Chapter 8 Post-Treatment Surveillance and Prevention and Treatment of Recurrence

- **Introduction**

The high recurrence rate of hepatocellular carcinoma (HCC), even after curative therapy, is a widely known yet unresolved problem. Unlike other cancers, HCC is unique in that if recurrence occurs, the same treatment options that were available at initial onset can be used; furthermore, a greater therapeutic effect than that observed for recurrence from other types of cancer can be expected. In other words, it is important to devise a treatment strategy for HCC recurrence that is similar to the strategy planned at the time of onset.

The 1st (2005) and 2nd editions (2009) of these guidelines lacked sufficient evidence pertaining to treatment for HCC recurrence, resulting in a tendency to focus on initial HCC treatment. The only Clinical Question (hereafter referred to as "CQ" or "Research Question" in the 1st edition) related to the treatment of recurrence was "What is the effective treatment for recurrent HCC?" in Chapter 3 on surgery. The recommendation for this question (2nd edition) was "It is recommended that a treatment policy for recurrent HCC be decided on the basis of the same criteria used for primary HCC. In other words, liver resection is a standard treatment, and, in particular, repeat liver resection is recommended for patients with single HCC and good liver function (noncirrhotic liver or Child class A disease; Recommendation Grade B)."

Because of recent advancements in nonsurgical treatments, accumulation of evidence for diagnostic methods, and implementation of follow-up after initial curative therapy, it was determined that this information should be consolidated and incorporated into the 3rd edition of the guidelines titled "Chapter 8 Post-Treatment Surveillance, Prevention, and Treatment of Recurrence." Liver resection, percutaneous ablation therapy, and liver transplantation were chosen as curative therapies, and after each therapy, three suggestions were proposed in the form of follow-up (surveillance for detecting recurrence), recurrence prevention, and selection of

treatment for recurrence. Namely, a total of 9 CQs were newly constructed on the basis of literature searches that were extended to articles published before June 2007. During the analysis process, these 9 CQs were consolidated for several reasons, resulting in 6 CQs. For instance, liver resection and percutaneous ablation therapy were performed concomitantly in many studies reporting post-treatment surveillance and recurrence prevention. Therefore, evidence for the two methods could not be separated easily, and each procedure was treated as its own CQ. Because no reports that focused primarily on recurrent HCC during post-transplantation surveillance were found, the entire CQ was deleted. In addition, adjuvant chemotherapies for preventing recurrence were discussed under the CQ "Adjuvant Therapy" in "Chapter 3 Surgery", similar to the 1st and 2nd editions. In addition, any other applications were discussed in Chapter 8.

There is insufficient evidence for all 6 CQs discussed in this chapter. We would like to wait for further evidence to accumulate and continue the discussion in the next edition.

CQ52　How should patients be followed up after liver resection and percutaneous ablation therapy?

Recommendation

After liver resection or percutaneous ablation, strict follow-up is recommended with the concomitant use of tumor marker analysis and imaging tests. Follow-up should be conducted according to the surveillance methods used in extremely high-risk cases at the time of onset **(Grade C1)**.

- **Scientific Statement**

Unlike surveillance for the initial onset of HCC, no documents that compared test intervals or established proper follow-up procedures to follow liver resection or percutaneous ablation therapy were found. We were therefore unable to recommend a strongly supported follow-up procedure.

- **Explanation**

Patients with type C cirrhosis belong to the group of patients with an extremely high risk of developing HCC, and they have an annual cancer incidence rate of approximately 8% (LF02190[1] Level 2a). In contrast, the annual recurrence rate after liver resection for HCC is over 10% and increases to 70%–80% after 5 years. In addition, a study performed ultrasound and dynamic computed tomography (CT) at 4-month intervals following percutaneous ablation therapy (LF11906[2] Level 4), and the cumulative HCC recurrence rate was demonstrated to be 18.6% after 1 year and 72.0% after 5 years. There is insufficient evidence to support that early detection of recurrence after liver resection and percutaneous ablation therapy improves prognosis. However, studies reporting long-term outcomes of liver resection or percutaneous ablation therapy have regularly performed repeat liver resection and repeated percutaneous ablation therapy for recurrence. It is therefore important to conduct post-treatment surveillance that is similar to initial surveillance in order to maximize the potential of curative therapy. At the very least, treatment must be followed by the strict surveillance of extremely high-risk patients.

The surveillance algorithm in these guidelines recommended regular screening of patients in the extremely high-risk group, with focus on ultrasound testing and tumor marker measurements every 3─4 months combined with dynamic CT/magnetic resonance imaging (MRI). A follow-up study that performed ultrasound at 3, 6, 12, and 24 months after radiofrequency ablation (RFA; L3H00023[3] Level 3) demonstrated that 78% of recurrent HCC lesions could be detected. After liver resection, however, ultrasound evaluation was difficult to perform in some patients because of the surgical wound and adhesions. Even after percutaneous ablation therapy, post-therapy changes could be difficult to distinguish from local recurrent lesions. Considering those difficult cases, imaging tests such as dynamic CT or dynamic MRI (including Gd-EOB-DTPA-enhanced MRI) as well as tumor marker measurement and ultrasound every 3–4 months are proposed as a regimen for post-treatment follow-up. The incidence of postoperative recurrence will likely increase, depending on the stage of HCC at onset and fibrosis in the liver; however, it appears

unrealistic to enforce stricter screening because of the cost of testing and radiation exposure. Early detection of extrahepatic recurrence may broaden treatment options and improve prognosis. However, if clinical symptoms are not observed, there are no recommended imaging tests to check for extrahepatic recurrence. If clinical symptoms such as pain in the extremities and neurological symptoms develop, or if tumor markers increase despite the absence of recurrence in the liver, extrahepatic metastasis should be suspected and CT/MRI or bone scintigraphy should be considered.

