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Review

Review on transarterial chemoembolization in hepatocellular carcinoma: Palliative, combined, neoadjuvant, bridging, and symptomatic indications

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ABSTRACT

The current review provides an overview on the palliative, combined, neoadjuvant, bridging, and symptomatic indications of transarterial chemoembolization (TACE) in patients with hepatocellular carcinoma (HCC). It is based on an analysis of the current literature and the experience of the authors on the topic. Chemoembolization combines the infusion of chemotherapeutic drugs with particle embolization. Tumor ischemia raises the drug concentration compared to infusion alone, extends the retention of the chemotherapeutic agent and reduces systemic toxicity. Palliatively, TACE is performed to control symptoms and prolong survival in HCC patients; in some indications TACE allows a local tumor control of 18–63%. For combined indications, excellent results were achieved by combined therapies, such as percutaneous ethanol injection (PEI)/TACE, radiofrequency ablation (RF)/TACE, and laser-induced thermotherapy (LITT)/TACE. As a neoadjuvant therapy prior to liver resection TACE showed 70% tumor control. Though debatable, TACE still plays a role as a bridging tool before liver transplantation. Symptomatic indication of TACE in ruptured HCC showed 83–100% control of bleeding but survival was poor. Thus, TACE represents an important therapeutic tool against HCC in general in addition to its special role in cases of unresectable HCC.

Contents

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1. Introduction

Recently published data indicate that the incidence and mortality rate of HCC have been increasing in North America and Europe [1]. Although there are several treatment options for patients with HCC, the long-term prognosis is generally poor. Surgical resection is usually the standard treatment modality. However, resection can only be performed in a minority of patients due to the presence of multifocal tumors or limited hepatic reserve at the time of diagnosis. Liver transplantation is another treatment option especially for patients with decompensated cirrhosis, but potential recipients outnumber donors by far. For patients with unresectable diseases, the goal of palliative treatment is to control symptoms, improve life quality and prolong survival. Data from several recently published studies are more encouraging and suggesting that TACE is superior to conservative treatment for HCC patients [2,3]. The efficacy of TACE for HCC has also been validated in a recent meta-analysis which re-examined the results of previous studies using stricter criteria [4]. These data indicate that a better outcome can be expected in properly selected patients with TACE as a palliative treatment for inoperable HCC. The goal of this review is to provide an overview on the role of TACE and its indication as a palliative, combined, neoadjuvant, bridging, or symptomatic treatment option in patients with hepatocellular carcinoma.

2. Principle of transarterial chemoembolization

In contrast to the normal liver which has dual blood supply, hepatocellular carcinoma is supplied almost exclusively by arterial supply. This provides the rationale for therapeutic local chemotherapy and hepatic artery obstruction of intermediate stage tumors via trans-catheter arterial embolization (TAE) and TACE [5]. In TACE, a solution of chemotherapy (frequently Doxorubicin or Cisplatin) suspended in lipiodol, an oily contrast medium selectively retained within the tumor, is injected into the feeding hepatic arteries directly supplying the tumor [5]. The aim of combining chemotherapeutic drugs with embolic material is to cause ischemia and to extend contact of the chemotherapeutic agent with the tumor. Such mixtures can drastically increase the local concentration of the chemotherapeutic agent. This is followed by the obstruction of the feeding arteries with an embolizing agent. The technique is tailored according to the number and location of lesions, especially in patients with the presence of multiple feeders.

3. Patient selection

According to the guidelines published by the American Association for Study of Liver Diseases (AASLD) [6] and the European Association for the Study of the Liver (EASL) [7] TACE is recommended as first-line non-curative therapy for non-surgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread (level I). According to the Japanese Guidelines published in 2007 [8], hepatectomy or hepatic artery embolization is recommended if there are 2 or 3 tumors of $\leq$3 cm in diameter, if there are more than 4 tumors, transarterial chemoembolization or hepatic arterial infusion chemotherapy is recommended.

Exclusion criteria in most trials were: advanced liver disease (Child–Pugh C), active gastrointestinal bleeding, encephalopathy, refractory ascites, presence of vascular invasion or portal vein occlusion due to liver tumor, extrahepatic metastases, portosystemic shunt, hepatofugal blood flow, any contraindication to an arterial procedure (impaired clotting tests and renal failure), WHO performance stages 3 or 4, and end-stage tumorous disease (Okuda III). However, some of these exclusion criteria should not be regarded as absolute contraindications to TACE; Kothary et al. [9] performed 65 high-risk procedures on 52 patients and showed a 30-day mortality rate of 7.7% and a procedure-related morbidity rate of 10.8%. They concluded that TACE in patients considered at high risk does not necessarily incur a higher incidence of morbidity or mortality. Patient selection should be based on the extent of the disease, and these tumors should be treated selectively at a segmental level if possible.

4. Procedure and drugs

The arterial system is accessed using the Seldinger technique and a catheter is advanced in the aorta. First selective celiac trunk and superior mesenteric arteriography should be performed with late-phase imaging of the portal venous anatomy. This step serves the following: (1) determines the arterial supply to the tumor, (2) detects possible variations in hepatic arterial supply, (3) identifies the arteries that should be avoided during treatment delivery, e.g. right gastric and supraduodenal arteries, (4) determines the patency of the portal vein or the presence of hepatopetal flow through collaterals to the liver in case of portal vein tumor thrombosis. Once the arterial anatomy is clearly understood, a catheter is advanced superselectively into the right or left hepatic artery, depending on which lobe contains the greatest tumor volume. A 4F hydrophilic cobra catheter used with a hydrophilic guide-wire suffices for about half of cases. Use of a standard lumen catheter allows rapid injection of the viscous chemoembolic emulsion and is unlikely to clog with particles. However, the catheter should not be used in vessels less than twice its diameter, as the catheter will cause a partial occlusion of the vessel lumen, resulting in pseudo-stasis. Withdrawal of the catheter then results in reflow to the tumor. Small vessels and branches which cannot be accessed with a standard angiographic catheter can be catheterized with a variety of microcatheters designed for hepatic chemoembolization. These catheters differ from standard microcatheters in that they have a slightly larger inner lumen and shorter overall length, which makes the injection of viscous chemoembolic emulsions easier. There are many microcatheter choices designed for this purpose these include the Cragg wire (Boston Scientific), the Turbo Tracker Infusion Catheter (Boston Scientific), and the Renegade Hi-Flo (Boston Scientific) microcatheters. Numerous wire choices are also available. These include the 0.018- or 0.025-in. glide wires, glide gold wire (Boston Scientific), Seeker 0.014 or Seeker 0.016 wire (Boston Scientific), and Headliner wire (Boston Scientific). The Cragg wire catheter is the only one that can accommodate a 0.025 in. guide wire. Microcatheters can be power-injected at 2.5–4.0 cm^3/s after lowering the pressure threshold on the injector to 300 psi. The choice of the catheter/Guide-wire combination is usually related to the interventionist preference. When the catheter

