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 first and second editions of the Guidelines (2005 and 2009 versions, 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 third edition of the Guidelines (2013 version). In the third edition, 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 third edition, 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 current fourth edition (2017 version), 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 current Guidelines. As for the recurrence of HCC after transplantation, the third edition recommended resection whenever possible; the recommendation was modified slightly in the current edition to introduce molecular targeted therapy for unresectable HCC, in order to reflect the publication of studies using molecular targeted drugs.

None of the 5 CQs in this chapter are supported by sufficient evidence. However, the quality of data has improved gradually since the the third edition was published, and more evidence is expected to become available before the next revision.

CQ51 How should patients be followed up after hepatectomy and percutaneous ablation?

Recommendation

Strong recommendation: As in surveillance of extremely high-risk patients at onset, follow-up with tumor marker tests and imaging-based screening are recommended.

■ 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 CQ52 in the third edition. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 612 articles. This was narrowed down to 33 in the first screening and to 9 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 the 3 articles from the third edition, a total of 12 articles are cited for CQ51 in the current edition. Unlike the literature search for surveillance of primary HCC, the literature search for follow-up did not extract any studies that compared screening tests or intervals for recurrence after hepatectomy or percutaneous ablation or showed high-quality evidence about the sensitivity and specificity of the tests[1-12].

■ 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. There is currently insufficient evidence that the early detection of recurrence after hepatectomy or percutaneous ablation improves prognosis, but studies of long-term outcomes after these procedures consistently mention repeat hepatectomy and repeated percutaneous ablation. From the perspective of curative therapy, this suggests that surveillance for recurrent HCC is as important as that for primary HCC. Therefore, post-treatment surveillance should be strict enough to apply to the extremely high-risk group.

The surveillance algorithm proposed in the current Guidelines recommends screening with US and tumor markers every 3-4 months as the core surveillance protocol for patients at extremely high risk of developing HCC, with the addition of dynamic CT/MRI every 6-12 months. 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 the stage of primary HCC and the severity of fibrosis in the background liver. However, from the perspective 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 for extrahepatic tumor recurrence. Indeed, 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 the surveillance of HCC recurrence after locoregional therapy, without citing references. The AASLD Guidelines propose follow-up with dynamic CT/MRI every 3-4 months as one follow-up protocol, with the possibility of extending the interval if no recurrence is seen for 2 years. The EASL Guidelines propose screening with US every 3-4 months. In a long-term follow-up study of patients with ≥ 5-years of disease-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; $p = 0.045$)[6]. This suggests that the testing interval can be extended to 6 months at most.

In summary, follow-up consisting of imaging and tumor marker testing is recommended, as in surveillance of extremely high-risk patients with primary HCC.

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CQ52 What methods are effective for preventing recurrence after hepatectomy and percutaneous ablation?

Recommendation

Weak recommendation: In patients with HCC associated with viral hepatitis, antiviral therapy may effectively suppress recurrence and improve survival after hepatectomy or percutaneous ablation.

■ 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 CQ29 and CQ53 in the third edition. A literature search conducted with a newly created search query and a publication date between January 1, 2012 and June 30, 2016 extracted 949 articles. This was narrowed down to 29 in the first screening and to 12 in the second screening based on the following inclusion criteria: RCT or meta-analysis. A total of 38 articles, including 26 of the 34 articles from the third edition, are cited for CQ52.

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]. 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[7]. As a special case, postoperative transportal therapy and TACE were effective in patients with HCC accompanied by portal vein tumor thrombus[8]. Even though administration of iodine-131-labeled Lipiodol into the hepatic artery improved short-term prognosis[9], it had no effect on long-term prognosis in a continuation study[10].

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[11-14], although these beneficial effects were observed in only a particular subgroup of patients in other studies[15,16]. Three meta-analyses of a small number of RCTs have all verified the efficacy of interferon α[17-19]. Also, an RCT of adefovir administration in 2 groups of HBV-positive patients who underwent R0 resection (N = 200) showed that adefovir improves recurrence-free survival (hazard ratio 0.651) and cumulative survival (hazard ratio 0.420)[20].

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)[21]. 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[22]. In addition, after a 1996 report of significantly improved recurrence-free and cumulative survival with the administration of acyclic retinoids[23], 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[24]. The results of 4 RCTs found no benefit of vitamin K administration as post-treatment adjuvant therapy[25-27]. A meta-analysis of acyclic retinoid and vitamin K showed a positive effect and no effect, respectively, as a vitamin analogue[28]. Whether survival is improved by long-term administration of branched-chain amino acids is currently unclear[29]. 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[30]. Another RCT recently showed suppression of recurrence with the cyclooxygenase-2 inhibitor meloxicam, but there was no significant change in the cumulative survival rate[31]. In addition, 2 RCTs showed improved recurrence-free survival and overall survival with adjuvant iodine-125 brachytherapy in patients with small HCC (≤ 3 cm)[32,33]. Furthermore, recurrence-free survival and overall survival were both improved in RCTs administering *Kampo* (Cinobufacini + Jiedu granules)[34], cytokine-induced killer cells[35], or iodine-131-labeled metuximab[36] as postoperative adjuvant therapy. In contrast, no improvement in

recurrence-free survival or overall survival was observed in an RCT of pre-hepatectomy TACE[37] or lymph node dissection accompanying hepatectomy[38] performed not as postoperative adjuvant therapy.