Although the American Associated for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) guidelines also indicate surveillance for recurrence after local therapy, no evidence-based document has been presented. The AASLD guidelines propose that dynamic CT or dynamic MRI be performed at 3–4-month intervals as follow-up, and they are examining the possibility of extending the screening interval for patients who remain relapse-free for 2 years. The EASL also recommends ultrasound at 3–4-month intervals.

- **References**

1) LF02190 Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma; national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Inhibition of Hepatocarcinogenesis by Interferon Therapy. Ann Intern Med 1999;131(3):174-81.
2) LF11906 Tateishi R, Shiina S, Yoshida H, Teratani T, Obi S, Yamashiki N, et al. Prediction of recurrence of hepatocellular carcinoma after curative ablation using three tumor markers. Hepatology 2006;44(6):1518-27.
3) L3H00023 Eisele RM, Schumacher G, Lopez-Hänninen E, Neuhaus P. Role of B-mode ultrasaound screening in detection of local tumor recurrence in the first year after radiofrequency ablation in the liver. Cancer Detect Prev 2007;31(4):316-22.

CQ53　What methods are effective for preventing recurrence after liver resection and percutaneous ablation therapy?

Recommendation

In patients with hepatitis-positive HCC, interferon therapy after liver resection and percutaneous ablation may inhibit recurrence and improve the survival rate. Treatment may be administered while monitoring adverse events **(Grade C1)**.

There are other methods that are reportedly useful for preventing recurrence. However, there is not enough evidence to recommend them at this time **(Grade C1)**.

- **Scientific Statement**

Several randomized controlled trials (RCTs) have shown the prevention of recurrence and/or improved survival rates after interferon therapy (α or β) was administered as adjuvant therapy after liver resection or percutaneous ablation therapy in HCC patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) positivity (LF10626[1)] Level 1b, LF11764[2)] Level 1b, L3F05468[3)] Level 1b). Nevertheless, there are reports of improved survival rates and prevention of recurrence only in a certain subgroup of patients (LF10137[4)] Level 1b, LF10556[5)] Level 1b). Recently, three meta-analyses that consolidated the results of previous small-scale RCTs (L3F05580[6)] Level 1a, L3F00592[7)] Level 1a, L3F05630[8)] Level 1a) were reported, and all results support the efficacy of interferon α therapy.

Although adoptive therapy is reported to be effective for preventing postoperative recurrence (LF01855[9)] Level 1b), the survival rates have not improved significantly. Recurrence has also been inhibited by acyclic retinoid, with improved survival rates (LF01582[10)] Level 1b). The sample size of each comparative study, however, was small; therefore, it is too early to recommend these treatments as post-treatment adjuvant therapy at this time. Vitamin K has been studied in three RCTs, although its efficacy is unfavorable (L3F01663[11)] Level 1b, LF10719[12)]

Level 1b, L3F01766[13] Level 1b). A meta-analysis integrated and analyzed the efficacy of acyclic retinoid and vitamin K as vitamin analog agents, and the results showed the former to be effective and the latter to be ineffective (L3F05447[14] Level 1a). It is unclear whether long-term treatment with branched-chain amino acid monotherapy improves the survival rate (LF00440[15] Level 1b). Although an RCT has indicated that combination treatment with branched-chain amino acids + ACE inhibitors is effective, it was a single report with a small number of patients; therefore, its results cannot be considered conclusive (L3F00664[16] Level 1b).

- **Explanation**

Because the recurrence rate for HCC is high, even after curative liver resection or percutaneous ablation therapy, prevention of recurrence is essential for long-term survival. In the past, antiviral therapy seemed to aid in the prevention of hepatitis B and C virus-related HCC recurrence, and supporting evidence is gradually being provided, including RCT results. For this CQ, therapies for preventing recurrence after curative therapies such as liver resection and percutaneous ablation therapy were examined, excluding treatments that were expected to yield direct antitumor effects (see CQ29).

Two RCTs have respectively demonstrated that postoperative interferon therapy for HBV-positive HCC and HCV-positive HCC have improved survival rates. However, the improved survival rate observed in the RCT on HBV-positive HCC was only observed in advanced HCC patientsl, and recurrence was prevented in HCV-positive HCC in the relatively early stages of disease in the other trial. The recommendation level until the 2nd edition (2009 edition) remained at Grade C1 because a sufficient number of patients were not examined in the first two RCTs, and the results of the latter 2 RCTs supported the efficacy of interferon only after subgroup analysis. Although the recent results of meta-analyses have strongly indicated the efficacy of this therapy, two of these analyses integrated the results of RCTs and prospective cohort studies (L3F00592[7] Level 1a, L3F05630[8] Level 1a). Therefore, these results should be interpreted with care. A meta-analysis of only RCTs (L3F05580[6] Level 1a) appears unconvincing because a difference in the 1-year

survival rate was already evident, despite the fact that the majority of patients had Child–Pugh class A disease. The formal results of the meta-analysis were classified as Level 1a; however, this should apply only to data obtained from properly designed RCTs that were integrated using strict statistical methods. Even if the title of the document uses the term "meta-analysis," each study should be properly evaluated to determine whether the rating is truly appropriate. None of these three documents were worthy of a Level 1a designation and were assigned a Grade C1 recommendation. Nonpegylated interferon had been used in the past, yet recent reports that comparatively analyzed treatments for virus eradication have indicated the efficacy of pegylated interferon (L3F05582[17] Level 2b) and small-dose, long-term administration (L3F05680[18] Level 3). Further studies are required, however, as the evidence level needs to be higher.