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is positioned for treatment, it is important to perform an arteriogram to confirm the anatomy before injecting any chemotherapy. This superselective injection may reveal findings not depicted in the celiac or superior mesenteric artery injection, such as cystic, right gastric or falciform arteries arising from the target hepatic artery, or guide-wire induced spasm in the target artery. The end point of the TACE procedure is visualization of the complete blockage of the tumor-feeding branch [10]. It is essential to check for extrahepatic collateral arterial supply to the HCC. The findings that suggest an external collateral artery (ExCA) supplying a tumor are a subcapsular location or exophytic tumor growth, a peripheral iodized oil retention defect within the tumor or a peripherally located portion of viable tumor on a follow-up CT scan. There are also findings like hypertrophied ExCAs around the tumor on CT scan, and the presence of a peripheral tumor-staining defect according to hepatic arteriography [11]. Due to a close contact between the liver and the diaphragm, the blood supply to the diaphragm can reach the liver by direct adherence. Thus, the right inferior phrenic artery is the most common collateral pathway [12]. Modification of TACE in patients with hepatic arteriovenous shunt (AV shunt) can be performed using balloon occlusion of the hepatic vein draining the shunt [13].

After the procedure, vigorous hydration, antiemetic therapy and optional antibiotics are continued. Narcotics, perchlorpromazine, and acetominophen are supplied for control of pain, nausea, and fever. The patient is discharged as soon as oral intake is adequate and parenteral narcotics are not required for pain control. After 3–4 weeks the patient returns for a second procedure directed at the other segment or lobe of the liver. Depending on the arterial anatomy, two to four procedures are required to treat the entire liver. Thereafter response is assessed by repeated imaging studies and tumor markers.

5. Chemotherapeutic and embolization agents

A recent systematic review of cohort and randomized studies described the commonly used anticancer agents [14]. The most common sole-agent anticancer drug was doxorubicin (36%), followed by cisplatin (31%), epirubicin (12%), mitoxantrone (8%), mitomycin C (8%), and SMANCS (5%). SMANCS is a chemical conjugate of a synthetic copolymer of styrene maleic acid (SMA) and a proteinaceous anticancer agent neocarcinostatin (NCS).

Lipiodol (iodized oil) (Guerbet/France) is an oily contrast medium which persists more selectively in tumor nodules for a few weeks up to some months when injected into the hepatic artery. It is used as a vehicle to carry and localize chemotherapeutic agents inside the tumor. Recent studies have tried to develop new formulations: a lipiodol–pirarubicin emulsion seems to be more effective and more stable in vitro than the classic doxorubicin-lipiodol [15]. A novel lipophilic platinum complex (SM-11355), which is a derivative of cisplatin developed for lipiodol suspension, has been shown in a phase-I clinical study to determine a lower plasma platinum concentration but a longer half-life, reflecting the sustained release properties of this formulation [16].

Hepatic artery obstruction is usually achieved by Gelfoam particles, but polyvinyl alcohol (PVA), starch microspheres, metallic coils and autologous blood clots have also been used [14]. Gelfoam is the most commonly used embolizing agent. This only occludes the artery temporarily [17] with recanalization taking place within 2 weeks. Autologous blood clot could be also used as an embolizing agent. It achieves the same temporary artery occlusion as gelatine sponge and, since the clot is lysed faster after embolization, there might be less chance of arterial thrombosis after several sessions of TACE [18]. Polyvinyl alcohol (PVA) particles can cause a permanent or semi-permanent arterial occlusion [17] and achieve more distal obstruction because of their smaller size (50–250 μm in diameter). A recent comparative nonrandomized study [19] by Brown et al. showed no difference in patient survival between TACE performed using gelatine sponge particles ($n = 41$) and TACE using PVA particles ($n = 40$). Embospheres (100–700 μm) were used in two recent studies [20,21] (4%). These are trisacryl gelatine microspheres able to penetrate deeper and to embolize smaller and more peripheral vessels than PVA particles; these characteristics are related to their lack of aggregation, their smooth and hydrophilic surface, and their deformability, all of which result in a lower rate of catheter occlusion and more distal penetration into the small vessels [20].

Drug-eluting beads (DEB) are a novel system consisting of PVA beads (500–700 μm) that are specifically designed to release chemotherapy at a slow rate. In a recent study TACE performed using DEB loaded with doxorubicin has been shown to modify the pharmacokinetics of the injected chemotherapy, thus reducing the drug-related side effects, while maintaining the same therapeutic efficacy as TACE [22].

6. Palliative indications

As systemic therapies did not show any survival benefit [21] the attention has been focused on locoregional approaches for palliative indication in HCC in recent years (Fig. 1). Although TACE is widely used in the palliative treatment of unresectable HCC, its role remains controversial (Table 1). O'Suilleabhain et al. [23] evaluated the long-term survival of TACE in patients with unresectable HCC and suggested that a cure for unresectable HCC may be possible with TACE, although this is rare. They identified twenty-five 5-year survivors (8%) (8 of which had tumors more than 10 cm in diameter) among a cohort of 320 patients treated with TACE for inoperable HCC. Hashimoto et al. [24] have also reported 4 patients with advanced HCC and portal vein branch involvement who survived for more than 5 years. Taniguchi et al. [25] showed a long-term survival and marked TACE-induced tumor necrosis in patients with unresectable HCC. A recent report on randomized controlled trial showed that TACE with doxorubicin and gelatine sponge offered survival benefits to patients with unresectable HCC compared with conservative management. In a large scale study of 8510 patients who underwent TACE, the median and 1-, 3-, 5-, and 7-year survival rates were 34 months, 82%, 47%, 26%, and 16%, respectively. Multivariate analyses revealed the following 5 variables to be independent predictors of patient prognosis: degree of liver damage, maximum tumor size, number of lesion(s), portal vein invasion, and AFP value [26]. Portal vein invasion showed much higher risks than the other 4 variables. Thus, patients with unresectable HCC should be offered TACE as a palliative treatment, provided that the treatment regimen is tolerated and the patients are carefully selected, as there is a small but definite possibility of long-term survival [24].

Use of a repetition policy tailored to tumor response and a technique of selective segmental chemoembolization has recently led to a significantly improved survival benefit with TACE compared with conservative treatment for inoperable HCC in a prospective randomized trial [27].

