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Article

Chemoembolization for Hepatocellular Carcinoma: A Critical Review of The 2021 CIRSE Recommendations with Presentation of A Technique for A Degradable Starch Microsphere - Chemoembolization

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Abstract

Transarterial chemoembolization (TACE) has been used to treat hepatocellular carcinoma (HCC) for more than 4 decades. So far, there is no consensus on which substances and which method should be used for the most effective treatment. A publication commissioned by CIRSE 2021 attempted to formulate recommendations. However, only the spectrum of currently implemented procedures is outlined. No recommendation was made as to how the various patients should be treated. In this article, therefore, basic considerations regarding the technique of chemoembolization are presented. Additionally, the authors discuss fundamental considerations about the embolism materials used, the cytostatic drugs and their dosage, as well as about pain therapy during treatment. Then, a technique is presented which used degradable starch microspheres (DSM) as an embolic agent. This technique allows multiple treatments over a longer period. The aim is to provide interventionalists with a decision-making aid for the TACE technique. A major problem when evaluating publications from different working groups is that the technology used is not adequately described and the individual studies are therefore not comparable. Therefore, a classification is presented that systematizes the possible different techniques. Future randomized trials should use this classification. Hopefully, if they are carried out on a sufficient number of patients, it will finally be possible to identify what is the best TACE procedure for individual patients. Until then the technique proposed by the authors can be applied.

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Keywords: TACE; technique; classification; chemoembolization; HCC; postembolization syndrome

Introduction

Chemoembolization for the treatment of malignant liver tumors like HCC has been performed for many years. However, to date, there has been no consensus on which substances and which method should be used for the most effective treatment. In a publication [1] entitled 'CIRSE Standards of Practice on Hepatic Transarterial Chemoembolisation', published in late 2021, an attempt was made to formulate recommendations. However, the document in fact only outlines the range of procedures currently performed. There is no analysis of the advantages and disadvantages of these different methods. Furthermore, there are no clear recommendations for which substances to use or in which order. The paper also neglects to mention which method should be used for which type of tumor and in which clinical circumstances. Another publication from 2021 [2] presents the results of a European study in which degradable starch microspheres (DSM) were used as an embolic agent. However, no Lipiodol is used as a marker substance in this technique.

In this publication, we want to discuss the basics of TACE and propose a technique that allows TACEs to be performed over a longer period with very few undesirable side effects. We also propose a classification of the possible different TACE techniques.

Definition

According to Lewandowski et al. [3] and the Society for Interventional Radiology, the term "chemoembolisation" ('TACE' - derived from **t**rans**a**rterial **c**hemo**e**mbolisation) refers to the application of a mixture consisting of a chemotherapeutic agent with an embolic agent, either with or without lipiodol. Due to the wide range of embolic and chemotherapeutic agents, this term is used in conjunction with several different treatment methods.

Technique

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Although chemoembolisation has been dedicated to treat malignant liver tumors for many years, neither Marelli et al. 2007 [4], in their overview of the chemotherapeutic and embolic agents used, nor Craig et al. (5) in their 2019 questionnaire campaign, were able to find out a standardized procedure from their answers. Lucatelli et al. [1] make a laudable attempt at bringing some order to TACE procedures by adding prefixes to the TACE procedures. They defined cTACE (conventional chemoembolisation) as the mixture of Lipiodol with a chemotherapeutic agent, combined with subsequent embolisation (mostly with degradable gelatin sponge - Gelfoam®). Lucatelli et al. [1] refer to the use of chemotherapeutically loaded microcapsules as DEM-TACE (chemotherapy-releasing, non- degradable microcapsules). Chemoembolisation with degradable starch particles (degradable starch microspheres - Embocept®S) became termed DSM-TACE. When using micro balloons to interrupt blood flow, the procedure was classed as b-TACE. With the chosen form of classification, however, it is not clear that permanent occlusion material is used in DEM-TACE (DEM-TACE). Consequently, the prefix p should be added to DEM-TACE (pDEM-TACE). Since, in some applications of DSM-TACE, microspheres are added after the chemotherapeutic agent has been administered, the term for this method should be prefixed with an s (sequential) (sDSM-TACE) to distinguish it from the original method (DSM-TACE, mixing the chemotherapeutic agent with the cytostatic agent). If DSM-TACE is combined with Lipiodol as an embolic agent, it should be prefixed with L-DSM-TACE. When Lipiodol is only used as a blood flow marker it should get the prefix *l* (*l*- DSM-TACE). Due to this improved classification, the TACE results of different studies can be better compared. Ultimately, since an abbreviation does often only insufficiently describe the method applied in an individual case – in everyday practice it is best if the method is described in detail.