Acyclic retinoid and adoptive immunotherapy are promising therapies, and one RCT each has reported on its treatment efficacy. Nevertheless, because these were single reports of small-scale RCTs, a large-scale comparative study based on these reports is necessary in the future. A single, small-scale RCT showed vitamin K resulted in a significant difference in relapse-free survival. However, it did not remain a significant factor after multivariate analysis; therefore, this should probably be considered as a negative study (LF10719[12] Level 1b). The efficacy of vitamin K monotherapy seems negligible according to the results of an RCT with an adequate sample size (L3F01766[13] Level 1b).

Within the time-frame of our search, no solid evidence regarding the direct effects of nucleoside analogs on recurrence prevention after therapy in HBV DNA-positive HCC patients was found. On the other hand, there are several studies in which post-therapy survival was better in the nucleoside analog group; therefore, the effects of nucleoside analogs on improving and maintaining hepatic functional reserve may be indirectly reflected in the survival rate (L3F01644[19] Level 2b, L3F01308[20] Level 2b, L3F01752[21] Level 1a). However, although these reports contain one meta-analysis, further studies are necessary because the analysis is nothing more than an integration analysis of cohort studies and does not include RCT evidence.

- **References**

1) LF10626 Sun HC, Tang ZY, Wang L, Qin LX, Ma ZC, Ye QH, et al. Postoperative interferon alpha treatment postponed recurrence and improved overall survival in patients after curative resection of HBV-related hepatocellular carcinoma: a randomized clinical trial. J Cancer Res Clin Oncol 2006;132(7):458—65.
2) LF11764 Kubo S, Nishiguchi S, Hirohashi K, Tanaka H, Shuto T, Kinoshita H. Randomized clinical trial of long-term outcome after resection of hepatitis C virus-related hepatocellular carcinoma by postoperative interferon therapy. Br J Surg 2002;89(4):418-22.
3) L3F05468 Lin SM, Lin CJ, Hsu CW, Tai DI, Sheen IS, Lin DY, et al. Prospective randomized controlled study of interferon-alpha in preventing hepatocellular carcinoma recurrence after medical ablation therapy for primary tumors. Cancer 2004;100(2):376—82.
4) LF10137 Lo CM, Liu CL, Chan SC, Lam CM, Poon RT, Ng IO, et al. A randomized, controlled trial of postoperative adjuvant interferon therapy after resection of hepatocellular carcinoma. Ann Surg 2007;245(6):831-42.
5) LF10556 Mazzaferro V, Romito R, Schiavo M, Mariani L, Camerini T, Bhoori S, et al. Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. Hepatology 2006;44(6):1543—54.
6) L3F05580 Zhang CH, Xu GL, Jia WD, Ge YS. Effects of interferon alpha treatment on recurrence and survival after complete resection or ablation of hepatocellular carcinoma: a meta-analysis of randomized controlled trials. Int J Cancer 2009;124(12):982-8.
7) L3F00592 Singal AK, Freeman DH Jr, Anand BS. Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma. Aliment Pharmacol Ther 2010;32(7):851-8.
8) L3F05630 Shen YC, Hsu C, Chen LT, Cheng CC, Hu FC, Cheng AL. Adjuvant interferon therapy after curative therapy for hepatocellular carcinoma (HCC): a meta-regression approach. J Hepatol 2010;52(6):889-94.

9) LF01855 Takayama T, Sekine T, Makuuchi M, Yamasaki S, Kosuge T, Yamamoto J, et al. Adoptive immunotherapy to lower postsurgical recurrence rates of hepatocellular carcinoma: a randomised trial. Lancet 2000;356(9232):802-7.

10) LF01582 Muto Y, Moriwaki H, Ninomiya M, Adachi S, Saito A, Takasaki KT, et al. Prevention of second primary tumors by an acyclic retinoid, polyprenoic acid, in patients with hepatocellular carcinoma. Hepatoma Prevention Study Group. N Engl J Med 1996;334(24):1561-7.

11) L3F01663 Hotta N, Ayada M, Sato K, Ishikawa T, Okumura A, Matsumoto E, et al. Effect of vitamin K2 on the recurrence in patients with hepatocellular carcinoma. Hepatogastroenterology 2007;54(79)2073-7.

12) LF10719 Kakizaki S, Sohara N, Sato K, Suzuki H, Yanagisawa M, Nakajima H, et al. Preventive effects of vitamin K on recurrent disease in patients with hepatocellular carcinoma arising from hepatitis C viral infection. J Gastroenterol Hepatol 2007;22(4):518-22.

13) L3F01766 Yoshida H, Shiratori Y, Kudo M, Shiina S, Mizuta T, Kojiro M, et al. Effect of vitamin K2 on the recurrence of hepatocellular carcinoma. Hepatology 2011;54(2):532-40.

14) L3F05447 Chu KJ, Lai EC, Yao XP, Zhang HW, Lau WY, Fu XH, et al. Vitamin analogues in chemoprevention of hepatocellular carcinoma after resection or ablation-a systematic review and meta-analysis. Asian J Surg 2010;33(3):120—6.

