Chapter 6:
Transcatheter Arterial Chemoembolization and Transcatheter Arterial Embolization

● Introduction

CQs related to TACE have gradually evolved since the second edition (2009 version) and the third edition (2013 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?”, and 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?”. The CQ37 through CQ40 in the third edition remained in use in the fourth edition although the wording was slightly changed to 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?”

In the current fifth edition (2021 version), no new CQ has been adopted, CQ39 in the fourth edition “What factors determine the timing of re-embolization?” has been deleted, and the remaining 5 CQs in the fourth edition have been left unchanged.

With regard to CQ33 “Which patients are eligible for TACE or TAE?” in the current edition, the recommendation differs little from that in the fourth edition, but more concrete conditions have been added to the recommendation on the basis of the

subsequently collected additional evidence, while deleting the description about the BCLC staging system.

With regard to CQ34 “What is the most appropriate method for selecting embolic agents and anticancer drugs for TACE or TAE?” and CQ35 “What imaging modalities are useful for assessing treatment response to TACE?”, several new pieces of evidence have been added to each of them, but the recommendations remain unchanged from the fourth edition. Regarding CQ35, care needs to be taken of the fact that dynamic MRI encompasses also contrast-enhanced MRI with Gd-EOB-DTPA, similar to the suggestion given in the fourth edition.

CQ36 “Is it appropriate to combine embolization and molecular-targeted therapy?” in the current edition is equal to CQ41 in the fourth edition. However, the recommendation about this CQ has been changed from “Combination therapy with embolization and molecular-targeted drugs is not recommended because of insufficient scientific evidence to verify that combination therapy improves survival. (Weak Recommendation)” in the fourth edition to “Combination therapy with embolization and molecular-targeted drugs deserves consideration. (Weak Recommendation)” in the fifth edition. The phrase “deserves recommendation” has been adopted for recommendation about CQ39 for the following reasons: (1) More scientific evidence is now available for the therapy combining primarily sorafenib with TACE/transcatheter arterial embolization (TAE) than at the time of publication of the fourth edition, including also reports demonstrating extended progression-free survival (although unable to show overall survival extension); and (2) further research for evaluation of the efficacy of this kind of combination is expected from now on.

The recommendation in the current edition about CQ37 “What are the clinical features of TACE failure?” is almost the same as CQ42 in the fourth edition. However, new evidence based on more advanced verification of the conditions for failure, as compared to the evidence in the fourth edition, has been adopted in the current edition (CQ37: Reference 26, OPTIMIS Study). At the meeting for finalizing recommendations, the Revision Committee decided that the recommendation be kept “Weak” for the time being because OPTMIS Study was a non-interventional study using propensity score matching.

Although not a few pieces of evidence for TACE/TAE have been firmly verified, establishment of the evidence is now under way concerning combination with molecular-targeted drugs (a relatively new concept of treatment) or the concept “TACE failure” involving the awareness of switching to molecular-targeted treatment. These circumstances had some effects in forcing weak recommendations, instead of stronger recommendations, in the fourth and fifth editions. Addition of more concrete conditions

to the recommendations based on the data/findings collected from now on is expected to allow stronger recommendations.

CQ33 Which patients are eligible for TACE or TAE?

Recommendations

1. TACE or TAE is recommended for patients with Child-Pugh A/B hypervascular HCCs (4 or more lesions, or 1-3 lesions > 3 cm) that are inoperable and are not indications for percutaneous ablation. (Strong Recommendation, Evidence Level A)
2. TACE or TAE may be considered for patients with inoperable hypervascular HCC accompanied by portal vein tumor thrombus. (Weak Recommendation, Evidence Level C)

■ Background

In the treatment algorithm of the current Guidelines, TACE/TAE is positioned as a valid alternative for treatment comparable to surgical therapy, RFA and drug therapy. In principle, hypervascular HCCs with hyperintense signals on hepatic arteriographic images are indications for TACE/TAE, such as classic HCCs (moderately and poorly differentiated HCCs) or part of early-stage HCCs. However, treatment should be selected based on staging, which includes patient factors as well as tumor factors. Here, the selection criteria for TACE/TAE in current clinical practice are discussed.

■ Scientific Statement

This CQ is a slight modification of CQ37 adopted in the fourth edition. A literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 557 articles. This was narrowed down to 20 in the first screening based on the inclusion criteria of studies that discussed the indications for TACE/TAE. The 20 articles were further narrowed down to 4 in the second screening to extract studies with high-quality evidence. Furthermore, 4 articles published in and after July 2016 were extracted by hand search, and 10 of the 16 articles used in the fourth edition were adopted. In total, 18 articles are cited for CQ33.

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[3,4]. 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)[5]. According to a systematic review by Lencioni et al., the median survival after Lip-TACE (TACE with the use of Lipiodol emulsion and gelatin sponge) was 19.4 months, with the survival rates at 1, 3 and 5 years being 70.3, 40.4 and 32.4%, respectively[6]. As adverse events, post-embolization syndrome involving chill, fever, abdominal pain, vomiting, etc. (4.77%) and exacerbation of liver function (52%) were seen frequently, while the incidence of hepatic failure and death was low (1.0% and 0.6%, respectively).

In Japan, Takayasu et al. reported the results of two large-scale prospective cohort studies designed to determine factors affecting the prognosis of unresectable HCC after Lip-TACE conducted within the framework of the nationwide follow-up survey of primary liver cancer by the Liver Cancer Study Group of Japan[7,8]. 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) three independent prognostic factors, i.e. (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).

Although the presence of intravascular 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)[9,10]. In addition, several meta-analyses showed that TACE/TAE improves prognosis in patients with advanced HCC[11]. The survival rates at 1, 3 and 5 years were 29, 4 and 1%, respectively, in total of these studies, higher than the rates after the best supportive care (BSC), and the incidence of liver failure after TACE/TAE was 1%. The five-year survival rate was 6% in cases where the tumor had not invaded beyond the primary portal vein branch, higher than the rate (0%) in cases with tumor invasion of the portal vein trunk (p < 0.001).

■ Explanation

TACE/TAE is indicated for hypervascular HCCs with hyperintense signals on hepatic

arteriographic images, including classic HCCs (moderately and poorly differentiated HCCs) and part of early-stage HCCs[1,2]. If the BCLC staging system, used in many countries overseas, is applied, the indications for TACE/TAE are confined to Child-Pugh A/B performance status (PS) 0 HCCs at Stage B (intermediate stage)[2]. These cases are approximately equivalent to Child-Pugh A/B HCCs (≥ 4 tumors of any size or 1-3 tumors > 3 cm). Because no article with high-quality evidence has been published since 2005 concerning expansion of the indications for TACE/TAE on the basis of analysis of patients with homogeneous features, TACE/TAE it not recommendable for cases with poor liver function (Child-Pugh C) or extrahepatic metastasis[12].

The criteria for indications of TACE/TAE in the current guidelines involve tumor factors and indicators of hepatic reserves each of which has a wide eligible range. To enable more concrete determination of the indications for TACE/TAE, several attempts of subgrouping have been reported[13-15]. From this point of view, a proposal has been made about the condition unlikely to manifest maximum responses to TACE/TAE even when it is within the eligible range, i.e., the proposal of the concept "TACE failure"[16,17]. The recommendations in the current edition do not refer to this concept because its validity has not yet been endorsed by sufficient evidence.

In addition to TACE/TAE, hepatectomy and drug therapy are indicated for HCCs with intravascular tumor thrombus. In the current edition, TACE/TAE for unresectable HCCs with portal vein tumor thrombosis is recommended weakly, considering that no article with high-quality evidence is available concerning the comparison of TACE/TAE with drug therapy and because the survival rate after TACE was lower than that after hepatectomy in a meta-analysis comparing TACE/TAE with hepatectomy[18].

Voting results

◎ Regarding the statement of recommendation 1 "TACE or TAE is recommended for patients with Child-Pugh A/B hypervascular HCCs (4 or more lesions, or 1-3 lesions > 3 cm) that are inoperable and are not indications for percutaneous ablation", its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
95.8% (23 members)	4.2% (1 member)	0% (0 members)	0% (0 members)

Total voters: 24 members

Voting results

◎ Regarding the statement of recommendation 2 “TACE or TAE may be considered for patients with inoperable hypervascular HCC accompanied by portal vein tumor thrombus”, its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
0% (0 members)	92.0 (23 members)	8.0% (2 members)	0% (0 members)

Total voters: 25 members

■ References

17) Japan Society of Hepatology (edt.). Liver Cancer Management Manual 4th Edition, Tokyo: IGAKU-SHOIN Ltd, 2020 (Japanese)

CQ34 What is the most appropriate method for selecting embolic agents and anticancer drugs for embolization therapy?

Recommendation

Conventional TACE (cTACE) with Lipiodol® (ethiodized oil) and porous gelatin particles or TACE with drug-eluting beads (DEB-TACE) is recommended. (Strong Recommendation, Evidence Level B)

■ Background

The treatment algorithm in the Guidelines specifies embolization therapy as the treatment for unresectable HCC. Once embolization therapy 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 embolization therapy during their period of follow-up observation. Various types of embolic agents and anticancer drugs are available for embolization therapy, and the combinations are even more diverse. With this in mind, here we reviewed the optimal ways to select embolic agents and anticancer drugs.

In the Guidelines, TAE indicates the method of treatment intended to embolize the vessels and blood sinuses nourishing the HCCs with the use of embolic agents such as Lipiodol®,

small pieces of gelatin sponge, porous gelatin particles and embolic beads. TACE denotes the treatment method using anticancer drugs simultaneously with the afore-mentioned embolic agents. cTACE indicates TACE using anticancer drug-combined Lipiodol emulsion and porous gelatin particles. Since embolic beads began to be covered by the National Health Insurance system in Japan (NHI) in 2014, it is now possible to apply TACE (DEB-TACE) using drug-eluting beads (DEB) or TAE using embolic beads alone (bland TAE).

■ Scientific Statement

This CQ is a continuation of CQ38 in the fourth edition. A literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 269 articles. This was narrowed down to 35 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 35 articles were further narrowed down to 8 in the second screening by excluding case studies as well as prospective studies with ≤ 30 patients. Adding one article extracted by hand search and 31 of the 47 articles from the fourth edition, a total of 40 articles are cited for CQ34.

●Selection of embolic agents

1) Lipiodol® and porous gelatin particles

A questionnaire survey conducted in 2008 showed that Lipiodol® was used in ≥ 90% of TACE cases in Japan[1].

Significantly better survival rates have been reported after TAE with Lipiodol® and small pieces of gelatin sponge as compared to TAE using small pieces of gelatin sponge alone[2,3].

In 2006, porous gelatin particles serving as a somewhat standardized aseptic spherical embolic agent (particle size 1 mm and 2 mm: Gelpart®) began to be covered by the NHI. At present, porous gelatin particles are used instead of small pieces of gelatin sponge. There is a report that the response to treatment and the incidence of adverse reactions differ little between small pieces of gelatin sponge and porous gelatin particles[4].

2) Spherical embolic agents

The DEB, prepared by pre-immersing beads (an embolic agent) in drug(s), releases the drug(s) into the surrounding tissues after embolization. A short-term study demonstrated high levels of anticancer drug(s) remaining in the tumor, without outflow into peripheral blood, thus making DEB a highly effective means of treatment less likely to cause systemic adverse reactions to the anticancer drug(s) used[5].

A study that compared DEB-TACE and bland TACE revealed a significantly higher rate

of tumor necrosis after DEB-TACE than after bland TAE[6].

Although the overall survival did not differ significantly between cTACE and DEB-TACE in many retrospective studies[7-17], there is a prospective study demonstrating a significantly higher complete response rate to cTACE[18].

With regard to adverse events, the level of anticancer drugs released into blood was higher following cTACE[19], and the incidence of post-embolization syndrome such as abdominal pain and fever was significantly higher following cTACE than following DEB-TACE[8,9,12,14,20]. On the other hand, bile duct disorders occurred more frequently following DEB-TACE[12].

In analysis of the relationship between the size of beads and the response to treatment, the response rate to TACE with DC Beads® did not differ between sizes 100-300 μm and 300-500 μm, while the incidence of post-embolization syndrome was lower in the smaller size group (100-300 μm)[21]. A comparison of the DC Beads® 100-300 μm with the smaller DC Beads® 75-150 μm showed the smaller bead was associated with a higher incidence of biliary complications, with no significant difference in response rates[22]. HepaSphere® microspheres are associated with less frequent leakage of anticancer drugs into systemic blood compared with cTACE, but there is no study comparing conventional beads (50-100 μm) with smaller microspheres (30-60 μm)[19].

In Europe, the cost for DEB-TACE did not differ markedly from that for cTACE[23].

●Selection of drugs for TACE

In an RCT, patients underwent embolization with small pieces of gelatin sponge after administration of epirubicin or doxorubicin in Lipiodol emulsion[24]. There was no significant difference in drug side effects between the two groups. The survival rate among low-risk patients was better in the doxorubicin group ($p = 0.018$) although this parameter among all patients did not differ between the epirubicin group and the doxorubicin group.

Other studies reported significantly better survival rates in patients who underwent embolization (using small pieces of gelatin sponge) after the administration of low-dose cisplatin in Lipiodol emulsion, compared with doxorubicin-Lipiodol emulsion (cisplatin 31% vs. doxorubicin 50%, $p < 0.05$)[25] and the beneficial effects of HAIC with fine cisplatin powder in Lipiodol suspension for patients with unresectable advanced HCC[26,27]. However, none showed high-quality evidence.

When TACE using cisplatin-Lipiodol suspension was compared with TACE using doxorubicin-Lipiodol suspension, some studies reported significantly higher responses to the former[28,29] while another study reported no significant difference[30].

A superior response to TACE with the addition of embolization using cisplatin-Lipiodol

suspension and gelatin sponge such as porous gelatin particles was reported over that to HAIC without embolization[26].

In a prospective study comparing TACE using miriplatin (a lipophilic platinum compound that is easily suspended in Lipiodol®) with TACE using epirubicin, the overall survival did not differ significantly between the two groups, but the incidence of adverse reactions was lower in the group using miriplatin[31].

■ Explanation

Because Lipiodol® is trapped and retained in the tumor vessels and sinusoids, the Lipiodol emulsion containing anticancer drug(s) plays the role of a carrier for the drug delivery system[32,33]. In Japan, spherical embolic agents began to be covered by the NHI as specific insurance-covered healthcare materials early in 2014. At present, 3 products of spherical embolic agents are available for use. Spherical embolic agents without the drug-releasing potential are called bland beads, while drug-releasing spherical embolic agents are called DEB. DEB-TACE, i.e. TACE with DEB, is more frequently used for HCCs than bland TACE (TACE with bland beads).

With regard to comparison between TACE and TAE, the meta-analysis in 2002 failed to prove superiority of TACE over TAE in terms of survival rate of advanced HCC patients. This result may be closely related to the hazardous effects of TACE (applied to approximately entire liver) on the tumor-free liver tissues[34]. In Japan, selective or super-selective cTACE is predominantly used at present, making it impossible to apply directly the results of meta-analysis of the past data from previously predominant entire-liver TACE. Thus, meta-analysis of TACE outcomes needs to be carried out in a manner reflecting the current way of TACE.

The embolization therapy using spherical embolic agents made of the β-emitting radionuclide yttrium-90 is called transarterial radioembolization (TARE) and is being established as a new embolization therapy with a combination of embolizing effects and in-tumor irradiation primarily in Europe and the USA[35], although this has not yet been approved in Japan. Its efficacy was comparable to cTACE, but particularly high responses to this therapy are expected in less hypervascular HCCs and advanced HCCs with vascular invasion.

In Japan, cTACE using Lipiodol® is predominant, while DEB-TACE is predominant in Europe and the USA. No evident difference in efficacy has been shown between these two therapies. During clinical practice, one of these two therapies is often selected in a manner tailored to the features of individual patients, rather than one of them is selected in an exclusive manner. With this borne in mind, the present edition recommends using

either Lipiodol® or DEB as an embolic agent on the ground that there is no consensus over superiority/inferiority between these two agents when used for embolization therapy. Diverse anticancer drugs have been used in the form of Lipiodol emulsion, including epirubicin, doxorubicin, mitomycin C, cisplatin and neocarzinostatin[24,33,36-40]. In addition, cisplatin for intraarterial infusion with improved water solubility began to be used in 2024, followed by marketing of miriplatin (a platinum preparation easy to suspend in Lipiodol®) in 2010. However, no difference in response has been reported between any two of these drugs used for TACE[31], and no report with high-quality evidence is available concerning differences in safety among these drugs. At present, therefore, there is no specific anticancer drug deserving recommendation for use in TACE although it is sure that TACE should use anticancer drug(s).

The voting at the Revision Committee after the above-mentioned discussions adopted a strong recommendation of applying cTACE or DEB-TCE. The recommendation in this edition does not cite any anticancer drug because no specific drug to be recommended has been identified.

Voting results

◎ Regarding the statement of recommendation “Conventional TACE (cTACE) with Lipiodol® (ethyl esters of iodized fatty acids of poppy seed oil) and porous gelatin particles or TACE with drug-eluting beads (DEB-TACE) is recommended”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
100% (24 members)	0% (0 members)	0% (0 members)	0% (0 members)

Total voters: 24 members

■ References

4) Yamada R, Sawada S, Uchida H, Kumazaki T, Hiramatsu K, Ishii H, et al. A clinical trial on porous gelatin particles for transcatheter arterial embolization (YM670). Jpn. J. Cancer Chemother. 2005; 32: 1431-6.

CQ35 What imaging modalities are useful for assessing treatment response to TACE?

Recommendation

Dynamic CT and dynamic MRI are recommended as useful imaging modalities for assessing treatment response to TACE. (Strong Recommendation, Evidence Level A)

■ 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 fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 381 articles. This was narrowed down to 29 in the first screening and to 8 in the second screening under the criteria “laying emphasis on studies of modalities for assessing the response to TACE and permitting selection of large-scale studies on the response to TACE so that the response assessment modalities employed in such studies may be used as reference information.” A total of 28 articles, including 20 from fourth edition, are cited for CQ35.

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]. A study published after release of the third edition of the Guidelines attempted creation of an iodine map by using dual-energy CT to allow for visualization of recurrent HCC after TACE in patients with Lipiodol® accumulation[3]. However, no new article regarding dual-energy CT as a means of treatment response assessment was adopted during the current revision. Regarding assessment with CT, qEASL has been reported as more sensitive in judging survival rates and detecting recurrence during assessment of treatment response as compared with RECIST, modified RECIST and EASL criteria[4].

The diagnostic accuracy of contrast-enhanced US was superior to contrast-enhanced CT in detecting residual tumor after TACE[5], 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[6]. Also during the current revision, additional reports showing superiority of contrast-enhanced US to contrast-enhanced CT in detecting residual tumor after TACE were collected[7-9]. However, there was also a report showing higher specificity of contrast-enhanced CT than contrast-enhanced US in identifying residual tumors[7]. Cone-beam CT performed during TACE shows an association between marginal contrast saturation and treatment response to TACE[10] and parenchymal blood volume estimated on cone-beam CT images allows for the assessment of residual HCC[11]. However, no comprehensive reports of treatment response to TACE have been published to date. Two studies using perfusion CT for assessing the response to TACE with drug-eluting spherical embolic agents (DEB-TACE) revealed useful perfusion CT parameters, but these studies involved no comparison with other imaging modalities[12,13].

The utility of dynamic MRI in assessing the post-TACE treatment response was first reported in the mid 1990s[14,15]. Compared with dynamic MRI, dynamic CT tended to underestimate residual lesions[16], and histopathological findings from resection specimens obtained at the time of transplantation showed the superiority of MRI to CT in sensitivity and specificity[17]. Dynamic MRI was also superior to Lipiodol CT and power Doppler US in sensitivity, specificity, and diagnostic accuracy[18]. 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[19]. In the meta-analysis of 13 articles newly adopted during the current revision, dynamic MRI was shown to be useful in assessing the post-TACE response, although there was no comparison with other imaging modalities[20].

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[21], whereas no significant difference was found between diffusion-weighted MRI and Lipiodol CT in predicting post-TACE recurrence[22]. 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, resulting in no difference in diagnostic accuracy in total of these changes[23]. 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[24] and that patients with low ADC levels before and after TACE responded poorly to TACE[25,26].

A study published after the release of the third edition reported a correlation between survival period and the assessment of treatment response on FDG-PET soon after TACE[27].

Also, FDG-PET was more useful than CT in assessing residual lesions after TACE in patients with high levels of Lipiodol® accumulation[28].

