Chapter 6:

Transcatheter Arterial Chemoembolization and Transcatheter Arterial Embolization

● Introduction

CQs related to TACE have gradually evolved since the second edition (2009 version) of the Clinical Practice Guidelines for Hepatocellular Carcinoma. Seven CQs related to TACE were included in the second edition: CQ41. “Who are eligible for TACE/TAE?” CQ42. “What embolic agents are needed for TACE/TAE?” CQ43. “Which vessels should be (chemically) embolized in TACE/TAE?” CQ44. “Is it essential to inject an iodized oil (lipiodol) and emulsions containing anticancer drugs in TACE?” CQ45. “What anticancer drugs should be used to in Lipiodol emulsion (a mixture of Lipiodol and anticancer drugs)?” CQ46. “When should repeat TACE/TAE be scheduled?” and CQ47. “Is combining TACE/TAE with other treatment modalities effective?” Of these, CQ41 was used without any modification as CQ37 in the third edition (2013 version), whereas CQ42 through CQ45 were integrated to create CQ38. “What type of embolic material or anticancer agent should be used for TACE/TAE?” Also, CQ46 became CQ39. “How should repeat TACE/TAE be scheduled?” Lastly, CQ47. “Is it effective to combine TACE/TAE with other treatment modalities (RFA, surgery, and arterial infusion)?” was deleted from Chapter 5 and was incorporated into another treatment modality in a different chapter. A new CQ was created in the third edition and was designated CQ40. “What types of diagnostic imaging techniques are useful for evaluation of the treatment effects of TACE?”

Although the wording may differ slightly from that used in the third edition, the following 4 questions remain in use in the current fourth edition. CQ37. “Which patients are eligible for TACE or TAE?” CQ38. “What is the most appropriate method for selecting embolic agents and anticancer drugs for TACE or TAE?” CQ39. “What factors determine the timing of re-embolization?” and CQ40. “What imaging modalities are useful for assessing treatment response to TACE?” Also, 2 newly created CQs were designated CQ41. “Is it appropriate to combine embolization and molecular-targeted therapy?” and CQ42. “What are the clinical features of TACE failure?”

Although the content of CQ37 in the current edition is virtually the same as that in the third edition, what is new in CQ37 is the use of the internationally recognized BCLC staging system as a reference. CQ38 contains descriptions of DEB-TACE and miriplatin, which were not mentioned in the third edition due to insufficient data. The content of CQ39 is also virtually the same as that in the third edition, but “elevated tumor marker level” was excluded from the requirements for determining the timing of re-embolization. Again, the content of CQ40 is practically identical to that in the third edition, but it should be kept in mind that Gd-EOB-DTPA is one of the contrast agents used in the mandatory screening modality dynamic MRI. Newly established CQ41 and CQ42 explain how and when molecular-targeted therapy should be administered, which was not mentioned in the third edition.

In addition to scientific evidence, consensus among hepatologists and other specialists is reflected in the current version of the Guidelines. However, some treatment modalities and regimens

are not supported by sufficient evidence and consensus, such as those used for portal vein tumor thrombus, anticancer drugs used in TACE, combination therapy with TACE and molecular-targeted drugs, and the definition of TACE failure that informs the timing of when to initiate molecular-targeted therapy. Accordingly, in the current edition of the Guidelines, the recommendations for these remain weak, but it is expected that these issues will be resolved in the future as more data are accumulated from high-quality prospective studies.

CQ37 Which patients are eligible for TACE or TAE?

Recommendations

Strong recommendation: TACE or TAE is recommended for patients with BCLC stage B (intermediate stage; PS 0, Child-Pugh A/B, and 4 or more lesions) hypervascular HCCs that are inoperable and are not indications for percutaneous ablation.

Weak recommendation: TACE or TAE may be considered for patients with BCLC stage C (advanced stage) and inoperable hypervascular HCC accompanied by portal vein tumor thrombus.

■ Background

This CQ was established based on CQ37 in the third edition, with slightly modified wording. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 254 articles. This was narrowed down to 37 in the first screening based on the inclusion criteria of studies that discussed the indications for TACE/TAE. The 37 articles were further narrowed down to 6 in the second screening to extract studies with high-quality evidence. Ten articles with high-quality evidence were similarly extracted from 21 articles used in the third edition, and thus 16 articles are cited here.

Together with surgery and RFA, TACE/TAE is a valid treatment option. In principle, lesions with hyperintense signals on hepatic arteriographic images are indications for TACE/TAE, such as tumors (i.e., lesions that appear like classic HCCs [moderately and poorly differentiated HCC]) or a concentration of early-stage HCCs. However, treatment should be selected based on staging, which includes tumor factors as well as patient factors. Here, the selection criteria for TACE/TAE in current clinical practice are discussed.