7. Combined TACE with other interventional treatments

TACE combined with other local therapeutic options such as percutaneous ethanol injection (PEI), radiofrequency (RFA) or laser ablation (LITT) increases the effectiveness of the treatment, in addition better results were reported with the combination treatment than with either of these therapies alone [28,29] (Table 2). Fig. 2 is an example of TACE combined with laser thermal ablation. Evidence-based practice (EBP) techniques were used to establish

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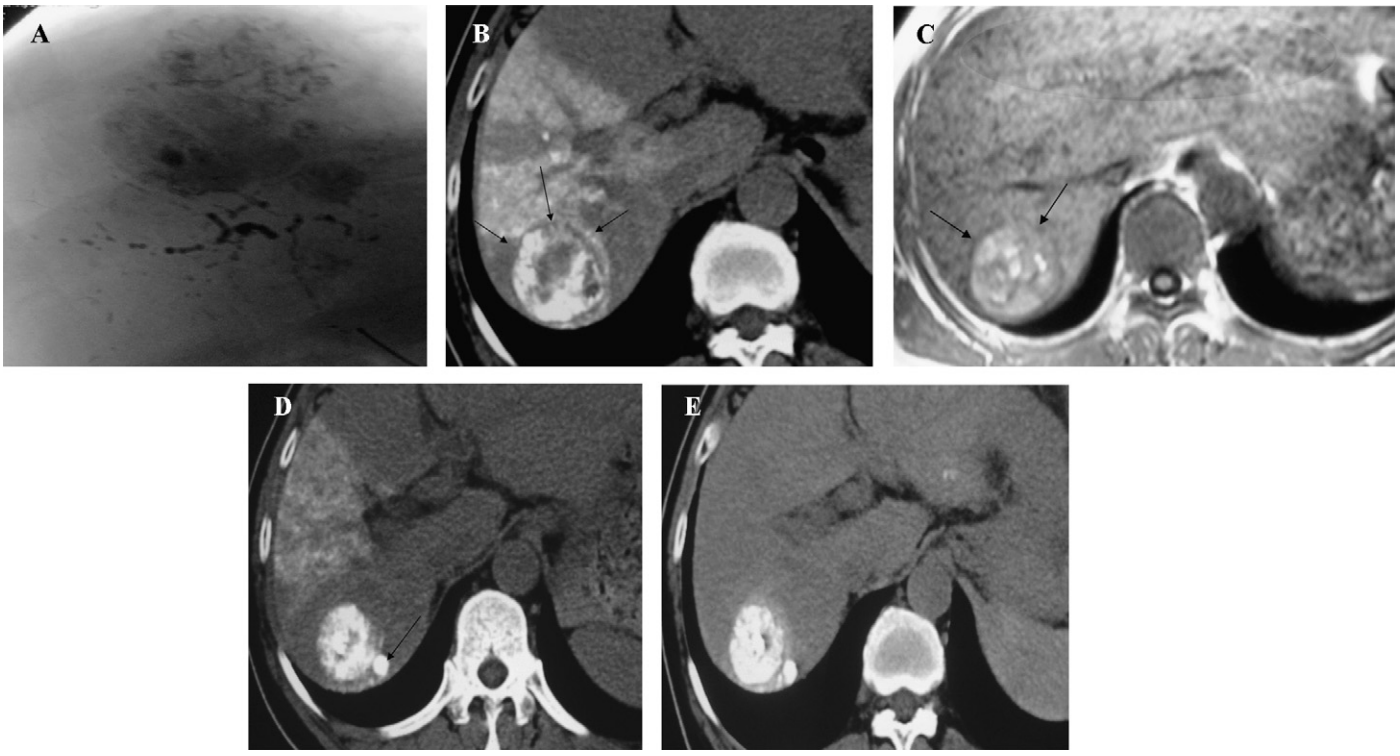

Fig. 1. A 57-year-old female patient with multicentric HCC in segments 5, 6, 7, and 8 (only two lesions are seen in segment 7). Palliative indication for TACE. (A) Post-TACE angiographic image showing a high degree of lipiodol uptake by the target tumor which appears well circumscribed. Note also multiple satellite HCC nodules. (B) CT post-TACE with inhomogeneous lipiodol uptake of tumor (arrows) and satellites as well as cirrhotic liver parenchyma. TACE sessions were performed in 4-week intervals. (C) Axial T1 MRI of the liver post-TACE shows partial lipiodol uptake in the tumor (arrows) resulting in an increased signal intensity. (D) Unenhanced MDCT after second course of TACE shows tumor shrinkage, a more homogeneous uptake and a better demarcartion of a satellite (arrow). (E) Unenhanced MSCT 1 year after 3rd cycle of TACE with persistent homogeneous lipiodol concentration of tumor and satellite.

Table 1
Studies on TACE as a palliative treatment of HCC

	No. of patients	Staging (*n*) Ok: I/II/III Ch: A/B/C	Anticancer	1-Year survival (%)	2-Year survival (%)	3-Year survival (%)	5-Year survival (%)
Huang et al. [74]	26	Ch: 23/8	Adriamycin	42		13	7
Llovet et al. [4]	112	Ok: 65/35/0	Doxorubicin	96	77	47	
O'Suilleabhain et al. [23]	320	Ch: 260/56/4	Cisplatin	31		11	8
Lo et al. [73]	79	Ok: 37/42/0	Cisplatin	57	31	26	
Ernst et al. [75]	160	Ok: 72/88		I: 58, 89 II: 19, 48	28, 68 0, 31	11, 39 0, 15	
Lee et al. [76]	31		Adriamycin	–	–	–	
Pelletier et al. [77]	42	Ok: 26/52/22	Doxorubicin	24			
Group d'etude et de traitment du carcinome hepatocellulare [78]	96	Ok: 90/10/0	Cisplatin	62	38		

Note: Especially the studies with a high patient inclusion. Child–Pugh classification (Ch). Okuda stage (Ok).

which patients with inoperable HCC will survive longer when they are treated with TACE alone; the results indicate that only those who meet the inclusion criteria used in two randomized controlled trials (RCTs) published in 2002 should receive this treatment [30]. These criteria include patients with diagnoses of unresectable hepatocellular carcinoma based on histology, cytology, or persistently elevated serum alphafetoprotein levels more than 400 ng/mL with typical imaging findings [27]. There was no evidence to support the use of TACE alone in patients with inoperable HCC. The results of this evidence-based evaluation suggest that TACE alone

Table 2
Studies on neoadjuvant TACE combined with other minimal-invasive methods of treatment of HCC

	No. of patients	Combined modalities	Staging Ch: A/B/C; Ok: I/II/III	1-Year survival (%)	2-Year survival (%)	3-Year survival (%)	5-Year survival (%)
Yamakado et al. [34]	64	TACE + RF	Ch: 12/59/2	98			
Pacella et al. [39]	45	TACE + LITT	Ch: 20/10/0	92	68	40	
Koda et al. [32]	26	TACE + PEI	Ch: 19/5/0	100		80	40
Tanaka et al. [79]	83	TACE + PEI	Ch: 48/35/0			68	35