15) LF00440 The San-in Group of Liver Surgery. Long-term oral administration of branched chain amino acids after curative resection of hepatocellular carcinoma: a prospective randomized trial. Br J Surg 1997; 84(11):1525-31.

16) L3F00664 Yoshiji H, Noguchi R, Ikenaka Y, Kaji K, Aihara Y, Yamazaki M, et al. Combination of branched-chain amino acids and angiotensin-converting enzyme inhibitor suppresses the cumulative recurrence of hepatocellular carcinoma: a randomized control trial. Oncol Rep 2011;26(6):1547-53.

17) L3F05582 Hagihara H, Nouso K, Kobayashi Y, Iwasaki Y, Nakamura S, Kuwaki K, et al.

Effect of pegylated interferon therapy on intrahepatic recurrence after curative treatment of hepatitis C virus-related hepatocellular carcinoma. Int J Clin Oncol 2011;16(3):210-20.

18) L3F05680 Kudo M, Sakaguchi Y, Chung H, Hatanaka K, Hagiwara S, Ishikawa E, et al. Long-term interferon maintenance therapy improves survival in patients with HCV-related hepatocellular carcinoma after curative radiofrequency ablation. A matched case-control study. Oncology 2007;72 (Suppl 1) :132-8.

19) L3F01644 Chuma M, Hige S, Kamiyama T, Meguro T, Nagasaka A, Nakanishi K, et al. The influence of hepatitis B DNA level and antiviral therapy on recurrence after initial curative treatment in patients with hepatocellular carcinoma. J Gastroenterol 2009;44(9):991-9.

20) L3F01308 Chan AC, Chok KS, Yuen WK, Chan SC, Poon RT, Lo CM, et al. Impact of antiviral therapy on the survival of patients after major hepatectomy for hepatitis B virus—related hepatocellular carcinoma. Arch Surg 2011;146(6):675-81.

21) L3F01752 Wong JS, Wong GL, Tsoi KK, Wong VW, Cheung SY, Chong CN, et al. Meta-analysis: the efficacy of anti-viral therapy in prevention of recurrence after curative treatment of chronic hepatitis B-related hepatocellular carcinoma. Aliment Pharmacol Ther 2011;33(10):1104-12.

CQ54 What methods are effective for preventing recurrence after liver transplantation?

Recommendation

Immunosuppressive drug selection and dose adjustments reportedly contribute to the prevention of recurrence after liver transplantation **(Grade C1).**

- **Scientific Statement**

The correlation between immune suppression and tumor progression has long been indicated. Pinna et al. conducted a retrospective study of 70 deceased liver transplant recipients (recurrence

occurred in seven cases) who had been treated with the immunosuppressive agent cyclosporine A (CyA), and they examined factors such as compliance with the Milan criteria, pathological vascular invasion, and histological differentiation of HCC. Multivariate analysis showed that strong exposure to CyA increased the risk of recurrence. The amount of exposure was defined as the area under the blood concentration time curve (AUC), determined by the trapezoidal rule based on the blood concentration of CyA and the time at each measurement point, with data omitted from the observation period (L3F06349[1)] Level 2b). This group later performed a follow-up study using a combination of CyA (79 patients) and tacrolimus (Tac; 60 patients), in which 220 ng/mL CyA and 10 ng/mL Tac were set as threshold values and analyzed in the same manner. The results showed that excessive exposure to the calcineurin inhibitor was associated with the recurrence rate (L3F01744[2)] Level 2b). Although the methods for measuring blood concentration were standardized and multivariate analysis was performed with factor analysis, death from other diseases was excluded and there were no detailed descriptions pertaining to transplant rejection.

The *in vitro* antitumor effects of mammalian target of rapamycin (mTOR) inhibitors are well known, and reports of their use are continuing to accumulate in western countries. Toso et al. treated 70 deceased liver transplant recipients with sirolimus (SRL) and observed no difference in the 4-year relapse-free survival rates between 34 patients who fulfilled the Milan criteria and 36 who did not (73% and 75%, respectively). SRL was also found to be useful for liver transplantation in terms of decreased adverse effects (LF11013[3)] Level 2b). Vivarelli et al. conducted a matched cohort study of 31 patients treated with SRL and reported a 3-year relapse-free survival rate of 86% in the SRL group and 56% in the non-SRL group, demonstrating that SRL may significantly decrease the recurrence rate (L3F00628[4)] Level 2b). Furthermore, a large-scale database from the United States was used to analyze 2,491 patients who underwent solitary liver transplantation for HCC, and it was demonstrated that 109 patients treated with SRL had a 5-year survival rate of 83.1%, whereas 2,382 patients who were not treated with SRL had a

5-year survival rate of 68.7%. A multivariate analysis revealed that SRL is an independent factor that aids in the prevention of recurrence, along with antibody induction therapy using anti-CD25 monoclonal antibody (L3F05168[5] Level 2b).

In addition, a meta-analysis including the above studies found that patients treated with mTOR inhibitors had improved 1-year (odds ratio: 4.53, 95% confidence interval: 2.31–8.89), 3-year (odds ratio: 1.97, 95% confidence interval: 1.29–3.00), and 5-year survival rates (odds ratio: 2.47, 95% confidence interval: 1.72–3.55) compared with those who were not treated with mTOR inhibitors. Patients treated with mTOR inhibitors also experienced a decreased recurrence rate (odds ratio: 0.42, 95% confidence interval: 0.21–0.83) compared with those who were not (L3F05229[6] Level 2b).

