Chapter 2:

Treatment Algorithm

● Introduction

The evidence-based treatment algorithm has been the most cited aspect of the Clinical Practice Guidelines for Liver Cancer. It is also frequently used in actual clinical settings. It was developed for use in the 2005 version (the first edition) of the Guidelines, with liver damage, tumor number, and tumor size as core factors, and has been used to determine treatment strategy because it incorporates the latest evidence. Developed under the guidance of the first Group Leader, Masatoshi Makuuchi, the algorithm recommended up to 2 treatment modalities that closely reflected actual hepatology treatment strategies in clinical practice in Japan. Only 3 articles were used as sources of evidence in the first edition (hepatectomy and percutaneous ablation by Arii et al., transcatheter arterial embolization (TAE) by Llovet et al., and liver transplantation by Mazzaferro et al.). However, the number of articles increased with each revision of the Guidelines, and the 2013 version (third edition) cites 10 articles. The algorithm itself was modified in the 2009 version (second edition) by introducing treatments for HCC with accompanying vascular invasion and extrahepatic metastasis and in the 2013 version (third edition) by ranking treatments. Only these minor changes, and no major changes, have been made to the basic treatment strategies.

Similarly, the consensus-based treatment algorithm published in 2007 has had the support of many physicians, especially hepatologists. Treatment was recommended based on a combination of 5 core factors: extrahepatic lesion, vascular invasion, hepatic functional reserve, tumor number, and tumor size. The algorithm proactively introduced treatment modalities with poor evidence and underwent multiple revisions prior to publication of the latest 2015 version (third edition). Learning from the Barcelona Clinic Liver Cancer (BCLC) staging classification and treatment schedule developed in Europe, the JSH introduced multiple treatment modalities to each category, and the 2015 version recommends 5 types of treatment modalities under each condition.

In the latest revision of the current Guidelines, the JSH led a project to develop a novel treatment algorithm that merged the evidence-based algorithm reflecting the evidence reported in articles with the consensus-based algorithm reflecting consensus reached based on actual clinical practice and by incorporating the GRADE system. The biggest change was establishing the CQ system, which underpins the new algorithm. In CQ11-16, we specify conditions related to tumor and liver function and we conducted literature searches of published articles. The first screening with keywords extracted 168-578 articles as candidates for each CQ, and these were eventually narrowed down to 4-19 articles.

The treatment algorithm in this 2017 version recommends treatments based on the combination of 5 core factors: hepatic functional reserve, extrahepatic metastasis, vascular invasion, tumor number, and tumor size. Future challenges include refining the treatment algorithm based on constructive feedback and suggestions from large numbers of clinicians.

Explanation of the treatment algorithm for HCC

Recommendation

The treatment algorithm in the Guidelines is recommended as criteria for selecting the treatment modality best suited to the pathological condition of HCC.