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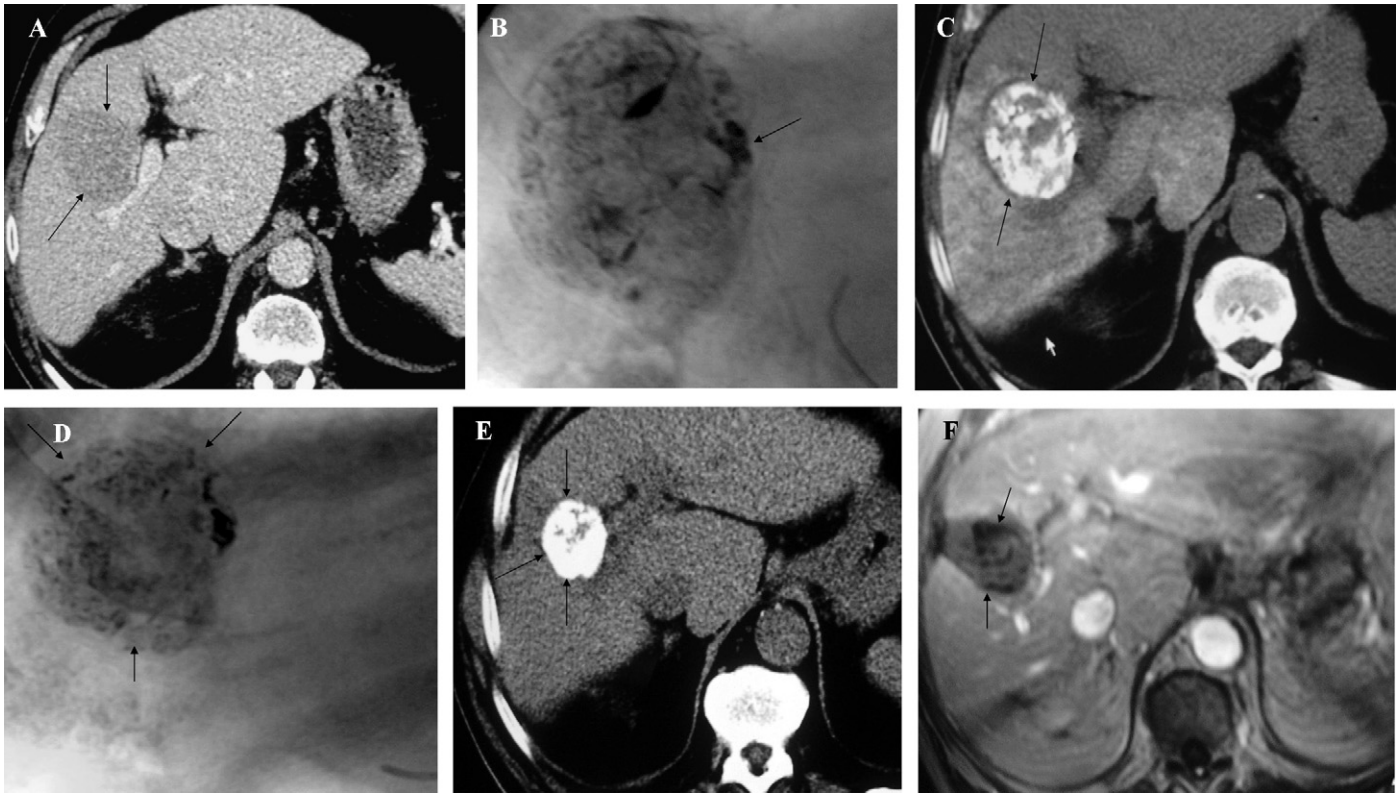

Fig. 2. A 74-year-old male patient with oligonodular HCC in segments 5 and 6. (A) MDCT shows a well-defined rounded hypodense mass with unsharp delineation. HCC: neoadjuvant indication. (B) Post-TACE angiographic image. Note the peripherally dominant lipiodol uptake with filling up of geographic spaces (arrow). (C) Post-TACE MDCT showing good lipiodol uptake of the tumor (black arrows) with low uptake in the central area. (D) Post-TACE angiography after 2nd TACE cycle shows a more central lipiodol distribution and homogeneous inner structure (arrows). (E) MDCT 5 weeks after the 3rd TACE cycle with a nearly homogeneous lipiodol distribution intratumorally (arrows). (F) Contrast-enhanced MRI: Gradient-echo-sequence TR/TE = 30/17, Gd-DTPA 24 h post-thermal ablation with MR-guided LITT. Note the sharp demarcation of the thermal necrosis (arrows) with a slightly hyperintense surrounding margin.

can no longer be regarded as the best therapy for inoperable HCC.

7.1. Combined TACE and PEI

The combination of TACE and repeated PEI has shown superior results compared to PEI or TACE alone [31,32]. Koda et al. [32] showed superior survival after 1, 3, and 5 years (100%, 80%, and 40%) for patients after combination treatment (vs. PEI alone), and Kamada et al. [31] recorded 1-, 3-, and 5-year survival rates of 90%, 65%, and 50% after combination treatment.

A recent study showed that the overall observed 1- and 3-year survival of 101 patients was 72% and 47%, respectively. Kaplan–Meier analyses revealed a 1-, 3-, and 5-year survival probability of 90%, 52%, and 43% after initial treatment with TACE followed by PEI and of 65%, 50%, and 37% after PEI alone [33].

7.2. Combined TACE and RFA

Radiofrequency ablation is designed to destroy tumors by heating tissue to temperatures exceeding 60 °C. Blockage of the hepatic artery increases the size of the area of thermal ablation by eliminating convection by blood flow and decreasing impedance in the tumor [28]. Tissues with low impedances tend to exhibit large areas of coagulation necrosis. Yamakado et al. [34] have shown that chemoembolization followed by RF ablation is a useful therapeutic method in controlling nodular HCC lesions not only for lesions ≤3 cm in size but also for lesions >3 cm. However, for nodular HCC lesions ≤3 cm, good treatment results have been reported with the use of RF ablation alone [35]. Considering that chemoembolization is associated with increased cost and patient discomfort, it may be reasonable to restrict combined use of chemoembolization to nonnodular HCC lesions if tumors are ≤3 cm. Combined use of chemoembolization, conversely, may be useful to prevent neoplastic seeding when tumors are in the subcapsular regions even when lesion size is ≤3 cm because seeding frequently occurs in subcapsular HCCs as a result of tumor bleeding caused by puncture [35]. Theoretically, chemoembolization seems to decrease the risk of neoplastic seeding. Regarding the effect of combined TACE and RF therapy concerning the quality of life (QOL) a recent trial concluded that the TACE/RFA group had significantly higher QOL scores than the TACE group [36] alone.