Furthermore, with advancements in immunosuppressive therapies, new clinical trials using additional molecular-targeted drugs are currently under way. A Spanish multicenter cooperative study was performed in 31 patients to confirm the safety of mTOR inhibitors combined with sorafenib therapy against recurrent HCC after liver transplantation. The results showed that the median survival time after recurrence was 19.3 months (95% confidence interval: 13.4–25.1 months), and the median time to progression was 6.8 months (95% confidence interval: 2.3–11.1 months). Therefore, combined treatment was possible without any serious risk of toxicity (L3F04273[7] Level 2b).

- **Explanation**

Immunosuppressive agents are essential for preventing post-transplantation rejection. The selection of immunosuppressive agents and adjustment of maintenance-level blood concentrations are performed according to the disease state. In addition, excessive administration of such agents is usually avoided in order to proactively prevent the risk of developing infection due to life-long immunosuppression and accumulation of adverse effects such as renal dysfunction. There is no point in testing excessively low doses to prevent recurrence if the graft is rejected; therefore, it is certainly not beneficial to expect recurrence prevention by adjusting only the concentration of a

specific immunosuppressive agent. The use of drugs such as mTOR inhibitors is extremely limited in Japan at present. However, the use or combined use of drugs with different effects can largely influence recurrence prevention. Positive results are anticipated from large-scale, multicenter studies in the future (L3F00575[8]). The recommendation grade was set as C1 after considering CyA and Tac dose adjustments and because the National Health Insurance has not approved the use of mTOR inhibitors for liver transplantation in Japan.

- **References**

1) L3F06349 Vivarelli M, Cucchetti A, Piscaglia F, La Barba G, Bolondi L, Cavallari A, et al. Analysis of risk factors for tumor recurrence after liver transplantation for hepatocellular carcinoma:key role of immunosuppression. Liver Transpl 2005;11(5):497-503.

2) L3F01744 Vivarelli M, Cucchetti A, La Barba G, Ravaioli M, Del Gaudio M, Lauro A, et al. Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors:reassessment of risk factors for tumor recurrence. Ann Surg 2008;248(5):857-62

3) LF11013 Toso C, Meeberg GA, Bigam DL, Oberholzer J, Shapiro AM, Gutfreund K, et al. De novo sirolimus-based immunosuppression after liver transplantation for hepatocellular carcinoma: long-term outcomes and side effects. Transplantation 2007;83(9):1162-8.

4) L3F00628 Vivarelli M, Dazzi A, Zanello M, Cucchetti A, Cescon M, Ravaioli M, et al. Effect of different immunosuppressive schedules on recurrence-free survival after liver transplantation for hepatocellular carcinoma. Transplantation 2010;89(2):227-31.

5) L3F05168 Toso C, Merani S, Bigam DL, Shapiro AM, Kneteman NM. Sirolimus-based immunosuppression is associated with increased survival after liver transplantation for hepatocellular carcinoma. Hepatology 2010;51(4):1237-43.

6) L3F05229 Liang W, Wang D, Ling X, Kao AA, Kong Y, Shang Y, et al. Sirolimus-based immunosuppression in liver transplantation for hepatocellular carcinoma: a meta-analysis. Liver Transpl 2012;18(1):62-9.

7) L3F04273 Gomez-Martin C, Bustamante J, Castroagudin JF, Salcedo M, Garralda E,

Testillano M, et al. Efficacy and safety of sorafenib in combination with mammalian target of rapamycin inhibitors for recurrent hepatocellular carcinoma after liver transplantation. Liver Transpl 2012;18(1):45-52.

8) L3F00575 Schnitzbauer AA, Zuelke C, Graeb C, Rochon J, Bilbao I, Burra P, et al. A prospective randomised, open-labeled, trial comparing sirolimus-containing versus mTOR-inhibitor-free immunosuppression in patients undergoing liver transplantation for hepatocellular carcinoma. BMC Cancer 2010;10:190.

CQ55 What treatments are effective against recurrence after hepatectomy?

Recommendation

When treating recurrence after hepatectomy, a treatment plan should be designed on the basis of the same criteria used for treating HCC at the initial onset. Repeat resection is recommended in patients with a single recurrence and good liver function **(Grade B)**.

- **Scientific Statement**

Treatment outcomes were compared between patients who underwent re-resection for recurrent HCC (single intrahepatic recurrence) after liver resection and those who did not undergo resection, and the prognosis was found to be favorable in the resection group (LF00243[1)] Level 2b, LF11269[2)] Level 2b). However, the actual number of recurrent cases indicated for liver resection did not exceed 11%–30% of the total number of cases. In addition, prognostic factors after repeat liver resection were the same as those after the first liver resection and included vascular invasion, residual hepatic function, and tumor number (LF00243[1)] Level 2b, LF11269[2)] Level 2b, LF00343[3)] Level 2b, LF11799[4)] Level 2b, L3F01716[5)] Level 2b). However, it was consistently reported that the time to recurrence was short and the prognosis was poor (LF00243[1)] Level 2b, LF11269[2)] Level 2b, LF11799[4)] Level 2b, L3F01716[5)] Level 2b). Percutaneous ablation therapy

for recurrent HCC was only documented in a Level 4 report (LF11814[6] Level 4), and there is no high-level evidence comparing liver resection and percutaneous ablation therapy for recurrent HCC. Although the only documentation for TACE is also a Level 4 report (L3F00150[7] Level 4), it can be deduced that TACE can extend the survival duration if recurrence is limited to the liver, according to Level 1b evidence on the efficacy of TACE for unresectable initial HCC. In order to discuss the pros and cons of performing liver transplantation for recurrent HCC after liver resection, we return to the issue of determining whether resection or transplantation should be performed as initial treatment, and this topic is discussed in a separate section. It is believed that extrahepatic recurrence or recurrence with extrahepatic lesions should be treated using the same treatment strategy used for initial therapy; however, in case of recurrence with single metastatic lung lesions, lung resection may be indicated depending on the patient (LF10099[8] Level 2b).