■ 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], and because the recommendation was graded C1 in the third edition of the Guidelines, the Revision Committee has decided to grade the recommendation weak in the current edition. When compiling the third edition, we had expected additional RCTs would report on the long-term low-dose administration of interferon or interferon PEG preparation, but the latest literature search extracted no additional RCTs, presumably because DAAs were introduced after the third edition was published.

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) but not on preoperative adjuvant therapies. However, because standard protocols have not yet been established irrespective of the route or procedure of administration, further studies are needed.

The utility of adefovir was shown for the first time after a long period without any RCTs on the administration of nucleos(t)ide analogues as post-treatment adjuvant therapy in patients with HBV-positive HCC. However, a single study does not offer sufficient evidence and more studies are warranted. Other RCTs individually evaluated the efficacy of vitamin K, adoptive immunotherapy, acyclic retinoid, COX2 inhibitors, branched chain amino acids, and iodine-125 brachytherapy, but these treatments are not recommended because of either negative findings or the small number of RCTs conducted to date.

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CQ53 What methods are effective for preventing recurrence after liver transplantation?

Recommendation

Weak recommendation: After liver transplantation, management with mTOR inhibitors may suppress the recurrence of HCC.

■ Background

This CQ corresponds to CQ54 in the third edition of the Clinical Practice Guidelines for Hepatocellular Carcinoma. 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 third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 116 articles. This was narrowed down to 21 in the first screening, from which 2 RCTs, 2 meta-analyses, and 4 retrospective cohort studies (8 articles in total) were extracted for use in this CQ, along with 6 of the 8 articles used in the third

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. Geissler et al. conducted a multicenter collaborative RCT of the mTOR inhibitor sirolimus in 525 patients after liver transplantation[1]. 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. Toso et al. administered sirolimus to 70 patients with HCC who had undergone deceased donor liver transplantation and found no significant difference in the 4-year recurrence-free survival rate between patients with HCC within the Milan criteria (73%, n = 34) and those with HCC beyond it (75%, n = 36)[2]. Their findings also suggested the utility of sirolimus in liver transplantation from the perspective side effects. In a matched cohort study by Vivarelli et al., the 3-year recurrence-free survival rate was 86% in the sirolimus group (n = 31) and 56% in the no-sirolimus group (n = 31), suggesting significant suppression of recurrence by sirolimus[3]. A large database analysis of 2,491 recipients of isolated liver transplantation for HCC conducted in the United States showed that 5-year survival was 83.1% in the sirolimus group (n = 109) and 68.7% in the no-sirolimus group (n = 2,382), and multivariate analysis revealed only anti-CD25 antibody induction and sirolimus-based maintenance therapy as independent factors positively associated with the suppression of recurrence[4]. In a study by Álamo et al., recurrence decreased significantly after administration of mTOR inhibitors (n = 16) compared with after administration of calcineurin inhibitors (CNI, n = 89) (6.2% vs. 19.1%), and there were no rejections, adverse events, or deaths in the mTOR group[5]. A meta-analysis of the studies mentioned above 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[6]. 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 CNI administration[7].

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[8]. 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 tacrolims (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[9]. 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[10].

■ 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. The recommendation was modified in the current edition because the utility of sirolimus has been verified by the RCT of mTOR inhibitors.

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[11] and a systematic review[12] have reported the utility of postoperative adjuvant therapy with cytotoxic agents 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 interferon therapy[13] and perioperative administration of prostaglandin E1[14] after liver transplantation for HCV-related HCC because both were from retrospective single-center studies. Although the utility of mTOR inhibitors has been verified, they are currently not covered by the National Health Insurance system and therefore are in limited use. So, the recommendation is

graded weak in the current Guidelines.

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CQ54 What treatment modalities are effective against recurrence after hepatectomy and percutaneous ablation?

Recommendation

Strong recommendation: The treatment algorithm used for primary HCC should also be used for the treatment of recurrent HCC after hepatectomy or percutaneous ablation.

■ 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 by combining CQ55 and CQ56 in the third edition. A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 148 articles. This was narrowed down to 32 in the first screening and to 13 in the second screening based on the following 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 the 11 articles from the third edition, a total of 24 articles are cited in CQ54. Among the articles cited in the third edition, one on percutaneous ablation for recurrent HCC and another on TACE for unresectable primary HCC were excluded from the current edition because they were single-arm trials. One article was added to the current edition to show treatment outcomes of hepatectomy for HCC—this study reported how technological advances in treatment modalities for recurrent HCC after primary HCC treatment contributed to improved long-term prognosis[1]. Also included was an article published in September 2016 that described novel prognostic factors associated with treatment modalities for extrahepatic lesions[2].