■ Scientific Statement

In general, HCCs that are indications for TACE or TAE are classic HCCs (moderately and poorly differentiated HCC) or a focus of early-stage HCCs, and they display as hyperintense signals on hepatic arteriographic images[1-3]. According to the BCLC staging system, which is commonly used

overseas, stage B HCC (intermediate stage; PS 0, Child-Pugh A/B, and 4 or more lesions) is an indication for TACE/TAE[4]. In the third edition of the Guidelines, indications for TACE/TAE included the presence of 2-3 HCCs > 3 cm or multiple HCCs (4 or more lesions, regardless of size) and liver damage grade A or B (corresponding to the Child-Pugh classes).

■ Explanation

TACE/TAE is essential for advanced inoperable HCCs that are not indications for percutaneous ablation and especially for hypervascular HCCs with hyperintense signals on hepatic arteriographic images; TACE/TAE is currently the standard treatment modality in the United States and Europe[1,2].

Two RCTs conducted in the early 2000s have shown that TACE/TAE improves the prognosis of advanced HCC[5,6]. Both RCTs were characterized by the exclusion of Okuda stage III and Child-Pugh C and by chemoembolization that is minimally invasive to non-cancerous liver tissue and is performed under selective catheterization of specific hepatic segmental arteries nourishing the HCC lesions. This is similar to how the study of TACE/TAE was conducted in Japan. Also, in a meta-analysis of 18 studies, Cammà et al. showed that the overall 2-year mortality rate was significantly lower in the TACE/TAE group than in the non-treatment group (OR, 0.54; 95% CI, 0.33-0.89; p = 0.015)[7]. They also stated that whenever possible, TACE/TAE should be performed consistently in RCTs in terms of methods (repeated regularly or not, selective or non-selective catheterization, and with which embolization agents) and tumor progression (e.g., tumor number and size)[7].

Since 2005, no studies have reported high-quality evidence about eligibility criteria among homogeneous patients. Therefore, in line with the exclusion criteria used in the RCTs reporting that TACE/TAE improves the prognosis of advanced HCC, the Revision Committee recommends the exclusion of non-selective TACE/TAE and patients with poor liver function such as Okuda stage III and Child-Pugh C.

When the SHARP study results on unresectable advanced HCC were published in 2008[8], sorafenib became the standard drug treatment for advanced HCC. This led to modification of the BCLC staging system and the development of numerous guidelines. Today, stage B HCC (intermediate stage; PS 0, Child-Pugh A/B, and 4 or more lesions) is the only indication for TACE/TAE in the Quality Improvement Guidelines for Transarterial Chemoembolization and Embolization of Hepatic Malignancy published by the Society of Interventional Radiology and the American Association for the Study of Liver Diseases (AASLD) Guidelines for the Treatment of Hepatocellular Carcinoma[4]. BCLC stage B HCC patients are equivalent to patients with 2-3 HCCs > 3 cm or multiple HCCs (4 or more lesions, regardless of size) and liver damage grade A or B (corresponding to the Child-Pugh classes) in the third edition of the Guidelines[2].

The Liver Cancer Study Group of Japan performed 2 large-scale prospective cohort studies to

determine factors that affect prognosis in unresectable HCC after Lip-TACE (with Lipiodol emulsion and gelatin sponge), and the results were published by Takayasu et al. in 2006[9] and 2012[10]. The first study examined 8,510 patients between 1994-2001 and showed (1) a 5-year survival rate of 25%, indicating that Lip-TACE is a safe treatment modality for unresectable HCC, and (2) independent prognostic factors of (i) liver damage grade, (ii) tumor stage, and (iii) serum AFP level (≥ or < 401 ng/mL). The second study examined 4,966 patients between 2000-2005 and reported (1) a 5-year survival rate of 34%, which was higher than in previous studies, and (2) the addition of PIVKA-II to the list of independent prognostic factors (liver damage grade, stage, and serum AFP levels). This study from 2012 revealed a significant difference in treatment outcomes between the TACE group and non-TACE group (surgical resection and locoregional therapy) and elucidated the outcome of TACE (which was one of the treatment options in the 2005 version [first edition] of the Guidelines). This suggests that the recommendation of TACE in the Guidelines is a valid treatment algorithm. Therefore, the Revision Committee strongly recommends that TACE be included in the current Guidelines.

However, because BCLC stage B (intermediate stage) covers a wide range of pathologies in terms of tumor factors and hepatic functional reserve, several studies have attempted to objectively subgroup the indications for TACE/TAE, but none has generated high-quality evidence[11,12].

Although the presence of intravascular tumor thrombus (especially portal vein tumor thrombus) is often regarded as a contraindication[2], there have been some cases of long-term survival after combination therapy with TACE/TAE and other treatment modalities, even though the patients had mild liver failure and highly advanced lesions (e.g., HCC with intravascular tumor thrombus or giant HCC ≥ 10 cm)[13]. In addition, several meta-analyses showed that TACE/TAE improves prognosis in patients with advanced HCC[14-16], making it difficult to deny the validity of TACE/TAE even in patients with stage C HCC (advanced stage) accompanied by intravascular tumor thrombus (especially portal vein tumor thrombus) but not extrahepatic metastasis. However, no previous studies have shown high-quality evidence for TACE/TAE compared with sorafenib, which is regarded as the standard treatment globally. Therefore, due to insufficient scientific evidence for its utility, the recommendation for TACE/TAE is graded only as weak for patients with HCC accompanied by intravascular tumor thrombus.

Future challenges in applying TACE/TAE for advanced HCC include the indications for TACE/TAC in the subgroup of patients with BCLC stage B and the utility of TACE/TAE and combination therapy with molecular-targeted drugs centering around sorafenib in patients with stage C HCC (advanced stage) accompanied by intravascular tumor thrombus (especially portal vein tumor thrombus).

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CQ38 What is the most appropriate method for selecting embolic agents and anticancer drugs for TACE or TAE?

Recommendations

Strong recommendation: Conventional TACE (cTACE) with Lipiodol® and porous gelatin particles (Gelpart®, Astellas Pharma Inc., Japan) or TACE with drug-eluting beads is recommended.

Weak recommendation: No anticancer drug is recommended specifically for use in TACE or TAE.

■ Background

The treatment algorithm in the Guidelines specifies TACE or TAE as the treatment for unresectable HCC. Once TACE/TAE is selected for the treatment of patients with HCC, usually they undergo the treatment multiple times over a relatively long period. So a certain proportion of patients with HCC finally undergo TACE/TAE during their period of follow-up observation. Various types of embolic agents and anticancer drugs are available for TACE/TAE, and the combinations are even more diverse. With this in mind, here we reviewed the optimal ways to select embolic agents and anticancer drugs.

■ Scientific Statement

This CQ was established based on CQ38 in the third edition, with slightly modified wording but the same meaning. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 143 articles. This was narrowed down to 15 articles in the first screening based on the following inclusion criteria: studies that compared the outcomes of treatment with or without embolic agents or anticancer drugs or compared treatment response to different anticancer drugs. The 15 articles were further narrowed down to 10 in the second screening by excluding those with ≤ 30 patients. A total of 47 articles, including 37 articles from the third edition, are cited for CQ38.

The iodized oil Lipiodol® is characteristically trapped and immobilized in tumor vessels and sinusoids *in vivo*. Taking advantage of this feature, Lipiodol is used to prepare an emulsion by mixing with anticancer drugs, and thus serves as a carrier in the drug delivery system[1,2]. Drug-eluting beads (DEB), which are spherical embolic agents impregnated with drugs, also serve as a form of carrier.

A questionnaire survey conducted in 2008 showed that Lipiodol® was used in ≥ 90% of TACE cases in Japan[3], so it is a common drug of choice for TACE. Although spherical embolic agents had

not been introduced in Japan at the time the third edition was published, they were later covered as special treatment agents by the National Health Insurance system, which enabled DEB to be used in TACE (DEB-TACE) or spherical embolic agents to be used in TAE (bland TAE), as permitted in the United States and Europe.

Two studies that compared DEB-TACE and bland TACE produced contrasting findings. One found no significant difference in the efficacy or incidence of adverse events[4], whereas the other showed a significantly higher rate of tumor necrosis after DEB-TACE than after bland TAE[5]. Overall, DEB-TACE is regarded as the standard method with spherical embolic agents. Additionally, no significant difference was found between cTACE and DEB-TACE[6-9], although cTACE resulted in the release of a larger amount of anticancer drugs into the systemic circulation[10] and adverse events were more frequent[7,8]. The costs did not appear to differ much between the treatments in Europe[11].

Spherical embolic agents of smaller size than the products first placed in the market were introduced more recently. Comparison by size revealed that the DC bead® (100-300 μm in diameter) was associated with a lower incidence of post-embolization syndrome, with no significant difference in response rates between 100-300 μm and 300-500 μm[12]. However, a comparison of the DC bead® 100-300 μm with the smaller DC bead® 7-150 μm showed the smaller bead was associated with a higher incidence of biliary complications, with no significant difference in response rates[13]. HepaSphere® microspheres are associated with less frequent leakage of anticancer drugs into systemic blood compared with cTACE, but no previous studies have compared conventional beads (50-100 μm) with smaller microspheres (30-60 μm)[10].

The anticancer drugs epirubicin, doxorubicin, mitomycin C, cisplatin, and neocarzinostatin have been used in Lipiodol emulsion for cTACE[2,14-19].

In an RCT, patients underwent embolization with small pieces of gelatin sponge after administration of epirubicin or doxorubicin in Lipiodol emulsion[20]. There was no significant difference in survival rate between the groups, although the rate was better in low-risk patients in the doxorubicin group ($p = 0.018$). There was also no significant difference in drug side effects between groups. Other studies have reported significantly better survival rates in patients who underwent embolization (using small pieces of gelatin sponge; cisplatin 31%; doxorubicin 50%) after the administration of low-dose cisplatin in lipiodol emulsion, compared with doxorubicin-lipiodol emulsion ($p < 0.05$)[21], and the benefit effects of TAI with fine cisplatin powder in lipiodol suspension (IA-call®) for patients with unresectable advanced HCC[22,23]. However, none showed high-quality evidence.

A superior response to TACE with the addition of embolization with cisplatin-lipiodol suspension and gelatin sponge such as porous gelatin particles was reported over that to TAI without embolization[24]. Two studies reported significantly better response to TACE with cisplatin-Lipiodol suspension over to TACE with doxorubicin-Lipiodol suspension[25,26], but this was not found not in

another study[27].

There is also a report of the utility of miriplatin (Miripla®)[28,29], a lipophilic platinum compound that is easily suspended in Lipiodol®, but high-quality evidence has yet to be shown.

Studies comparing cTACE with Lipiodol® and small pieces of gelatin sponge and TAI with Lipiodol® without gelatin sponge have reported controversial results: cTACE significantly improved the survival rate in one study[30], but no significant difference was observed in another study[31].

In a study conducted in Japan, TACE with degradable starch microspheres had comparable efficacy and a safety profile similar to that of cTACE in patients with metastatic liver cancer, but not in patients with HCC[32]. Although the β-emitting radionuclide yttrium-90 (Y-90) is not approved for clinical application in Japan, radioembolization with Y-90 microspheres was found to be superior to cTACE in regard to the number of treatment sessions, rate of adverse events, and total hospitalization stay, even though overall survival and time-to-progression (TTP) were comparable[33].

■ Explanation

Recent technological advances in catheterization, guidewire systems, and imaging devices used, for example, in CT/angiography systems, have improved the identification of arterial branches that supply liver cancer. This has brought us superselective catheterization and, in turn, the superselective injection of a large amount of chemoembolization agents into not only the branches of the hepatic artery, but also those of the hepatic portal vein in the area surrounding the tumor[1,34]. Through these catheterization techniques, it is possible to inject highly concentrated anticancer drugs into tumors while simultaneously blocking both the hepatic artery and portal vein, likely generating local effects called catheter ablation. As a result, it is possible to enhance anticancer effects and preserve the function of liver tissues not affected by cancer, thereby substantially improving prognosis after TACE/TAE[1,18,35,36]. However, HCC spanning different liver segments or near the liver surface is generally supplied by multiple blood vessels, including collateral vessels, and is associated with a high incidence of local recurrence[34,37]. Despite many reports of favorable survival rates, no studies have provided high-quality evidence for superselective TACE/TAE[38, 39].

Prognosis is favorable after cTACE in patients with advanced HCC and good liver function and in patients with small HCC, and the pathological assessment of post-cTACE resection specimens shows high antitumor efficacy[40,41]. Additionally, Cox's proportional hazards regression analysis shows a significant difference in survival between cTACE and TAE ($p < 0.01$)[41]. A meta-analysis did not show that patients with advanced HCC have better prognosis after TACE than after TAE[29], and the lack of benefit shown for cTACE can be considered the technical difference between superselective cTACE and techniqes used in RCTs. In other words, cTACE was performed in almost all of the livers in the RCT, likely damaging non-cancerous liver tissue and decreasing survival rate[42].

Small pieces of gelatin sponge have been used conventionally as an embolic agent in TACE/TAE for HCC in Japan[43]. In 2006, Gelpart® consisting of porous gelatin particles (a sterile, moderately standardized, and spherical embolic agent 1 and 2 mm in diameter) was approved for National Health Insurance coverage in Japan, and the administration of gelatin sponge (Spongel®, Gelfoam®) into blood vessels was contraindicated in October of the same year. It should be noted that porous gelatin particles may be used in TACE/TAE for HCC, but not for other diseases or in organs other than the liver[44,45]. In a previous study of TACE/TAE, there was no significant difference in short-term treatment response or in the incidence of side effects between the porous gelatin particles and the once-popular small pieces of gelatin sponge[45]. Therefore, at present, cTACE in the Guidelines refers to TACE with Lipiodol emulsion containing anticancer drugs and porous gelatin particles.

Many types of spherical embolic agents using different materials such as acrylic, polyvinyl alcohol, and gelatin have been developed overseas[20, 46, 47]. In Japan, three types of spherical embolic agents were approved as special treatment materials in early 2014. In general, DEBs are beads that release drugs, and bland beads are not impregnated with, and so do not release, drugs. Because the embolic agents are impregnated with drugs in advance, drug-eluting spherical embolic agents slowly release drugs into the surrounding area after blocking blood vessels. A pharmacokinetic study showed that the high concentration of anticancer drugs released from DEBs remains inside the tumor without dispersing into peripheral blood vessels, which provides an excellent short-term treatment response to DEB with a low incidence of systemic side effects[47]. Examination of resection specimens after liver transplantation in patients with HCC showed a significantly higher tumor necrosis rate after DEB-TACE than after bland TAE[5], and DEB-TACE is used as the standard treatment more often in the United States and Europe.

Two types of DEBs (DC bead® and HepaSphere®) are approved for clinical application in Japan. These embolic agents are spherical and permanent and are available in a range of particle sizes, with smaller diameter products used more often. Although products with much smaller diameters are available on the market in the United States and Europe, their utility has not been clarified. In general, from a technical standpoint, superselective TACE is performed using fewer anticancer drugs in Japan than in the United States and Europe, but it is currently unclear if there is a significant difference in efficacy between DEB-TACE and cTACE performed in the Japanese clinical setting. Although not approved in Japan, transarterial radioembolization with Y-90 microspheres, which are made from the radionuclide Y-90 and spherical embolic agents, is becoming popular in Western countries as a novel agent for embolization and intratumoral radiation therapy[33]. Even with efficacy comparable to that of cTACE, it is expected to produce a favorable response in patients with relatively less hypervascular HCC and in those with advanced HCC accompanied by vascular invasion.

cTACE is currently the major treatment modality in Japan, while DEB-TACE is common in the United States and Europe. Because no studies have clearly shown a significant difference in their efficacy, this has led to the conclusion that the two modalities are comparable in TAE. Thus, treating HCC with either one is strongly recommended.

Various drugs have been used as anticancer drugs in Lipiodol emulsion, such as epirubicin, doxorubicin, mitomycin C, cisplatin, and neocarzinostatin[2, 14-19]. Furthermore, IA-call® (a hydrophilic cisplatin product for arterial embolization) and miriplatin (a pro-Lipiodol® platinum product) have been used since 2004 and 2010, respectively, in Japan. However, no studies have shown high-quality evidence for their efficacy or safety, suggesting the lack of specific anticancer drugs to be recommended. Therefore, the Revision Committee grades the recommendation weak.

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CQ39 What factors determine the timing of re-embolization?

Recommendation

Strong recommendation: Local recurrence of hypervascular HCC after embolization therapy and the occurrence of a second primary hypervascular HCC in another part of the liver are the factors determining the timing of re-embolization.

■ Background

It is important to clarify whether re-embolization should be repeated regularly or performed on demand following tumor enlargement. Here, we investigated factors determining the timing of re-embolization by comparing the treatment outcomes of regularly repeated embolization (scheduled embolization) or on-demand embolization.

■ Scientific Statement

Wording in CQ39 in the third edition was slightly modified in this CQ. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 234 articles. This was narrowed down to 28 in the first screening and to 1 in the second screening based on the following inclusion criteria: studies that discussed determinants for the timing of re-embolization and compared outcomes of scheduled TACE and on-demand TACE. A total of 18 articles, including the 17 articles from the third edition, are cited for CQ39.

In 1991, Ikeda et al. reported the efficacy of regularly repeated embolization (scheduled embolization) every 3 months, finding a significantly higher number of patients with complete necrosis after scheduled embolization[1]. Subsequently, several RCTs were conducted to compare the efficacy of symptomatic therapy and scheduled embolization repeated every 2-3 months in patients with advanced HCC, but none showed improvement in prognosis, even though antitumor effects were observed[2-6].

In terms of the efficacy of on-demand TACE, 3-year survival rates were 78% and 77.1% with superselective embolization on demand following tumor enlargement[7,8]. Another study showed that embolization repeated on demand for recurrent HCC extended survival periods after curative treatment[9]. In another study, TACE repeated on demand combined with radiation therapy improved survival for HCC with portal vein tumor thrombus and preserved liver function[10].

Despite many reports of improved survival after on-demand embolization following tumor enlargement or elevated levels of tumor markers[11,12], no RCTs have compared survival between scheduled embolization every 2-3 months and on-demand embolization following tumor enlargement[13].

Ernst et al. retrospectively compared scheduled embolization repeated at least 3 times at 2-month intervals and on-demand embolization performed following tumor enlargement, and they found that compared with on-demand re-embolization, scheduled re-embolization was associated with many complications ($p < 0.001$) and lower cumulative survival rates ($p < 0.001$), suggesting that it is important to perform superselective embolization on demand following tumor enlargement[11]. Review articles published after 2002 also recommend performing re-embolization on demand following tumor enlargement[12-16]. There has been an attempt to assess the validity of re-embolization by establishing a scoring system for predicting prognosis by incorporating risk factors associated

with re-embolization[17].