Up to date, there are no known valid studies with enough patients, in which there was a prospective comparison of different embolic agents. They were previously administered more or less upon the basis of personal experience or clinical tradition. This also explains why there were such inconsistencies in the conclusions about the impact of chemoembolisation on survival. As an example of studies that can only be used to a limited extent the publication by Taguchi et al. from 1992 [6] will be described: 60 patients were randomized: 30 received intra-arterial doxorubicin (< 30 mg/m^2 body surface area) mixed with DSM every two weeks, the control

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group received the chemotherapy agent without DSM. The response rate in the patients who received the DSM-doxorubicin mixture was significantly higher than in the patients who received the doxorubicin injection alone. Survival data were not given. Injection of a chemotherapeutic agent into a hepatic artery without an embolic agent is unlikely to have any local effect because the agent enters the circulation quickly and has more of a systemic effect. In addition, there was no differentiation between the patients regarding liver function and tumor burden.

In 2002, Ramsey and Geschwind [7] analyzed the existing data. They stated that, from several non-randomized trials, it was determined that chemoembolisation resulted in high survival rates. However, they noted critically that the number of patients examined in these studies was too low and that, overall, there were significant weaknesses in the methodology used. Ramsey & Geschwind [7] concluded that "New RCTs examining the impact of chemoembolisation on survival are urgently needed...".

Embolic agents

Despite the lack of studies, some basic considerations are possible (which are not fully covered by references) which basic attributes an optimal embolic agent should have in the chemoembolization of malignant liver tumors:

1) What should be the effect of an embolic agent?

An embolic agent basically has two different purposes:

- When mixed with the chemotherapeutic agent, it should ensure that the latter is not immediately flushed out of the liver with the bloodstream. During the period of blood stasis in the treated vascular region, the chemotherapeutic agent must remain there for a significant period for it to be best absorbed by the tumor cells (based upon the premise that normal liver cells primarily draw their supply from the portal vessels; but tumor cells draw it from the arteries – [8]).
- The embolisation-dependent ischemia phase should last long enough to affect the tumour cells.

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2) What further characteristics should an embolic agent have?

The regional treatment of malignant liver tumors usually requires multiple (sequential) rounds of treatment. If a permanent embolic agent is used, only the developed collateral arteries can be used for any further necessary treatment. These collateral arteries are, however, often exceedingly small and only reach parts of the tumor. During a subsequent chemoembolisation it is therefore often not possible to administer a therapeutic dose. A temporary embolic agent that restores blood flow after about 1 - 2 hours in the treated section of the vessel would therefore be of great benefit. The particles should not be so large that they block the segmental arteries, because that would cause the collaterals in the liver to open and no ischemia to occur. If the embolic agent is so small that it only occludes the vessels at the capillary level, two scenarios are possible: there are often small A-V fistulas in the tumor, which means there is a risk of an increased number of particles entering the circulation. It is also possible for such small particles to induce excessive necrosis with e.g., the formation of an abscess. Taking the above into consideration, the ideal embolic agent should occlude the vessels at the precapillary level. Capillaries have a diameter of 5 to 10 µm, a size of about 50 µm is therefore desirable.

3) Avoiding damage to the residual liver tissue

Since it is generally not possible to apply chemoembolisation with absolute precision (even if extremely selective cannulation of the artery supplying the tumor is possible), a degradable embolic substance should be used to minimize damage to the surrounding liver tissue, particularly considering that in a prospective study [9] could not find an advantage for a permanent embolic agent.

Which substances are most applicable based upon these considerations?

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Temporary embolic agents should be used as a preference. In 2018, Ebert wrote an overview of the currently used embolic agents [10]. According to this, there are currently only two substances that close vessels temporarily: Gelatine (usually known as 'Gelfoam™' or 'Gel-Bead™ Embolisation Spheres') and 'starch particles' (degradable starch microspheres). Lipiodol® can also be considered as a temporary embolic agent (but it is not approved for such use). Although Lipiodol® has been used for many years; the problem is that it is still not clear how best to administer it and what effect it has. Some of the publications on the use of Lipiodol® in chemoembolization have considerable methodological weaknesses and can therefore only be used to a limited extent [e.g.: 1, 11, 12, 13, 14, 15]. It would be worth discussing how Lipiodol® is to be administered: it can either be injected alone (sequentially small amounts next to the actual chemoembolic agent) or mixed with the chemotherapeutic agent. The Lipiodol® and the chemotherapeutic agent are mixed by connecting the two syringes filled with the substances via a three-way stopcock and then mixing the contents of the syringes by quickly emptying one of the syringes alternately. It is assumed that the frequency and speed with which the syringes are emptied influences the size of the oil droplets and their stability [14, 15, 16]. However, the size of the droplets in individual cases cannot be predicted. Due to its lipophilic coating, the emulsion consisting of oil droplets and the chemotherapeutic agent is thought to lead the tumor cell to absorb a larger amount of the chemotherapeutic agent [12]. Irrespective of the discussion about these possible effects, however, Lipiodol® has two undisputed marker functions: even small amounts of Lipiodol® can be recognized very well under fluoroscopy (even under very unfavorable conditions - e.g. obese patient) and the Lipiodol® is degraded very slowly in tissues without a RES (which is true for malignant tumors) and can be detected there (with a native CT) for up to several months [17]. In practice, this means that with the help of the Lipiodol®, the blood flow can be checked under fluoroscopy, and it can be ensured that there is always antegrade flow in the treated hepatic arteries. Stasis in the vascular bed is detected early and retrograde flow into extrahepatic vessels is avoided. Lipiodol® is quickly degraded in the liver cells, while it remains in tumors, especially in the necrotic part, for a long time and can be easily detected there in a (native) CT.