- **Explanation**

After liver resection for HCC, recurrence is reported to occur in 50% patients after 2 years and 80% patients after 5 years. Recurrence after liver resection for HCC is characterized by highly frequent intrahepatic recurrence, and at least 90% of first recurrences are intrahepatic metastases, most of which appear to be single lesions in the liver. Intrahepatic recurrence following liver resection is not only associated with metastasis but also contributes to the development of new HCC from liver tissue that remains after liver resection (metachronous multicenter recurrence). The treatment strategy for metachronous multicenter recurrence is theoretically the same as initial treatment (if it is assumed that the risk of carcinogenesis in the liver has not changed over time). Nevertheless, regular clinicopathological examination has shown that such events are difficult to distinguish from recurrent metastasis in the liver. Therefore, the mechanism by which the treatment strategy should be altered from the initial treatment plan for HCC remains unknown. Studies comparing treatment and nontreatment of single intrahepatic recurrence and studies comparing liver resection with other therapies were ranked no higher than Level 2b; therefore, candidate selection for each therapy led to a study bias. Several studies conducted multivariate

analyses of background factors, and all showed that re-resection was an independent positive prognostic factor compared with nonresection (LF00243[1] Level 2b, LF11269[2] Level 2b), but the possibility of publication bias should be considered. Prognostic factors for repeat liver resection in patients with recurrent HCC were analyzed in Level 2b and Level 4 reports that examined 40–80 patients. These reports found that the vital prognosis after re-resection was nearly identical to that after first resection following HCC onset at the same facility. Because the time from first resection to re-resection was largely ignored in these comparison studies, it is conceivable that the favorable results achieved after re-resection reflect a selection bias. It is presumed that patient selection using the same criteria used after the initial onset results in the selective resection of patients with recurrence from metachronous multicentric carcinogenesis. Vascular invasion is a common prognostic factor after first resection, and the time interval from first resection to recurrence (categorized as <1 year or ≥1 year) is also often reported to be a prognostic factor, which appears to support the aforementioned speculations. According to the above findings, it is recommended that treatment strategies for recurrent HCC should use the same criteria as those used for initial HCC. However, if recurrence develops shortly after resection, it may be appropriate to adopt a different approach from the initial treatment strategy. Repeat liver resection for recurrent HCC, however, has mostly been reported in Asia, including Japan, in the past. Reports have recently emerged from western countries as well (L3F01716[5] Level 2b), although the scale of the study was far too small in terms of patient numbers.

There are several Level 4 reports regarding percutaneous ablation therapy for recurrent HCC after first resection. The prognostic factors were tumor diameter and alpha-fetoprotein (AFP) level, and prognosis was often influenced by the time period from first resection to recurrence, similar to that in patients who undergo repeat liver resection (LF11793[9] Level 4). There were no strongly supported studies that compared liver resection with percutaneous ablationl therapy for recurrent HCC. The prognosis did not differ between a transcatheter chemoembolization (TACE) group and both groups in studies that compared a variety of therapies for recurrence after resection. A

difference in prognosis was instead observed with the number of treatments (L3F00289[10] Level 2b), indicating that proactive intervention for recurrence may be linked to an improved prognosis. Studies of TACE treatment for recurrent HCC are ranked at no higher than Level 4 (L3F00150[7] Level 4), yet one study has reported that the time to recurrence is a prognostic factor in the latter. The efficacy of TACE for unresectable HCC has been supported by several reports with Level 1b evidence, and TACE was documented as the first-choice therapy for treating patients with unresectable recurrent HCC, which constitutes more than 50% patients with recurrence. Comparative studies with molecular-targeted therapy are a subject of future investigation.

In consideration of the overwhelming shortage of deceased liver donors for liver transplantation, the standard policy asserts that HCC should initially be treated with liver resection followed by patient monitoring, and if recurrence is observed and the tumor meets the selection criteria (Milan criteria), transplantation is performed. This method is referred to as "salvage transplantation." There are some issues associated with this method, however. If both resection and liver transplantation are indicated for initial HCC, there is some debate as to whether liver transplantation or resection should be performed first. This issue is discussed in a separate section. On the other hand, the pros and cons of liver transplantation should be discussed for patients who meet tumor-based selection criteria at the time of recurrence but were not indicated for liver transplantation at the time of initial liver resection. This has been discussed in a single report in which liver transplantation was performed in 5 patients, and all patients survived 18 months of follow-up (four patients with no recurrence, one with recurrence at 16 months; L3F01485[11] Level 2b). This is a topic for future investigation.

After the liver, the lung is the second most common site of recurrence following liver resection. In principle, curative therapies are ineffective against recurrent HCC with extrahepatic lesions, and treatment strategies do not differ much from those used at onset. One report, however, has emphasized the efficacy of resection for a limited number of solitary pulmonary metastases (LF10099[8] Level 2b). A comparison with molecular-targeted drugs is a topic for future investigation.

- **References**

1) LF00243 Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Intrahepatic recurrence after curative resection of hepatocellular carcinoma: long-term results of treatment and prognostic factors. Ann Surg 1999;229(2):216-22.

2) LF11269 Chen WT, Chau GY, Lui WY, Tsay SH, King KL, Loong CC, et al. Recurrent hepatocellular carcinoma after hepatic resection: prognostic factors and long-term outcome. Eur J Surg Oncol 2004;30(4):414-20.

3) LF00343 Shimada M, Takenaka K, Taguchi K, Fujiwara Y, Gion T, Kajiyama K, et al. Prognostic factors after repeat hepatectomy for recurrent hepatocellular carcinoma. Ann Surg 1998;227(1):80-5.

4) LF11799 Minagawa M, Makuuchi M, Takayama T, Kokudo N. Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. Ann Surg 2003;238(5):703-10.

5) L3F01716 Roayaie S, Bassi D, Tarchi P, Labow D, Schwartz M. Second hepatic resection for recurrent hepatocellular cancer: a Western experience. J Hepatol 2011;55(2):346-50.

6) LF11814 Choi D, Lim HK, Rhim H, Kim YS, Yoo BC, Paik SW, et al. Percutaneous radiofrequency ablation for recurrent hepatocellular carcinoma after hepatectomy: long-term results and prognostic factors. Ann Surg Oncol 2007;14(8):2319-29.

7) L3F00150 Choi JW, Park JY, Ahn SH, Yoon KT, Ko HK, Lee do Y, et al. Efficacy and safety of transarterial chemoembolization in recurrent hepatocellular carcinoma after curative surgical resection. Am J Clin Oncol 2009;32(6):564-9.

8) LF10099 Tomimaru Y, Sasaki Y, Yamada T, Eguchi H, Takami K, Ohigashi H, et al. The significance of surgical resection for pulmonary metastasis from hepatocellular carcinoma. Am J Surg 2006;192(1):46-51.

9) LF11793 Yang W, Chen MH, Yin SS, Yan K, Gao W, Wang YB, et al. Radiofrequency ablation of recurrent hepatocellular carcinoma after hepatectomy: therapeutic efficacy on

early- and late-phase recurrence. AJR Am J Roentgenol 2006;186 (5 Suppl):S275-83.

10) L3F00289 Kishi Y, Saiura A, Yamamoto J, Koga R, Seki M, Morimura R, et al. Repeat treatment for recurrent hepatocellular carcinoma: is it validated? Langenbecks Arch Surg 2011;396(7):1093-100.

11) L3F01485 Facciuto ME, Koneru B, Rocca JP, Wolf DC, Kim-Schluger L, Visintainer P, et al. Surgical treatment of hepatocellular carcinoma beyond Milan criteria. Results of liver resection, salvage transplantation, and primary liver transplantation. Ann Surg Oncol 2008;15(5):1383-91.

CQ56 What treatments are effective against recurrence after percutaneous ablation therapy?

Recommendation

When treating recurrence after percutaneous ablation, a curative treatment strategy that takes hepatic functional reserve into account should be designed **(Grade B)**.

- **Scientific Statement**

Rossi et al. studied 696 patients treated with repeat RFA for HCC and found that after initial therapy, the 3- and 5-year recurrence rates were 70.8% and 81.7%, respectively (the annual rates were 6.2% for local recurrence and 35% for distant recurrence). The 3- and 5-year overall survival and disease-free survival rates were 67.0%, 40.1%, 68.0%, and 38.0%, respectively (L3F05870[1)] Level 2a).

In addition, Portolani et al. studied patients in the following groups: group 1 patients treated with liver resection for recurrence after percutaneous ablation therapy (24 patients treated with PEI, 12 with RFA), group 2 patients treated with re-resection for recurrence after liver resection (26 patients), and group 3 patients treated with percutaneous ablation therapy for recurrence after liver

resection (31 patients). No significant differences were observed between groups in terms of 1-, 3-, and 5-year survival rates (Group 1: 92%, 73%, and 43%; Group 2: 95%, 73%, and 31%; Group 3: 96%, 78%, and 41%, respectively; L3F05638[2] Level 2b).

Furthermore, according to Okuwaki et al., distant recurrence was observed in 59 of 115 patients (51.3%) who underwent RFA for HCC, and the 1-, 3-, and 5-year survival rates after distant recurrence were 92.7%, 55.4%, and 43.7%, respectively. In addition, the survival rate was significantly higher in the RFA-treated group than in the TACE-treated group (3-year survival rate: 77.2% vs. 28.5%, respectively; L3F00093[3] Level 2b).

- **Explanation**

Percutaneous ablation therapies, including RFA, are safe to perform in patients with cirrhosis and poor liver function. Therefore, percutaneous ablation therapy can be useful for controlling HCC recurrence in patients who are contraindicated for liver resection. At present, no studies have thoroughly and comparatively analyzed liver resection and percutaneous ablation therapy as treatments for recurrence after percutaneous ablation therapy. Therefore, treatment should be selected in line with the initial treatment after considering curability and hepatic functional reserve.

- **References**

1) L3F05870 Rossi S, Ravetta V, Rosa L, Ghittoni G, Viera FT, Garbagnati F, et al. Repeated radiofrequency ablation for management of patients with cirrhosis with small hepatocellular carcinomas: a long-term cohort study. Hepatology (Baltimore, Md) 2011;53(1):136-47.

2) L3F05638 Portolani N, Baiocchi GL, Coniglio A, Grazioli L, Frassi E, Gheza F, et al. Sequential multidisciplinary treatment of hepatocellular carcinoma: the role of surgery as rescue therapy for failure of percutaneous ablation therapies. J Surg Oncol 2009;100(7):580-4.