In cases where embolization was performed as initial treatment and subsequent embolization was performed on demand, complete response rates were 48% after the first embolization, 52% after the second embolization, and 55% after the third embolization; recurrence rates at 6 months were 37% after the first embolization and 40% after the second embolization; median overall survival was 32 months; and complete response and recurrence rates after the first and second embolization were comparable[18].

■ Explanation

No RCTs have compared treatment outcomes between scheduled embolization and on-demand embolization following tumor enlargement. However, retrospective studies and recent reviews strongly suggest that if the background liver condition is suitable to perform embolization therapy, re-embolization should be considered in cases where previously treated HCC recurs locally or newly developing hypervascular HCC appears on diagnostic imaging.

The elevation of tumor marker levels was included as one of the factors that determine the timing of re-embolization up to and including the third edition. However, treatment is rarely initiated based solely on tumor marker elevation and is instead generally initiated after confirming recurrence on images, so for this fourth edition of the Guidelines, the Revision Committee decided, following debate at the meeting for finalizing recommendations, to exclude elevated tumor marker levels. Instead, local recurrence of hypervascular HCC and the appearance of new hypervascular HCC are strongly recommended as factors determing the timing of re-embolization.

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CQ40 What imaging modalities are useful for assessing treatment response to TACE?

Recommendation

Strong recommendation: Dynamic CT and dynamic MRI are recommended as useful imaging modalities for assessing treatment response to TACE.

■ Background

Various modalities have been used to assess the effect of TACE, so it is important to elucidate which diagnostic imaging modalities are supported by high-quality evidence and are therefore strongly recommended. Here, we reviewed diagnostic imaging modalities useful for assessing the effect of TACE.

■ Scientific Statement

A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 247 articles. This was narrowed down to 35 in the first screening and to 9 in the second screening to extract studies that assessed the effect of TACE using appropriate modalities. A total of 20 articles, including 11 from the third edition, are cited for CQ40.

It is generally agreed that CT is the first imaging modality of choice for TACE. In Lipiodol CT, response to TACE is evaluated based on the pattern of Lipiodol® accumulation. For example, necrosis was observed in 98% of the lesion when Lipiodol® accumulation was virtually complete, whereas 64% was necrotized when the accumulation was incomplete[1]. Incomplete intratumoral Lipiodol® accumulation makes it difficult to distinguish inhomogeneous Lipiodol® accumulation from the enhancement by contrast agents. It also makes it challenging to diagnose neoplastic changes on the basis of contrast-enhancement when intratumoral hemodynamics is affected by the accumulation of Lipiodol®[2]. However, a study published after the third edition of the Guidelines were released showed that an iodine map created by using dual-energy CT allows for diagnosis of recurrent HCC after TACE in patients with Lipiodol® accumulation[3].

The diagnostic accuracy of contrast-enhanced US was superior to contrast-enhanced CT in detecting residual tumor after TACE[4], and contrast-enhanced US performed 1 day after TACE was more sensitive than contrast-enhanced CT performed 1 month after TACE in detecting residual HCC[5].

Cone-beam CT performed during TACE shows an association between marginal contrast saturation and treatment response to TACE[6] and parenchymal blood volume estimated on cone-beam CT images allows for the assessment of residual HCC[7]. However, no comprehensive reports of treatment response to TACE have been published to date.

The utility of dynamic MRI in assessing the post-TACE treatment response was first reported in the mid 1990s[8,9]. Compared with dynamic MRI, dynamic CT tended to underestimate residual lesions[10], and histopathological findings from resection specimens obtained at the time of

transplantation showed the superiority of MRI over CT in sensitivity and specificity[11]. Dynamic MRI was also superior to Lipiodol CT and power Doppler US in sensitivity, specificity, and diagnostic accuracy[12]. In another study, the area of contrast enhancement on dynamic MRI at 1 month after TACE correlated strongly with the site of recurrence detected 6 months after TACE, suggesting that tumor recurrence can be predicted with dynamic MRI[13].

In a study that used histopathologic findings of the explanted liver as reference, dynamic contrast-enhanced subtraction MRI was superior to diffusion-weighted MRI in assessing tumor necrosis[14], whereas no significant difference was found between diffusion-weighted MRI and Lipiodol CT in predicting post-TACE recurrence[15]. The addition of diffusion-weighted imaging to dynamic MRI improves its sensitivity for post-TACE recurrence of HCC, but this in turns decreases its specificity, although without affecting diagnostic accuracy[16]. To date, no studies have verified the significant utility of diffusion-weighted imaging. Previous studies evaluated treatment response to TACE using the apparent diffusion coefficient (ADC), a parameter of diffusion-weighted imaging, and found that ADC was useful in assessing treatment response soon after TACE[17] and that patients with low ADC levels before and after TACE responded poorly to TACE[18].