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This leaves Gelfoam and starch particles as temporary embolic agents. Although the use of blood clots as embolic material has been written about, they cannot be considered for general use as it is impossible to control the size of the clots. Therefore, they find no further mention here:

- Gelfoam is made from pig skin. It is available as a spongy structure that can be cut into small, different-sized pieces – e.g., 2.5 - 5 mm in length – or as a powder (Gelfoam®, Gel-Block®). Until the endemic occurrence of "spongiform bovine encephalopathy" (in the 1990s), the substance was made from cattle skin, but pig skin was used from the early 2000s due to fears of eventual transmission of the disease to humans [18]. The literature reports both the use of Gelfoam in powder form and Gelfoam sponges cut into small pieces [4, 5, 19, 20]. The use of pieces of Gelfoam [5, 13, 18] is ineffective if the embolic agent is to be mixed with the chemotherapeutic agent. Only Gelfoam® powder can be used as part of a mixture. The questions that remain to be answered are how large the Gelfoam particles must be (i.e., at what level they block the arteries) and how long the blockage lasts. It is difficult to pre-determine the size of individual particles of the powder as it is made by grinding pieces of Gelfoam sponge. The size of such particles would need to be determined ex vivo. However, since Gelfoam swells in the blood, this data are irrelevant. In animal experiments (with rabbits), Cho and Lunderquist [21] demonstrated that intrahepatic arteries with a diameter of 50 - 150 µm were occluded by the gel foam powder. Louail et al. [18] reported that in pigs even renal arteries with a diameter of 350 - 500 µm were occluded. There are no known studies on humans in this area. Regarding the second question: how long the vessels should remain closed by the Gelfoam: the data that has been published on this are inconsistent. The results range between 2 weeks for pieces of Gelfoam [19] to 3 days for powder [18].

- **Starch particles:** There is currently only one product on the market in Europe that consists of starch particles (= amilomer = EmboCept®S). The starch particles (microspheres, degradable starch microspheres = DSM) are degraded in the blood by amylases. When assessing the substance, it should be noted that a product manufactured in Sweden (Spherex®) was on the market until

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the early 2000s but was then no longer available in Europe (only in Asia). In 2006, however, a new product became available on the market (EmboCept®, in 2009 it was replaced by EmboCept® S, which has a shorter half-life). EmboCept®S consists of particles with a size of 50 µm, the half-life in the blood is about 30-40 minutes. The embolic agent is available as a substance consisting of 7.5 ml fluid which contains 450 mg particles (as specified by the manufacturer).

One of the first publications on the use of starch particles (Spherex®) in the chemoembolisation of malignant liver tumors was published by Dakhil et al., [22]. This publication reports on five patients with a malignant liver tumor: In these patients, the level of the chemotherapeutic agent used was measured in the peripheral blood - once after administration of the chemotherapeutic agent without the addition of an embolic product and once as a mixture with the Amilomer. In comparison, the peripheral blood levels were 30-90% lower following the use of the Amilomer mixture. Angiographically, the blood flow in the treated hepatic arteries returned to normal about 30 minutes after the administration of the cytostatic-Amilomer mixture. Pohlen et al. [23] investigated the dependence of the concentration of the chemotherapeutic agent (carboplatin) applied to the tumor on the embolic agent used in VX2 tumors of rabbit's livers. Compared to when applied alone, the concentration of cytostatic in the tumor tissue was 12.1 times higher after mixing with gel foam powder and 12.8 times higher after mixing with DSM (Spherex®). Pieper et al. [24] investigated in pigs how long blood stasis persists after the embolisation of the hepatic arteries with EmboCept®S. They were able to demonstrate that flow through the hepatic arteries was demonstrable after around 30 minutes. However, the findings from animal testing can only be transferred to humans to a limited extent since amylase activity in animals (particularly pigs) differs from that in humans.