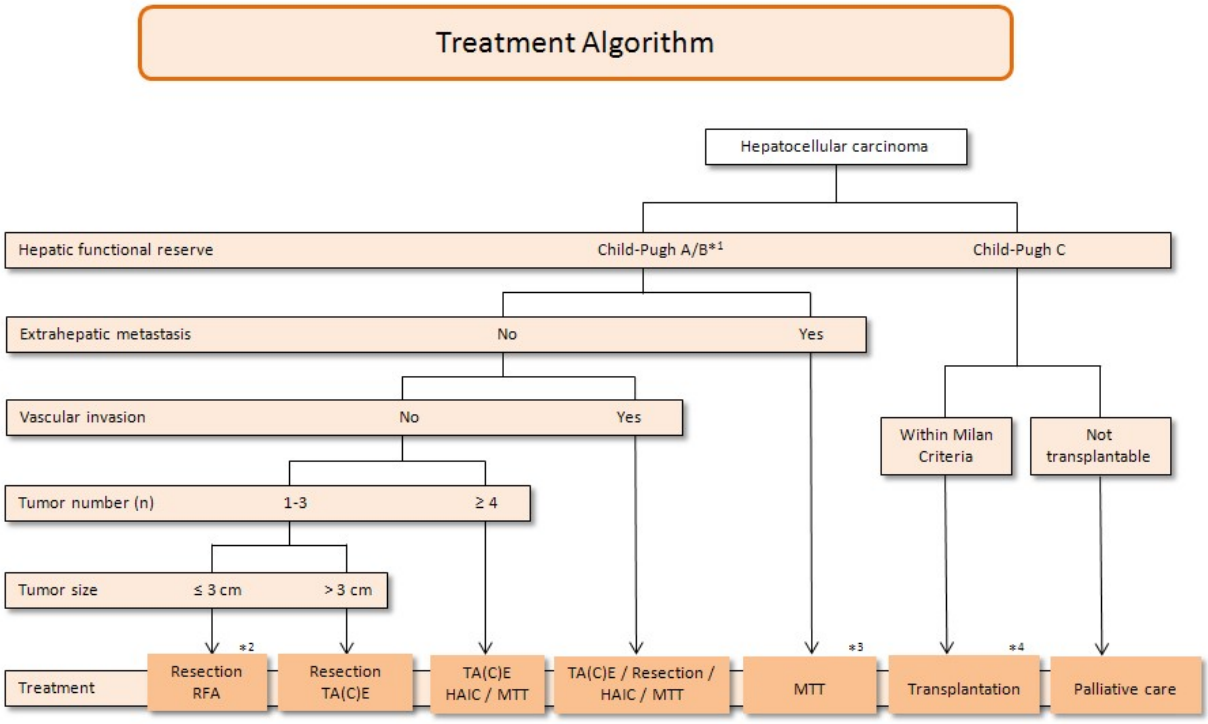
Explanation

The treatment algorithm for HCC was established based on the 5 core factors of hepatic functional reserve, extrahepatic metastasis, vascular invasion, tumor number, and tumor size. Hepatic functional reserve is evaluated based on the Child-Pugh classification. When hepatectomy is being considered, the final decision is made based on liver damage grade, which includes consideration of ICG test results. Extrahepatic metastasis, vascular invasion, tumor number, and tumor size are assessed based on pre-treatment diagnostic imaging findings.

Three treatments are recommended for HCC patients with Child-Pugh A/B liver function without extrahepatic metastasis or vascular invasion. (1) Hepatectomy or RFA is recommended for up to 3 HCCs ≤ 3 cm, but hepatectomy is recommended as first-line therapy for solitary HCC regardless of size (see CQ11). (2) Hepatectomy is recommended as first-line therapy and TACE or TAE as second-line therapy for up to 3 HCCs > 3 cm (see CQ11 and 12). (3) TACE is recommended as first-line therapy and transcatheter arterial infusion chemotherapy (TAI) or molecular-targeted therapy as second-line therapy for up to 4 HCCs (see CQ13).

Molecular-targeted therapy is recommended for HCC patients with Child-Pugh A liver function and extrahepatic metastasis (see CQ15-2). For HCC patients with vascular invasion and no extrahepatic metastasis, individualized treatment strategies are established based on liver function, the condition of HCC, and the extent of vascular invasion. Among many treatment modalities reported in recent articles, the Guidelines recommend embolization, hepatectomy, TAI, and molecular-targeted therapy because of their high levels of evidence and superior applicability in Japan (see CQ16).

Liver transplantation is recommended for HCC within the Milan criteria (solitary HCC lesion ≤ 5 cm or up to 3 HCCs ≤ 3 cm) in Child-Pugh C patients aged ≤ 65 years (see CQ14). When transplantation is not indicated, palliative care is recommended for patients with HCC and Child-Pugh C liver function. Untransplantable cases include incompatible tumor conditions or liver function as well as lack of a matching donor. When considering treatments other than liver transplantation, patients and treatment modalities should be carefully selected and some treatments have been reported to be effective. At present, however, there is insufficient evidence to recommend any treatment other than transplantation.



Abbreviations; RFA: radiofrequency abration, TA(C)E: transcatheter arterial (chemo) embolization, HAIC: hepatic arterial infusion chemo therapy, MTT: molecular-targeted therapy

[1] Assessment based on liver damage is recommended in the case of hepatectomy.

[2] For solitary HCC, resection is recommended as first-line therapy and ablation as second-line therapy.

[3] Patients with Child-Pugh A only.

[4] Patients age ≤ 65 years.

CQ11 What treatment modalities are recommended for solitary HCC?

Recommendation

Strong recommendation: Hepatectomy is recommended as first-line therapy. For HCC ≤ 3 cm, percutaneous ablation is recommended as second-line therapy.

■ Background

Several algorithms recommend treatment modalities for solitary HCC. Here, we investigated the efficacy of treatment modalities by reviewing previous evidence.

■ Scientific Statement

A literature search conducted with a publication date between January 1, 1982 and June 30, 2016 and the keywords “hepatectomy”, “surgical resection”, “RFA”, “solitary HCC”, “tumor number and size”, “Child-Pugh classification”, and “liver damage grade” extracted 227 articles that reported the outcome of treatment for solitary HCC. This was narrowed down to 15 articles in the first screening. A total of 11 articles with ambiguous conclusions were excluded, and the remaining 4 articles and another 6 new hand-searched articles are cited for CQ11.