A study published after the third edition was released reported a correlation between survival period and the assessment of treatment response on FDG-PET soon after TACE[19]. Also, FDG-PET was more useful than CT in assessing residual lesions after TACE in patients with high levels of Lipiodol® accumulation[20].

■ Explanation

Assessment of response to TACE involves not only assessing the therapeutic effect on the lesion, but also establishing the treatment strategy. Serum AFP is a marker for HCC, but many patients do not have elevated AFP levels at the time of recurrence after TACE and imaging findings are therefore clearly crucial for the assessment of clinical response. Although dynamic CT is commonly used to assess the therapeutic effect of TACE, it is sometimes difficult to evaluate local recurrence due to the high attenuation of Lipiodol® and the beam hardening effect it causes. Studies on the usefulness of dual-energy CT for Lipiodol® accumulation are expected to continue in the future. In MRI, Lipiodol® does not interfere with the visualization of lesions, and the residual lesions are visualized as hyperintense signals by contrast agents. Also, high-speed 3D MRI generates thin slices comparable to those generated by CT, which in turn allows for the capture of minute contrast enhancements without being affected by partial volume effect. Another advantage is the lack of exposure to ionizing radiation. The use of MRI including the ADC, will certainly be a further topic of investigation. Cone-beam CT, FDG-PET, and contrast-enhanced US have been studied and may be applied as auxiliary modalities. Prediction of the final therapeutic effect based on the assessments made immediately after TACE will be an option for assessing tumor response to TACE.

From the viewpoint of examination costs and time, it is not realistic to assess treatment response with MRI in all cases. CT-based assessment of treatment response does have clinical merits. As a result, in the Guidelines the Revision Committee strongly recommends both dynamic CT and dynamic MRI as modalities to assess the therapeutic effect of TACE.

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CQ41 Is it appropriate to combine embolization and molecular-targeted therapy?

Recommendation

Weak recommendation: Combination therapy with embolization and molecular-targeted drugs is not recommended because of insufficient scientific evidence to verify that combination therapy improves survival.

■ Background

This CQ was newly established in the current edition because of the now widespread use of molecular-targeted therapy with sorafenib and reports of positive outcomes when used in combination with locoregional therapy.

■ Scientific Statement

A literature search conducted with a publication date between January 1, 1982 and June 30, 2016 extracted 105 articles. This was narrowed down to 45 in the first screening and to 15 in the second screening based on the following inclusion criteria: studies that used combination therapy of embolization and systemic chemotherapy with sorafenib, which is covered by the National Health Insurance system as a molecular-targeted therapy for HCC.

Many studies have reported the effects of TACE and sorafenib combination therapy in recent years. In 2011, a prospective phase II trial of DEB-TACE and sorafenib in patients with unresectable HCC showed that the combination is well tolerated and safe, but the study had a small number of patients[1]. Chao et al. performed a multicenter phase II study of combination therapy with cTACE and sorafenib in patients with unresectable HCC and reported a 3-year survival of 86.1%[2]. Other phase II studies also showed the overall safety and efficacy of combination therapy with DEB-TACE/cTACE and sorafenib[3–5].

Lencioni et al. conducted a placebo-controlled phase II RCT of combination therapy with DEB-TACE and sorafenib (the Sorafenib or Placebo in Combination with TACE for Intermediate Stage HCC study) in patients with BCLC stage B HCC (intermediate stage), but sorafenib did not improve TTP in a clinically significant manner compared with DEB-TACE alone[6]. In contrast, a single-center placebo-controlled RCT of combination therapy with cTACE and sorafenib in patients with similar pathological conditions (HCV-related intermediate-stage HCC) demonstrated significant improvement in TTP after the combination therapy[7]. In a placebo-controlled phase III study of sorafenib after TACE in Japanese and Korean patients with unresectable HCC, sorafenib administered after cTACE had no significant effect on TTP, but the result might have been affected by the timing of sorafenib administration after TACE as well as the study design[8].

A large-scale observational registry study conducted in different regions worldwide (Global Investigation of Therapeutic Decisions in Hepatocellular Carcinoma and of its Treatment with Sorafenib study) suggested that combination therapy with TACE and sorafenib is a viable treatment approach, but the study did not offer sufficient evidence because of the difference in patient backgrounds between the combination therapy and monotherapy with sorafenib groups[9]. Some studies suggest the efficacy of combination therapy with TACE and sorafenib in patients with BCLC stage C HCC (advanced stage), which is normally the indication for sorafenib, but they were mostly retrospective cohort studies and not RCTs[10-13]. Two of the articles cited for CQ41 report the results

of meta-analyses, but because the analyses included a limited number of RCTs, the level of evidence is less than optimal[14, 15].