There are also several clinical publications on "DSM-TACE". In a prospective study [25] 45 patients with HCC were divided into three groups: - the first group received cisplatin and lipiodol, the second, cisplatin and DSM (presumably Spherex®), and the third group cisplatin, DSM and lipiodol. The results showed that the patients treated with the combination of cisplatin, DSM and lip-

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iodol had the longest “progression-free survival time”. Unfortunately, there is no information on how the patients were randomized and at what time intervals the treatment was repeated. The number of patients (= 15 in each group) is also exceedingly small to draw a widely valid conclusion. Two publications that retrospectively examined TACE with DSM should be mentioned here. Minici et al. [26] studied 50 of their own patients who received a total of 142 treatment procedures from 2015 to 2020. Treatment consisted of a mixture of DSM, non-ionic contrast medium and doxorubicin (50 mg) – but without lipiodol. Unfortunately, there is no information about the dose in which the DSM was given. When no stasis occurred following the application of the doxorubicin-DSM mixture, DSM was injected additionally, until there was complete blood stasis in the treated area. The authors concluded that “DSM-TACE” is an effective and safe treatment method for patients with intermediate-stage HCC, since there were only two serious side effects.

Ludwig et al. [2] published the retrospective results of a multi-center study (three clinics in Europe). The patients were treated between 2009 and 2018. There was no control group. A total of 121 patients were evaluated, all of whom had unresectable HCC. In all three clinics, a mixture of non-ionic contrast medium, DSM and an anthracycline (Doxorubicin or Epirubicin) was injected as selectively as possible (without Lipiodol®). In each of the three clinics, different doses of cytostatic and starch particles were used. Lipiodol® was only injected as an additional embolic agent if stasis did not occur after the planned dose had been administered. A total of 585 treatment procedures were recorded. There were relatively few side effects, except duodenal ulcers (in 0.2% of treatment procedures). Duodenal ulcers occur when a stasis occurs in the hepatic artery during treatment and the chemoembolizate drains retrograde into the gastroduodenal artery. This leads to slow healing and painful defects in the mucous membrane of the duodenal wall. Ludwig et al., [2] concluded that DSM-TACE is a good option for patients with HCC for whom there is no other possible treatment. However, Lipiodol was not used as a marker substance in the study and the aim was complete stasis in the treated vascular bed.

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In the presented studies, DSM was always mixed with the chemotherapy drug. We believe this is the right approach. The methodological shortcomings of the two studies are excluded from this. In addition, in our opinion, the addition of Lipiodol as a marker for the direction of the blood flow in the treated arteries makes the treatment safer.

The above-mentioned characteristics of an optimal embolic agent are all fulfilled by starch particles: they have the correct and stable size; they can be mixed well with a chemotherapeutic agent and are safely dissolved in the blood. The short ischemia time leads to only minimal damage to the remaining liver tissue. Further treatment sessions are then possible.

Postembolization Syndrome

This term includes symptoms such as pain, nausea, vomiting and fever that occur after the treatment. Above all, the pain affects the patient severely, which is why the following treatment method is recommended:

The authors of this paper have particularly good experiences with the intra-arterial injection of 50 mg pethidine (Dolantin®). After positioning the tip of the catheter in the target vessel, 50 mg pethidine is slowly applied to the vessel bed that is to be treated. The injection must be carried out very slowly. If it is administered to quickly, the patient fields severe pain (which, however, subsides quickly). The injection is best carried out in such a way that the patient – who has been informed about it beforehand – feels at most a very slight sensation of pressure. This treatment has led to a significant reduction in the pain medication required following TACE. Undesirable side effects have not been identified – with correct usage [27]. It is not known how this medication works precisely; its effectiveness may be related to the morphine receptors in the liver [28].

Here is our treatment suggestion based on the facts described above: In general, it should not be forgotten that the chemoembolisation of malignant liver tumors is always palliative. It must also be repeated several times (like in systemic

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administrations). Therefore, all procedures must be taken to ensure that the multiple courses of treatment required have as little negative effect on the patient's quality of life as possible. Unfortunately, the following suggestions cannot be backed up by the results of prospective randomized studies. The authors performed at least 1500 chemoembolization over a 30-year period. Our suggestions are therefore based on the combination of the results of published scientific studies and years of personal experience with chemoembolization (i.e., evidence- and eminence-based):

- Dexamethasone medication as an antiemetic is not required.
- An Anthracycline (e.g., Doxorubicin or Epirubicin) should be used as a first choice. The first dose should not be higher than 50 mg for the initial chemoembolisation of HCC. If this is ineffective, the dose may be increased up to 100 mg. The total dose of 700 mg/m² should not be exceeded due to the risk of cardiomyopathy. Although this dosage rate comes from systemic chemotherapy, the patient's cardiac function should be checked after two-three rounds of chemoembolisation as a precaution. If changes are detected, the recommendation is to switch to cisplatin 50 mg. This also becomes necessary if the tumor shows signs of progression. Neurotoxicity, nephrotoxicity, and cardiotoxicity must be expected from a cumulative dose of 400 mg/m² of Cisplatin [29].
- Before each chemoembolization, a 3rd generation bile-permeable cephalosporin (e.g., Ceftriaxone) should be given once to prevent the possible infection of necrosis occurring because of the chemoembolization
- Before the treatment, the patient should be hydrated intravenously with 1000 ml physiological NaCl solution, provided the kidney function is not impaired.
- Administration of an antiemetic (e.g., Ondansetron 4 mg before and after chemoembolization) is usually only necessary if Cis-platin is used.
- During treatment, the patient should be sedated, e.g., with a mixture of 100 mg Pethidine + 1000 mg Novaminsulfon and 10 mg of Midazolam diluted in 500 ml of physiologic NaCl. This mixture is infused slowly, whereby oxygen saturation and blood

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pressure are monitored continuously. This medication relaxes the patient and Midazolam (often) leads to antegrade amnesia. When the patient regains consciousness, they will be glad to discover that the procedure is already over.

- The artery supplying the tumor should be cannulated as selectively as possible. If several tumors located in different parts of the liver need to be treated, the respective arteries must be probed individually. Depending on the patient's condition and liver function, treatment can also be spread across two separate sessions (especially in the initial stage of treatment, where it is not known how the patient will respond to the therapy).
- Diagnostic angiography must be performed prior to any chemoembolization. In addition to identifying the arteries supplying the tumor(s), larger A-V shunts must be ruled out. If such a shunt is discovered, it must be embolized (e.g., with pieces of gel foam or with coils). This also applies to atypical vessels that may arise from the aorta, from the inferior phrenic artery or from other regional arteries.
- Once the tip of the (most often coaxial) catheter has been placed into the artery supplying the tumor, 50 mg of pethidine are slowly injected.
- EmboCept®S is supplied in a 7.5 ml bottle (with 450 mg of Amilomer dissolved in physiological NaCl). Doxorubicin and Epirubicin should be used as a powder. 50 mg of powder are dissolved in the Amilomer liquid. The resulting fluid is usually too highly concentrated and must be diluted. The type of dilution depends on the vascular situation: a large tumor with rapid blood flow in the supplying arteries may not require dilution. The slower the blood flow is (especially if several sessions of treatment have already carried out), the greater the liquid needs to be diluted with physiological NaCl. When blood flow is slow (and tumors are small), for example, only 3 ml of the Amilomer liquid should be used, the cytostatic must dissolved in it and then diluted again with 12 ml of physiological saline solution. The resulting 15 ml liquid can then be injected slowly.

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- The starch particles, which are heavier than water, sediment very quickly. It therefore makes sense to fill only one (insulin) syringe at a time and to stir the mixture thoroughly before filling the next syringe with the “Anthracycline-EmboCept®S” mixture.
- In addition to the mixture consisting of the chemotherapeutic drug and EmboCept®S, lipiodol is injected at regular intervals. As lipiodol has a relatively high viscosity and can therefore only be injected with high pressure through the small lumen of the coaxial catheter, it makes sense to first heat the lipiodol: A heat lamp (infrared lamp) is placed over the table on which the bowl containing lipiodol has been placed.
- Insulin (Luer-lock) syringes are required for the injection of the substances. The mixture of Amilomer and chemotherapeutic agent is drawn up in one syringe and lipiodol in the second. The two syringes and the therapy catheter are connected via a three-way stopcock (Fig. 1).
- During treatment, the "anthracycline-amilomer mixture" and some of the lipiodol are injected alternately by turning the three-way stopcock. In most cases, a ratio of four parts "anthracycline-amilomer mixture" to one-part lipiodol is sufficient to determine the rate of blood flow. Only about 0.05 ml of Lipiodol should be injected as a bolus. If blood flow is slow, the dose of lipiodol can be slightly reduced. By administering lipiodol, blood flow becomes clearly visible through fluoroscopy even in very adipose patients. In addition, the distribution of substances in the tumor to be tracked easily. If there is stasis in the vascular bed, e.g., if the injection is carried out too rapidly, this can be recognized immediately. In this way, retrograde flow in the hepatic arteries and the possible transfer of the liquid into the gastroduodenal artery is reliably prevented.
- The chemoembolizate is injected until there is a significant slowdown in the blood flow in the treated arteries or when the 50 mg of the chemotherapy drug (i.e., anthracycline or cisplatin) has been injected. It is not necessary to increase the dose up until the point of complete blood stasis. There is a high risk that blood stasis in the treated arteries will damage the vessel wall (e.g.,

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due to the cytostatic agent that is present there in relatively high concentration). It is absolutely necessary to protect the arteries of the liver as much as possible, for the subsequent treatments.