In patients with HCC and good hepatic functional reserve, those with no distant metastasis or vascular invasion are candidates for curative therapy. Patients with poor liver function are eligible for transplantation or palliative care.

The previous versions of the Guidelines recommend hepatectomy and RFA for HCC in patients with liver damage grade A as well as in some patients with liver damage grade B. However, hepatectomy is excluded from the treatment options for patients with Child-Pugh B/C liver function and portal hypertension in the United States and Europe[1]; the BCLC staging system recommends treatment other than hepatectomy[2]. In Japan, Ishizawa et al. have performed small liver resections safely in patients with portal hypertension[3].

A comparison of treatment outcomes by tumor number has shown the utility of hepatectomy for solitary HCC compared with multiple HCCs[4]. Using the database of the Liver Cancer Study Group of Japan, Arii et al. compared the outcomes of hepatectomy and percutaneous ethanol injection (PEI) for HCC in patients with liver damage grade A/B and showed the utility of hepatectomy[5]. Also using the database of the Liver Cancer Study Group of Japan, Hasegawa et al. retrospectively compared the outcomes of hepatectomy (n = 5361), RFA (n = 5548), and PEI (n = 2059) for solitary HCC (≤ 3 cm) and found significantly better prognosis after hepatectomy[6]. This led to the recommendation of hepatectomy as first-line therapy and RFA as second-line therapy, respectively, in this group of patients.

Four RCTs have compared the outcomes of hepatectomy and RFA[7–10]. Two found significantly

better prognosis after hepatectomy, while the remaining 2 showed no significant difference between the treatments. All 4 RCTs had problems associated with study design or background factors, and they did not reflect actual clinical situations in Japan.

■ Explanation

When selecting a treatment strategy for HCC, hepatic functional reserve is evaluated based on the Child-Pugh classification, and when hepatectomy is being considered, a final decision is made based on liver damage grade, which includes ICGR15. The Guidelines recommend hepatectomy for patients with good liver function. However, treatment strategies for patients with portal hypertension (presence of esophageal varices and platelet count $\leq 10 \times 10^4/\mu L$) vary between Japan and the United States and Europe. The BCLC staging system used in the United States and Europe recommends avoiding hepatectomy and instead selecting liver transplantation or RFA for patients with portal hypertension[2]. In Japan, hepatectomy is performed safely by combining pre-hepatectomy endoscopic treatment of esophageal varices and systematic segmentectomy.

As described above, after Hasegawa et al. retrospectively examined the largest number of patients treated by hepatectomy, RFA, or PEI, they recommend hepatectomy as first-line therapy[6]. However, no prospective studies have clearly presented evidence for which is more effective, surgery or other treatment. Therefore, the Guidelines recommend hepatectomy as first-line therapy for solitary HCC and percutaneous ablation as second-line therapy for HCC $\leq$ 3 cm. Because Hasegawa et al.'s study is a large-scale study of patients in the Liver Cancer Study Group of Japan database and the level of evidence is high, the strength of recommendation is therefore rated "strong". In contrast, the RCTs described above do not reflect actual clinical situations in Japan. The results of an ongoing RCT on the utility of hepatectomy and RFA (SURF-RCT*, UMIN000001795) in Japan are eagerly awaited.

■ References

1) Bruix J, Castells A, Bosch J, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. *Gastroenterology* 1996; 111: 1018-22. PMID: 8831597

2) Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; 53: 1020-2. PMID: 21374666

3) Ishizawa T, Hasegawa K, Aoki T, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology* 2008; 134: 1908-16. PMID: 18549877

4) Ho MC, Huang GT, Tsang YM, et al. Liver resection improves the survival of patients with multiple hepatocellular carcinomas. *Ann Surg Oncol* 2009; 16: 848-55. PMID: 19159983

5) Arii S, Yamaoka Y, Futagawa S, et al. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. *Hepatology*

2000; 32: 1224-9. PMID: 11093728

6) Hasegawa K, Kokudo N, Makuuchi M, et al. Comparison of resection and ablation for hepatocellular carcinoma: a cohort study based on a Japanese nationwide survey. *J Hepatol* 2013; 58:724-9. PMID: 23178708

7) Huang J, Yan L, Cheng Z, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann Surg* 2010; 252: 903-12. PMID:21107100

8) Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. *Ann Surg* 2006;243: 321-8. PMID: 16495695

9) Feng K, Yan J, