocol, 60 % would accept cTACE with lipiodol and doxorubicin or epirubicin, 29 % would accept DSM-TACE with starch particles, 20 % would accept bland embolization without cytostatic agents, and 19 % would accept cTACE with lipiodol and cisplatin. 6 % of those surveyed would prefer to participate in studies with individual TACE protocols such as combinations of lipiodol, doxorubicin, and cisplatin, combinations of alcohol and lipiodol, or microspheres in combination with chemotherapeutic agents.

**Discussion**

In recent years, the Barcelona Clinic Liver Cancer (BCLC) classification has become established in Europe for determining the suitable treatment regime for HCC. Depending on the stage of the disease, different treatment options are preferred (\textit{Fig. 6}).

For early stages of HCC (stage 0 = very early stage and stage A = early stage), local ablative treatment methods \[15\], surgical resection, and liver transplantation are the treatments of choice.

Liver transplantation is the preferred treatment for patients with liver cirrhosis and early-stage HCC. However, due to the increasing demand for donor organs, the wait time for an organ in Europe is approximately 6 – 24 months \[16\]. Over the course of this wait time, some patients may no longer meet the transplantation criteria due to tumor progress.

In the intermediate stage of HCC (stage B), TACE is the standard treatment, particularly in the case of preserved liver function (Child Pugh Turcotte A-B) with no clinically relevant extrahepatic tumor manifestation. A meta-analysis of 6 randomized controlled studies showed an extended long-term survival for TACE compared to best-supportive care or other suboptimal treatments in patients with unresectable HCC lesions \[17\].

Against the background of the broad indication spectrum for performing TACE and the continually growing TACE instrumentarium, there is currently no consensus as to which TACE protocol in which stage of disease is the ideal procedure particularly while no chemoembolization method could be established as the superior treatment protocol in the aforementioned meta-analysis by Marelli et al. \[9\].

However, there is consensus that TACE should be performed as selectively as possible according to the tumor vascularization pattern and growth pattern and depending on the tumor location \[18\]. The results of this national survey which can be considered representative in light of the participation rate of 61 % also show the trend toward selective application of embolic agents and chemotherapeutic agents.

With respect to survival, there are currently no randomized controlled studies that have shown a definitive advantage for a particular cytostatic agent, an embolic agent, or a de-
fined combination of a chemotherapeutic agent and embolic agent. However, a survival advantage for cTACE compared to best-supportive care was able to be shown in two randomized controlled studies [3, 4].

In general, simultaneous, intraarterial application of a combination of cytostatic agents and embolic agents is recommended in order to devascularize the tumor tissue to the greatest extent possible via TACE. Intraarterial chemotherapy alone is generally not considered to be useful especially since no survival time extension could be shown in retrospective case series in patients with advanced HCC [3].

For doxorubicin-loaded microspheres, a reduction of the systemic toxicity of doxorubicin compared to conventional TACE with a lipiodol emulsion and subsequent gel foam particle embolization could be shown. Moreover, a higher local effectiveness could be shown on the basis of the degree of tumor devascularization and tumor necrosis [19]. Whether comparable results can be achieved with the new DSM-TACE method with temporary vascular occlusion via starch microspheres has not yet been systematically examined. However, growth-retarding effects in HCC could be shown for DSM-TACE [20].

The results of this survey reflect the current situation: There is no generally preferred TACE protocol with respect to the materials used in Germany even if DEB-TACE and conventional cTACE with a combination of lipiodol and chemotherapeutic agent are the most frequently used and favored protocols.

Although TACE is one of the most frequently used minimally invasive tumor treatments, there is no agreement about the exact procedures regarding the type and quantity of embolic agent or cytostatic agent and no standardized guidelines for follow-up examinations and peri-interventional adjuvant therapy.

As a rule, transarterial chemoembolization can be performed repeatedly after initial response to treatment. The interval between two interventions can be between four weeks and three months depending on the tolerability and systemic side effects of the chemotherapeutic agent. TACE should be repeated until complete devascularization of all tumor foci is seen in multiphase magnetic resonance imaging or multiphase computed tomography. Continuation of TACE is indicated if hypervascularized HCC lesions persist or new treatable HCC lesions arise after initial response to treatment.

SIRT is also available as a minimally invasive treatment option at a high percentage of the surveyed departments (37.5%). There is currently no definitive data regarding the superiority of chemoembolization over radioembolization in the intermediate stage of HCC. This is probably due to the large number of patients (> 1000) required for such a direct comparison. However, with the results of their multicenter retrospective study, Sangro et al. highlight the importance of SIRT in patients not responding to TACE treatment or in patients for whom TACE does not seem promising, i.e., in bilobar or multinodular cases [21]. The results of this survey show that different treatment strategies are used with respect to the time point and number of reinterventions. While the time point of re-TACE is between one and two months at 77% of the surveyed departments, reinterventions are performed at shorter time intervals of two to four weeks in 15.5% of the departments. With respect to the number of chemoembolization procedures per patient, TACE treatment is repeated per patient in most surveyed departments while one TACE is performed per patient in only 1.5% of the departments. According to the results of this survey, at least 58% of the surveyed departments schedule intermediate staging between four weeks and three months after an intervention. Whether and to what extent the 40 remaining departments in Germany schedule re-staging in this time window cannot be derived from this data but it is clear that there is no standard for follow-up examinations after chemoembolization.

The mRECIST classification (modified Response Evaluation Criteria In Solid Tumors) [22] and the EASL classification (European Association for the Study of the Liver) are used...
to evaluate the local response after TACE [23]. However, there is no uniform recommendation as to which of the different classification systems for which different applications, definitions, and limitations apply is to be used [24]. A reevaluation of the treatment regime should be performed by the tumor board both in the case of progress in the form of a good response to treatment as well as in the case of worsening of the liver function.

Fortunately all surveyed departments with only one exception indicated their willingness to participate in a multicenter study with a standardized treatment protocol to be used to treat at least 75% of the treatable patients. The preferred protocols are DEB-TACE and conventional TACE with lipiodol in combination with another cytostatic agent. The disproportionately large number of university hospitals among the participating departments and the exclusive focus of the survey on chemoembolization against the background of multimodal treatment concepts for HCC limit the applicability of this study. However, this DEGIR survey does provide an overview of the current status of TACE in Germany.

**Conclusion**

The results of this survey show the heterogeneity of the current radiological interventional treatment situation for intermediate HCC via TACE in Germany. It seems possible to recruit a sufficient number of study centers for multicenter national studies in order to answer important questions (e.g. optimum treatment protocols, optimum particle size, application form).

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