7.3. Combined TACE and LITT

Repeated sessions of TACE can be used with the aim of downsizing the tumor thus reaching a tumor size that can be ablated with LITT. Zangos et al. [37] performed repeated TACE (mean, 3.5 treatments per patient) in 48 patients, to reach a favorable size for LITT (the largest lesion was between 50 and 80 mm in diameter, and there were no more than five lesions). After the diameter of the tumors had decreased to less than 50 mm, the patients were treated with MR-guided LITT 4–6 weeks after embolization. Repeated TACE reduced the tumor size in 32 patients (66.7%), forming the basis for performing MR-guided LITT procedures. They concluded that TACE appears to be an effective treatment of large-sized HCC, which extends the indication for MR-guided LITT. The same combination was used by Vogl et al. [38] who showed that TACE can be used as

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a downsizing tool before LITT. Whereas Vogl et al. and Zangos et al. used TACE as a downsizing tool before LITT, Pacella et al. [39] performed LITT before TACE in thirty large HCCs of 3.5–9.6 cm in diameter (mean diameter, 5.2 cm). After combined treatment, complete response was achieved in 27 (90%) of the 30 large HCCs. Partial response was obtained in the remaining three (10%) tumors. Their rationale for combining two techniques is based on the fact that LITT reduces the volume of viable tissue and brings the lesion back within the range of TACE effectiveness.

7.4. Combined TACE and 3DCRT

The combined effect of TACE and 3D Conformal Radiotherapy (3DCRT) reduces or delays the tendency of multifocality of the HCC; results in a well-delineated tumor margin which facilitates the RT planning by checking the tumor coverage and observation of the patient set up error; and detects the intrahepatic spread of HCC. These rationales of combined TACE and RT are due to the effect of deposited iodised oil in the hepatic lesions [40]. The overall survival rates at 1, 2 and 3 years were 60%, 38% and 28%, respectively, with a median survival period of 17 months. Irradiation dose, T stage and hepatic cirrhosis were identified as independent predictors for overall survival by Cox proportional regression analysis. The 1-, 2-, and 3-year local progression-free rates were 74%, 57% and 38%, and the 1-, 2-, and 3-year distant metastases rates were 15%, 21% and 40%, respectively. Cheng treated HCC by RT with or without TACE, and obtained promising results for 2-year survival (41%) and for median survival time (19 months) [41].

8. Neoadjuvant indications

A possible survival advantage has also been reported in patients treated with TACE before resection of HCC when compared with resection alone [42]. TACE after radical excision of hepatoma can efficiently destroy remnant cancer cells, decrease recurrence, and increase survival rate [43]. However, it was reported that TACE can damage hepatic and immunologic function, thus decreasing the survival rate [44].

8.1. Preoperative TACE

Zhang et al. [45] retrospectively analyzed the therapeutic results of 1457 HCC patients treated with hepatectomy 120 of whom had received TACE before hepatectomy. They showed that the 5-year disease-free survival rates of the patients who received more than 2 sessions of TACE, those who received one session of TACE, and no TACE patients were 51.0%, 35.5%, and 21.4%, respectively, and that the mean disease-free survival times of the three groups were 66.4, 22.5 and 12.5 months, respectively. They concluded that effective preoperative TACE may be one of the best methods, which can be clinically performed at present, for resectable HCCs including small HCCs for improving disease-free survival after hepatectomy. On the other hand Choi et al. [46] studied 273 patients who underwent curative resection for HCC; 120 of them underwent preoperative TACE. The 1-, 3-, and 5-year disease-free survival rates were 76.0%, 57.7%, and 51.3%, respectively, in the TACE group and 70.9%, 53.8%, and 46.8%, respectively, in the non-TACE group. Although a difference was noted between the TACE and non-TACE groups it was not significant.

8.2. Postoperative TACE

Xi et al. [47] studied 823 patients with hepatocellular carcinoma who underwent curative liver resection and 126 patients (15.3%) received TACE post-operation. They showed that postoperative TACE had not decreased the recurrence rate in patients with a tumor diameter less than 3 cm, while TACE increased the disease-free survival for patients with tumor diameter of 3–10 cm, positive in alphafetoprotein (AFP), presented vascular invasion or patients with tumor diameter larger than 10 cm, positive in AFP, multinodular, presented vascular invasion, resection margin less than 1 cm. In patients with HCC combined with portal vein tumor thrombus, postoperative TACE improved the survival and reduced tumor recurrence. Fan et al. [48] investigated postoperative chemotherapy for patients with HCC complicated by portal vein tumor thrombosis (PVTT). Hepatic resection combined with thrombectomy was performed in 179 patients with HCC and PVTT. The survival rates at 6 months, 1, 2, and 3 years after surgical resection with postoperative chemotherapy (TACE and/or PVC) were 55.8%, 39.3%, 30.4%, and 15.6%, respectively, which were significantly higher than those of the other group without adjuvant chemotherapy.

Li et al. [49] described the results of their recent comparative study of patients who underwent surgery with and without TACE and PVC. The 1–3, and 5-year disease-free survival rates in Group A (resection only, $n = 37$) were 50.7, 17.8, and 0%, respectively; in Group B (resection + TACE, $n = 35$) they were 62.3, 23.7, and 4.0%, respectively, and in Group C (resection + TACE + PVC, $n = 40$) increased to 74.4, 46.1, and 11.5%, respectively.

9. Bridging indications

Liver transplantation is the only curative method for HCC (Table 3). The rationale for using TACE as a bridging therapy (Fig. 3) prior to orthotopic liver transplantation (OLT) is two-fold: to control tumor growth while the patient awaits an organ and to cause significant tumor necrosis, which may reduce tumor dissemination during surgery. In addition, some have argued that TACE may achieve tumor downstaging in patients with advanced HCC, allowing to safely expand the current criteria for OLT in patients with HCC. TACE is also sometimes used to gain time and learn more about the natural history of a particular tumor prior to OLT [50]. Pérez Saborido et al. [51] studied 46 patients undergoing LT for HCC, 18 of whom received one session of pretransplant TACE (Group A) and 28 had no pretransplant TACE (Group B). The recurrence rate in Group A was 16% and in Group B 36% ($p = 0.16$). In group A patients, mean survival was 89.3 ± 21.7 months with 1-, 3-, and 5-year survival rates of 83.3%, 60.5%, and 60.5%, respectively. In group B patients, mean survival was 75.1 ± 19.1 months with 1-, 3-, and 5-year survival rates of 77.2%, 58.7%, and 38.1%, respectively. The differences in mean survival were not statistically significant ($p = 0.56$). Similarly in their case–control study Decaens et al. [52] included 100 patients who received TACE before LT and 100 control patients who

Table 3
Results of liver transplantation for hepatocellular carcinoma in the last 6 years