3) L3F00093 Okuwaki Y, Nakazawa T, Kokubu S, Hidaka H, Tanaka Y, Takada J, et al. Repeat radiofrequency ablation provides survival benefit in patients with intrahepatic distant recurrence of hepatocellular carcinoma. Am J Gastroenterol 2009;104(11):2747-53.

CQ57　What treatments are effective against recurrence after liver transplantation?

Recommendation

Resection of recurrent lesions after liver transplantation may be considered when possible **(Grade C1)**.

- **Scientific Statement**

Recurrence after liver transplantation is considered to be a link in a chain of systemic disseminated lesions. Treatment is extremely difficult, similar to that for systemic disseminated lesions in nontransplanted patients. No effective systemic therapies have been reported. There are reports of resection, although they are rare.

In the United States, Schwartz et al. consolidated data for 57 patients who developed recurrence from among 311 patients who underwent liver transplantation for HCC and reported 18 patients who underwent resection (including five resections). In addition, multivariate analysis showed that resection is an independent factor that improves the survival duration after recurrence (LF11493[1] Level 2b). In the United Kingdom, Heaton et al. reported that of 3,017 liver transplant patients, 11 underwent liver resection after liver transplantation for several reasons, of which four patients were treated for intrahepatic recurrence of HCC. After the recurrent lesions were removed, two patients died from additional recurrence 9 months and 30 months after the procedure, respectively, one was lost to follow-up, and one was documented as surviving at the 1-year point (L3F02098[2] Level 5). Catalano et al. similarly performed liver resection after liver transplantation in 12 of 367 patients who underwent liver transplantation, and two of these patients were being treated for recurrent lesions. Eighteen and 20 months after resection, both patients died from recurrence (LF11598[3] Level 2b). Bates et al. reported five patients who underwent resection for pulmonary metastasis. Pulmonary metastases were discovered at an average of 500 days after liver transplantation; one resection patient died from recurrence 38 months later and four survived

through the 12-, 38-, 54-, and 80-month time points, respectively (L3F03948[4] Level 5). Although living donor liver transplantation is commonly performed in Japan, long-term survival has been achieved with the resection of recurrent lesions. Furthermore, Taketomi et al. performed resection in 9 of 17 patients with recurrent HCC after liver transplantation and reported 1-, 3-, and 5-year relapse-free survival rates of 55.6%, 11%, and 11%, respectively, whereas patients who could not undergo resection had 1-, 3-, and 5-year relapse-free survival rates of 12.5%, 0%, and 0%, respectively (L3F01731[5] Level 2b).

- **Explanation**

Liver transplantation is the ultimate form of liver resection. In regular liver resection, a part of the liver tissue that is the origin of HCC must be spared in order to preserve liver function for patient survival. In liver transplantation, the carcinogenic areas of the liver are completely removed, followed by orthotopic transplantation. Therefore, any recurrent lesions that arise after such treatment are treated as a link in a chain of systemic disseminated lesions, even if lesions are seen in the liver. In addition, because malignant tumors under immunosuppression rapidly progress interdependently, the effects of local therapies are extremely limited. In recent years not included in the literature search period, mTOR inhibitors have continued to be used in patients with recurrence, and the same can be said for molecular-targeted therapies among nontransplanted patients. Further reports are anticipated.

- **References**

1) LF11493 Roayaie S, Schwartz JD, Sung MW, Emre SH, Miller CM, Gondolesi GE, et al. Recurrence of hepatocellular carcinoma after liver transplant: patterns and prognosis. Liver Transpl 2004;10(4):534-40.

2) L3F02098 Marangoni G, Faraj W, Sethi H, Rela M, Muiesan P, Heaton N. Liver resection in liver transplant recipients. Hepatobiliary Pancreat Dis Int 2008;7(6):590-4.

3) LF11598 Catalano G, Urbani L, Biancofiore G, Bindi L, Boldrini A, Consani G, et al. Hepatic resection after liver transplantation as a graft-saving procedure: indication criteria,

timing and outcome. Transplant Proc 2004;36(3):545-6.

4) L3F03948 Bates MJ, Farkas E, Taylor D, McFadden PM. Pulmonary resection of metastatic hepatocellular carcinoma after liver transplantation. Ann Thorac Surg 2008;85(2):412-5.

5) L3F01731 Taketomi A, Fukuhara T, Morita K, Kayashima H, Ninomiya M, Yamashita Y, et al. Improved results of a surgical resection for the recurrence of hepatocellular carcinoma after living donor liver transplantation. Ann Surg Oncol 2010;17(9):2283-9.

Comments from the Health Economics Committee

Health Economics Perspective on Clinical Practice Guidelines for Hepatocellular Carcinoma, 2013 Edition

– **Regarding CQ43 in Particular –**

Center for Public Health Informatics, National Institute of Public Health

Takashi Fukuda

Systemic chemotherapy with sorafenib is recommended for unresectable hepatocellular carcinoma (HCC), and the drug expenses for sorafenib monotherapy are approximately 540,000 yen per month. When better and more effective medical care is available, it should be implemented. However, countries where drug expenses are covered by the public health care system are evaluating the cost-effectiveness of treatment.

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) evaluates the cost-effectiveness of new medical technologies and pharmaceutical products and provides counselling on whether its use should be recommended to the public health care system, the National Health Service (NHS). Sorafenib therapy was not recommended for unresectable HCC