■ Explanation

Assessment of response to TACE involves not only assessing the therapeutic effect on the lesion, but also establishing the treatment strategy. Following recent advances in drug therapy, multiple alternatives are now available for treatment after TACE failure, and evaluation of the response to TACE has been becoming increasingly more important. 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 due to Lipiodol® accumulation and the beam hardening effect it causes. Studies on the usefulness of dual-energy CT for Lipiodol® accumulation are now under way. 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. Not only the hemodynamic assessment of lesions, but also diffusion-weighted MRI and evaluation with the ADC map are reported to be useful in assessing the lesions remaining or recurring after TACE. Furthermore, treatment of HCC with TACE and other techniques will need multiple sessions of diagnostic imaging, and evaluation by MRI will become more desirable from the viewpoint of reducing exposure to radiation. So, further studies are needed on evaluation by MRI. Contrast-enhanced US is useful because it is superior to contrast-enhanced CT in terms of less radiation exposure and better assessment of treatment response. However, because its diagnostic capability can vary greatly depending on the examiner's skill, it is realistic to use contrast-enhanced US as an auxiliary modality from the viewpoint of ensuring objectivity of assessment. Prediction of the final therapeutic effect based on the cone-beam CT 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.

Voting results

◎ Regarding the statement of recommendation “Dynamic CT and dynamic MRI are recommended as useful imaging modalities for assessing treatment response to TACE”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
100% (24 members)	0% (0 members)	0% (0 members)	0% (0 members)

Total voters: 24 members

■ References

CQ36 Is it appropriate to combine embolization and molecular-targeted therapy?

Recommendation

Combination therapy with embolization and molecular-targeted drugs deserves consideration. (Weak Recommendation, Evidence Level B)

■ Background

This CQ was established in the fourth edition because of the 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 July 1, 2016 and January 31, 2020 extracted 252 articles. This was narrowed down to 54 in the first screening and to 15 in the second screening based on the inclusion criteria “Selection of original studies comparing the responses to embolization therapy applied independently or in combination with molecular-targeted drug therapy (either one molecular-targeted drug or multiple molecular-targeted drugs), with priority given to the studies using treatment methods feasible in Japan.” A total of 26 articles, including 11 of the 15 articles from fourth edition, are cited for CQ36.

Many studies have reported the effects of TACE and sorafenib combination therapy in recent years. In 2011, a single-arm 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 included only 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 acceptable safety and promising 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: SPACE Study) in patients with BCLC stage B HCC (intermediate stage), but sorafenib did not improve the time to progression (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 study design (e.g., the timing of sorafenib administration after TACE)[8]. Later, a placebo-controlled phase III study of combination therapy with DEB-TACE and sorafenib was reported from Europe/USA but it failed to show significant improvement in TTP[9]. However, a recent phase II study of combination therapy with cTACE and sorafenib in Japan demonstrated significant improvement in TTP as compared to the cTACE monotherapy group, thus endorsing the add-on effect of sorafenib for the first time. One factor pointed out to have enabled such a result is the study design which permitted the protocol treatment to be continued until treatment with TACE became difficult to continue[10].

Some retrospective cohort studies suggested the efficacy of combination therapy with TACE and sorafenib in patients with BCLC stage C HCC (advanced stage), which is normally the indication for conventional molecular-targeted therapy[11-13], followed by the report of a single-arm phase II study in Japan demonstrating that this therapy had no safety problem and was promising as an effective therapy[1]A large-scale cohort study also reported significantly longer survival after the combination therapy than after sorafenib monotherapy[15]. However, an RCT comparing combined cTACE + sorafenib therapy with sorafenib monotherapy failed to demonstrate significant improvement in survival despite longer TTP in the combination therapy group[16].

Factors reported to determine the utility of combined TACE + sorafenib therapy include the presence of portal vein tumor thrombus and the onset of sorafenib-related skin

disorders, hypertension or other comorbidities after the start of treatment[17-21]. Another study of the combination therapy with molecular-targeted drugs involved comparison of the outcomes of cTACE with or without sorafenib or sunitinib, demonstrating longer survival and higher tolerability in the cTACE + sorafenib therapy group[22].

■ Explanation

Combination therapy with TACE and sorafenib is unquestionably safe and tolerated. Many studies have suggested its efficacy, but these are mostly retrospective cohort studies or single-arm phase II studies. Although several RCTs demonstrated extension of TTP, no study reported longer survival after TACE + sorafenib therapy than after sorafenib monotherapy[6-10,16], and the same can be said of meta-analyses involving RCTs[23-26]. Still more, there is no prospective study demonstrating the efficacy of TACE combined with other molecular-targeted drugs. However, in view of the possibility for publication of new reports suggesting the efficacy of this kind of combination therapy, voting was made about adoption of this recommendation on combination therapy with embolization (TACE) and molecular-targeted drugs.

Voting results

◎ Regarding the statement of recommendation “Combination therapy with embolization and molecular-targeted drugs deserves consideration”, its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
9.1% (2 members)	90.9% (20 members)	0% (0 members)	0% (0 members)

Total voters: 22 members (abstention because of COI: 2 members)

■ References

CQ37 What are the clinical features of TACE failure?

Recommendation

HCC is 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. (Weak Recommendation, Evidence Level C)

■ 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. Furthermore, multiple molecular-targeted drugs for use in the treatment of HCC recently began to be covered by the NHI in Japan. Therefore, a clear definition of TACE failure is essential for determining the appropriate timing to switch to second-line therapy.

■ Scientific Statement

In the fifth edition, a literature search conducted with a publication date between July 1, 2016 and January 31, 2020 and the keywords “hepatocellular carcinoma”, “TACE/embolization”, and “refractory/failure” extracted 112 articles. This was narrowed down to 21 articles in the first screening and 14 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. A total of 30 articles, including 5 articles extracted by hand search and 11 articles from the fourth edition, are cited for CQ37.

In 2012 and 2014, the following definition of HCC unresponsive to TACE was proposed by expert consensus in Japan[1,2]: (1) 2 or more consecutive insufficient responses of the treated tumor (viable lesion > 50%) or 2 or more consecutive increases in the number of intrahepatic tumors when assessing treatment response with CT or MRI at 1-3 months after adequately performing TACE with changed chemotherapeutic agents and/or reviewed feeding artery; (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.

There is no clear scientific evidence for the timing of diagnosing TACE failure. However, it has been shown that the overall survival is poor in cases where HCC has recurred within 5 months of TACE and that treatment methods other than TACE should be selected upon

recurrence within 5 months of TACE[3,4]. Another study reported that 2 or more TACE sessions within 6 months is considered to be a poor prognostic factor and associated with TACE failure in patients with HCC who underwent curative resection[5]. There is a report that even if the first TACE is unsuccessful, prognosis improves if HCC responds favorably to the second TACE[6]. If the feeding artery is reviewed or the drug used is changed during 2 sessions of TACE, the response to TACE can differ. Therefore, it is reasonable to make a diagnosis of TACE failure based on treatment response after 2 or more TACE sessions[7]. Some studies repeated TACE after TACE failure based on this assumption and overall survival improved from 11.5 months to 15.3 months[8-10]. These studies, although retrospective in nature, also reported better prognosis (through preservation of hepatic reserves and extension of the time to progression of HCC) with sorafenib after TACE failure than with repeated TACE[8,9] or with TACE and sorafenib combination therapy than with TACE alone[10,11].

After TACE failure, sorafenib therapy was more useful than intraarterial infusion chemotherapy with 5-FU[12,13], and the possibility for improved prognosis by switching to an appropriate second-line therapy has been suggested[14,15]. In studies evaluating sorafenib versus repeated TACE after TACE failure, median survival increased from 24.7 months to 25.4 months in patients who were treated with sorafenib after becoming unresponsive to TACE[8,9]. Treatment response also improved when, instead of applying sorafenib therapy, the anticancer drug used for TACE was changed from epirubicin to a platinum-based drug[16] or when spherical embolic agents were used for embolization[17]. At the same time, effectiveness of sorafenib has been reported also in cases of DEB-TACE failure[18]. The articles on the response of TACE failure cases to sorafenib include a report that sorafenib therapy at dose level ≥ 400 mg can be continued if ChE level is ≥ 220 U/L[19] and a report that prognosis is poor if portal vein invasion is noted after sorafenib therapy[20]. These reports suggest the importance of selecting appropriate drug therapy in individual cases.

Recent studies have shown that hypoxia-inducible factor (HIF)-1α, VEGF, and C-Met are involved in TACE failure[21,22]. There are also reports that preoperative levels of biomarkers such as interleukin-8 (IL-8) and miR-122[23] were used to predict TACE failure[24,25].

■ Explanation

The definition of TACE failure that is currently in use was proposed following expert consensus. Its validity was verified in a prospective study (OPTIMIS Study)[26]. At the meeting for finalizing recommendations, the Revision Committee decided on a weak

recommendation of the definition because, despite some validity of the definition of TACE failure currently in use, the OPTMIS Study was designed for prospective but non-interventional analysis through case accumulation and because the articles adopted for the current revision included no RCT.

Although there is global consensus over the necessity of immediately switching TACE to drug therapy if TACE failure is diagnosed, it is not uncommon that the reduction in hepatic reserves makes switching to drug therapy difficult if TACE is continued until the current criteria for TACE failure are met. Because multiple alternatives are now available for drug therapy after TACE failure, it is desirable to apply TACE in a more appropriate manner than before, preserving the hepatic reserves as far as possible. Specifically, it is required to select ultra-selective TACE (using the supportive software for identification of the feeding artery installed in the angiograph or the like and employing a small-diameter microcatheter) or balloon-occluded TACE (B-TACE; using a micro-balloon catheter capable of changing the hemodynamics of the area to be treated or injecting the embolic agent) tailored to the features of individual cases or lesions, while preserving the hepatic reserves as far as possible.

Based on expert consensus, it was recently proposed to avoid application of TACE to "TACE ineligible" cases (patient who are likely to have Child–Pugh B liver condition after TACE or those in whom response to TACE cannot be expected)[27,28]. The "TACE ineligible" conditions include: (1) conditions likely to fail in responding to TACE (tumor size/number not satisfying the up-to-seven criteria or the like), (2) conditions likely to result in reduced hepatic reserves (not satisfying the up-to-seven criteria, albumin-bilirubin [ALBI] grade 2 or lower), and (3) conditions not expected to respond to TACE (capsule-free tumor forms often accompanied by microvascular invasion such as proliferative single nodular type, confluent multinodular type, massive type, infiltrative type and diffuse type as well as nodular expression forms such as poorly differentiated HCC). According to expert opinions, the TACE ineligible conditions are not TACE contraindications but should be controlled while preserving the hepatic reserves by applying drug therapy with lenvatinib, etc. (drugs to which a high response rate is expected) prior to TACE or by a combination of drug therapy and TACE[29,30].

What is desired from now on is to apply TACE and judge TACE failure appropriately so that TACE can be switched to drug therapy at an appropriate timing after TACE failure. Also after switching to drug therapy, appropriate addition of TACE should be considered if drug therapy is continued or the response to drug therapy is poor.

Voting results

◎ Regarding the statement of recommendation “HCC is 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”, its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
9.1% (2 members)	86.4% (19 members)	4.5% (1 member)	0% (0 members)

Total voters: 22 members (abstention because of COI: 2 members)

■ References

28) Japan Society of Hepatology (edt.). Liver Cancer Management Manual 4th Edition, Tokyo: IGAKU-SHOIN Ltd, 2020 (Japanese)

Chapter 7:
Drug Therapy

● Introduction

The first evidence for drug therapy for HCC was yielded from the SHARP Study (a double-blind RCT comparing sorafenib with placebo) reported in 2008, demonstrating better survival in the sorafenib group compared to the placebo group. Following this finding, sorafenib was adopted as the standard drug for first-line drug therapy for advanced HCC and began to be covered by the National Health Insurance system (NHI) in Japan in May 2009.

Later, numerous studies for developing other first-line drug therapies were carried out, with sorafenib serving as the control. Still, none of those therapies was shown to be either superior or non-inferior to sorafenib. In 2017, however, non-inferiority of lenvatinib to sorafenib was reported, resulting in coverage of lenvatinib under the NHI in March 2018. In 2019, combination therapy with atezolizumab (an immune checkpoint inhibitor) and bevacizumab (vascular endothelial growth factor inhibitor) was shown to have extended patients' survival compared to the sorafenib group in RCT, resulting in coverage of this combination therapy under NHI in September 2020. Multiple phase III trials designed to evaluate the efficacy of combination therapies involving immune checkpoint inhibitors are under way.

Studies for developing second-line drug therapy after sorafenib therapy have also been carried out. In 2017, regorafenib was reported to have extended the survival of patients with PD (progressive disease) in response to preceding sorafenib therapy, resulting in this drug coverage under NHI in June 2017. In addition, ramucirumab, used for second-line drug therapy after sorafenib therapy, was reported to have extended the survival of patients with alpha-fetoprotein (AFP) $\geq$ 400 ng/mL in an RCT, resulting in NHI coverage in June 2019. Cabozantinib was additionally shown in a placebo-controlled RCT of post-sorafenib second-line drug therapy to have extended the survival of patients, resulting in NHI coverage in November 2020.

Thus, sorafenib, lenvatinib, and atezolizumab + bevacizumab are now available in first-line drug therapy. And regorafenib, ramucirumab, and cabozantinib can be used for second-line drug therapy.

In Japan, intrahepatic progression has conventionally been treated with hepatic arterial infusion chemotherapy (HAIC). Although HAIC is now applied less frequently than before in the presence of multiple systemic drug therapies, it is still used during clinical practice primarily for cases with tumor invasion of major vessels.

During the current revision, CQs were reviewed. CQ43 “Is molecular-targeted therapy recommended for unresectable advanced HCC?” in the fourth edition (2017 version) has been divided into CQ39 “What drugs are recommended as first-line drug therapy for unresectable advanced HCC?” and CD40 “What drugs are recommended as second-line and subsequent drug therapies for unresectable advanced HCC?”. CQ45 “What factors predict treatment response to drug therapy?” and CQ47 “How should the side effects of drug therapy be managed?” in the fourth edition have been deleted. As a CQ related to indications for drug therapy, CQ38 “Which patients are eligible for drug therapy?” has been newly adopted. Still more, considering the availability of multiple drug therapies mentioned above, “Algorithm for drug therapy” has been added to the current edition.

In the current revision process, 2 committee members independently performed a literature search of English articles published by January 31, 2020, using the search query developed for each CQ. The first screening was conducted through Web-based evaluation with the use of Guideline Manager, and the articles thus extracted were subjected to the second screening based on evaluation of their abstracts. Disagreements were resolved by discussion. As in previous editions, studies were excluded that reported treatment involving embolization or perioperative drug therapy and studies equivalent to a phase I or II clinical study that used drugs still in development or no longer in use. Also excluded were studies that described indeterminate antitumor effects and systematic reviews with insufficient or redundant data. Articles describing the results of a large-scale RCT published after January 31, 2020 and critical articles or conference reports not extracted with the search query were added by hand search. The articles after the first screening are summarized in Abstract Table.

The evidence level was decided through discussion at the Revision Committee on the basis of the Evidence Table. Recommendations were drafted by the staff in charge and adopted through discussions after evaluation of the evidence level at the recommendation finalizing meetings. The strength of recommendation was decided by voting.

The algorithm for drug therapy newly prepared for the current edition was drafted by the staff in charge of drug therapy, followed by preparation of the final draft through discussions among the Revision Committee members primarily via Email and by subsequent discussions and voting at the Revision Committee meeting.

A number of studies for developing drug therapy for HCC are now underway. Several new evidences are expected to be yielded from these studies before the next revision of the Guidelines, accompanied by coverage of some of these drugs in the NHI. These new drugs will be evaluated as to their evidence, reflected into the recommendations and made public in the JSH webpage soon after they are approved for NHI coverage, rather than

when they are presented at professional society meetings or published in journals, similar to the way adopted after publication of the fourth edition.

Explanation of Algorithm for Anti-HCC Drug Therapy

With the advance in drug therapies for HCC, six drug therapies have already been covered by the NHI in Japan, and we have created the algorithm for drug therapy. When dealing with patients eligible for the drug therapy recommended in CQ38, it is recommended to judge the presence or absence of indication for the combination therapy with atezolizumab and bevacizumab and, if judged “present,” to apply this combination therapy as the first-line drug therapy. For patients not indicated for the therapy because of comorbidity (e.g., autoimmune disease), treatment with sorafenib or lenvatinib is recommended. About second-line and subsequent drug therapies, treatment with sorafenib, lenvatinib, regorafenib, ramucirumab, and cabozantinib deserve consideration. However, evidence supporting the use of these drugs after the combination therapy with atezolizumab plus bevacizumab is unavailable. As second-line and subsequent therapies after sorafenib therapy, evidence supporting the use of regorafenib, ramucirumab, and cabozantinib is available, allowing us to recommend using these drugs. In Japan, treatment with lenvatinib also deserves consideration, although evidence is not available. Regarding second-line and subsequent drug therapies after lenvatinib therapy, treatment with sorafenib, regorafenib, ramucirumab, and cabozantinib deserve consideration, although evidence supporting their use is not available.

Some members of the Revision Committee voiced a view that the algorithm should include only the drugs for which evidence is available or that if the algorithm is prepared under such a policy, clinicians using this algorithm may misunderstand that drugs not supported by evidence cannot be used. There were also opinions that sufficient descriptions would be needed on the drugs without sufficient supportive evidence. The algorithm should add a comment of not intending to discourage the use of drugs without evidence as long as they are covered under the NHI. As a result of these discussions, it was decided to mark the drugs supported by evidence with solid fonts and underlines. The thus prepared algorithm was adopted by a majority of the votes at the Revision Committee.

(61)

Algorithm for Drug Therapy

Hepatocellular Carcinoma

- Advanced HCC not indicated for surgical resection, liver transplantation, percutaneous ablation, TACE, etc.
- Good performance status (PS)
- Child-Pugh A liver function

Indication for combination therapy with atezolizumab and bevacizumab

(62)

Present Absent

(63)

First-line drug therapy

Second-line and subsequent drug therapies

(64)

Atezolizumab + Bevacizumab

Sorafenib

Lenvatinib

Regorafenib

Ramucirumab

Cabozantinib

(65)

Sorafenib

Regorafenib

Ramucirumab

Cabozantinib

Lenvatinib

(66)

Lenvatinib

Sorafenib

Regorafenib

Ramucirumab

Cabozantinib

(67)

TACE: transcatheter arterial chemoembolization, PS: performance status

Solid font and underlines indicates the availability of evidence from randomized controlled trials

CQ38 Which patients are eligible for drug therapy?

Recommendation

Drug therapy is recommended for patients with advanced HCC not indicated for surgical resection, liver transplantation, percutaneous ablation, TACE, etc., but with good PS and hepatic reserves (Child-Pugh A liver function). (Strong Recommendation, Evidence Level A)

■ Background

HCC tends to repeatedly recur at high rates and often progresses to advanced disease without clear indications for surgical resection, liver transplantation, percutaneous ablation, or TACE. Systemic drug therapy is applied to such cases. When applying such therapy, however, the patient's performance status (PS) and organ function need to be taken into consideration from the viewpoints of drug metabolism and adverse events, because poor systemic condition and/or compromised organ function prevails in patients with advanced HCC. Here, recommendation related to the indications for drug therapy was reviewed.

■ Scientific Statement

Under the section of CQ43 in the fourth edition "Is molecular-targeted therapy recommended for unresectable advanced HCC?", recommendation of each drug was described, including the indications of such therapy. Following subsequent advances in drug therapy, the number of drugs covered by the NHI has increased, making the therapy more complicated. In the fifth edition (2021 version), the CQ has been divided into three parts: CQ38 "Which patients are eligible for drug therapy?", CQ39 "What drugs are recommended as first-line drug therapy for unresectable advanced HCC?" and CD40 "What drugs are recommended as second-line and subsequent drug therapies for unresectable advanced HCC?".

On the thus adopted new CQ39, a literature search setting the publication date between January 1, 2000 and January 31, 2020 extracted 363 articles. This was narrowed down to 25 articles in the first screening and 6 articles in the second screening. A total of 7 articles, including one article extracted by hand search, are cited here for CQ38.

The eligibility criteria for the clinical trials (phase III trials) of various drugs deserve reference when discussion over this CQ. The eligibility criteria adopted in the clinical trials on each drug are cited below.

In a phase III trial comparing combined atezolizumab plus bevacizumab therapy with sorafenib therapy as the first-line drug therapy, the eligibility criteria were systemic

therapy naïve patients, unresectable or metastatic HCC having measurable lesion(s), Child-Pugh A liver function, and ECOG performance status 0 or 1[1].

In another phase III trial, comparing lenvatinib with sorafenib used for first-line drug therapy, unresectable HCC, Child-Pugh A liver function, and ECOG performance status 0 or 1 were eligibility criteria[2].

In two other phase III trials comparing sorafenib with placebo used for first-line drug therapy, drug-therapy naïve unresectable HCC, Child-Pugh A liver function, and ECOG performance status 0 or 1 were eligibility criteria[3,4].

In a phase III trial comparing regorafenib with placebo used for second-line drug therapy, advanced HCC not indicated for resection, percutaneous ablation and embolization, tolerability with sorafenib, response "PD (progressive disease)" to sorafenib rated by diagnostic imaging, Child-Pugh A liver function, and ECOG performance status 0 or 1 were eligibility criteria[5].

In another phase III trial comparing ramucirumab with placebo used for second-line drug therapy, response "PD" or intolerability to/with sorafenib, AFP ≥ 400 ng/mL, unresectable HCC, Child-Pugh A liver function, and ECOG performance status 0 or 1 were eligibility criteria[6].