	Year	No. of patients	Recurrence rate (%)	5-Year disease-free survival (%)	5-Year survival (%)
Foxton et al. [80]	2004	146	19	72	66
De Carlis et al. [81]	2003	121		86	61
Margarit et al. [82]	2002	103	15		58
Figueras et al. [83]	2001	307	21	58	63

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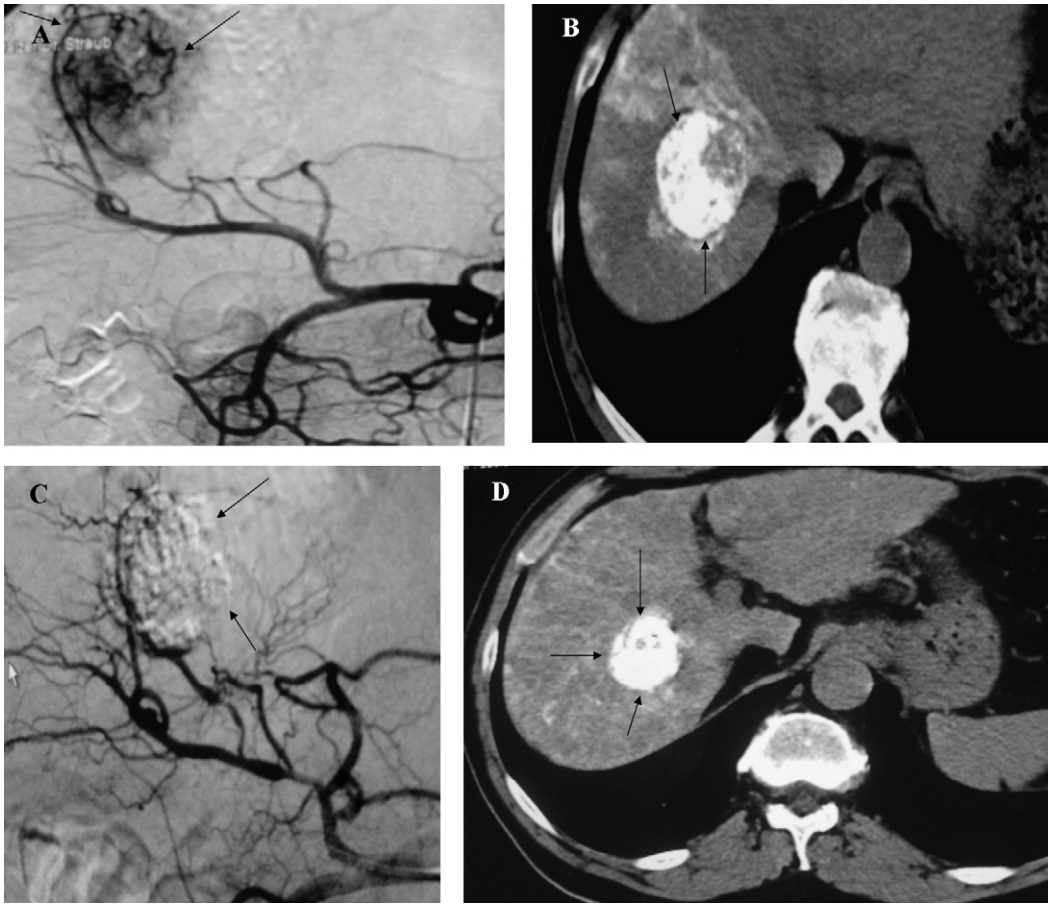

Fig. 3. A 57-year-old male patient with nodular HCC in segments 5, 6, and 7. Bridging indication for TACE pre-liver transplantation. (A) Angiographic evaluation with a tumor blush and verification of a large lateral and smaller medial tumor-feeding artery (arrows). (B) MDCT post-1st TACE cycle with a tumorous uptake (arrows) and a focal area with low uptake. (C) Angiographic evaluation post-3rd cycle of TACE. Note some vascular spasms in the medial supplying arteries (arrows). (D) MDCT post-3rd TACE with now homogeneous lipiodol distribution. 8 weeks post-TACE a liver transplantation was performed, verifying total tumor necrosis without vital parts (arrows).

did not receive TACE. Overall 5-year survival was 59.4% with TACE and 59.3% without TACE. They concluded that with a mean waiting period of 4.2 months and 1 TACE procedure, pre-LT TACE does not influence post-LT overall survival and disease-free survival. Even studies which showed survival difference between the TACE and non-TACE groups denied the role of TACE on improving survival as what was reported by Stockland et al. [53] who reported survival at 1, 3, and 5 years to be 91%, 80%, and 72% in the patients in whom TACE was performed on elective basis, 79%, 58%, and 39% in the patients in whom TACE was performed on urgent basis, and 69%, 61%, and 41% in the non-TACE group, respectively, and they concluded that despite this difference, the decreased survival in the urgent TACE and non-TACE groups was due to non-cancer-related deaths. Although there was no sufficient evidence to support the concept that TACE prior to OLT can improve long-term survival other studies still emphasize its role in preventing tumor progression during the waiting time for transplantation. Graziadei et al. [54] included 48 OLT-eligible patients in his study (41 had already received OLT and 7 were still waiting). The 41 patients who underwent transplantation had an average of 2.5 ± 1.6 sessions of TACE and spent 178 ± 105 days on the waiting list before OLT, while the 7 patients who were still on the waiting list, had a mean period of 173 ± 70 days without any evidence of tumor progression. None of the patients meeting the selection criteria had tumor progression. As a downstaging tool in his study Graziadei et al. [54] also included 15 advanced HCC patients not eligible for transplantation who received 5.1 ± 2.7 cycles of TACE (range, 2–12). 3 patients were removed due to tumor progression. 11 showed a partial response of >50% necrosis and 1 < 50%. 10 patients underwent OLT and showed 30% HCC recurrence rate. Thus, despite successful downstaging before OLT, patients with primarily advanced HCC had a significantly less favorable outcome in the intent-to-treat analysis as well as in the posttransplantation survival compared with patients with early-stage HCC (31% vs. 94% at 5 years, $p < 0.001$ and 41% vs. 94% at 5 years, $p < 0.001$). Other studies tried to use the response to TACE as selection criteria for OLT thus introducing a biological selection criterion as suggested by Otto et al. [55] who concluded that the sustained response to TACE is a better selection criterion for LT than the initial assessment of tumor size or number. In spite of all this debate it is still not acceptable for most medical teams not to offer some form of tumor treatment to patients with HCC on the waiting list, and TACE represents the most acceptable bridging tool in this context especially as it does not expose liver transplant recipient to additional risk at surgery [50] (Tables 4 and 5).

10. Symptomatic indications

Ruptured HCC following TACE is a rare but serious complication. Large tumor size, male sex, and exophytic growth of tumor may be predisposing factors for rupture [56], although a prospective randomized study to validate its efficacy is impossible. Liu et al. [57] described 42 patients who had received TAE for treatment of rup-

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Table 4
Randomized controlled studies in arterial embolization/chemoembolization versus conservative management

	No. of patients	Staging Okuda: I/II/III	Drugs used	Tumor response (%)	1-Year survival (%)	2-Year survival (%)
Llovet et al. [72]	112; 40 (TACE)	65/35/0	Gelfoam + Doxorubicin	35	82	63
Lo et al. [73]	79; 40 (TACE)	47/53/0	Gelfoam + Cisplatin	27	57	31
Pelletier et al. [84]	73; 37 (TACE)	60/40/0	Gelfoam + Cisplatin + Tamoxifen	24	51	24
Bruix et al. [85]	80; 40 (TAE)	67/23/0	Gelfoam + Coil	55	70	49
Group d'etude et de Traitment du Carcinome Hepatocellulaire [78]	96; 50 (TACE)	90/10/0	Gelfoam + Cisplatin	16	62	38

Table 5
Preoperative TACE as a bridge to transplantation or resection

	No. of patients	Staging (n) Ok: I/II/III; Ch: A/B/C	Recurrence	1-Year survival (%)	2-Year survival (%)	3-Year survival (%)	5-Year survival (%)
Decaens et al. [52]	100	Ch: 62/37/10	13%				59
Graziadei et al. [54]	41	Ch: 24/23/1	$N = 1$	98	98		93
Venook et al. [86]	13		No recurrence			76	
Perez et al. [87]	18			83	60	60	
Oldhafer et al. [88]	21			60		48	

tured HCC. 35 (83%) of them had successful hemostasis. However, due to hypovolemic shock caused by ruptured tumor as well as the ischemic effect on the cirrhotic liver, liver failure after TAE was a significant complication and was frequently the cause of mortality. Ten (29%) of the 35 patients who had successful hemostasis after TAE in the present series died of liver failure within 1 month. The survival rate was not different from that of the 466 patients with no history of rupture who received TACE as the primary definitive treatment of HCC during the same study period. In patients who underwent hepatic resection, more widespread metastases could be expected in the rupture group compared with the patients without complication.

11. Complications and management

The main complication of TACE is the postembolization syndrome (PES). PES is characterized by nausea, vomiting, abdominal pain, and fever, occurring in 2–7% of patients after the procedure [58]. The etiology of PES is not fully understood but it is thought to be caused by a combination of tissue ischemia and an inflammatory response to chemoembolization. Although PES is a self-limited event that can be managed supportively, it remains the major impact on the need for and length of postprocedural hospitalization. Embolization of the viscerally innervated gallbladder, which lacks a dual blood supply from the portal vein, is associated with right upper quadrant pain [59]. A similar study found no difference in the severity of PES in patients who received embolization combined with chemotherapeutic agents compared with those who received embolization alone [60]. A large embolized volume and a low percentage of tumor volume would be associated with an increased risk of PES because of the larger amount of normal liver being embolized. Previous embolization was found to be associated with a reduced risk of PES. This may, in part, be an effect of the trend towards a decreased chemoembolic dose required when treating a previously embolized region. The most serious complication of TACE is hepatic insufficiency. Chan et al. [61], identified the factors that appear to predispose patients to the development of irreversible acute hepatic decompensation after TACE, namely a high dosage of cisplatin (9.5 ± 5.9 mg), high basal levels of bilirubin (23 μmol/L (range, 5–45 μmol/L), prolonged prothrombin time (14 ± 2.1 s), and advanced cirrhosis. Pretreatment liver function and the stage of cirrhosis have always been the main considerations for patients receiving TACE. They stated that 20% of the patients involved in their study developed acute hepatic decompensation after TACE. However, in the majority of patients, the liver function returned to its pretreatment level before the next course of TACE was initiated. Only a minority of patients eventually developed irreversible liver failure. A rare complication of TACE is cerebral lipiodol embolism. 5 cases of cerebral lipiodol embolism have been reported. An intracardiac right-to-left shunt via a patent oval foramen or intrapulmonary AV shunt can lead to cerebral lipiodol embolism [62]. In the presence of AV shunt there is a potential risk of pulmonary embolism or infarction because the iodized oil can pass through the shunt. The incidence of pulmonary oil embolization increases to 43% when a large amount of iodized oil is used for TACE [63]. Furthermore, when the AV shunt or the inferior phrenic artery to pulmonary artery shunt are present, the incidence of serious complications such as respiratory arrest, massive atelectasis, and hydropneumothorax caused by the tissue toxicity from doxorubicin and oil embolism is increased up to 33% [63].

12. TACE and tumor recurrence

Lee et al. [64] suggested that the overall cumulative recurrence rate of HCC patients with initial remission following TACE was 23% after 1 year, 55% after 2 years and 67% after 3 years in their series. These data are quite similar to the results reported by Yoshikawa et al. [65]. Both studies also showed that patients with multinodular HCC had a recurrence more frequently than those with single nodular type of tumors. The recurrence rate of patients with portal vein thrombosis appeared to be very high even though they had been in initial remission. It is not difficult to understand the increased chance of recurrence in patients with portal vein thrombosis because hematogenous seeding of cancer cells can precede initial remission by TACE in these patients. It is also possible that a certain type of HCC that is more unresponsive to the therapy can more easily spread and may have an increased tendency to recur following TACE.

Thus, closer surveillance and combined systemic treatment [66] should be considered in patients with multinodular HCC or portal vein thrombosis even if they were in remission radiologically after TACE. Patients with heterogeneous Lipiodol uptake on CT scan had higher tendency of recurrences during the follow-up period than those with homogeneous uptake.

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Table 6
Prognostic factors affecting the response to TACE