- A non-enhanced CT scan of the liver is performed on the day after chemoembolization. Lipiodol is rapidly metabolized from the liver cells themselves (by the RES system). The Lipiodol, which is detected on these CT scans, must therefore be inside the tumour and it can be determined whether the tumor area has been adequately reached by the treatment. Such a CT is also necessary if another artery had to be probed during the course of treatment.
- Most contributors agree that chemoembolization must be repeated regularly in patients with HCC. The necessary frequency and the necessary intervals between the individual sessions have not yet been the subject of controlled studies. The authors have had good experiences with the following scheme: "initial therapy" and "maintenance therapy". "Initial therapy" consists of the first three sessions of treatment, which are carried out at intervals of between two and a maximum of four weeks (depending on the patient's condition and liver function tests results). This is followed by "maintenance therapy", which is carried out twice a year if no further tumor growth can be detected. Restaging is performed before every “maintenance therapy”. If restaging shows renewed tumor growth, an “initial therapy cycle” is repeated. However, every patient should be seen by the general practitioner at least every three months. In addition, the patient is instructed to present himself immediately if his general condition changes.

Summary

Liver chemoembolisation is the preferred method for treating inoperable HCC. Although it has been carried out for many years, there is no treatment regimen that has been validated by prospective studies and is generally accepted as a standard procedure. In our opinion, it is of greatest importance how the treatment is performed, i.e., which substances in what mixture and sequences are used and how often the treatment is repeated. The previously known studies were carried out using different techniques and different

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substances. They do not allow a valid comparison of different studies. We present an easy-to-perform TACE technique using DSM as the embolic agent and Lipiodol® as the marker substance that is easy to perform, can be repeated often, and is very well tolerated by patients.

As long as there are no prospective studies in which e.g., different mixtures of substances and time sequences are examined, our recommendation is to employ our proposed treatment scheme. There is an urgent need to establish a scientifically based treatment for patients with HCC. We appeal to all who have the necessary resources and are interested in making progress, to implement randomized and controlled studies with a sufficient number of patients.

Extra box:

Summary of supportive measures:

Before the treatment:

- hydrate the patient intravenously with 1000 ml physiological NaCl solution.
- a 3rd generation bile-permeable cephalosporin (e.g., Ceftriaxone) given once intravenously.
- Antiemetic drug (e.g., Ondansetron 4 mg) if Cisplatin is used.
- Slowly inject 50 mg of pethidine into the artery supplying the tumor prior to the administration of the chemoembolizate.

During the treatment

- sedate the patient, e.g., with a mixture of 100 mg Pethidine + 1000 mg Novaminsulfon and 10 mg of Midazolam diluted in 500 ml of physiologic NaCl.

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- Continuous monitoring of the patient using pulse oximetry and regular blood pressure measurement
- starch particles sediment very quickly. The mixture of the chemotherapeutic drug and starch particles must be shaken or stirred regularly and frequently.

After the treatment:

- Administration of an antiemetic (e.g., Ondansetron 4 mg) if cisplatin is used.
- The patient should be hydrated intravenously with 1000 ml physiological NaCl solution.
- If the patient still complains of pain, continue slowly administering the mixture of 100 mg Pethidine + 1000 mg Novaminsulfon and 10 mg Midazolam diluted in 500 ml physiological saline solution intravenously.
- When sedated, continuous monitoring of the patient using pulse oximetry and regular blood pressure measurement.

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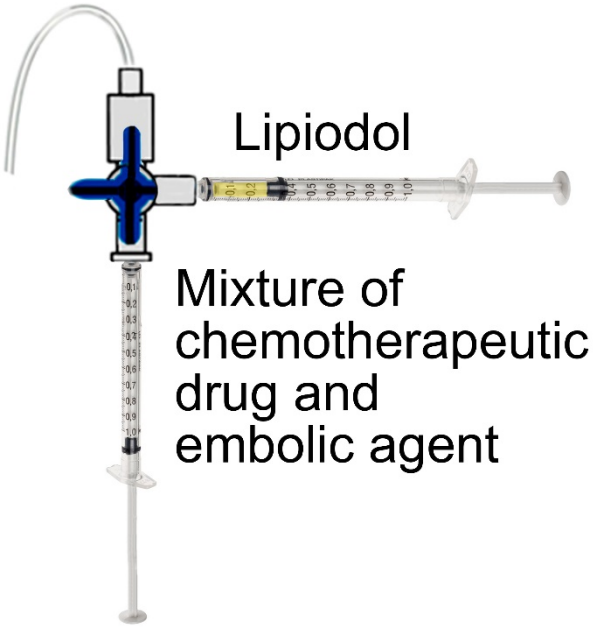

Fig. 1: Treatment situation: Two insulin syringes are connected via a three-way stopcock: either the chemoembolizate or the lipiodol is injected by turning the stopcock.