In the phase III trial comparing cabozantinib with placebo used for second-line or third-line drug therapy, unresectable HCC with prior treatment (prior systemic therapy with up to 2 drugs, including sorafenib, is acceptable), Child-Pugh A liver function, and ECOG performance status 0 or 1 were eligibility criteria[7].

Thus, all of the trials conducted to develop the drug therapies (adopted by the NHI to date) were common in terms of three eligibility criteria: 1) unresectable HCC, 2) hepatic reserves equivalent to Child-Pugh A, and 3) ECOG performance status 0 or 1.

■ Explanation

So that the efficacy and safety of new drug therapy under development may be verified, an appropriate setting of the criteria for eligible subjects is essential. The target of drug therapy for HCC can be roughly divided into 1) suppression of recurrence or exacerbation of tumors eligible for locoregional therapy such as resection, and 2) control of tumors difficult to treat with locoregional therapy. Numerous attempts to develop drug therapies with these targets have been made to date. Still, the drug therapies targeting only the latter have come to be covered by the NHI in Japan, and no adjuvant chemotherapy to be combined with such drug therapies has yet been established. Namely, the drugs currently covered by the NHI were developed by trials setting the targets (eligibility criteria) as "unresectable HCC."

Furthermore, two additional criteria (ECOG performance status 0 or 1, and hepatic reserves equivalent to Child-Pugh A) were adopted as eligibility criteria for the clinical trials (phase III trials) on these drugs. The recommendation on CQ38 has thus been set as "Drug therapy is recommended for patients with advanced HCC not indicated for surgical resection, liver transplantation, percutaneous ablation, TACE, etc. but having good PS and good hepatic reserves (Child-Pugh A liver function)." In other words, the efficacy and safety of drug therapy have been verified, i.e., assured, only under the conditions specified here.

It is difficult to determine the evidence level for this recommendation in the absence of phase III clinical trial comparing this set of conditions with another set. However, considering that the articles on various drug therapies adopted during discussions over indications of drug therapy were phase III RCTs, the evidence level was set as A.

Voting results

◎ Regarding the statement of recommendation "Drug therapy is recommended for patients with advanced HCC not indicated for surgical resection, liver transplantation, percutaneous ablation, TACE, etc. but having good PS and good hepatic reserves (Child-Pugh A liver function)", its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
100% (20 members)	0% (0 members)	0% (0 members)	0% (0 members)

Total voters: 20 members (abstention because of COI: 4 members)

During the Revision Committee meeting, there was a voice that referring to "TACE, etc." might be unnecessary because situations "not indicated for TACE, etc." are rare. However, considering that many of the past clinical trials adopted "not indicated for TACE, etc." as one of the eligibility criteria, we decided to incorporate this into the conditions for this recommendation.

■ References

CQ39 What drugs are recommended as first-line drug therapy for unresectable advanced

ICC?

Recommendations

1. Combination treatment with atezolizumab plus bevacizumab is recommended as first-line drug therapy for unresectable advanced HCC. (Strong Recommendation, Evidence Level A)

2. Treatment with sorafenib or lenvatinib is recommended if atezolizumab plus bevacizumab is not indicated because of comorbidity such as autoimmune disease. (Strong Recommendation, Evidence Level A)

■ Background

HCC often repeats recurrence, eventually leading to advanced HCC not indicated for surgical resection, liver transplantation, percutaneous ablation, and TACE. The effectiveness of sorafenib, a molecular-targeted drug, against such unresectable HCC was reported in 2008. It was the first report on drug therapy compared with placebo. Later, regorafenib, lenvatinib, ramucirumab, cabozantinib, and atezolizumab + bevacizumab were shown to be effective as drug therapy for HCC. Here, what drugs are recommendable for first-line drug therapy were reviewed.

■ Scientific Statement

CQ43 in the fourth edition, “Is molecular-targeted therapy recommended for unresectable advanced HCC?” has been divided in the current edition into CQ39 and CD40, corresponding to first-line drug therapy and second-line drug therapy, respectively. The literature search query employed in the fourth edition was modified to simultaneously allow the search for articles related to CQ39 and CQ40. A literature search conducted with this query and a publication date between July 1, 2016 and January 31, 2020 extracted 124 articles. This was narrowed down to 11 in the first screening, focusing on RCT, and then to 9 in the second screening. Of these 9 articles, 6 had already been adopted in the revised fourth edition (revised 2017 version), and the remaining 3 were newly added articles. In addition, one report at a professional society meeting was adopted as a critical article. In total, 4 articles were newly adopted for the current edition. These 4 articles plus 17 of the 20 articles from the revised fourth edition (excluding 3 articles on sub-group analysis, etc.) were adopted for Q39 + CQ40 (21 articles in total). Of these articles, 11 articles on first-line drug therapy were adopted for CQ39.

Sorafenib significantly improved the survival, as compared to the placebo group, when used in patients with good performance status (PS) and Child-Pugh A liver function among the patients not indicated for surgical resection, liver transplantation, percutaneous

ablation and TACE[1,2]. The efficacy and safety of sorafenib were endorsed also in a systematic review[3].

RCTs comparing sorafenib with sunitinib, brivanib or linifanib used for first-line drug therapy failed to demonstrate superiority or non-inferiority of sorafenib to any of these drugs[4-6]. An RCT, designed to evaluate the effect of adding erlotinib to the sorafenib therapy, did not significantly improve survival[7]. Lenvatinib was compared to sorafenib as a control in an RCT, demonstrating non-inferiority in terms of survival prolongation[8]. Another RCT, evaluating the effect of adding doxorubicin to the sorafenib therapy, failed to demonstrate significant improvement in survival, either[9]. Nivolumab did not significantly improve survival in an RCT adopting sorafenib as a control[10]. Combination treatment with atezolizumab and bevacizumab prolonged the survival as compared to the sorafenib group in an RCT[11].

■ Explanation

There have recently been remarkable advances in the development of drug therapies for HCC. After publication of the fourth edition of the Guidelines, 4 RCTs on first-line drug therapy have been reported, dealing with lenvatinib, sorafenib + doxorubicin, nivolumab and atezolizumab + bevacizumab. In the presence of these numerous RCT reports, the 3 articles adopted in the fourth edition, dealing with sub-group analysis of sorafenib, etc., have been deleted from the current edition because they did not provide high-quality evidence.

Sorafenib was shown in 2008 to improve the survival as compared to the placebo group (SHARP Study) and in 2009 to improve the survival (Asia-Pacific Study)[1,2]. The effectiveness of sorafenib was shown also in a subsequent systematic review mentioned above[3]. Thus, reports with high-quality evidence are available concerning the efficacy of sorafenib against unresectable HCC. In Japan, the use of this drug for unresectable HCC began to be covered by the NHI in May 2009.

The reports on effectiveness of sorafenib against advanced HCC triggered subsequent attempts of evaluating molecular-targeted drugs (sunitinib, brivanib and linifanib), sorafenib + erlotinib and sorafenib + doxorubicin in comparison to sorafenib monotherapy. However, none of these RCTs demonstrated superiority or non-inferiority to sorafenib monotherapy in terms of survival extension (a primary endpoint)[4-7,9].

Lenvatinib, on the other hand, was shown to be non-inferior to sorafenib in terms of survival extension (a primary endpoint)[8] and its use for unresectable HCC began to be covered by the NHI in March 2018. As a result, it is now possible in Japan to use not only sorafenib but also lenvatinib for first-line drug therapy.

Now, development of new regimens of anti-cancer drug therapy using immune checkpoint inhibitors is active. Nivolumab, an immune checkpoint inhibitor, was evaluated as a means of first-line drug therapy for HCC, but it did not improve the survival in comparison to the sorafenib therapy group in an RCT[10]. Later, the combination treatment with atezolizumab (an immune checkpoint inhibitor) and bevacizumab (a neovascularization inhibitor) extended the survival in comparison to sorafenib in an RCT[11], allowing this combination treatment for unresectable HCC to be covered by the NHI in September 2020. Conventionally, sorafenib or lenvatinib has been used for first-line drug therapy. However, considering that combined atezolizumab + bevacizumab therapy has been shown to extend the survival significantly as compared to sorafenib and that lenvatinib has been shown to be non-inferior, rather than superior, to sorafenib (although no RCT directly comparing combined atezolizumab + bevacizumab therapy with lenvatinib has been conducted), it was decided to recommend combined atezolizumab + bevacizumab for first-line drug therapy in the current edition.
However, for cases judged as ineligible for this combination treatment because of comorbidity (e.g., autoimmune disease), the conventionally used sorafenib or lenvatinib is recommended.

Voting results

◎ Regarding the statement of recommendation 1 “Combination treatment with atezolizumab and bevacizumab is recommended as first-line drug therapy for unresectable advanced HCC”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
100% (19 members)	0% (0 members)	0% (0 members)	0% (0 members)

Total voters: 19 members (abstention because of COI: 4 members)

Voting results

◎ Regarding the statement of recommendation 2 “Treatment with sorafenib or lenvatinib is recommended if the above-cited therapy is not indicated because of comorbidity such as autoimmune disease”, its adoption was strongly recommended by voting of committee members.

Strongly	Weakly	Weakly	Strongly

recommended to adopt	recommended to adopt	recommended not to adopt	recommended not to adopt
100% (19 members)	0% (0 members)	0% (0 members)	0% (0 members)

Total voters: 19 members (abstention because of COI: 4 members)

■ References

CQ40 What drugs are recommended as second-line and subsequent drug therapies for unresectable advanced HCC?

Recommendation

In cases shown by radiological progression as progressive disease after sorafenib therapy but tolerable with sorafenib (Child-Pugh A liver function), treatment with regorafenib is recommended. Ramucirumab is recommended for cases with Child-Pugh A liver function and AFP ≥ 400 ng/mL who were shown by diagnostic imaging as PD after sorafenib therapy or those where sorafenib was discontinued due to side effects. Cabozantinib is recommended for cases with Child-Pugh A liver function having a history of sorafenib treatment and rated as PD after systemic drug therapy. (Strong Recommendation, Evidence Level A)

■ Background

HCC often repeats recurrence, eventually leading to advanced HCC not indicated for surgical resection, liver transplantation, percutaneous ablation and TACE. Effectiveness of sorafenib, a molecular-targeted drug, against such unresectable HCC was reported in 2008. Later, regorafenib, lenvatinib, ramucirumab, cabozantinib and atezolizumab + bevacizumab were shown to be effective as drug therapy for HCC. Here, what are recommendable for second-line drug therapy were reviewed.

■ Scientific Statement

CQ43 in the fourth edition “Is molecular-targeted therapy recommended for unresectable advanced HCC?” has been divided in the current edition into CQ39 and CD40, corresponding to first-line drug therapy and second-line drug therapy, respectively. The literature search query employed in the fourth edition was modified to allow search for articles related to CQ39 and CQ40 simultaneously. A literature search conducted with this

query and a publication date between July 1, 2016 and January 31, 2020 extracted 124 articles. This was narrowed down to 11 in the first screening, focusing on RCT, and then to 9 in the second screening. Of these 9 articles, 6 had already been adopted in the revised fourth edition, and the remaining 3 were newly added articles. In addition, one report at a professional society meeting was adopted as a critical article. In total, 4 articles were newly adopted for the current edition. These 4 articles plus 17 of the 20 articles from the revised fourth edition (excluding 3 articles on sub-group analysis, etc.) were adopted for Q39 + CQ40 (21 articles in total). Of these articles, 10 articles[1-10] on second-line drug therapy were adopted or CQ40.

RCTs using brivanib, everolimus, tivantinib, or S-1 compared with placebo as second-line drug therapy after progression or intolerant to sorafenib have been conducted, but all failed to demonstrate survival extension.[1-4]. In a placebo-controlled RCT, regorafenib was shown to significantly extend the survival of sorafenib-tolerable patients with Child-Pugh A liver function rated as PD by diagnostic imaging after sorafenib therapy (cases able to orally take 100 mg or more sorafenib per day for 20 days or longer during the 28-day period before completion of treatment)[5]. Ramucirumab failed to extend the survival of patients after sorafenib treatment in a placebo-controlled RCT[6], but sub-group analysis of the data from that study revealed survival extension in patients with high AFP levels (≥ 400 ng/mL). To endorse this result, a placebo-controlled RCT was carried out in patients after first-line drug therapy with sorafenib having high AFP (≥ 400 ng/mL) and Child-Pugh A liver function, revealing that the survival was extended by ramucirumab[7]. Cabozantinib was shown to extend the survival of patients having a history of sorafenib treatment, rated as PD after systemic drug therapy and classified as Child-Pugh A liver function in a placebo-controlled RCT[8]. ADI-PEG 20 (pegylated arginine deiminase) did not extend the survival of patients having undergone second-line or subsequent drug therapies in a placebo-controlled RCT[9]. Pembrolizumab did not extend survival in a placebo-controlled RCT involving patients after sorafenib treatment[10].

■ Explanation

There have recently been remarkable advances in the development of drug therapies for HCC. After publication of the fourth edition of the Guidelines, 4 RCTs on second-line drug therapy have been reported, dealing with ramucirumab, cabozantinib, ADI-PEG 20 and pembrolizumab.

Second-line drug therapy after sorafenib treatment, using a molecular-targeted drug (brivanib or everolimus) or a cytotoxic anti-cancer drug (S-1), was evaluated in comparison to placebo, but failed to be shown as superior in terms of survival (the primary

endpoint)[1-3]. Tivantinib failed to extend survival of HCC patients with high tumor tissue MET expression in a placebo-controlled RCT[4].

In a placebo-controlled RCT, regorafenib was shown to extend the survival of sorafenib-tolerable patients with Child-Pugh A liver function rated as PD by diagnostic imaging after sorafenib therapy (cases able to orally take 400 mg or more sorafenib per day for 20 days or longer during the 28-day period before completion of treatment)[5]. This was the first report of survival extension by means of second-line drug therapy. In June 2017, regorafenib was covered by the NHI for use in treatment of unresectable HCC having exacerbated after anti-cancer chemotherapy.

Ramucirumab failed to extend the survival of patients after sorafenib treatment in a placebo-controlled RCT, involving patients having prematurely quitted the sorafenib therapy for a reason of adverse evets as well as patients rated by diagnostic imaging as PD after sorafenib therapy[6], but an RCT involving patients with high AFP levels (≥ 400 ng/mL) revealed extended survival after ramucirumab treatment[7]. This drug began to be covered by the NHI in June 2019 for use in the treatment of unresectable HCC having exacerbated after anti-cancer chemotherapy and AFP ≥ 400 ng/mL.

Cabozantinib was shown to extend the survival of patients having a history of sorafenib treatment, having progressed after systemic drug therapy and classified as Child-Pugh A liver function in a placebo-controlled RCT. Of all patients enrolled to that study, 27% had received systemic therapy with one drug other than sorafenib and undergone therapy with cabozantinib as third-line drug therapy[8]. In Japan, this drug began to be covered by the NHI in November 2020 with indications of unresectable HCC having exacerbated after anti-cancer chemotherapy.

In a placebo-controlled RCT, ADI-PEG 20 did not extend the survival of patients having previously undergone systemic therapy with one or more drugs (including systemic therapy with drug(s) other than sorafenib)[9]. Pembrolizumab extended the overall survival and the progression-free survival (both the primary endpoints) of patients after preceding sorafenib treatment in a placebo-controlled RCT, but the extent of survival extension was not large enough to satisfy the preset statistical significance level, thus failing to demonstrate effectiveness[10].

Thus, survival extension has been achieved by second-line drug therapy using one of the three drugs (regorafenib, ramucirumab and cabozantinib). The second-line drug therapy using these drugs was evaluated in RCTs involving patients having received the first-line drug therapy with sorafenib, instead of the first-line combined drug therapy with atezolizumab + bevacizumab or the first-line monotherapy with lenvatinib.

Some of the overseas guidelines describe sorafenib or lenvatinib as a means of treatment

succeeding to combined atezolizumab + bevacizumab therapy. However, in the absence of reports with evidence levels high enough to be recommended as second-line drug therapy after combined atezolizumab + bevacizumab therapy or lenvatinib monotherapy, no regimen is now unconditionally recommendable as the second-line drug therapy after such first-line drug therapies. Thus, the current edition recommends regorafenib, ramucirumab and cabozantinib as a possible means of second-line drug therapy after sorafenib therapy for patients satisfying the eligibility criteria employed in the corresponding RCTs.

Voting results

◎ Regarding the statement of recommendation "In cases shown by diagnostic imaging as PD (progressive disease) after sorafenib therapy but tolerable with sorafenib (Child-Pugh A liver function), treatment with regorafenib is recommended. Ramucirumab is recommended for cases with Child-Pugh A liver function and AFP ≥ 400 ng/mL who were shown by diagnostic imaging as PD after sorafenib therapy or those where sorafenib was discontinued due to side effects. Cabozantinib is recommended for cases with Child-Pugh A liver function having a history of sorafenib treatment and rated as PD after systemic drug therapy", its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
100% (18 members)	0% (0 members)	0% (0 members)	0% (0 members)

Total voters: 18 members (abstention because of COI: 5 members)

This recommendation does not intend to deny second-line drug therapy after combined atezolizumab + bevacizumab or lenvatinib monotherapy. If either combined atezolizumab + bevacizumab or lenvatinib monotherapy has been applied as first-line drug therapy during clinical practice, drugs other than those used in the first-line drug therapy are likely to be selected for the second-line drug therapy. However, since there is no sufficient evidence serving as the rationale for selecting drugs for the second-line drug therapy after the first-line therapy using atezolizumab + bevacizumab or lenvatinib alone, no drug is definitely recommended for the second-line drug therapy in the current edition. We expect evidence related to the selection of drugs for second-line drug therapy after first-line drug

therapy is reported.

In recent years, organ-agnostic genomic-based treatment has advanced, allowing pembrolizumab to be covered by the NHI in December 2018 for use in the treatment of standard therapy-refractory advanced/recurrent solid cancers with microsatellite instability (MSI)-high that have exacerbated after anti-cancer therapy. In June 2019, entrectinib also began to be covered by the NHI for use in the treatment of neurotrophic receptor tyrosine kinase (NTRK) gene fusion-positive advanced/recurrent solid cancers. Through discussions during the Revision Committee meetings, it was decided to avoid referring to such organ-agnostic genomic-based treatment in the recommendation because: 1) HCC patients had not been included in the subjects of the clinical trials on pembrolizumab used for treatment of MSI-high solid cancers; 2) MSI-high is quite rare among HCC patients[11]; and 3) atezolizumab, which is an anti-PD-L1 antibody acting on the same pathway as pembrolizumab, is available for use. The recommendation also avoided referring to the use of entrectinib for treatment of NTRK gene fusion-positive advanced/recurrent solid cancers because HCC patients had not been included in the subjects of the clinical trials concerned[12] and because NTRK gene fusion is quite rare among HCC patients[13]. However, this drug may serve as an alternative treatment in cases where these genetic anomalies are detected by the gene panel test with tumor tissue or blood, and standard therapy is difficult to apply.

■ References

CQ41 Is HAIC recommended for unresectable advanced HCC?

Recommendation

HAIC may be performed for advanced HCC accompanied by multiple intrahepatic lesions or vascular invasion, which are not indications for surgical resection, liver transplantation, locoregional therapy, and TACE. (Weak Recommendation, Evidence Level B)

■ Background

Despite the need for specific skills, many patients have been treated by HAIC in Japan. It allows highly concentrated anticancer drugs to be administered directly into the HCCs, preventing the systemic administration of a high concentration of drugs and thus suppressing the incidence of adverse effects. Here, we reviewed the recommendation of

HAIC for unresectable advanced HCC.

■ Scientific Statement

A literature search conducted with a newly created search query and a publication date between July 1, 2016 and January 31, 2020 extracted 63 articles. This was narrowed down to 28 in the first screening. Nine articles that each reported ≥ 50 HAIC cases were extracted in the second screening. In addition, 2 articles were hand-searched from those published after February 2020. With the inclusion of 7 articles (quoted in the Scientific Statement for CQ44 in the fourth edition) from the 26 articles adopted until the fourth edition, excluding those adopted only for the appendix tables of the fourth edition, a total of 18 articles are cited here for CQ41.

In a small-scale RCT, combination therapy with systemic administration of interferon and cisplatin arterial infusion significantly improved median overall survival compared with cisplatin arterial infusion chemotherapy or BSC alone[1]. Combination therapy with interferon and 5-FU arterial infusion also significantly improved overall survival compared with historical controls[2]. In a study using data from primary HCC cases recorded in the database from the nationwide follow-up survey of primary liver cancer by the Liver Cancer Study Group of Japan, treatment outcomes were compared between HAIC with 5-FU and cisplatin and BSC in two groups of patients matched by propensity score[3]. Compared with BSC, HAIC had a good treatment outcome (hazard ratio 0.60; $p < 0.0001$) even in patients with 4 or more nodules or portal vein tumor thrombus[3].