	Studies	No. of patient	Survival (years)	*p*-Value (Ikeda: UV/MV) (CLIP: UN)
Age (years)	Ikeda et al. [68]			
>60		90	3	0.47/0.02
<60		38	3.8	
Sex	Ikeda et al. [68]			
F		26	3.3	0.60/0.27
M		102	3.4	
HBV	Ikeda et al. [68]			
+		21	2.9	0.82/0.97
–		107	3.3	
HCV	Ikeda et al. [68]			
+		101	3.4	0.14/0.02
–		26	2.9	
Alcohol abuse	Ikeda et al. [68]			
+		30	3.8	1.10/0.57
Bilirubin (mg/dL)	Ikeda et al. [68]			
>2.0		7	2.7	0.81/0.63
<2.0		121	3.3	
Albumin (g/dL)	Ikeda et al. [68]			
>3.5		93	3.5	0.02/<0.01
<3.5		35	2.7	
GOT/ALT (IU/L)	Ikeda et al. [68]			
>82		44	3	0.41/0.19
<82		84	3.5	
GPT/AST (IU/L)	Ikeda et al. [68]			
>70		54	3.5	0.74/0.60
Lactic dehydrogenase (IU/L)	Ikeda et al. [68]			
>500		26	3	0.38/0.32
<500		102	3.3	
Cholinestrase (IU/L)	Ikeda et al. [68]			
>100		115	3.4	0.05/0.71
<100		11	2.5	
Alphafetoprotein	Ikeda et al. [68] (U/L)			
>400		26	1.4	<0.01/0.02
<400		101	3.5	
<10	CLIP [89] (ng/dL)	129		<0.0001
11–400		193		
>400		100		
Prior hepatectomy	Ikeda et al. [68]			
+		62	3.8	0.12/0.71
–		66	2.8	
Tumor no.	Ikeda et al. [68]			
Multi		90	3	0.76/0.17
Single		38	3.8	
Tumor distribution	Ikeda et al. [68]			
Bilobe		55	2.9	0.01
Unilobe		73	3.8	
<50%	CLIP [89]	331		<0.0001
>50%		89		
Tumor size	Ikeda et al. [68]			
>25%		18	1.0	0.78/0.16
<25%		110	3.5	
Tumor type	CLIP [89]			<0.0001
Uninodular		204		
Multinodular		181		
Massive		42		
Child A/B/C	CLIP [89]			<0.0001
A		166		
B		192		
C		69		
Okuda I/II/III	CLIP [89]			<0.0001
I		161		
II		175		
III		46		

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Table 6 (*Continued*)

	Studies	No. of patient	Survival (years)	*p*-Value (Ikeda: UV/MV) (CLIP: UN)
PV Thrombosis	Ikeda et al. [68]			
Yes		4	0.8	0.52/0.10
No		124	3.3	
Yes	CLIP [89]	46		<0.0001
No		361		
Distant metastases	CLIP [89]			0.03
No		421		
Yes		14		
Systemic treatment	CLIP [89]			0.89
No		348		
Yes		80		
Anticancer agents	Ikeda et al. [68]			
MMC + ADR		17	2.9	0.54/0.59–/0.52
SMANCS		24	3.5	
ADR		87	3.5	
Locoregional treatment	CLIP [89]			<0.0001
No		182		
Yes		247		
TACE		75		
Surgery		12		
PEI		138		
>1		22		

UV: Univariate analysis, MV: Multivariate analysis, CLIP: Cancer of Liver Italian Program. Ch: Child–Pugh classification, Ok: Okuda classification, MCC: Mitomycin, SMANCS: Zinostatin stimilamar, ADR: Doxorubicin, ALT: Alanin aminotransferase, AST: Aspartate aminotrasferase, GOT, Glutamic oxalacetic transaminase, GPT: Glutamic pyruvic transaminase.

13. Prognostic factors affecting TACE efficacy

The prognosis of HCC patients can be best assessed by taking tumor stage, liver function and physical status into account in the staging system. The impact of treatment should also be considered when estimating life expectancy. Currently, the Barcelona Clinic Liver Cancer (BCLC) staging system is the only staging system that accomplishes these aims (level II-2). The TNM system has been repeatedly modified and still does not have adequate prognostic accuracy. In addition, its use is limited because it is based on pathological findings, and liver function is not considered. The Okuda classification takes tumor size (imaging/surgery) and liver function into account. It allows the identification of end-stage disease, but it cannot adequately stratify patients with early or intermediate stage disease. The Child–Pugh system and the MELD score only consider liver function. Thus, they cannot be accurate. The main advantage of the BCLC staging system is that it links staging with treatment modalities and with an estimation of life expectancy that is based on published response rates to the various treatments. It identifies those with early HCC who may benefit from curative therapies, those at intermediate or advanced disease stage who may benefit from palliative treatments, and those at end stage with a very poor life expectancy.

Local recurrence rate was compared using 12 possible prognostic factors: patient age, hepatitis C infection, modified Child–Pugh classification, number of tumors, size of tumor nodule, serum alphafetoprotein level, serum albumin level, platelet count, homogeneity of iodized oil accumulation within the nodule, tumor location in segmental border zone, tumor location in subcapsular area, and contact of tumor with adjacent vessels [67]. Two important prognostic factors related to Lipiodol uptake and tumor location. A recent study showed that the local tumor recurrence rate was higher for the tumors showing inhomogeneous iodized oil uptake. Tumor location in a segmental border zone was proved to be another risk factor for local tumor recurrence after segmental TACE for HCC by both the univariate and multivariate analyses. Most of the recurrent tumors were supplied by feeders from the adjacent segmental arteries, and most of the originally occluded segmental arteries had not reopened, as was seen on the follow-up hepatic angiograms [67]. Ikeda et al. [68] found that HCVAb positivity was one of the factors that contributed to a better outcome. This was partly due to residual confounding, because HCVAb positivity was strongly associated with favourable tumor-related factors, such as smaller tumor size and tumor number (data not shown). Of tumor-related factors, serum AFP level was identified as significantly associated with shorter survival times in the multivariate analysis. These findings were compatible with previous reports [69]. Multivariate analyses revealed the following 5 variables to be independent predictor of patient prognosis: degree of liver damage, maximum tumor size, number of lesion(s), portal vein invasion, and AFP value. Portal vein invasion showed a much higher hazard ratio than the other 4 variables [70]. The staging system for the liver cirrhosis is a very important prognostic factor that influences survival in patients with HCC treated by TACE since the aim is to prolong survival while increasing the quality of life. The combined staging systems MELD and CLIP were identified as significant variables associated with survival [71].

The benefits of chemoembolization should not be offset by treatment-induced liver failure. Predictors of outcome are related to tumor burden (tumor size, vascular invasion, and AFP levels), liver functional impairment Child–Pugh, bilirubin, ascites), health status (constitutional syndrome, Karnofsky index, PST), and response to treatment [72,73] (Table 6).

14. Summary

Transarterial chemoembolization is the first line of treatment in inoperable hepatocellular carcinoma and should be tailored according to the individual patient's condition. It is useful in local tumor control, prevents tumor progression, prolongs patients' life and controls patient symptoms. TACE alone or combined with minimally invasive procedures is used as a neoadjuvant therapy or as a bridge to liver transplantation or resection. In the latter condition it prevents tumor progression and patient drop out from the wait-

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ing list of liver transplantation. Newly introduced medications like Sorafenib may provide new hope for HCC patients although their role in combination with TACE has not yet been investigated. Many complications for TACE are mostly controllable and can be reduced by strict selection of the candidates and application of the recommended inclusion and exclusion criteria as well as proper technique and follow-up. The effectiveness of TACE is to be estimated accordingly by plotting the treatment strategy linked to tumor staging and other prognostic factors affecting the impact of TACE on the survival rates.

Conflict of interest

None.

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