Author contributions

The two authors have seen and agreed with the contents of the manuscript. All authors contributed to the compilation and analysis of the data and the preparation of the manuscript.

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References

1. Lucatelli P, Burrel M, Guiu B, de Rubeis G, van Delden O, Helmberger T: CIRSE standards of practice on hepatic transarterial chemoembolisation. Cardiovasc Intervent Radiol 2021; 44:1851-1867, https://doi: 10.1007/s00270-021-02968-1.
2. Ludwig JM, Iezzi R, Theysohn JM, Albrecht T, Posa A, Gross A: European Multicenter Study on Degradable Starch Microsphere TACE: The Digestible Way to Conquer HCC in Patients with High Tumor Burden. Cancers 2021; 13:5122, https://doi: 10.3390/cancers13205122.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 November 2022 doi:10.20944/preprints202211.0065.v1

3. Lewandowski RJ, Geschwind, JF, Liapi E, Salem R: Transcatheter Intraarterial Therapies: Rationale and Overview. Radiology 2011, 259: 641-657. https://doi:10.1148/radiol.11081489.
4. Marelli L, Stigliano R, Triantos C, Senzolo M, Cholongitas E, Davies N, Tibballs J, Meyer T, Patch DW, Burroughs A: Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. Carciovasc Intervent Radiol 2007; 30: 6-25.
5. Craig P, Young S, Golzarian J: Current trends in the treatment of hepatocellular carcinoma with transarterial embolization: Variability in technical aspects. Cardiovasc Intervent Radiol, 2019; https://doi.org/10.1007/s00270-019-02232-7.
6. Taguchi T, Ogawa N, Bunke B, Nilson B, and DSM Stud Group (Japan). The use of degradable starch microspheres (Spherex) with intra-arterial chemotherapy for the treatment of primary and secondary liver tumours – results of a phase III trial. Reg Cancer 1992; 4:161-165.
7. Ramsey DE, Geschwind JFH: Chemoembolization of hepatocellular carcinoma - what to tell the skeptics: review and meta-analysis. Tech Vasc Interv Radiol 2002; 5:122-126, https://doi: 10.1053/tvir.2002.36418.
8. Breedis C, Young G: The blood supply of neoplasms in the liver. Am J Pathol 1954; 30: 969-985.
9. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, Pitton K, Sergent G, Pfammatter T, Terraz S, Benhamou Y, Avajon Y, Gruenberger T, Pomoni M, Langenberger H, Schuchmann M, Dumortier J, Mueller C, Chevallier P, Lencioni R, on behalf of the PRECISION V investigatos. 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.
10. Ebert J: Embolisate. In: Regionale und lokale Therapie von malignen Lebertumoren – eine Bestandsaufnahme. Hrgs: Boese-Landgraf J, Fobbe F, Uni-Med Verlag Bremen 2018. German.
11. Nakamura H, Hashimoto T, Oi H, Sawada S: Transcatheter oily chemoembolisation of hepatocellular carcinoma. Radiology 1989; 170:783-786, https://doi:10.1148/radiology.170.3.2536946.
12. Kruskal, JB, Hiatky L, Hahnfeldt P, Teramoto K, Stokes KR, Clouse ME: In vivo and in vitro analysis of the effectiveness of doxorubicin combined with temporary arterial occlusion in liver tumors. JVIR 1993; 4: 741–747, https://doi:10.1016/S1051-0443(93)71965-X.
13. Chung JW: Transcatheter arterial chemoembolization of hepatocellular carcinoma. Hepato-Gastroenterology 1998; 45:1236-1241.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 November 2022 doi:10.20944/preprints202211.0065.v1