In a retrospective cohort study of HAIC and sorafenib in HCC patients, the response rate to HAIC was higher than that to sorafenib[4,5] (particularly higher in cases sensitive to TACE and vascular invasion positive[6]). In a meta-analysis comparing the outcomes of HAIC and sorafenib in advanced HCC cases, HAIC was more effective and resulted in better prognosis as compared to sorafenib[7]. In a retrospective analysis of the outcomes of HAIC and sorafenib therapy for advanced HCC cases matched by propensity score, there was no significant difference in prognosis between the two therapies in the studies conducted until 2015[8.9], while HAIC resulted in better prognosis than sorafenib in larger-scale cohort studies reported after 2016[10]. (particularly better in cases free of extrahepatic lesions[11] and cases free of extrahepatic lesions and vascular invasion positive[12]).

In a phase II trial designed to evaluate the add-on effect of HAIC with cisplatin in advanced HCC patients receiving sorafenib therapy, survival was longer following sorafenib + HAIC than following sorafenib monotherapy[13]. However, in a phase III trial evaluating the add-on effect of HAIC using 5-FU and cisplatin, there was no significant improvement in survival in the sorafenib + HAIC group as compared to the sorafenib

monotherapy group[14]. In another phase III trial evaluating the add-on effect of HAIC using FOLFOX in patients with advanced HCC accompanied by portal vein tumor thrombus, the prognosis was better in the sorafenib + HAIC group than in the sorafenib alone group[15].

Other than these studies, a retrospective analysis comparing the outcomes of HAIC in patients with HCC accompanied by extrahepatic metastasis revealed better prognosis in cases with non-pulmonary metastasis than in cases with pulmonary metastasis[16]. In another retrospective analysis comparing the outcomes of HAIC in HCC patients by hepatic reserves, the prognosis was better in cases Child-Pugh score lower than 8 than in cases with the score ≥ 8 or 9[17,18].

■ Explanation

Eleven articles adopted in the current edition mostly reported analyses of the outcomes of HAIC and sorafenib therapy for advanced HCC cases. To be specific, 9 articles were trials adopting sorafenib as a control in comparison to HAIC. Seven of them simply compared outcomes of HAIC with sorafenib therapy, and the remaining 2 articles (RCTs) compared sorafenib + HAIC as with sorafenib monotherapy. Eight of the 9 articles demonstrated better outcomes of HAIC as compared to sorafenib therapy.

The Explanation in the fourth edition states: “To verify the prognostic benefits of HAIC, it is desirable to conduct high-quality comparative studies that use molecular-targeted drugs like sorafenib as a control, but the difficulty associated with this means that there have been no such studies carried out as yet.” Facing difficulty in carrying out such a comparison, the Revision Committee adopted 2 RCTs. Both were designed to evaluate the add-on effect of HAIC in advanced HCC patients receiving sorafenib therapy. One of them reported: “In cases accompanied by portal vein tumor thrombus, the prognosis was better after sorafenib + HAIC than after sorafenib monotherapy.” The other showed: "The survival was not significantly improved by sorafenib + HAIC as compared to sorafenib monotherapy.”

The articles simply comparing HAIC with sorafenib therapy often report that the prognosis of patients free of extrahepatic lesions or vascular invasion positive is better following HAIC than following treatment with sorafenib alone.

Some RCTs, however, failed to demonstrate superiority of HAIC to sorafenib therapy. Still more, the reports demonstrating better outcomes of HAIC as compared to sorafenib monotherapy often limited applicability of this finding to patients satisfying “conditions” such as “accompanied by portal vein tumor thrombus,” “free of extrahepatic lesions” and “vascular invasion positive.” Reflecting this fact, the current revision modified the

recommendation in the fourth edition “HAIC may be performed for advanced HCC accompanied by progressive intrahepatic lesions ---” (Weak Recommendation) into “HAIC may be performed for advanced HCC accompanied by multiple intrahepatic lesions or vascular invasion ---.” The decision as to the strength of recommendation was assigned to voting by the Revision Committee members.

Voting results

◎ Regarding the statement of recommendation “HAIC may be performed for advanced HCC accompanied by multiple intrahepatic lesions or vascular invasion, which are not indications for surgical resection, liver transplantation, locoregional therapy and TACE”, its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
15.0% (3 members)	85.0% (17 members)	0% (0 members)	0% (0 members)

Total voters: 20 members (abstention because of COI: 3 members)

■ References

CQ42 How should tumor response to drug therapy be assessed?

Recommendation

Tumor response to drug therapy should be assessed using RECIST or modified RECIST. (Strong Recommendation, Evidence Level A)

■ Background

RECIST, which assesses tumor shrinkage in one direction, is often used to evaluate treatment response to conventional chemotherapy[1,2]. However, typical HCC is hypervascular, and the response of HCC to treatment is sometimes expressed as reduction in intratumoral blood flow. So, modified RECIST (mRECIST) specific to HCC has also been used[3]. Here, we investigated the recommendation for assessing the response of HCC to drug therapy, taking into consideration the methods employed in RCTs for assessing the response of 6 efficacy-endorsed drug therapy regimens, i.e., combined atezolizumab

+ bevacizumab[4], sorafenib[5,6], lenvatinib[7], regorafenib[8], ramucirumab[9,] and cabozantinib[10].

■ Scientific Statement

A literature search conducted with a publication date between July 1, 2016 and January 1, 2020 extracted 52 articles. This was narrowed down to 15 in the first screening, focusing on RCTs. This was narrowed further to 5 articles in the second screening. Two RCTs were additionally adopted by review of the articles adopted in the fourth edition. With the addition of one RCT and 7 articles on methods for response evaluation extracted by hand search, a total of 15 articles are cited for CQ42. The articles involving retrospective analysis adopted in the fourth edition were excluded from the current edition. Among the criteria for assessment of response to drug therapy in general, RECIST1.1 is currently the most commonly used[2]. This set of criteria is designed to evaluate tumor shrinkage in one direction, covering 2 lesions at maximum per organ, without considering intratumoral blood flow reduction. However, the criteria used more often to determine the tumor response of HCC are the mRECIST[3], EASL[11], RECICL[12], and Choi criteria[13], which evaluate decreases in intratumoral blood flow as well. Recently, iRECIST, which also considers a definite assessment of cancer progression, has also begun to be used following the clinical introduction of immune checkpoint inhibitors[14]. Table 1 lists the methods employed for assessing HCC response to 6 efficacy-endorsed drug therapy regimens in 7 RCTs[4-10].

In all of these 7 studies, RECIST was used for response assessment. In the 3 studies on combined atezolizumab + bevacizumab, lenvatinib and regorafenib, mRECIST was additionally employed.

■ Explanation

When sorafenib was clinically introduced as standard therapy for HCC, the importance of assessing reduction in intratumoral blood flow was also pointed out, partly because tumor shrinkage is difficult to achieve with this type of cancer[15]. Among others, lenvatinib treatment often leads to the disappearance of high intensity of the tumor, and there arose many voices recommending a check for this change in the evaluation of HCC response to this drug. As a result, mRECIST also began to be used[7]. The fourth edition recommended using criteria that consider the intratumoral blood flow. However, following the recent clinical introduction of combined immunotherapy such as atezolizumab + bevacizumab therapy[4], tumor shrinkage can be expected even in cases of HCC, resulting in a voice that RECIST solely assessing tumor shrinkage without considering the disappearance of intratumoral blood flow will suffice. RECIST requires

only simple measurement, which is less likely to cause inter-examiner errors, and thus allows easy comparison among different studies. We can also expect tumor shrinkage from drug therapy for HCC. With this in mind, the use of RECIST or mRECIST for assessing response to drug therapy is recommended.

Table 1. Methods for assessment of the response of unresectable HCC to drug therapy (68)
Anti-cancer drug/Regimen
Method 1
Method 2
Study
Reference
(69)
Sorafenib
Sorafenib
Lenvatinib
Atezolizumab + Bevacizumab
Regorafenib
Ramucirumab
Cabozantinib

Voting results

◎ Regarding the statement of recommendation “Treatment response to drug therapy should be assessed using RECIST or modified RECIST”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
95.5% (21 members)	4.5% (1 member)	0% (0 members)	0% (0 members)

Total voters: 22 members (abstention because of COI: 3 members)

■ References

Chapter 8:
Radiation Therapy

● Introduction

Radiotherapy can be characterized by minimal invasiveness and stress-less adaptability even for elderly patients and patients with complications. It is currently selected as a means of radical treatment for many types of malignant neoplasm and is used extensively also for treatment aimed at alleviating the tumor-caused symptoms.

Until around the 1970s when two-dimensional irradiation using fluoroscopy for treatment planning had prevailed, radiotherapy for HCC had been applied seldom. This was because precise targeting of the intrahepatic tumor was difficult with the technology in those days, forcing irradiation to a wider area of the lesions and posing a concern over the risk of liver damage arising from high-dose curative irradiation.

Three-dimensional conformation radiotherapy began to be applied around the 1980s. With this technique, the tumor within the liver can be identified three-dimensionally by CT scan, thus contributing to marked decrease of the intact liver volume exposed to unnecessary irradiation. It simultaneously enabled quantitative evaluation and prediction of the risk for hepatopathy with the use of dose volume histograms. As a result, radiotherapy began to be applied, with major targets set at cases difficult to treat with other treatment methods (e.g., vascular invasion-positive HCC). However, it was still difficult in those days to attempt complete local control by radiotherapy alone.

In recent years, advances in computer technology have enabled improvements in treatment planning algorithms, accompanied by development of intensity modulated radiotherapy (IMRT; enabling dose concentration tailored to the tumor morphology), high-precision guiding with 3-dimensional images and timeline-based countermeasures against respiration-caused bodily movements during radiotherapy. These improvements, combined with technological innovations related to medical devices, have enabled reducing the radiation dose to surrounding intact tissues while precisely identifying the changing tumor location and applying a curative dose to the lesions. New techniques of radiation developed include stereotactic body radiation therapy (SBRT) which can precisely apply radiation at a single dose higher than that of conventional fractionated radiotherapy (2 Gy/dose) as well as particle radiotherapy (proton beam therapy, heavy-ion radiotherapy). These new techniques have been utilized for various diseases and conditions also in Japan. For radical treatment of HCC, SBRT and particle radiotherapy are predominantly used from the viewpoint of a balance between dose distribution and liver damage.

In the previous edition, radiotherapy for HCC was divided into two categories, i.e., SBRT/particle radiotherapy as high-intensity modalities aimed at complete local control and three-dimensional conformation radiotherapy (ordinary fractionated radiotherapy) as auxiliary therapy for patients receiving surgery, TACE or the like. A new feature of the systematic review during the current revision lies in that there were data from RCTs comparing SBRT or particle radiotherapy with other standard therapies (percutaneous ablation, TACE, etc.) and the articles dealing with such comparison based on propensity score. None of these studies or reports demonstrated inferiority of SBRT or particle radiotherapy to existing standard therapies, and they were shown to be comparable (superior in some endpoints) to the standard therapies. Considering these findings and the expectation of further evidence accumulated from now on, the high-precision radiotherapy by means of SBRT or particle radiotherapy is adopted in a CQ, in continuation from the fourth edition (2017 version). Meanwhile, three-dimensional conformation radiotherapy, which is slightly lower in control rate because of lower dose intensity, has been deleted from the CQ in the current edition after discussions at the Revision Committee, in view of the fact that the number of reports on this modality has decreased considerably under the trend of its replacement by SBRT and particle radiotherapy aimed at complete local control.

Radiotherapy for metastatic tumors has been usually applied regardless of the primary site of tumor. Although there is little evidence specific to HCC, the CQ on bone metastasis and brain metastasis is adopted in a CQ, in continuation from the fourth edition, in view of the fact that the Guidelines will be utilized by a broad range of clinicians.

It is clinically known that certain time is taken until tumor shrinkage is achieved after radiotherapy for HCC and that the speed of shrinkage varies among individual cases. So, a new CQ about the method for response assessment after radiotherapy has been adopted, based on the awareness that an idea/view differing from that for other treatment methods seems necessary for radiotherapy.

The systematic review during the current revision revealed the availability of data from RCTs comparing radiotherapy aimed at radical treatment with other standard therapies as well as abstracts showing such a comparison based on propensity score. This suggests that the evidence for radiotherapy in this field is being established. Clinical studies on combination of drug therapy and radiotherapy and so on are now under way, allowing us to expect that the roles of radiotherapy in the treatment of HCC will be further clarified from now on.

CQ43 Which patients are eligible for stereotactic body radiotherapy?

Recommendation

Stereotactic body radiotherapy may be performed in patients with 1-3 HCCs difficult to treat with resection or percutaneous ablation, Child-Pugh A/B (score 7) liver function and tumor diameter ≤ 5 cm, regardless of presence/absence of vascular invasion. (Weak Recommendation, Evidence Level B)

■ Background

Stereotactic body radiotherapy (SBRT) is a radiation therapy method that precisely delivers a high dose per fraction to a localized target tumor in a small number of fractions. It can achieve higher local control and reduce the adverse events in the surrounding organs as compared to conventional fractionated radiotherapy. SBRT is also applicable to HCC cases difficult to undergo surgery or percutaneous ablation for medical reasons (surgery: e.g., intolerable, percutaneous ablation: e.g., target tumor too close to the large vessel, bile duct or diaphragm, target tumor invisible on ultrasonography)[1]. Because of these advantages, SBRT has recently been becoming popular as a mean of local treatment of HCC. In this CQ, which HCC patients are eligible for SBRT were reviewed. Although this CQ pertains to the indications for SBRT, the methods for dose fractionation and prescription for SBRT are also described, with the expectation that the Guidelines are referred to by clinicians when performing SBRT.

■ Scientific Statement

This CQ is a continuation of CQ48 in the fourth edition. A literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 235 articles. This was narrowed down to 50 in the first screening. Then, the content of each article was examined, and 4 articles were extracted in the second screening (3 articles of phase I or II trials on SBRT for HCC and 1 article of a meta-analysis). With the addition of 5 articles on phase I or II trials from the fourth edition and one article on RCT comparing sorafenib with conventional fractionated radiotherapy with TACE for HCC with vascular invasion extracted by hand search, a total of 10 articles[2-11] are cited for CQ43.

Eight articles on phase I or II trials[2-9] among these 10 articles yielded the following findings.

The 2-/3-year local control rate was 94.6-97%/90-96.3%, and the 2-/3-year overall survival rate was 68.7-84%/66.7-76%[2-4,6,9], respectively, in the articles reporting 2-year

or longer outcomes in all patients with HCC who underwent SBRT.

With regard to the number of tumors eligible for SBRT, only patients with solitary HCC were treated in 3 articles[2,3,9], and patients with 1 to 3 or 4 HCCs were treated in 2 articles[5,8]. The remaining 3 articles imposed no restriction on the number of HCCs[4,6,7] , and 2 of them reported the number of HCC treated with SBRT, with up to 2 or 3 HCCs treated[4,6].

With regard to eligibility for surgery or percutaneous ablation, 7 articles applied SBRT to patients judged difficult to receive surgery or percutaneous ablation for medical reasons[2-8], and the remaining article applied SBRT to patients judged difficult to receive surgery or percutaneous ablation for medical reasons or having refused to receive these treatment methods[9].

With regard to liver function, 2 articles applied SBRT only to patients with Child-Pugh A liver function[2,7]. The remaining 6 articles applied it to patients with Child-Pugh A or B liver function[3-6,8,9,] including 5 articles which applied SBRT to patients with Child-Pugh A or B (score 7) liver function[4-6,8,9]. Grade 3 or higher elevation of hepatobiliary enzymes was 1.7-28.6%[2,4-7,9] , and an increase of Child-Pugh score by 2 or more after SBRT was 1.7-34.3% [2,4,5,9]in the reports of SBRT applied to patients with Child-Pugh A or A/B (score 7) and involving analysis of adverse events in all patients enrolled.

With regard to the tumor size, 4 articles applied SBRT only to HCCs not exceeding 4-6 cm[2,3,8,9] and the remaining 4 articles applied it to HCCs not exceeding 10-15 cm or without imposing any size restriction (applicable also to giant HCCs)[4-7]. With regard to the total of tumor diameters in individual patients, one of the 5 articles applying SBRT to multiple HCCs imposed a restriction of 1-3 HCCs with the total diameter not exceeding 6 cm[8]. The remaining 4 articles imposed no restriction on the total of tumor diameters[4-7].

Total dose, dose per fraction, and dose prescription methods of SBRT varied among reports[2-9]. The total dose was 24-60 Gy, the dose per fraction was 4-20 Gy, and the number of fractions was 3-6[2-9].

In a RCT involving HCC patients with vascular invasion (portal vein tumor thrombus and/or hepatic vein tumor thrombus), the conventional fractionated radiotherapy with TACE group showed significantly higher progression-free survival rate at 12 weeks after treatment (86.7% vs. 34.3%, $p < 0.001$), response rate at 24 weeks after treatment (33.2% vs. 2.2%, $p < 0.001$), and median overall survival (55.0 weeks vs. 43.0 weeks, $p = 0.04$) as compared to the sorafenib group[10].

A meta-analysis of prospective and retrospective reports on vascular invasion (portal vein tumor thrombus) positive HCC patients (only retrospective reports for the SBRT group) revealed a significantly higher response rate in the SBRT group than in the conventional fractionated radiotherapy with/without TACE group (70.7% vs. 51.3%, $p = 0.031$)[11].

■ Explanation

Regarding the outcome of HCC treatment with SBRT, multiple prospective studies revealed a high local control rate (at 2/3 years: 94.6-97%/90-96.3%) and a high overall survival rate (at 2/3 years: 68.7-84%/66.7-76%)[2-4,6,9]. In most of these prospective studies, SBRT was applied to patients judged difficult to receive surgery or percutaneous ablation[2-8], suggesting that SBRT provides a valid means of local treatment for those patients. Furthermore, many of the prospective studies reported a high local control rate with SBRT applied not only to local treatment-naïve HCC cases but also to TACE refractory cases and cases of recurrence after local therapy with radiofrequency ablation (RFA), TACE, surgery, etc.[3-8]. This suggests that SBRT is indicated well also in cases refractory or recurrent after local therapy as salvage therapy. There is no published RCT reporting outcomes comparing SBRT with local treatments other than radiotherapy, chemotherapy, and observation. In studies involving retrospective comparison of the outcome of SBRT and RFA using propensity score matching, with the BCLC-factor serving as a matching factor, SBRT was reported to achieve significantly better local control and similar survival compared to RFA[12,13]. These results suggest that SBRT is comparable to RFA in terms of efficacy. Regarding HCC with tumor diameter ≥ 2-3 cm, better local control with SBRT than with RFA has been suggested by multiple retrospective propensity score-matched analyses[13,14]. Furthermore, retrospective analyses of the outcome of SBRT and TACE with propensity score matching revealed significantly better local control[15-18] and overall survival[15,17,19] with SBRT than with TACE, suggesting that SBRT is more effective as a means of local treatment for HCC than TACE.

No strict criteria have been established for the number of HCC tumors that are indicated for SBRT. SBRT was applied to cases with multiple lesions in many of the prospective studies,[4-8]. The majority of those studies limited the number of tumors to four or less. The largest number of tumors treated in those studies was up to four.[5]. Considering the number of HCC tumors in the prospective studies and the consistency with the Guidelines' treatment algorithm, the Revision Committee decided to recommend cases of 1-3 HCCs as an indication of SBRT.

Since liver dysfunction is one of the adverse events arising from SBRT, the liver function should be taken into account when considering the indication for SBRT. Most prospective studies have treated HCC patients with Child-Pugh A/B (score 7) and reported liver dysfunction after SBRT with low severity and frequency[2,4-7,9]. Therefore, the Revision Committee decided to recommend Child-Pugh A/B (score 7) as the liver function requirement for performing SBRT safely. In addition, because high-dose irradiation to the

gastrointestinal tract may cause bleeding, ulceration, or perforation[1,20], the distance between the target tumor and the gastrointestinal tract should be taken into account when considering whether SBRT can be performed and the dose fractionation.

There are no strict criteria also on the HCC size indicated for SBRT. In some prospective studies, SBRT was applied even to giant HCC with size over 10 cm[4-7]. In the prospective studies reported from Japan, on the other hand, SBRT was applied to HCC with tumor diameter not exceeding 4-5 cm[3,9]. Bearing in mind this finding and the NHI's coverage of SBRT in Japan (covering only HCC with diameter not exceeding 5 cm), the Revision Committee decided to recommend HCC with tumor diameter not exceeding 5 cm as an indication for SBRT. As the number and tumor size of HCC treated with SBRT increase, the irradiation dose to the normal liver tends to be higher. Therefore, it is essential to perform SBRT under appropriate dose constraints that consider the dose to the normal liver.

There is no strongly recommended dose fractionation or dose prescription method for SBRT for HCC. From Japan, Takeda et al. reported a single-center phase II study of SBRT in 35-40 Gy/5 fractions for HCC[3], and Kimura et al. reported a multicenter phase II study of SBRT in 40 Gy/5 fractions (STRSPH study)[9], respectively. Dose prescription in both studies was designed to cover 95% of the planning target volume (PTV) at the prescribed dose, fitting the isodose line of 60-80% (the former study) or 70% (the latter study) of the maximum dose to the PTV periphery.