Compared with no resection, repeat resection improved prognosis in patients with intrahepatic recurrence after hepatectomy for HCC[3,4]. 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[3-7], although an association between short recurrence-free survival and poor prognosis has been consistently reported[3,4,6,7].

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[8,9]. In a study by Kishi et al. that compared patients who underwent hepatectomy, TACE, PEI/RFA, or other treatment modalities for HCC recurrence after hepatectomy, it was found that hepatectomy, TACE, and PEI/RFA improved prognosis compared with other treatment modalities and were of clinical significance especially in patients with small-sized tumor, long recurrence-free interval, and no extrahepatic metastasis[10]. A study that compared hepatectomy and percutaneous ablation for HCC recurrence after hepatectomy revealed comparable results between the 2 treatment modalities[11,12]. However, TACE was found to be inferior to hepatectomy and percutaneous ablation[13], and better prognosis was found after hepatectomy than after TACE in a meta-analysis[14]. When recurrence occurred soon after surgery, comparable outcomes of TACE, hepatectomy, and percutaneous ablation were also reported[15]. The merits of liver transplantation for recurrent HCC after resection are not discussed in this chapter because it comes back to the question of whether resection or transplantation should be selected as the first treatment option. However, a study that compared hepatectomy, liver transplantation, RFA, TACE, and chemotherapy in patients with recurrent HCC after hepatectomy has reported comparable outcomes between hepatectomy and liver transplantation[16].

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%)[17]. 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)[18]. 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[19]. Overall survival 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).

Imai et al. found no significant difference in disease-free survival or cumulative overall survival between hepatectomy and RFA for recurrent HCC after RFA[20]. 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[21]. 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.

The literature search extracted 2 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[22], while 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[23].

■ Explanation

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, 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[3,4]; 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 40-80 retrospective cohort studies or perioperative comparative effectiveness studies. In these studies, 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. Based on the above, it was concluded that the best treatment strategy for recurrent HCC needs to be

developed using criteria similar to those used for primary HCC. However, in the case of recurrence shortly after resection, it may be reasonable to establish a treatment strategy different from that used for primary HCC.

Several studies have investigated the outcomes of percutaneous ablation for recurrent HCC after the first resection, mostly reporting that prognosis depends on tumor diameter, AFP levels, and time from first resection to recurrence, as in the case of repeat hepatectomy[24].

Except for one study that found no difference in prognosis between hepatectomy, RFA, and TACE[25], other studies have shown that TACE is inferior to hepatectomy and RFA for treating recurrence after resection[11-13]. However, the levels of evidence in these studies are not high, suggesting that the criteria used for primary HCC should be used to select treatment modalities.

The overwhelming lack of deceased donors in liver transplantation has led to a novel transplantation method—salvage 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. It is essential though to discuss here the pros and cons of liver transplantation for recurrent HCC that meets the eligibility criteria even though primary HCC did not meet the eligibility criteria for liver transplantation at the time of first hepatectomy. This was addressed in a study that followed up 5 patients after liver transplantation and reported all patients were alive 18 months after the procedure (4 without recurrence, and 1 with recurrence after 16 months)[26]. Further study is warranted of this issue.

In the current edition of the Guidelines, CQ15-2 was newly established to cover extrahepatic metastasis. Therefore, those who seek information and recommendations about extrahepatic recurrence should read to this CQ.

The latest literature search extracted 2 additional articles that compared the utility of surgical resection (including liver transplantation) and percutaneous ablation to treat recurrence after percutaneous ablation[20,21]. Both modalities had comparable results, suggesting that percutaneous ablation for recurrent HCC after percutaneous ablation needs to be considered based on curative potential and hepatic functional reserve.

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CQ55 What treatment modalities are effective against recurrence after liver transplantation?

Recommendation

Weak recommendation: Recurrent HCC after transplantation may be resected if resectable or treated with molecular-targeted drugs if unresectable.

■ Background

This CQ corresponds to CQ57 in the third 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 third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 127 articles. This was narrowed down to 21 in the first screening, eventually extracting 2 meta-analyses for use in CQ55. The remaining articles and the 5 articles cited in the third edition were excluded because they were retrospective studies and were included in the meta-analyses.

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 (MST) after recurrence was 12.97 months. After resection, 27 patients with localized extrahepatic or intrahepatic recurrence had an MST of 42 months, with no severe postoperative complications or postoperative death. In patients with systemic metastasis for whom resection was not indicated, MST 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, MST 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%).

■ 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 only meta-analyses of retrospective studies 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 RFA 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 MST compared with systemic chemotherapy with cytotoxic agents, but it was also associated with dose reduction and discontinuation of therapy due to adverse drug reactions. Also, despite improving MST, combination therapy with the immunosuppressant mTOR inhibitors was associated with death, suggesting that we should, for now, refrain from using these inhibitors, which are not covered by the National Health Insurance system, in Japan. Further study is needed to accumulate more evidence on these drug therapies.

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