14. de Baere T, Dufaux J, Roche A, Counnord JL, Berthault MF, Denys A, Pappas P: Circulatory alterations induced by intra-arterial injection iodized oil and emulsions of iodized oil and doxorubicin: experimental study. Radiology 1995; 194:165-170, https://doi: 10.1148/radiology.194.1.7997545
15. de Baere T, Arai Y, Lencioni R, Geschwind JF, Rilling W, Salem R, Matsui O, Soulen MC: Treatment of Liver Tumors with Lipiodol TACE: Technical Recommendations from Experts Opinion. Cardiovasc Intervent Radiol 2016; 39:334-343, https://doi: 10.1007/s00270-015-1208-y.
16. Deschamps F, Moine L, Isoardo T, Tselikas L, Paci A, Mir L. M, Huang N, Fattal E, de Baère T: Parameters for stable water-in-oil lipiodol emulsion for liver trans-arterial chemo-embolization. CVlR 2017; 40:1927-1932, https://doi:10.1007/s00270-017-1763-5.
17. Kan, Z, McCuskey A, Wright KC, Wallace S: Role of kupffer cells in iodized oil embolization. Invest Radiol 1994; 29: 990 - 993.
18. Louail B, Sapoval M, Bonneau M, Wasseff M, Senechal Q, Gaux JC: A new porcine sponge material for temporary embolization: an experimental short-term pilot study in swine. Cardiovasc Intervent Radiol 2006; 29:826-831, https://doi: 10.1007/s00270-004-0299-7.
19. Brown DB, Pilgram TK, Darcy MD, Fundakowski CE, Lisker-Melman M, Chapman WC, Crippin JS: Hepatic arterial chemoembolization for hepatocellular carcinoma: comparison of survival rates with different embolic agents. J Vasc Interv Radiol 2005; 16:1661-1666, https://doi: 10.1097/01.RVI.0000182160.26798.A2.
20. Rösch J, Keller FS, Kozak B, Niles N, Dotter CT: Gelfoam powder embolization of the left gastric artery in treatment of massive small-vessel gastric bleeding. Radiology 1984; 151: 365–370. https://doi:10.1148/radiology.151.2.6608749.
21. Cho KJ. Lunderquist A: Experimental hepatic artery embolization with Gelfoam® Powder. Investig Radiol 1983; 18:189-193. https://doi:10.1097/00004424-198303000-00017.
22. Dakhil S, Ensminger W, Cho K, Niederhuber J, Doan K, Wheeler R: Improved regional selectivity of hepatic arterial bcnu with degradable microspheres. Cancer 1982; 50:631-635, https://doi:10.1002/1097-0142(19820815)50:4<631::aid-cncr2820500403>3.0.co;2-m.
23. Pohlen U, Berger G, Binnenhei M, Reszka R, Buhr HJ: Increased carboplatin concentration in liver tumors through temporary flow retardation with starch microspheres (Spherex) and gelatin powder (Gelfoam): an experimental study in liver tumor-bearing rabbits. J Surg Res 2000; 92:165 - 170, https://doi: 10.1006/jsre.2000.5856, 2000.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 November 2022 doi:10.20944/preprints202211.0065.v1

24. Pieper CC, Meyer C, Vollmar B, Hauenstein K, Schild HH, Wilhelm KE: Temporary arterial embolization of liver parenchyma with degradable starch microspheres (EmboCept®S) in a swine model. Cardiovasc Intervent Radiol 2015; 38: 435 - 441, https://doi: 10.1007/s00270-014-0966-2.

25. Yamasaki T, Hamabe S, Saeki I, Harima Y, Yamaguchi Y, Uchica K, Terai S, Sakaida I: A novel transcatheter arterial infusion chemotherapy using iodized oil and degradable starch microspheres for hepatocellular carcinoma: a prospective randomized trial. J Gastroenterol 2011; 46:359-366, https://doi: 10.1007/s00535-010-0306-5

26. Minici R, Ammendola M, Manti F, Siciliano MA, Minici M, Komaei I, Currò G, Laganà D: Safety and Efficacy of Degradable Starch Microspheres Transcatheter Arterial Chemoembolization (DSM-TACE) in the Downstaging of Intermediate-Stage Hepatocellular Carcinoma (HCC) in Patients with a Child-Pugh Score of 8-9. Front Pharmacol 2021; 12:634087, https://doi: 10.3389/fphar.2021.634087.

27. Fobbe F, Boese-Landgraf J, Chen Y, Reichel M, Schmoll E, Wolf KJ: Intraarterielle Injektion von Pethidin zur Schmerzbehandlung bei der Chemoembolisation der Leber. RÖFO 1994; 161: 168 – 170. German.

28. Sánchez E, Tampier L, Mardones J: Receptors for morphine and opioids. Gen Pharmacol 1976; 7:107-110, https://doi: 10.1016/0306-3623(76)90044-6.

29. Wiggermann P: Chemotherapeutika. In: Regionale und lokale Therapie von malignen Lebertumoren-eine Bestandsaufnahme. Hrsg: Boese-Landgraf J, Fobbe F, Uni-Med Verlag Bremen 2018. German.