Conventional fractionated irradiation with/without TACE for HCC with vascular invasion has been performed, and results of several prospective studies have been reported[10,21-23]. Yoon et al. reported the results of an RCT that conventional fractionated irradiation with TACE achieved significantly better progression-free survival, median survival, and response rates than sorafenib for HCC with vascular invasion (portal vein tumor thrombus and/or hepatic vein tumor thrombus)[10]. Koo et al. reported in a prospective study that conventional fractionated irradiation with TACE achieved significantly better response rate (42.9% vs. 13.8%, $p<0.01$), progression-free survival rate (71.4% vs. 37.9%, $p<0.01$), and overall survival (median: 11.7 months vs. 4.7 months, $p<0.01$) than the historical control TACE group for HCC with inferior vena cava tumor thrombus.[21]. These findings suggest that radiotherapy may play a durable role in treating HCC with vascular invasion.

Recently, several retrospective studies of SBRT for HCC with vascular invasion have been reported[24,25]. Rim et al. conducted a meta-analysis of prospective and retrospective reports on HCC with portal vein tumor thrombus, reporting a significantly higher response rate in the SBRT group than in the conventional fractionated radiotherapy with

TACE group (70.7% vs. 51.3%, p = 0.031)[11] suggesting that SBRT more effective than conventional fractionated radiotherapy with TACE.
The Revision Committee discussed the recommendation for CQ43, considering that while SBRT has been reported to be highly effective for HCC, no RCTs have been reported to date showing that SBRT for HCC improves clinical outcomes compared to other local treatments, chemotherapy, or observation.

Voting results

◎ Regarding the statement of recommendation "Stereotactic body radiotherapy may be performed in patients with 1-3 HCCs difficult to treat with resection or percutaneous ablation, Child-Pugh A/B (score 7) liver function and tumor diameter ≤ 5 cm, regardless of presence/absence of vascular invasion", its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
8.7% (2 members)	91.3% (21 members)	0% (0 members)	0% (0 members)

Total voters: 23 members (abstention because of COI: 1 member)

■ References

CQ44 Which patients are eligible for particle radiotherapyy (proton beam therapy and heavy-ion radiotherapy)?

Recommendation
Particle radiotherapy (proton beam therapy and heavy-ion [carbon ion] radiotherapy) may be performed for HCCs that are not indicated for hepatectomy or percutaneous ablation. (Weak Recommendation, Evidence Level B)

■ Background
Charged particle beams have finite ranges, and because dose concentration is one of the physicochemical properties, compared with X-rays, charged particles deliver higher doses of radiation while also preserving liver function. Particle radiotherapy is now expected to provide a new alternative for locoregional treatment of HCC. Here, patients

likely to respond to this therapy were reviewed from the viewpoint of tumor features and patient background.

■ Scientific Statement

This CQ is a continuation of CQ49 in the fourth edition. A literature search conducted with the search query similar to the one used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 78 articles. This was narrowed down to 24 articles in the first screening and to 17 in the second screening based on the following inclusion criteria: RCTs or non-RCTs with recurrence-free survival or overall survival as the primary endpoint. With the addition of 1 RCT made public after the second screening and extracted by hand search and 18 articles from the fourth edition, a total of 36 articles are cited for CQ44.

Two RCTs were extracted. One of these articles describes a phase III RCT of proton beam therapy (70.2 Gy [relative biological effectiveness; RBE] in 15 fractions over 3 weeks) and TACE in 69 patients who had a clinical or pathologic diagnosis of HCC and met either the Milan criteria or University of California San Francisco (UCSF) transplant criteria. Interim analysis results showed a significantly higher 2-year local control rate in the proton beam therapy (88%) than in the TACE group (45%), even though there was no intergroup difference in the 2-year survival rate. Total days of hospitalization due to adverse events within 30 days of proton beam therapy or TACE was 24 and 113 days, respectively, indicating significantly fewer hospital days with proton beam therapy[1]. The other RCT was a phase III trial comparing proton beam therapy with RFA in patients with recurrent HCC (size $\leq$ 3 cm, tumor number $\leq$ 2). The local progression-free survival rate (a primary endpoint) was significantly higher in the proton beam therapy group (92.8%) than in the RFA group (83.2%), indicating non-inferiority of proton beam therapy to RFA[2].

The literature search extracted 9 prospective single-arm studies (six reporting the utility of proton beam therapy and 3 pertaining to heavy-ion radiotherapy)[3-10]. Most of these studies involved patients difficult to receive surgery or percutaneous ablation (including patients refusing such therapy). Proton beam therapy had a 2-year local control rate of 88-96% and a 5-year local control rate of 87.8-90.2%[3-7,11]. For heavy-ion radiotherapy, the 3- and 5-year local control rates were 81-95% and 90-95%, respectively[8-10]. A phase I study of proton beam therapy demonstrated the dose-dependency of local effect: the complete tumor response rate significantly improved as the radiation dose increased from 60 Gy (RBE) in 20 fractions to 66 Gy (RBE) in 22 fractions and then 72 Gy (RBE) in 24 fractions[11]. The overall survival rate after proton beam therapy was 59-66% at 2 years, 33% at 3 years, and 38.7-42.3% at 5 years[1,5-7,11], while the same parameter after heavy-

ion radiotherapy was 50% at 3 years and 25-36.3% at 5 years[8-10]. A single-center comparative study of proton beam therapy and heavy-ion radiotherapy reported no significant difference in local control rate or overall survival rate[12]. Three studies (using propensity sore, meta-analysis, etc.) reported comparison with X-ray therapy, demonstrating that particle radiotherapy caused less liver damage and improved the prognosis significantly[13-15].

Some retrospective studies suggested effectiveness against HCC with major vascular invasion, with the median survival of 13.2-22 months in cases with portal vein tumor thrombus[16-18], a 5-year survival rate of 34% in treatment-naïve HCC cases with major vascular invasion[19] and a 2-year survival rate of 64% in single HCC cases with inferior vena cava tumor thrombus[20].

As adverse events, hepatic failure, gastrointestinal disorders, rib fracture, pneumonitis, etc. have been reported. The incidence of Grade 3 or severer adverse events has been reported to be 3.2-8.1%[8-10,21-31]. According to multiple reports, liver function did not significantly exacerbate after this kind of therapy from the pre-treatment level[3,5,10,11,30]. Also in cases of HCC with a large diameter or located near the porta hepatis or the digestive tract, particle radiotherapy was safely administrated through adjustment of dose and field of irradiation, indicating no difference in prognosis depending on the location of lesions[21,30,32,33]. It has been reported that heavy ion radiotherapy was safely applicable also to elderly patients without causing acute adverse events, and there is no apparent deterioration in outcomes in patients with HCC complicated by sarcopenia[34,35]. Indocyanine green retention rate at 15 minutes (ICGR15) is an effective predictor of prognosis specifically in Child-Pugh A patients[36].

■ Explanation

Particle radiotherapy has been used to treat HCC since the 1980s. In the past, evidence for this therapy was limited because of a small number of institutions providing this therapy. In recent years, under the global trend of increase in the number of institutions providing this therapy, further better local control effects of particle radiotherapy have been endorsed by RCTs and prospective studies (Table 1).

Two RCTs demonstrated that proton beam therapy shortened the hospital stay period of HCC patients difficult to treat with resection or percutaneous ablation through manifestation of higher local control than TACE and that the therapy was non-inferior to RFA in terms of local effects on small-size HCC. Although studies at higher evidence levels are needed about the relationship of this therapy to other treatment methods, particle radiotherapy has been so far shown to have certain efficacy against HCC difficult

to treat with resection or percutaneous ablation. On the basis of such a finding and the low incidence of adverse events, the Revision Committee judged this therapy as recommendable.

Furthermore, usefulness of this kind of therapy in cases unlikely to be eligible for TACE (e.g., vascular invasion positive HCC and giant HCC) and vulnerable patients (e.g., elderly patients) has been shown in many retrospective observational studies, suggesting that particle radiotherapy may provide a valid alternative of treatment for these conditions to which availability of other curative treatment methods is limited. In all of these studies, Although the radiation dose of particle radiotherapy was higher than that adopted for X-ray radiotherapy in previous reports, , the incidence of adverse events was low.

Proton beam therapy differs from heavy-ion radiotherapy in terms of physical dose distribution, biological effects and the settings based on such parameters/features (e.g., total dose, number of fractions), but there is no evident difference between these two therapies in terms of the outcome of HCC treatment or the eligible conditions.

Table 1　Outcomes of prospective studies using particle therapy for HCC

(70)

Study design

Patients (n)

Dose per fraction (f)

Local control rate

Survival

Late adverse events

(71)

Proton therapy

Bush et al.[1]

Kim et al.[2]

Bush et al.[3]

Hong et al.[4]

Fukumitsu et al.[5]

Kawashima et al.[6]

Kim et al.[11]

Hong et al.[7]

Heavy particle therapy

Kato et al.[8]

Tsujii et al.[9]

Kasuya et al.[10]
(72)
Phase II clinical study
Phase I clinical study
Phase I clinical study
Phase I/II clinical study
Phase I/II clinical study
Phase II clinical study
Phase I/II clinical study
(73)
70.2 Gy (RBE)/15 f
66 Gy (RBE)/10 f
63 Gy (RBE)/15 f
58.05-67.5 Gy (RBE)/15 f
66 Gy (RBE)/10 f
76 Gy (RBE)/20 f
60 Gy (RBE)/20 f to 72 Gy (RBE)/24 f
45-75 Gy (RBE)/15 f
49.5-79.5 Gy (RBE)/15 f
48-70 Gy (RBE)/4-12 f
52.8 Gy (RBE)/4 f
52.8-69.6 Gy (RBE)/4, 8, 12 f
(74)
88% (2 years)
LPFS
92.8% (2 years)
85.8% (3 years)
83.0% (4 years)
60 of 76 patients
94.8% (2 years)
87.8% (5 years)
96% (2 years)
71.4-83.3% (3 years)
1 of 15 patients had recurrence at the margin
81% (3 years)
87% (3 years)

95% (3 years)
91.4% (3 years)
90.0% (5 years)
(75)
MST 30 months
PFS 48% (2 years)
OS 59% (2 years)

91.7% (2 years)
80.8% (3 years)
75.4% (4 years)

Median PFS 36 months

MST 49.9 months

38.7% (5 years)

66% (2 years)

42.3% (5 years)

33% (3 years)

25% (5 years)

26% (5 years)
35% (5 years)

50.0% (3 years)
25.0% (5 years)
(76)
Severe adverse events were rare; 2 patients were admitted for liver failure
None had ≥ Grade 3 adverse events
5 (of 76) patients had Grade 2 hematologic adverse events; none had significantly decreased liver function

4 patients had Grade 3 adverse events
3 patients had rib fracture; 1 patient had Grade 3 radiation pneumonitis; 8 patients had worsened CP class
8 patients had liver failure; no incidence of liver failure in 9 patients with ICGR15 < 20%
None had ≥ Grade 2 late adverse events; 4 patients had a decrease in CP score by 1 point
1 patient had Grade 1 gastrointestinal bleeding; 1 patient had Grade 5 gastrointestinal perforation
None had severe liver damage; none had a decrease in CP score by ≥ 2 points
(not listed)
(not listed)
4 patients had ≥ G3 non-hematological adverse events
(77)
MST, median survival time; PFS, progression free survival (rate/duration); OS, overall survival; LPFS, local progression-free survival rate; CP, Child-Pugh

Particle radiotherapy (proton beam therapy, heavy-ion radiotherapy) may thus be viewed as a minimally invasive treatment with high local effects applicable to HCC not indicated for standard locoregional therapy. Particle radiotherapy for unresectable HCC over 4 cm was approved for coverage by National Health Insurance system in Japan since 2022.

Voting results

◎ Regarding the statement of recommendation “Particle radiotherapy (proton beam therapy and heavy-ion [carbon ion] radiotherapy) may be performed for HCCs that are not indicated for hepatectomy or percutaneous ablation”, its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
8.7% (2 members)	91.3% (21 members)	0% (0 members)	0% (0 members)

Total voters: 23 members (abstention because of COI: 1 member)

■ References

CQ45 Is radiotherapy recommended for management of the symptoms of bone/brain metastasis from HCC?

Recommendation

1. Radiotherapy is recommended for management of the pain arising from bone metastasis. (Strong Recommendation, Evidence Level A)
2. Radiotherapy is recommended for patients with brain metastasis from HCC. (Strong Recommendation, Evidence Level A)

■ Background

There are many reports of RCTs where radiation therapy was administered for bone or brain metastasis without limiting the primary organ, suggesting that radiation therapy is the standard treatment. As far as solid tumors are concerned, there is no evidence to change the strategy of radiation therapy according to the primary organ or histological type. Here, we investigated the need for establishing treatment strategies specific to HCC.

■ Scientific Statement

This CQ is a continuation of CQ15-1 in the fourth edition. A literature search conducted with the search query similar to the one used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 303 articles. This was narrowed down to 57 based on the article titles and abstracts in the first screening. Then, in the second screening, the content of these 57 articles was reviewed carefully to select 31 articles, including retrospective studies that evaluated radiation therapy for bone and brain metastasis from HCC as well as RCTs and systematic reviews/meta-analyses (primarily involving RCTs) of bone and brain metastasis of unknown primary. With the addition of 19 articles from the fourth edition, a total of 50 articles are cited for CQ45.

No clinical studies have reported high-quality evidence for performing radiation therapy for bone metastasis solely from HCC. However, RCTs and a meta-analysis of bone metastasis from organs other than the liver have consistently reported the efficacy of radiation therapy in managing the pain associated with bone metastasis[1-4], although few of these RCTs included HCC cases. Whereas some retrospective studies have shown the beneficial effect of radiation therapy on pain management in bone metastasis from HCC[5-9], others have reported lower treatment efficacy and the need for higher radiation doses compared with radiation therapy for bone metastasis from other organs[10-15]. This suggests that radiotherapy with a different dose fractionation scheme may be appropriate for bone

metastases from HCC from that for bone metastases from other organs. Because the prognosis is usually poor in HCC patients having bone metastasis[16,17], single-dose 8Gy irradiation with a short treatment period has also been attempted[18-25].
Similarly, no clinical studies have reported high-quality evidence for performing radiation therapy for brain metastasis solely from HCC. However, the appropriate combination of whole brain radiotherapy and stereotactic radiotherapy has been established as the standard based on the findings from RCTs and a meta-analysis of patients with brain metastasis in general[26-41]. Even though brain metastasis from HCC has been investigated only in retrospective studies, some studies have shown that radiation therapy extends survival compared with no treatment[42-46]. Following advances in systemic treatment techniques, molecular-targeted drugs and immune checkpoint inhibitors have recently begun to be used, and there is a report that the safety is not reduced by the use of these drugs in combination with radiotherapy for brain metastasis[47].

■ Explanation
Important points to note about distant metastasis are the management and prevention of local tumor-associated symptoms. Particularly in patients with brain metastasis, suppression of tumor growth is directly associated with survival and therefore establishing a proper treatment strategy is extremely important. There are consistent results from many RCTs that evaluated radiation therapy for bone or brain metastasis without limiting the primary organ. Generally, there is insufficient evidence to change the indications for radiation therapy or the dose-fractionation scheme according to the organs of primary site or histological type. As far as this point is concerned, treatment strategy has been established based on sufficient evidence. However, as stated in the Scientific Statement section, patients with distant metastasis from HCC were seldom involved in high-quality studies, suggesting that these findings may not be applicable to distant metastasis from HCC.
Only a few retrospective studies have analyzed bone or brain metastasis from HCC, and therefore evidence is limited; however, none have refuted the significance of radiation therapy. This suggests that indications for radiation therapy may be established using the criteria for bone and brain metastasis from organs other than the liver. However, compared with bone and brain metastasis from other organs, the outcomes of radiation therapy for bone and brain metastasis from HCC are generally poor, prompting some studies to propose the use of intensified radiation therapy. Yet there have been no reports of the superiority of radiation therapy dose fractionation scheme to date.
Following recent advances in radiotherapy techniques, it is now possible to apply SBRT

by which local anti-tumor effects of radiotherapy can be elevated by a high single dose. Although it is still controversial whether or not locoregional treatment of distant metastasis can improve the prognosis, SBRT deserves consideration because its use in patients with oligo-metastasis (cases where other lesions remain controlled) began to be covered by the NHI in 2020. Careful judgment of its indication is essential in individual cases because some studies demonstrated bone density reduction and increase of fracture following SBRT[49,50] despite a report that SBRT manifested a higher pain-relieving effect than ordinary fractionated radiotherapy[48].

At the Revision Committee meetings, there was a voice that the evidence level for radiotherapy should be B because few RCTs had been reported concerning bone metastasis or brain metastasis from HCC. However, in the absence of a retrospective study of HCC cases demonstrating an outcome contradicting the results of RCTs carried out regardless of the type of cancers, the Revision Committee adopted evidence level A after discussions.

Voting results

◎ Regarding the statement of recommendation 1 “Radiotherapy is recommended for management of the pain arising from bone metastasis”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
91.7% (22 members)	8.3% (2 members)	0% (0 members)	0% (0 members)

Total voters: 24 members

◎ Regarding the statement of recommendation 2 “Radiotherapy is recommended for patients with brain metastasis from HCC”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
87.5% (21 members)	12.5% (3 members)	0% (0 members)	0% (0 members)

Total voters: 24 members

■ References

CQ46 How should treatment response to radiotherapy be assessed?

Recommendation

Dynamic CT or dynamic MRI is recommended when assessing treatment response to radiotherapy, thereby defining local control as no increase in the size or in early enhancement of the treated lesion for 6 months or longer. (Strong Recommendation, Evidence Level B)

■ Background

RECIST1.1, designed to evaluate tumor shrinkage, has been widely used as the criteria for the assessment of the treatment response of solid tumors[1]. On the other hand, HCC, which is typically hyper-vascularized, does not necessarily show tumor shrinkage. For this reason, modified RECIST[2] and RECICL[3] which incorporate the tumor-necrotizing effect into evaluation have been used. However, when radiotherapy is applied to HCC, the tumor tends to remain on radiological evaluation after treatment, and the extent and speed of tumor shrinkage vary greatly, making it difficult to correctly assess the response to treatment with the existing criteria, and there is a concern for erroneous judgment as "treatment failure." Here, the criteria for assessment of response to radiotherapy were reviewed.

■ Scientific Statement

This CQ has been newly adopted in the fifth edition (2021 version). A literature search conducted with a publication date between January 1, 2010 and January 31, 2020 extracted 440 articles on "evaluation of the response to radiotherapy" or "prospective evaluation of the efficacy of radiotherapy." This was narrowed down to 33 in the first screening, focusing on articles closely related to these topics. Then, in the second screening, 4 articles dealing with the methods for assessment of treatment response using diagnostic imaging as well as 9 articles on prospective studies (involving 20 or more cases) specifying the methods for assessing the treatment response were adopted. With the addition of 2 important articles extracted by hand searching, a total of 15 articles[4-18] are cited for CQ46.

• Studies on response to radiotherapy

Kimura et al. chronologically evaluated changes on dynamic CT findings in 59 patients

(67 lesions) with HCC following SBRT. In approximately 30% of these cases, early enhancement remained to be seen also at 3 months after treatment, but decrease in blood flow was noted in most cases at 6 months[4]. Sanuki et al. also reported that when the response to SBRT in 42 HCC cases with early enhancement was assessed by dynamic CT using modified RECIST, the complete response rate increased over time (24%, 67% and 71% at 3, 6 and 12 months, respectively) and early enhancement persisted for 2 years or longer in some cases[5]. Mendiratta-Lala et al. evaluated the response after SBRT on dynamic MRI or CT in 6 patients who underwent liver transplantation and 4 patients with normalized tumor markers, reporting that early enhancement on diagnostic images remain even at 12 months after treatment despite pathological or serological control of the tumor, and that persistent blood flow did not necessarily indicate residual viable tumor[6]. In addition, the same group followed 62 patients with 67 lesions by MRI and reported that 25% of these patients showed complete response and 75% remained unchanged when assessed with modified RECIST at 3-6 months after treatment and that early intensity enhancement remained in 58% of the patients 12 months after treatement[7].

• Prospective studies on efficacy of radiotherapy

Literature search with the above-mentioned criteria extracted only articles on SBRT or particle therapy[8-16]. All of these articles used dynamic CT or MRI for assessment. RECIST served as the criteria for response assessment in 4 articles, and modified RECIST served in 5 articles. Only one of these articles set the “response rate” as an endpoint. The other articles calculated “local control rate” on the basis of the view that the absence of progression in treated lesions indicated local control.