■ Explanation

Combination therapy with embolization and sorafenib is unquestionably safe and tolerated. Many studies have suggested its efficacy, but these are mostly retrospective cohort studies and single-arm phase II studies. Also, no large-scale phase III studies have demonstrated the efficacy of combination therapy relative to monotherapy with sorafenib. Therefore, at present, there is insufficient scientific evidence to suggest that combination therapy with embolization and molecular-targeted drugs improves survival. Although the recommendation for combination therapy is graded weak in the current Guidelines, it is possible that there will be many reports of its efficacy in the future.

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CQ42 What are the clinical features of TACE failure?

Recommendation

Weak recommendation: HCC is empirically considered unresponsive to TACE when any one of the following 3 conditions is met: (1) unsatisfactory improvement of the primary lesions or the appearance of new intrahepatic lesions after 2 TACE sessions, (2) vascular invasion or extrahepatic metastasis, or (3) persistently elevated levels of tumor markers.

■ Background

TACE is recommended for multiple HCCs where one measures > 3 cm or there are 4 or more HCCs in patients with Child-Pugh A/B liver function without vascular invasion. TACE is a valid treatment modality and improves prognosis. However, when repeated for recurrent tumors, TACE may not achieve effective control or may even exacerbate liver dysfunction. Since the introduction of molecular-targeted therapy in 2009, there have been reports of improved prognosis in cases of TACE failure following molecular-targeted therapy rather than repeat TACE. Therefore, a clear definition of TACE failure is essential for determining the appropriate timing to switch to second-line therapy. This CQ was newly established in the current Guidelines.

■ Scientific Statement

A literature search conducted with a publication date between January 1, 1982 and June 30, 2016 and the keywords “hepatocellular carcinoma”, “TACE/embolization”, and “refractory/failure” extracted 113 articles. This was narrowed down to 43 articles in the first screening and 11 articles in the second screening based on the following inclusion criteria: studies that defined TACE failure, those that evaluated treatment modalities and prognosis after diagnosis of TACE failure, and those that discussed factors predictive of TACE failure.

In 2012, the following definition of HCC unresponsive to TACE was proposed by expert consensus in Japan[1]: (1) poor intratumoral Lipiodol accumulation (≤ 50%) in the treated tumor or 2 or more consecutive incidences of intrahepatic lesions on CT for assessing treatment response immediately after adequately performing TACE; (2) appearance of vascular invasion; (3) appearance of distant metastasis; or (4) persistently elevated levels of tumor markers immediately after TACE even when a slight transient decrease is observed. The description of “intrahepatic lesions” in (1) was revised in 2014 to take into account the introduction of spherical embolic agents and timing of decision-making[2]: (1) 2 or more consecutive insufficient responses of the treated tumor (viable lesion >50%) even after changing chemotherapeutic agents and/or reanalyzing the feeding artery as seen on CT or MRI for assessing treatment response at 1-3 months after adequately performing TACE, or 2 or more consecutive increases in the number of intrahepatic tumors. The presumed rationale for 2 sessions of TACE is the varying effects due to different nutrient arteries and drugs.

There is no clear scientific basis for a definitive diagnosis of TACE failure. However, it has been shown that even if the first TACE is unsuccessful, prognosis improves if HCC responds favorably to the second TACE. Therefore, it is reasonable to make a diagnosis of TACE failure based on treatment response after 2 or more TACE sessions[3]. Some studies repeated TACE after TACE failure based on this assumption and overall survival improved from 11.5 months to 15.3 months[4-6]. These studies, although retrospective in nature, also reported better prognosis with sorafenib after TACE failure than with repeated TACE[4,5] or with TACE and sorafenib combination therapy than with TACE alone[6]. In studies evaluating sorafenib versus repeated TACE after TACE failure[4,5], median survival increased from 24.7 months to 25.4 months in patients who were treated with sorafenib after becoming unresponsive to TACE[4,5]. Together the 3 studies suggest that prognosis improves by switching to appropriate second-line therapy even after a diagnosis of TACE failure. Treatment response also improved when, in addition to the administration of sorafenib, the commonly used anticancer drug for TACE epirubicin was changed to a platinum-based drug[7] or when spherical embolic agents were used for embolization[8].

Recent studies have shown that hypoxia-inducible factor-1α, VEGF, and C-Met are involved in TACE failure[9,10]. In addition, research is currently underway to predict TACE failure based on

preoperative levels of biomarkers such as interleukin-8[11].

■ Explanation

The definition of TACE failure that is currently in use was provisionally proposed following expert consensus. Some validity was reported in previous studies, and the definition has been shown to help the transition to second-line therapy after TACE failure. However, scientific evidence is currently insufficient.

After debate at the meeting for finalizing recommendations, the Revision Committee decided on a weak recommendation of the definition because, despite some validity, the definition of TACE failure currently in use is supported only by retrospective studies.

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