■ Explanation

Because radiotherapy manifests its efficacy through inducing tumor cell damage (impairment of cell mitotic activity and subsequent cell death), necrosis and hypoperfusion do not necessarily occur soon after this therapy, unlike those changes seen after ablation or embolization. All of the articles employed in this revision to determine treatment efficacy after radiotherapy indicated that the tumor blood flow remained as long as 1 to 2 years, and that a long period of time was required to observe tumor shrinkage. For these reasons, it is difficult to assess the treatment response based on early enhancement, and it is desirable to define “local control” as absence of size increase (no progression) of the treated lesions when assessing the response to radiotherapy. When making assessment in this way, selection of criteria (RECIST, modified RECIST, etc.) is unlikely to affect the outcome. When “response rate” is evaluated, care needs to be taken of the timing for response evaluation. In view of the several reports suggesting that it

takes at least about 6 months to manifest the maximum response, and therefore it is desirable to set a sufficient period of time , based on an understanding of the features regarding the changes over time after treatment. The timing of imaging evaluation should be dynamic CT or MRI at intervals of 3-4 months (cf. CQ47). If there is a marked enlargement of the treated lesions, it is considered to be a “local recurrence” .
While dynamic CT or MRI is the basic evaluation modality for assessment, the usefulness of diffusion-weighted MRI not dependent on changes in tumor blood flow has also been reported[17,18], and is a subject for further studies.

Voting results

◎ Regarding the statement of recommendation “Dynamic CT or dynamic MRI is recommended when assessing treatment response to radiotherapy, thereby defining local control as no increase in the size or in early enhancement of the treated lesion for 6 months or longer.”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
95.5% (21 members)	4.5% (1 member)	0% (0 members)	0% (0 members)

Total voters: 22 members (abstention because of COI: 1 member)

■ References

Chapter 9:
Post-treatment Surveillance and Prevention and Treatment of Recurrent HCC

● Introduction

Despite immense advances made in therapeutic tools for HCC, the high rate of HCC recurrence even after curative therapy remains challenging for hepatologists to solve. On the other hand, a merit of HCC treatment is that the same treatment modality may be selected for the treatment of both primary and recurrent HCC and can be expected to produce some therapeutic effect. This is not the case with the treatment of other types of cancer. In other words, when treating HCC, the strategies used for recurrent HCC are as important as those used for primary HCC, and this point has been consistently emphasized since the first edition of the Guidelines.

Due to insufficient scientific evidence about the treatment of recurrent HCC, primary HCC was the key focus of the 2005 and 2009 versions of the Guidelines (first and second editions, respectively). “What is the most effective treatment for recurrent HCC?” in Chapter 3 on Surgery was the only CQ related to the treatment of recurrent HCC (“RQ” was used instead of CQ in the first edition), and the recommendation (second edition) was: “It is recommended that the treatment strategy for recurrent HCC is developed using the same criteria used for primary HCC. In other words, hepatectomy is the standard treatment modality for recurrent HCC, and repeat hepatectomy is recommended especially for patients with solitary HCC and good liver function (those with non-cirrhotic livers and Child-Pugh A liver function) (recommendation grade B)”.

However, with evidence growing on the treatment for recurrent HCC, the Revision Committee decided to create CQs related to clinical management following initial curative therapy. As a result, Chapter 8 “Post-treatment Surveillance, Prevention, and Treatment of Recurrence” was established in the 2013 version of the Guidelines (third edition). In the 2013 version, hepatectomy, percutaneous ablation, and liver transplantation were selected as curative treatment modalities, and three propositional CQs were established for each to address post-treatment follow-up (surveillance for recurrent HCC), preventive measures against recurrence, and the selection of treatment modalities for recurrent HCC. Thus, 9 CQs were newly established for the 2013 version, and a literature search of articles published even before June 2007 was conducted for these. Then, for several reasons, the 9 CQs were merged to generate 6 CQs for the third edition.

For the 2017 version (fourth edition), additional evidence for the 6 CQs was searched for in the literature that became available after the third edition was published. No additional

high-quality evidence was extracted for follow-up procedures after curative therapy. Therefore, the contents of the CQs remain similar to those in the third edition. The clinical significance of the use of cytotoxic anticancer drugs as a preventive measure against recurrence after curative therapy was almost completely refuted and the role of molecular targeted therapy in preventing recurrence of HCC was also refuted in the STORM (Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma) study. Accordingly, anticancer drug therapy is not actively recommended. In contrast, the introduction of DAAs means there has been steady progress in viral hepatitis treatment, which was primarily performed with interferon therapy at the time the third edition was published. Presently, there is insufficient evidence that DAAs directly prevent the recurrence of HCC through the management of hepatitis, but DAA use is at least expected to improve prognosis indirectly through maintenance and improvement of liver function. As for the prevention of recurrence after liver transplantation, the recommendation reflects study findings of effective postoperative management with mammalian target of rapamycin (mTOR) inhibitors. In the third edition, CQs related to treatment options for recurrent HCC were separated for resection and percutaneous ablation groups. However, because these treatment modalities have one thing in common—that is, primary and recurrent HCCs are treated under almost identical treatment strategies—the CQs were merged into a single CQ in the fourth edition. As for the recurrence of HCC after transplantation, the third edition recommended resection whenever possible; the recommendation was modified slightly in the fourth edition to introduce molecular targeted therapy for unresectable HCC, in order to reflect the publication of studies using molecular targeted drugs.

In the 2021 version (fifth edition), CQ50 “How should patients be followed up after liver transplantation?” was newly established, because none of the 5 CQs in the fourth edition were about follow-up after liver transplantation. Furthermore, the order of CQs was rearranged: the first half of the CQs (CQ47, 48, and 49) are related to “after hepatectomy and percutaneous ablation” and the second half of the CQs (CQ50, 51, and 52) are related to “after liver transplantation”. As in the fourth edition, literature searches extracted only a small number of studies showing high-quality evidence; therefore, recommendations for CQ47, 48, and 49 related to “after hepatectomy and percutaneous ablation” and CQ51 related to “after liver transplantation” were almost unchanged from the fourth edition. As for the newly created CQ50 “How should patients be followed up after liver transplantation?”, although the second screening extracted only 1 article and did not extract any articles with high-quality evidence, the Revision Committee had no objection to the importance of “as in surveillance of extremely high-risk patients at onset, follow-

up with tumor marker tests and imaging-based screening" and decided to grade the recommendation "strong". In addition, in CQ52 "What treatment modalities are effective against recurrence after liver transplantation?", studies have shown the utility of mTOR inhibitors in patients with recurrent HCC after liver transplantation, and a new recommendation for the use of mTOR inhibitors was added to the recommendation in the fourth edition.

None of the 6 CQs in this chapter are supported by sufficient evidence. However, the quality of data has improved gradually since the fourth edition was published, and more evidence is expected to become available before the next revision.

CQ47 How should patients be followed up after hepatectomy and percutaneous ablation?

Recommendation

It is recommended that follow-up with tumor marker tests and imaging-based screening according to the surveillance for primary HCC in extremely high-risk patients. (Strong Recommendation, Evidence Level C)

■ Background

Because of the high recurrence rate even after curative therapy, it is important to follow-up HCC carefully after hepatectomy or percutaneous ablation and select the most appropriate treatment modality after recurrence.

■ Scientific Statement

This CQ was established based on CQ51 in the fourth edition. A literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 356 articles. This was narrowed down to 14 in the first screening and to 9 in the second screening based on the following inclusion criteria: cohort studies or RCTs that described follow-up protocols and details of recurrent HCC (size, number, presence or absence of portal vein invasion). Along with the 12 articles from the fourth edition, a total of 21 articles are cited for CQ47 in the current edition. Unlike the surveillance of primary HCC, there is no literature with high-quality evidence that showed the optimal test methods and interval to detect recurrence after hepatectomy or percutaneous ablation. [1-21].

■ Explanation

The incidence of primary HCC is approximately 8% in patients with cirrhosis type C[1], who are at extremely high risk of developing HCC, whereas the recurrence rate of HCC after hepatectomy is ≥ 10% annually and increases to 70-80% over 5 years. In addition, a study that involved US and dynamic CT at 4-month intervals after percutaneous ablation showed a cumulative HCC recurrence rate of 18.6% at 1 year and 72.0% at 5 years[2]. There is currently insufficient evidence that the early detection of recurrence after hepatectomy or percutaneous ablation improves prognosis, but reports of long-term outcomes after these procedures consistently mention the implementation of repeat hepatectomy and percutaneous ablation. From the perspective of curative therapy, this suggests that post-treatment follow-up is as important as surveillance for primary HCC. Therefore, post-treatment follow-up should be strict enough to apply to the extremely high-risk group.

The surveillance algorithm proposed in the current Guidelines recommends regular screening with US and tumor markers every 3-6 months as the core surveillance protocol for patients at extremely high risk of developing HCC, with the addition of dynamic CT/MRI. In a previous study, US-based follow-up screening at 3, 6, 12, and 24 months after RFA detected 78% of cases of HCC recurrence[3]. Even though the diagnostic accuracy of contrast-enhanced US for intrahepatic recurrence after RFA is low compared with that of contrast-enhanced CT[4], follow-up screening with contrast-enhanced US may reduce the number of screenings with CT/MRI[5]. Therefore, a post-treatment follow-up protocol is recommended that consists of tumor marker testing every 3-4 months and screening with US (contrast-enhanced US) as well as dynamic CT or dynamic MRI (including Gd-EOB-DTPA-enhanced MRI).

The rate of postoperative recurrence depends on risk factors such as the preoperative stage of HCC and the severity of fibrosis in the background liver. In patients with high preoperative risk (multiple HCCs ≤ 3 cm or solitary HCC measuring 3-5 cm) who underwent curative percutaneous ablation, overall survival was significantly better in the group with short follow-up intervals (< every 4 months) than in the group with long follow-up intervals (every 4-6 months), while overall survival was not different according to the follow-up interval in patients with low preoperative risk (solitary HCC ≤ 3 cm) who underwent curative percutaneous ablation[6]. In patients at high risk based on age and prothrombin time-international normalized ratio (PT-INR) who underwent hepatectomy or percutaneous ablation, the group with a follow-up interval of 3 months had significantly better overall survival than the group with a follow-up interval of 6 months, while overall survival was not different according to the follow-up interval in patients at low risk[7]. On the other hand, there was no difference in overall survival between patients

followed up every 2-4 months after curative resection and those followed up every 4-6 months, regardless of the level of risk based on preoperative tumor size, number, and microvascular invasion[8]. In consideration of screening cost and radiation exposure, it is impracticable to develop a screening program more rigorous than that described above.

In patients with extrahepatic recurrence, early detection can offer more treatment options, which in turn can improve prognosis. However, for patients without clinical symptoms, there is no recommendation as to which imaging modality to use at what frequency for extrahepatic tumor recurrence. CT, MRI, FDG-PET, and bone scintigraphy are considered when patients have clinical symptoms of extrahepatic metastasis such as pain in the extremities and neurological symptoms or when no intrahepatic recurrence is observed after tumor marker levels become elevated again.

The AASLD and EASL Guidelines describe methods used in follow-up surveillance for HCC recurrence after locoregional therapy, without citing references. The AASLD Guidelines state that imaging and AFP measurement should be performed after hepatectomy at least every 3-6 months (shorter intervals are considered during the first 1 year) and that CT or MRI should be performed after percutaneous ablation at least every 3 months during the first 1 year and at least every 6 months thereafter. The EASL Guidelines propose follow-up every 3-4 months during the first 1 year after curative resection.

In a long-term follow-up study of patients with ≥ 5-years of relapse-free survival after hepatectomy, recurrent tumors were significantly smaller on detection in patients who underwent CT-based screening every 6 months than those who underwent screening every 12 months (1.1 cm vs. 3 cm, respectively; $p = 0.045$)[9]. In addition, in patients who developed HCC recurrence ≥ 2 years after surgery, the percentage of patients who underwent potentially curative treatment was significantly higher and survival was significantly longer in the group that underwent regular (6-monthly) follow-up with imaging and AFP than in the group that did not[10]. The percentage of patients who received regular follow-up (≤ every 6 months) was significantly higher in the group that survived ≥ 10 years after curative resection than in the group that survived < 10 years, indicating that regular follow-up is an independent prognostic factor associated with ≥ 10-year survival[11]. Therefore, follow-up at ≤ 6-month intervals is recommended even in long-term recurrence-free patients.

In summary, follow-up consisting of imaging and tumor marker testing is recommended after hepatectomy or percutaneous ablation, according to the surveillance for primary HCC in extremely high-risk patients.

Although the literature search did not extract any articles with high-quality evidence

about markers that predict the risk of recurrence after hepatectomy or percutaneous ablation, some studies have shown that no decrease (non-response) in AFP or AFP-L3 fraction after treatment predicts recurrence[12-15], suggesting that non-response patients require careful follow-up.

In the meeting for finalizing recommendations, the Revision Committee decided that at least follow-up as in surveillance of extremely high-risk patients at onset is desirable considering the extremely high recurrence rate after curative treatment of HCC although the literature search did not extract any studies with high-quality evidence about follow-up procedures after hepatectomy or percutaneous ablation. The Revision Committee also decided to rate the strength of evidence C considering that the strength of evidence on the surveillance for primary HCC in extremely high-risk patients is rated B and that the target population is different in this CQ, and then took a vote.

Voting results

◎ Regarding the statement of recommendation "It is recommended that follow-up with tumor marker tests and imaging-based screening according to the surveillance for primary HCC in extremely high-risk patients", its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
78.3% (18 members)	21.7% (5 members)	0% (0 members)	0% (0 members)

Total voters: 23 members

References

CQ48 What methods are effective for preventing recurrence after hepatectomy and percutaneous ablation?

Recommendation

In patients with HCC associated with viral hepatitis, antiviral therapy may effectively suppress recurrence and improve survival after hepatectomy or percutaneous ablation.
(Weak Recommendation, Evidence Level B)

Background

HCC has a high recurrence rate even after curative locoregional therapy. Survival is expected to improve through the prevention of recurrence. Here, we investigated the most effective preventive measures against recurrence.

Scientific Statement

This CQ was established by combining CQ28 and CQ52 in the fourth edition. A literature search conducted with a newly created search query and a publication date between July 1, 2016 and January 31, 2020 extracted 211 articles. This was narrowed down to 32 in the first screening and to 4 in the second screening based on the following inclusion criteria: RCT or meta-analysis exclusively of RCTs. A total of 40 articles, including 36 of the 38 articles from the fourth edition, are cited for CQ48.

Several RCTs evaluated postoperative adjuvant (cytotoxic) chemotherapy after curative hepatectomy, but only one reported improved recurrence-free survival[1]; the other RCTs had negative outcomes or reported poor prognosis due to worsening of liver function[2-4]. Similarly, RCTs that evaluated the effect of hepatic transarterial therapy, such as TAI and TACE, as postoperative adjuvant therapy specific to hepatectomy, mostly showed a significant improvement in recurrence-free survival but not in cumulative survival[3,5,6]. A recent RCT of patients after resection of HBV-positive HCC showed that postoperative TACE significantly improved recurrence-free survival (hazard ratio, 0.68) and 3-year survival rate (hazard ratio, 0.59)[7]. Improved cumulative survival was reported in a meta-analysis of hepatic transarterial adjuvant therapy, but differences in drug dosages and administration methods means the results should be interpreted with care[8]. As a special case, postoperative transportal therapy and TACE were effective in patients with HCC accompanied by portal vein tumor thrombus[9].

Some RCTs showed that interferon (α or β) therapy as adjuvant therapy after hepatectomy or percutaneous ablation effectively suppressed recurrence or improved survival in patients with HBV- or HCV-positive HCC[10-13], although these beneficial effects were observed in only a particular subgroup of patients in other studies[14,15]. Three meta-analyses of a small number of RCTs have all verified the efficacy of interferon α[16-18]. An RCT of HBV-positive patients who underwent R0 resection showed that adefovir improves recurrence-free survival and cumulative survival[19]. Treatment with nucleos(t)ide analogues after curative resection improved recurrence-free survival ($p = 0.016$) and cumulative survival ($p = 0.004$) even in patients with low HBV-DNA levels[20]. An RCT of 447 patients showed that the reduction rate of hepatitis B virus surface antigen

(HBs antigen), overall survival and recurrence-free survival were significantly better in the group that received a nucleos(t)ide analogue + peginterferon α for 48 weeks early after curative resection or percutaneous ablation (early combination group) than in the group that additionally received peginterferon α after 1 year of nucleos(t)ide analogue treatment (later combination group), nucleos(t)ide analogue monotherapy group and non-nucleos(t)ide analogue treatment group[21].

The application of molecular-targeted therapy as adjuvant therapy is expected. However, in 2015 the STORM study (a large-scale RCT of sorafenib as adjuvant treatment in the prevention of HCC recurrence after hepatectomy or percutaneous ablation in 1,114 patients treated at 202 institutions worldwide) reported no significant difference in the median recurrence-free survival, which was the primary endpoint of the study, between the sorafenib group (33.3 months) and placebo group (33.7 months)[22]. Cumulative survival also did not differ significantly.

In a randomized trial, adoptive immunotherapy administered to prevent recurrence after curative therapy suppressed recurrence but failed to significantly improve survival[23]. In addition, after a 1996 report of significantly improved recurrence-free and cumulative survival with the administration of acyclic retinoids[24], an RCT was conducted with 401 patients divided into 3 groups to receive 300 mg/day peretinoin, 600 mg/day peretinoin, or placebo. The results showed the recurrence-free survival rate differed significantly between the 600 mg peretinoin and placebo groups[25]. At present, a phase III study of patients after curative treatment of HBV-positive HCC is ongoing. The results of 4 RCTs found no benefit of vitamin K administration as post-treatment adjuvant therapy[26-28]. A meta-analysis of acyclic retinoid and vitamin K showed a positive effect and no effect, respectively, as a vitamin analogue[29]. Whether survival is improved by long-term administration of branched-chain amino acids is currently unclear[30]. One RCT showed that combination therapy with branched-chain amino acids and angiotensin converting enzyme (ACE) inhibitors suppresses recurrence, but the number of patients was small[31]. Another RCT showed suppression of recurrence with the cyclooxygenase-2 inhibitor meloxicam, but there was no significant change in the cumulative survival rate[32]. In addition, 2 RCTs showed improved recurrence-free survival and overall survival with adjuvant iodine-125 brachytherapy in patients with small HCC (≤ 3 cm)[33,34]. Furthermore, recurrence-free survival and overall survival were both improved in RCTs administering *Kampo* (Cinobufacini + Jiedu granules)[35], cytokine-induced killer cells[36], iodine-131-labeled metuximab[37], or Huaier granule[38] as postoperative adjuvant therapy. In contrast, no improvement in recurrence-free survival or overall survival was observed in an RCT of pre-hepatectomy TACE[39] or lymph node dissection accompanying hepatectomy[40].

■ Explanation

The extremely high HCC recurrence rate after curative resection or percutaneous ablation emphasizes the importance of preventing recurrence for long-term survival. Conventionally, antiviral therapy is performed in patients with HCC associated with HBV and HCV. RCTs of postoperative interferon therapy for HBV- or HCV-positive HCC have reported various findings, both positive and negative. In contrast, 3 meta-analyses reported improved recurrence-free survival or cumulative survival with interferon therapy performed after hepatectomy or percutaneous ablation, emphasizing its relevance. However, because some of the meta-analyses included results of prospective cohort studies as well as RCTs[18,19], the Revision Committee has decided to grade the recommendation weak as in the fourth edition. Because it is ethically difficult to conduct an RCT of DAA therapy in patients after curative treatment of HCV-positive HCC, no articles were extracted based on the inclusion criteria "RCT or meta-analysis exclusively of RCTs". Although 2 RCTs on the administration of nucleos(t)ide analogues other than adefovir in patients after curative treatment of HBV-positive HCC showed high-quality evidence, more studies are required to determine whether peginterferon should be additionally used early after surgery.

A literature search of articles related exclusively to hepatectomy (excluding percutaneous ablation therapies) extracted several RCTs on postoperative adjuvant therapies (including hepatic transarterial therapy such as TACE). However, because standard protocols have not yet been established irrespective of the route or procedure of administration, further studies are needed. Currently, clinical studies are ongoing to determine whether immune checkpoint inhibitors prevent recurrence after hepatectomy, percutaneous ablation, and TACE, and the results are awaited with interest.

RCTs individually evaluated the efficacy of vitamin K, adoptive immunotherapy, acyclic retinoid, COX2 inhibitors, branched chain amino acids, iodine-125 brachytherapy, and Huaier granule, but these treatments are not recommended because of either negative findings or the small number of RCTs conducted to date. No recommendable preoperative adjuvant therapies were identified.

Voting results

◎ Regarding the statement of recommendation "In patients with HCC associated with viral hepatitis, antiviral therapy may effectively suppress recurrence and improve survival after hepatectomy or percutaneous ablation", its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
28.6% (6 members)	71.4% (15 members)	0% (0 members)	0% (0 members)

Total voters: 21 members (abstention because of COI: 3 members)

References

CQ49 What treatment modalities are effective against recurrence after hepatectomy and percutaneous ablation?

Recommendation

The treatment algorithm used for primary HCC is recommended for the treatment of recurrent HCC after hepatectomy or percutaneous ablation.

(Strong Recommendation, Evidence Level C)

■ Background

With regard to the treatment response of HCC to hepatectomy, remarkable improvement was seen in the cumulative survival rate in the 1990s compared with the 1980s, but no significant improvement was seen in the recurrence-free survival rate after resection. This suggests that technological advances made in therapeutic modalities for recurrent HCC after the treatment of primary HCC contribute to improved long-term prognosis[1].

■ Scientific Statement

This CQ was established based on CQ54 in the fourth edition. A literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 403 articles. This was narrowed down to 38 in the first screening and to 13 in the second screening based on the following inclusion criteria: RCTs or non-RCTs with experimental, placebo, and no-treatment (control) groups and recurrence-free survival or overall survival as the primary endpoint. Along with 9 of the 16 articles in the third edition (CQ55, CQ56) and 12 of the 13 articles selected in the second screening in the fourth edition, a total of 34 articles are cited for CQ49 in the current edition.

The 13 articles selected in the second screening in the current edition consist of 1 RCT, 10 non-RCTs (6 with appropriate adjustment for bias), and 2 meta-analyses, and many studies had large sample sizes compared with the fourth edition. However, the literature search did not extract any articles on the treatment of recurrent HCC after RFA, and the articles used in the fourth edition are cited for CQ49 in the current edition. One article on the treatment of extrahepatic lesions cited in the fourth edition was excluded because CQ14 on extrahepatic metastasis covers extrahepatic recurrence.

The rate of recurrence is said to be around 50% and 80% at 2 years and 5 years after hepatectomy for HCC, respectively. The first recurrence after hepatectomy for HCC is characterized by a high frequency of intrahepatic lesions (≥ 90%), most of which are solitary HCCs. Intrahepatic recurrence after hepatectomy is attributable to intrahepatic metastasis or to new HCCs arising from the remnant liver after resection (i.e., metachronous multicentric recurrence). The treatment strategy for metachronous multicentric recurrence is theoretically the same as that for primary HCC, provided there is no change over time in the risk of HCC in the background liver. However, because of the difficulty differentiating metachronous multicentric recurrence from intrahepatic metastasis based on clinicopathologic test results in daily clinical practice, the challenge is to distinguish the extent to which the treatment strategy for primary HCC should be modified.

Comparison of the outcome of treatment with that of no treatment in patients with intrahepatic solitary recurrence and comparison of the outcome of hepatectomy with that of other treatment modalities has only been done in retrospective cohort studies thus far, which suggests some selection bias exists in these studies. Accordingly, there is a bias in selecting cases indicated for each treatment modality. Some of these retrospective cohort studies performed multivariate analysis and found that, compared with no resection, repeat hepatectomy is an independent prognostic factor for survival[2,3]; however, it may be necessary to account for potential publication bias here. Prognostic factors in cases of repeat hepatectomy for recurrent HCC have been investigated in several dozen retrospective cohort studies or perioperative comparative effectiveness studies, and survival after repeat hepatectomy was comparable to that after resection for primary HCC at the same institution. If we assume that time from first resection to repeat hepatectomy was ignored in the comparisons, the favorable outcomes after repeat hepatectomy are thought to reflect selection bias among patients who underwent repeat hepatectomy. It is highly likely that resection is selectively performed in patients with recurrent HCC which is in fact due to metachronous multicentric occurrence, because patients are selected based on the eligibility criteria used for patients with primary HCC. The fact that time

from the first resection to recurrence (< 1 year or ≥ 1 year) and vascular invasion, as with the first resection, are prognostic factors in many studies of repeat hepatectomy seems to offer supporting evidence of the assumption mentioned above.

Main treatment modalities for intrahepatic recurrence after treatment of HCC include hepatectomy, RFA, TACE, liver transplantation, and drug therapy, and many studies have compared the outcomes of the treatment modalities. The literature search extracted only 1 RCT reporting that cumulative survival and recurrence-free survival are comparable between repeat hepatectomy and repeat RFA for HCC within the Milan criteria[4]. The outcomes of TACE for primary HCC and for recurrent HCC were comparable after propensity score matching of patient characteristics, suggesting that TACE clinical practice guidelines for primary HCC could be applicable to recurrent HCC[5].

Recurrent HCC after hepatectomy

Some studies have compared treatment modalities for recurrent HCC (intrahepatic solitary recurrence) after hepatectomy. Compared with no resection, repeat resection improved prognosis[2,3,6]. However, the proportion of patients with recurrence for whom surgery was indicated was only about 11-30%. Prognostic factors after repeat hepatectomy are the same as those for hepatectomy for primary HCC, namely vascular invasion, residual liver function, and number of tumors[2,3,6-9], although an association between short recurrence-free survival and poor prognosis has been consistently reported[2,3,6,8,9]. Two articles concerning the association between prognosis and treatment modalities for HCC recurrence after hepatectomy both reported that treatment modalities for HCC recurrence are prognostic factors[10,11]. Several studies have investigated the outcomes of RFA for recurrent HCC after hepatectomy, mostly reporting that prognosis depends on tumor diameter, AFP levels, and time from first resection to recurrence, as in the case of repeat hepatectomy[12]. Studies that compared hepatectomy and RFA for HCC recurrence after hepatectomy revealed comparable results between the 2 treatment modalities[13,14]. Four studies have compared the outcomes of hepatectomy and TACE (TACE + RFA): one study reported better outcomes with hepatectomy than with TACE in patients with up to 3 intrahepatic recurrent tumors[15], and a meta-analysis reported better outcomes with hepatectomy than with TACE[16]. Yagi et al. proposed indication criteria using a prediction scoring system based on age and tumor size and number: hepatectomy should be performed in patients with score 0, TACE should be performed in patients with score 2/3, and treatment modality should be determined according to liver function in patients with score 1[17]. A study that compared hepatectomy and TACE + RFA for recurrent HCC ≤ 5 cm revealed comparable results between the 2 treatment modalities[18].

On the other hand, studies that compared hepatectomy, RFA and TACE reported comparable results between hepatectomy and RFA and inferiority of TACE to hepatectomy and RFA[11,19]. A comparison of sorafenib with sorafenib + TACE-RFA showed that sorafenib + TACE-RFA can prolong survival time when compared with that achieved with sorafenib monotherapy[20]. A comparison of TACE with TACE + sorafenib revealed better outcomes with TACE + sorafenib in patients with BCLC intermediate stage recurrent HCC with microvascular invasion after hepatectomy and those with advanced-stage recurrent HCC (accompanied by portal vein tumor thrombus or extrahepatic metastasis)[21].

Recurrent HCC after percutaneous ablation

Rossi et al. examined 696 patients who repeatedly underwent RFA for recurrent HCC after percutaneous ablation and found that the cumulative incidence of first recurrence at 3 years and 5 years was 70.8% and 81.7%, respectively (yearly rate: local recurrence rate of 6.2% and nonlocal recurrence rate of 35%)[22]. In addition, overall survival was 67.0% and 40.1% at 3 years and 5 years, respectively, and disease-free survival was 68.0% and 38.0%, respectively.

Portolani et al. compared 36 patients who underwent hepatectomy for recurrence after percutaneous ablation (Group 1: PEI, n = 24; RFA, n = 12), 26 patients who underwent re-resection after hepatectomy (Group 2), and 31 patients who underwent percutaneous ablation after hepatectomy (Group 3) and found no significant differences in 1-year, 3-year, or 5-year overall survival (Group 1: 92%, 73%, and 43%; Group 2: 95%, 73%, and 31%; Group 3: 96%, 78%, and 41%, respectively)[23]. According to Okuwaki et al., nonlocal recurrence occurred in 51.3% (59/115 patients) who underwent RFA for HCC, and their 1-year, 3-year, and 5-year overall survival rates were 92.7%, 55.4%, and 43.7%, respectively[24]. Overall **s**urvival was also significantly improved in patients who underwent RFA for nonlocal recurrence compared with those who underwent TACE (3-year survival rate, 77.2% vs. 28.5%, respectively).

Two studies have compared surgery (including transplantation) and percutaneous ablation for recurrent HCC after percutaneous ablation[25,26]. Imai et al. found no significant difference in disease-free survival or cumulative overall survival between hepatectomy and RFA for recurrent HCC after RFA[25]. Although resection was recommended for local recurrence in some patients, long-term prognosis after RFA was also within the permissible range. Xie et al. found no significant difference in disease-free survival or overall survival between surgical resection (including transplantation) and RFA for recurrent HCC after RFA[26]. They concluded that RFA should be the first treatment

modality of choice for local recurrence after RFA, but in the case of contraindication, resection should be considered. Both studies showed that the outcomes of percutaneous ablation and surgical resection were comparable.

Recurrent HCC after hepatectomy or percutaneous ablation

The literature search extracted 3 articles that summarized cases of intrahepatic recurrence after hepatectomy or RFA for HCC. Eisele et al. found no difference in prognosis between RFA and re-hepatectomy for intrahepatic recurrence[27]. Chan et al. reported that prognosis was better after liver transplantation and hepatectomy than after RFA, and that liver transplantation is a valid choice when hepatectomy is not feasible[28]. Ma et al. reported that disease-free survival and overall survival were better after salvage liver transplantation than after re-resection for intrahepatic recurrence after hepatectomy or RFA[29]. They emphasized the importance of timely salvage liver transplantation because of the high rate of non-transplantable recurrence after re-resection.

Recurrent HCC after percutaneous ablation or TACE

The latest literature search extracted 1 article on recurrence after RFA or TACE. Orimo et al. found comparable short- and long-term outcomes of hepatectomy between patients with intrahepatic recurrence after RFA or TACE and HCC patients without preoperative treatment and concluded that hepatectomy is acceptable for patients with intrahepatic recurrence after RFA or TACE[30].

Liver transplantation for recurrent HCC

The overwhelming lack of deceased donors in liver transplantation has led to a novel transplantation method—salvage liver transplantation—being proposed to promote hepatectomy for primary HCC and liver transplantation for recurrent HCC within the eligibility criteria for transplantation (the Milan criteria). However, the ethical dilemma with this proposal is related to the discussion of whether hepatectomy or liver transplantation should be performed from the outset in patients with primary HCC who are eligible for both methods. This is discussed in another section. It is essential though to discuss here the pros and cons of liver transplantation for recurrent HCC that meets the eligibility criteria. The literature search extracted 3 studies (including 2 meta-analyses) that compared liver transplantation and hepatectomy for recurrent HCC. Liver transplantation for recurrent HCC was comparable to hepatectomy in overall survival, inferior in surgery-related complications, and superior in disease-free survival[31-33]. A study that compared hepatectomy, liver transplantation, RFA, TACE, and drug therapy in

patients with recurrent HCC after hepatectomy has reported comparable outcomes between hepatectomy and liver transplantation[34]. Considering the current overall survival rates and lack of donors, hepatectomy still remains an important treatment option for recurrent HCC.

Extrahepatic recurrence

For extrahepatic recurrence, see CQ14 on extrahepatic metastasis.

■ Explanation

The evidence about the treatment of recurrent HCC after hepatectomy or percutaneous ablation reviewed in the above Scientific Statement section includes no reports on treatment modalities significantly inconsistent with the treatment algorithm used for primary HCC, suggesting that the treatment algorithm used for primary HCC should be used for the treatment of recurrent HCC after hepatectomy or percutaneous ablation. However, treatment different from the treatment algorithm may be considered depending on the time to recurrence (e.g., early recurrence immediately after treatment of primary HCC).

In the meeting for finalizing recommendations, the Revision Committee decided to rate the strength of "the overall evidence on the recommendation" "C" because there are no reports on whether the treatment algorithm used for primary HCC suppresses recurrence or prolongs survival when used for recurrent HCC and because there are few relevant RCTs and meta-analyses; however, the treatment algorithm has few disadvantages and is often used for the treatment of recurrent HCC in daily clinical practice. Considering the above, the committee members casted their votes.

Voting results

◎ Regarding the statement of recommendation "The treatment algorithm used for primary HCC is recommended for the treatment of recurrent HCC after hepatectomy or percutaneous ablation", its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
95.7% (22 members)	4.3% (1 member)	0% (0 members)	0% (0 members)

Total voters: 23 members

References

CQ50 How should patients be followed up after liver transplantation?

Recommendation
As in follow-up after hepatectomy or percutaneous ablation, follow-up with tumor marker tests and imaging-based screening used for surveillance of extremely high-risk patients at onset are recommended.
(Strong Recommendation, Evidence Level C)

■ Background
Because HCC recurs at a certain rate even after liver transplantation, it is important to follow-up HCC carefully after liver transplantation and select the most appropriate treatment modality after recurrence.

■ Scientific Statement
This CQ was newly established in the fifth edition. A literature search conducted with a publication date between January 1, 2000 and January 31, 2020 and the keywords “hepatocellular carcinoma”, “liver transplantation”, and “surveillance” extracted 341 articles. This was narrowed down to 7 in the first screening and to 1[1] in the second screening based on the following inclusion criteria: studies that described imaging modalities for follow-up. Although the literature search did not extract any articles with high-quality evidence about the optimal method of follow-up after liver transplantation, the importance of follow-up was uncontroversial, and the Revision Committee decided to add “observational studies or RCTs that described follow-up protocols to detect recurrent HCC and recurrence rate” to the inclusion criteria. Of the articles cited for CQ51 or CQ52 on the prevention or treatment of recurrent HCC after liver transplantation, respectively, 11[2-12] met the above criteria. Along with the 11 articles and a retrospective observational study on a follow-up protocol[13] cited in one of the articles[12], a total of 13 articles are cited for CQ50.
In the early days of clinical application of liver transplantation, the results of liver transplantation for HCC were poor because of frequent recurrence. However, establishment of eligibility criteria for liver transplantation in patients with HCC such as

the Milan criteria resulted in transplantation outcomes comparable to those in patients without HCC. On the other hand, the cumulative HCC recurrence rate after liver transplantation is not low (12.5-21.4%)[1-13]. In addition, screening with imaging and tumor markers at least every 3-6-months is often used as the core follow-up method early after surgery[1-13], but there is no standard protocol.

A single-center retrospective study by Liu et al. evaluated the utility of the follow-up protocol (chest and abdominal CT or chest CT + abdominal MRI every 3 months for 5 years after surgery, and every 6 months thereafter) in 125 HCC patients (including 37 [29.6%] with HCC beyond the Milan criteria) who underwent liver transplantation[1]. During a mean follow-up of 84.3 months, 24 patients (19.2%) had recurrence: 14 (11.2%) had recurrence within 2 years, 9 (7.2%) had recurrence 3-5 years after surgery, and 1 (0.8%) had recurrence after 5 years. Frailty model analysis revealed no difference in recurrence-free survival between 3-month interval surveillance and up to 12-month interval surveillance. In addition, all but one of the 24 patients with recurrent HCC received additional treatment, and the median survival after recurrence was 14 months. They concluded that less frequent imaging surveillance reduces the burden on patients associated with imaging without compromising surveillance benefits. However, considering the high recurrence rate and poor prognosis after recurrence, the results should be interpreted with care.

In a single-center retrospective study by Hwang et al., 334 patients who underwent living donor liver transplantation for HCC were followed up with tumor marker measurements every 1-3 months, abdominal and pelvic dynamic CT + chest radiography every 3-6 months and, as an additional test, plain chest CT every 4-12 months for 5 years after liver transplantation and with regular blood tests and imaging thereafter[13]. The results showed that 68 of the 318 patients (excluding 16 who died perioperatively) had HCC recurrence (21.4%) during a mean follow-up of 77 months. In addition, 36 of 243 patients who underwent liver transplantation for HCC within the Milan criteria had recurrence: most of them (30 patients) had recurrence within 3 years and thereafter only 6 sporadic recurrences were observed. On the other hand, all recurrences occurred within 3 years in patients with HCC beyond the Milan criteria; and among these patients, 3 of 33 within the Asan criteria (up to 6 tumors $\leq$ 5 cm each) had recurrence, while 29 of 42 beyond the Asan criteria had recurrence, with a significantly higher recurrence rate in patients beyond the Asan criteria. They proposed a risk-based screening protocol for HCC recurrence and emphasized the importance of careful follow-up for 3 years after surgery in high-risk patients and the necessity of long-term follow-up even in patients within the Milan criteria.

■ Explanation

Although there is insufficient evidence that early detection of recurrence after liver transplantation improves prognosis, follow-up after liver transplantation is as important as that after other curative treatment modalities for HCC, because resection could be considered and an opportunity for systemic drug therapy may be available in cases of localized recurrence. The United States National Comprehensive Cancer Network (NCCN) guidelines propose follow-up with AFP measurement, CT, and MRI every 3-6 months for 2 years after liver transplantation and every 6-12 months thereafter, without citing references.

There is insufficient evidence about follow-up procedures after liver transplantation, and there was some debate as to whether the recommendation should be rated strong or weak in the Revision Committee. The Revision Committee took into account the following points: the recurrence rate after liver transplantation is approximately 20%; adherence to the eligibility criteria for liver transplantation lowers the recurrence rate; the recurrence rate decreases further 1 year after liver transplantation; and extrahepatic metastasis is a common recurrence pattern. The Revision Committee eventually concluded that evidence obtained from patients who underwent hepatectomy or percutaneous ablation can be extrapolated to follow-up after liver transplantation, because the NCCN guidelines recommend follow-up with imaging every 3-6 months for 2 years after liver transplantation and because the same methodology is used to detect recurrent HCC after liver transplantation and after hepatectomy or percutaneous ablation, although treatment modalities for recurrent HCC after liver transplantation may be different from those after hepatectomy or percutaneous ablation; and then took a vote.

Voting results

◎ Regarding the statement of recommendation “As in follow-up after hepatectomy or percutaneous ablation, follow-up with tumor marker tests and imaging-based screening used for surveillance of extremely high-risk patients at onset are recommended”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
100% (25 members)	0% (0 members)	0% (0 members)	0% (0 members)

Total voters: 25 members

As in follow-up after hepatectomy or percutaneous ablation, follow-up after liver transplantation should be strict enough to apply to the extremely high-risk group.

References

CQ 51 What methods are effective for preventing recurrence after liver transplantation?

Recommendation
After liver transplantation, management with mTOR inhibitors suppresses the recurrence of HCC.
(Weak Recommendation, Evidence Level C)

■ Background
This CQ corresponds to CQ53 in the fourth edition. One of the problems associated with liver transplantation in patients with HCC accompanied by cirrhosis and liver failure is the recurrence of HCC. Although immunosuppressants are essential for preventing rejection after liver transplantation, they may contribute to tumor progression. Here, we reviewed the effect of different post-transplantation management of immunosuppressants on the prevention of recurrence.

■ Scientific Statement
A literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 108 articles. This was narrowed down to 11 in the first screening, from which 1 RCT, 1 meta-analysis, and 2 retrospective cohort studies (4 articles in total) were extracted. Along with the 14 articles from the fourth edition, a total of 18 articles are cited for CQ51 in the current edition.
A number of articles have recently reported on the utility of mTOR inhibitors with immunosuppressive and anticancer effects in the management of HCC recurrence after liver transplantation. Since around 2005, observational studies have suggested the possibility that mTOR inhibitors may reduce the recurrence rate of HCC after liver transplantation[1-4], but some studies do not support the possibility[5]. Geissler et al. conducted a multicenter collaborative RCT of the mTOR inhibitor sirolimus in 525 patients after liver transplantation[6]. In the sirolimus (n = 261) and non-sirolimus (n = 264)

groups, the 3-year recurrence-free survival rate after transplantation was 80.6% and 72.3%, respectively, and the 5-year recurrence-free survival rate was 79.4% and 70.3%, respectively, with statistically significant differences. However, there was no significant difference in recurrence-free survival or overall survival over the entire study period. Only the 1-year survival rate differed significantly (97.2% and 90.0%, respectively) in patients with HCC beyond the Milan criteria. Jeng et al. conducted a multicenter collaborative RCT to evaluate the safety and efficacy of the mTOR inhibitor everolimus[7]. A subgroup analysis of patients who had HCC before liver transplantation reveled that none of the 56 patients who received everolimus had HCC recurrence at 12 months after surgery, while that 8.1% of the 62 patients who did not receive everolimus had HCC recurrence.

In addition, a meta-analysis of the suppressive effect of sirolimus on HCC recurrence after liver transplantation revealed the sirolimus group had improved survival at 1 year (OR, 4.53; 95% CI, 2.31-8.89), 3 years (OR, 1.97; 95% CI, 1.29-3.00), and 5 years (OR, 2.47; 95% CI, 1.72-3.55) and reduced recurrence (OR, 0.42; 95% CI, 0.21-0.83) compared with the no-sirolimus group[8]. There was also no significant difference in post-transplantation complications, such as acute cellular rejection and hepatic artery thrombosis, between the 2 groups. A similar meta-analysis also revealed that sirolimus administration significantly reduced recurrence (OR, 0.30; 95% CI, 0.16-0.55), recurrence-related deaths (OR, 0.29; 95% CI, 0.12-0.70), and all deaths (OR, 0.35; 95% CI, 0.20-0.61) compared with calcineurin inhibitor (CNI) administration[9]. Furthermore, a recent meta-analysis reported that initiation of treatment with mTOR inhibitors including sirolimus and everolimus within 6 months of liver transplantation improves recurrence-free survival at 1-year (OR, 1.09; 95% CI, 1.01-1.08) and 3-years (OR, 1.1; 95% CI, 1.01-1.21) and overall survival at 1-year (OR, 1.07; 95% CI, 1.02-1.12), 3-years (OR, 1.1; 95% CI, 1.02-1.19), and 5-years (OR, 1.18; 95% CI, 1.08-1.29), with no significant increase in rejection[10].

On the other hand, CNI dosage and the association between CNI and recurrence have long been investigated. Vivarelli et al. retrospectively investigated 70 patients (7 had recurrence) who had undergone deceased donor liver transplantation and subsequent immunosuppression mainly with cyclosporine A (CyA), examining various factors such as within/beyond the Milan criteria, histological vascular invasion, and histological differentiation in HCC[11]. Based on multivariate analysis results, they concluded that exposure to high levels of CyA increases the possibility of recurrence. For each patient, they used the trapezoidal rule to calculate the area under the curve (AUC) of the CyA blood concentration versus the time course (CyA-AUC), and then calculated mean CyA

exposure by dividing the CyA-AUC by the time of exposure to CyA. In their subsequent study including patients treated with CyA (n = 79) and tacrolimus (n = 60), the same analyses using the cut-off values of 220 ng/mL for CyA and 10 ng/mL for tacrolimus revealed that overexposure to CNIs was associated with the rate of HCC recurrence[12]. Measurements of drug concentration in blood were consistent, and the multivariate analysis included various factors. However, death from other diseases was excluded, and there were no descriptions related to rejections. In a study by Rodríguez-Perálvarez et al., the mean 5-year recurrence rate was 22.0% in 36 patients with HCC within the Milan criteria who were exposed to high-dose CNIs (mean trough concentrations, > 10 ng/mL tacrolimus and > 300 ng/mL CyA), which was significantly higher than the rate of 7.0% in 106 patients exposed to low-dose CNIs[13].

■ Explanation

The recommendation in the third edition of the Guidelines was made based on reports that overexposure to CNIs is associated with recurrence of HCC after liver transplantation, and the recommendation was modified in the fourth edition because the utility of sirolimus had been verified by the RCT of mTOR inhibitors. Evidence supporting the utility of mTOR inhibitors was added to the current edition.

Immunosuppressants are absolutely necessary to prevent transplant rejection. Determining the type of immunosuppressant to choose and the blood concentration to maintain depend on the patient's pathological condition. It is common to avoid overdosing drugs so as to maximally prevent infection and side effects (e.g., kidney failure) attributable to lifelong immunosuppressants. However, this would amount to failing to see the wood for the trees if the transplanted organ were to be rejected merely because extremely low-dose immunosuppressants were used solely to prevent recurrence. Therefore, adjusting drug concentrations to suppress recurrence it is not a recommended strategy. Because mTOR inhibitors function as immunosuppressive anticancer drugs, they have potential as maintenance drugs after liver transplantation for HCC. Both an RCT[14] and a systematic review[15] have reported the utility of postoperative adjuvant therapy with cytotoxic anticancer drugs after liver transplantation for HCC, but the current Guidelines do not reflect this finding because of the lack of evidence on postoperative adjuvant therapy for HCC in Japan. Also, the current Guidelines do not reflect reports on a steroid-free immunosuppressive regimen after liver transplantation for HBV-related HCC[16] or interferon therapy[17] and perioperative administration of prostaglandin E1[18] after liver transplantation for HCV-related HCC because they were from retrospective single-center studies. Although the utility of mTOR inhibitors has been verified, they were covered by

the National Health Insurance system in February 2018 and therefore there is no long-term clinical experience. Considering the above, the committee members casted their votes.

Voting results

◎ Regarding the statement of recommendation “After liver transplantation, management with mTOR inhibitors suppresses the recurrence of HCC”, its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
4.2% (1 member)	91.7% (22 members)	4.2% (1 member)	0% (0 members)

Total voters: 24 members

References

CQ52 What treatment modalities are effective against recurrence after liver transplantation?

Recommendation

1. Recurrent HCC after transplantation may be resected if resectable or treated with drug therapy if unresectable.
(Weak Recommendation, Evidence Level C)
2. mTOR inhibitors may be administered to patients not receiving mTOR inhibitors.
(Weak Recommendation, Evidence Level C)

■ Background

This CQ corresponds to CQ55 in the fourth edition. HCC recurs at a certain rate after liver transplantation in patients with HCC, cirrhosis, and liver failure, but no treatment has been developed to address this problem. In general, treatment strategies are determined based on the patient’s condition at recurrence and the site of recurrence. Here, we discuss treatment modalities that are effective against recurrence after liver transplantation.

■ Scientific Statement

A literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 108 articles. This was narrowed down to 11 in the first screening, from which 2 retrospective studies on the administration of molecular-targeted drugs after recurrence were selected. Along with the 2 meta-analyses from the fourth edition, a total of 4 articles are cited for CQ52 in the current edition[1-4].

de'Angelis et al. performed a meta-analysis of 61 studies to search for and identify safe and effective treatment modalities for patients with recurrent HCC after liver transplantation[1]. The mean recurrence rate after liver transplantation for HCC was 16%, and the median time from transplantation to recurrence was 13 months (range, 2-132 months). The incidence of extrahepatic recurrence was 67%, and the median survival time after recurrence was 12.97 months. After resection, 27 patients with localized extrahepatic or intrahepatic recurrence had a median survival of 42 months, with no severe postoperative complications or postoperative death. In patients with systemic metastasis for whom resection was not indicated, the median survival was 12.1 months in 76 patients treated with sorafenib alone and 18.2 months in 68 patients treated with mTOR inhibitors. Major drug side effects were digestive symptoms, hand-foot syndrome, hypertension, and malaise, and adverse drug reactions resulted in dose reduction and therapy discontinuation in 42.1% and 9.6% of patients, respectively. Of 23 patients who received combination therapy with sorafenib and mTOR inhibitors, 6 had severe side effects and 4 died. In patients receiving other treatment modalities, the median survival was 11.2 months with TACE (n = 40), 5.79 months with systemic chemotherapy (n = 35), and 3.3 months with best supportive care (n = 54).

Mancuso et al. performed a meta-analysis of 17 studies to evaluate the safety and survival benefit of sorafenib for recurrent HCC after liver transplantation[2]. The median time from transplantation to recurrence was 13.6 months (range, 7-38.1 months), and the median frequency of intrahepatic recurrence, intra-/extrahepatic recurrence, and extrahepatic recurrence was 14.5%, 26.2%, and 56.8%, respectively. In patients treated with sorafenib, the median frequency of ≥ Grade 3 side effects was 16.1% for malaise, 18% for gastrointestinal toxicity, 22.5% for skin lesions, and 0% for cardiac events. Adverse drug reactions resulted in dose reduction and therapy discontinuation in 42.8% and 31.9% of patients, respectively. Because 2 of 113 patients who received combination therapy with mTOR inhibitors died (1.8%), caution must be observed when combining the two drugs. Survival status was listed only in 8 patients, whose mean 1-year survival rate was 63%

(18-90%).

After the publication of the above meta-analyses, Xu et al. reported that in patients who did not receive the mTOR inhibitor sirolimus as an immunosuppressant after living donor liver transplantation for HCC associated with cirrhosis, survival after HCC recurrence was significantly prolonged in the group that was switched to sirolimus after recurrence compared with the group that was not switched (median survival, 12 vs. 8 months; $p = 0.039$)[3]. In addition, Jung et al. evaluated the utility of sorafenib and mTOR inhibitors in patients with recurrent HCC after liver transplantation divided into 4 groups (139 who did not receive sorafenib or mTOR inhibitors, 16 who received mTOR inhibitors alone, 54 who received sorafenib alone, and 23 who received both sorafenib and mTOR inhibitors)[4]. Post-recurrence survival did not differ between patients receiving and not receiving sorafenib (hazard ratio, 1.25; 95% CI, 0.91-1.73; $p = 0.18$), while mTOR inhibitor administration significantly improved post-recurrence survival (hazard ratio, 2.25; 95% CI, 1.58-2.92; $p < 0.001$). In addition, there was no difference in post-recurrence survival between mTOR inhibitor subgroups receiving and not receiving sorafenib ($p = 0.26$).

■ Explanation

Liver transplantation involves the removal of neoplastic lesions as well as the background liver with chronic disease that is the underlying cause of the neoplastic changes, and the placement of the donor liver at the resection site. Any lesions occurring after liver transplantation are thought to be caused by disseminated cancer cells already circulating in blood. However, it is unclear whether intrahepatic recurrence is due to circulating disseminated lesions, hepatitis newly induced by grafts, or de novo malignant transformation accompanying the progression of cirrhosis. An increasing number of studies are reporting the treatment of recurrent HCC after liver transplantation, but none has been an RCT or large-scale prospective study to date. Therefore, the Revision Committee has decided to cite the meta-analyses of retrospective studies used in the fourth edition and 2 new retrospective studies that investigated the effect of mTOR inhibitors on prognosis after HCC recurrence, and to grade the recommendation “weak”. Comparison by treatment revealed that resection was the most effective treatment for intra-/extrahepatic solitary lesions, but due to relatively large bias associated with the type and site of recurrence and patient background, the phrase “if resectable” was added to the recommendation. Many studies have investigated TACE for the treatment of intrahepatic metastasis, and evidence is also accumulating about the treatment outcomes of RFA. Neither TACE nor RFA is associated with severe complications. However, given the

frequent need for not only duct-to-duct biliary anastomosis but also choledochojejunostomy in biliary reconstruction after liver transplantation, TACE and RFA may induce severe complications such as cholangitis and liver abscess. Therefore, TACE and RFA are not recommended in the current Guidelines.
In patients with completely disseminated metastases throughout the body, the molecular-targeted drug sorafenib extended the median survival time compared with systemic chemotherapy with cytotoxic anticancer drugs, but it was also associated with dose reduction and discontinuation of therapy due to adverse drug reactions. Also, combination therapy with the immunosuppressant mTOR inhibitors improves the median survival time. Therefore, switching to combination therapy with mTOR inhibitors may be considered for patients not receiving mTOR inhibitors. However, the safety and efficacy of combination therapy with sorafenib and mTOR inhibitors have not been established, and adverse events associated with the combination therapy include death; therefore, caution must be exercised when using the combination therapy. As for molecular-targeted drugs other than sorafenib, an observational study of regorafenib was reported; however, it was an uncontrolled single-arm study, and regorafenib is not recommended in the current edition[5]. Caution should be exercised when the immune checkpoint inhibitor atezolizumab is used in patients with a history of organ transplantation, because these patients were excluded from clinical studies, and because transplant rejection was observed in patients with a history of renal transplantation who received a similar drug, resulting in the categorization of transplant rejection as an important potential risk in the risk management plan (RMP). Because of the emergence of new drug therapies for advanced HCC, further study is needed to accumulate more evidence on the use of these drug therapies in patients with recurrent HCC after liver transplantation and to evaluate the prognosis.

Voting results

◎ Regarding the statement of recommendation 1 “Recurrent HCC after transplantation may be resected if resectable or treated with drug therapy if unresectable”, its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
4.2% (1 member)	95.8% (23	0% (0 members)	0% (0 members)

	members)		

Total voters: 24 members

Regarding the statement of recommendation 2 “mTOR inhibitors may be administered to patients not receiving mTOR inhibitors”, its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
0% (0 members)	100% (24 members)	0% (0 members)	0% (0 members)

Total voters: 24 members

References

External Review of the Clinical Practice Guidelines for Hepatocellular Carcinoma 2021

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Purpose

As in the first to fourth editions, this fifth edition of the Guidelines was reviewed externally before publication. In 2002, the Japan Council for Quality Health Care launched the Medical Information Network Distribution Service (MINDS) project to promote the development of EBM guidelines. In 2014, the MINDS project defined clinical practice guidelines as follows: a document that assists the decision-making process of patients and healthcare professionals for highly important medical procedures, presenting systematic reviews of clinical evidence and grading recommendations to achieve the best treatment outcome and emphasizing the importance of the balance between benefit and harm for patients[1]. In light of the above definition, the role of the External Review Panel is to objectively assess the current edition of the Guidelines from various perspectives and to feedback the findings to the Guidelines. However, as in the fourth edition, the fifth edition of the Guidelines was externally reviewed immediately before publication with the expectation that the results summarized will serve as references for the next revision.

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Assessment methods

The External Review Panel consisted of 3 hepatologists (specialists in internal medicine, surgery, and radiology) who were not involved in this revision of the Guidelines, 2 non-

hepatologists (specialists in internal medicine and surgery) with expertise in developing clinical guidelines, and 1 biostatistician. The 6 appraisers independently rated the Guidelines and the scores were combined and analyzed.

As for the fourth edition, the current Guidelines was externally reviewed using the Appraisal of Guidelines for Research and Evaluation II (AGREE II)[2] (Table 1). The AGREE II questionnaire categorizes items by domain and uses a 7-point rating scale. The AGREE II consists of 6 domains (a total of 23 items): Scope and Purpose (3 items), Stakeholder Involvement (3 items), Rigour of Development (8 items), Clarity of Presentation (3 items), Applicability (4 items), and Editorial Independence (2 items). Except for the last 2 items in the Overall Guideline Assessment domain, each item uses a 7-point rating scale, ranging from Strongly Disagree (1 point) to Strongly Agree (7 points). One of the two items in the Overall Guideline Assessment domain at the end of the questionnaire rates the overall quality of the guidelines on a 7-point rating scale, ranging from low (1 point) to high (7 points), and the other item on the level of recommendation (i.e., "I would recommend this guideline for use") is answered by selecting a response from the options "Yes", "Yes, with modifications", and "No" (Table 1). The total score for each domain is calculated from the individual item scores, and the maximum and minimum possible scores in each domain are also calculated. Then, scaled domain score (%) is calculated by dividing (Obtained score – Minimum possible score) by (Maximum possible score – Minimum possible score) and multiplying by 100. Scaled domain scores and comments from the appraisers, which are given in the space below each questionnaire item, are combined to reveal superior and inferior aspects of the Guidelines.

Because the fourth edition and the current fifth edition were reviewed externally by the same appraisers using the same assessment tool, the reviews of the fourth and the current editions were compared, and appreciable changes are mentioned in the Guidelines.

Results

Table 1 shows the scores for individual items and domains. Scores for Domain 4. "Clarity of Presentation" and Domain 5. "Applicability" by non-hepatologists were lower by 16% and 20%, respectively, compared with scores by hepatologists (Table 1). Analysis of the domain scores by all appraisers revealed that although Domain 2. "Stakeholder Involvement" (64%) and Domain 5. "Applicability" (53%) were poorly rated, the scores generally improved from the fourth edition (Figure 1).

Analysis of the individual item scores revealed that the number of items rated particularly poorly (score percentage, ≤ 60%) by all appraisers was 4, which decreased from 6 in the fourth edition. In Domain 2. "Stakeholder Involvement", Item 5. "The views and

preferences of the target population (patients, public, etc.) have been sought" was rated lower (19%) than in the fourth edition. This is because the Revision Committee did not include patient representatives as in the fourth edition and because the public hearing held during the Annual Meeting of the JSH and the call for public comments on the JSH webpage targeted JSH members, resulting in failure to improve the situation in which the Guidelines cannot reflect patients' opinions and comments. In Domain 3. "Rigour of Development", Item 11. "The health benefits, side effects, and risks have been considered in formulating the recommendations" was scored differently by hepatologists (67%) and non-hepatologists (44%), and in particular a non-hepatologist commented that "complications and side effects are poorly described compared with benefits in many CQs". In Domain 5. "Applicability", 2 of the 4 items were rated poorly. Item 18. "The guideline describes facilitators and barriers to its application" (56%) and Item 20. "The potential resource implications of applying the recommendations have been considered" (33%) were rated poorly as in the fourth edition because the Guidelines did not provide sufficient information about the percentage of medical institutions that can provide advanced and costly medical care such as liver transplantation, molecular-targeted therapy, and particle therapy or about National Health Insurance coverage status and cost-benefit of such medical care.

Compared with the fourth edition, Item 1. "The overall objective (s) of the guideline is (are) specifically described" and Item 3. "The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described" in Domain 1 were rated higher in the current edition, because both were described in General Statement at the beginning of the Guidelines. In addition, Item 7. "Systematic methods were used to search for evidence" (78%) and Item 8. "The criteria for selecting the evidence are clearly described" (86%) in Domain 3. "Rigour of Development" were rated higher compared with the fourth edition. This seems to reflect the fact that literature search queries were summarized, as in the third edition, in "Steps in the revision process" at the beginning of the Guidelines (Item 7) and the method for evaluating evidence using Abstract Table was described in detail (Item 8). However, appraisers commented that literature search engines (e.g., PubMed and Cochrane) used in the current edition should be described. The score for Item 21. "The guideline presents monitoring and/or auditing criteria" (61%) in Domain 5. "Applicability" also increased. Although Item 21 had the lowest score among all items in the fourth edition, it had a high score in the current edition, because the "Monitoring of the Guidelines after publication" section was established in General Statement. However, non-hepatologists rated Item 21 poorly (44%) and commented that "it is not specifically described how the Guidelines are monitored and audited".

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Table 1. Scores and percentages for the different AGREE II items
80
Hepatologists
Non- hepatologists
Overall
Reference
81
Points
Rate of agreement
Score by domain
Points
Rate of agreement
Score by domain
Points
Rate of agreement
Score by domain (fifth edition)
Score by domain in the fourth edition
82
Overall, Score by domain (fifth edition)
Reference, Score by domain in the fourth edition
83
Figure 1. Score by domain
84
Hepatologists
Non-hepatologists
Figure 2. AGREE II items scored differently by hepatologists and non-hepatologists
Green lines indicate items with ≥ 20% difference in scores.

Item scores differed ≥ 20% between hepatologists and non-hepatologists for 3 items: Item 19, “The guideline provides advice and/or tools on how the recommendations can be put into practice” in Domain 5. “Applicability”, in addition to the above-mentioned Item 11. “The health benefits, side effects, and risks have been considered in formulating the recommendations” in Domain 3. “Rigour of Development” and Item 21. “The guideline presents monitoring and/or auditing criteria” in Domain 5. “Applicability”. All the 3 items

were rated lower by non-hepatologists (Figure 2). In relation to Item 19, particularly non-hepatologists expressed the opinion that an educational tool, side reader for patients (e.g., publication on the website or pamphlet) or application should be developed so that everyone can understand how to put the recommendations into practice. The appraisers had the impression that because the Guidelines were generally developed for hepatologists, description is insufficient for non-hepatologists and patients.

Other noteworthy comments are as follows. First, there was a consensus that the title of the Guidelines should be changed to the "Clinical Practice Guidelines for Hepatocellular Carcinoma", because the Clinical Practice Guidelines for Intrahepatic Cholangiocarcinoma were compiled as described in General Statement.

In relation to Item 6, although the target users of the Guidelines are defined as "all clinicians, including hepatologists and physicians in other fields, who manage patients with liver cancer" in the current edition, there was a consensus that the target users should include not only other medical personnel but also patients and the general public, because team medicine is essential and patients select treatment modalities by themselves after informed consent in the current health care. In relation to Item 4, there was a comment that the guideline development group should include palliative care specialists, nurses, and patients. In Item 16, a member requested that the Guidelines describe how to take into account the patient condition such as age in selecting treatment modalities.

There were the following general comments: Specific statistical values for the main evidence on which the recommendations were based should be described in the Scientific Statement section for each CQ; and although the algorithm should be developed by summarizing the results of CQs, the "treatment algorithm" chapter was first created in which CQs about the algorithm were established, and some subsequent CQs for individual treatment modalities overlap with the CQs about the algorithm (e.g., CQs about indications for liver transplantation: CQ13 and CQ26). Also, although it is a detail, there was a comment that wording was not standardized (particularly wording of examinations).

In the Overall Guideline Assessment domain, Item 1. "Rate the overall quality of this guideline" had a score of 83%, which was higher than 75% in the fourth edition. Item 2. "I would recommend this guideline for use" was answered "Yes" by all the appraisers, and none answered "Yes, with modifications" or "No".

Summary

The 2021 version of the Clinical Practice Guidelines for Hepatocellular Carcinoma was externally reviewed based on the AGREE II tool. Suggestions thought to be valuable for

the next revision process are listed below.

The title of the Guidelines is changed to the “Clinical Practice Guidelines for Hepatocellular Carcinoma”.

The target users of the Guidelines should include not only clinicians but also patients and the general public, and an easy-to-understand explanation should be given to patients and the general public using a side reader on the website, pamphlet or application.

The Revision Committee of the Guidelines should include palliative care specialists, nurses, and patients.

It should be specified in advance how to monitor and audit the Guidelines.

The evidence from which the recommendations were derived should be explained in more detail in the Scientific Statement section.

Facilitators and barriers (cost, etc.) to the application of the Guidelines (e.g., in liver transplantation, molecular-targeted therapy, and particle therapy) need to be further discussed from the perspective of facility resources and health economics.

References

1) Toshio Morizane, Masahiro Yoshida, Noriko Kojimahara, edited. Minds Handbook for Clinical Practice Guideline Development 2014. Tokyo: IGAKU-SHOIN Ltd, 2014 (Japanese)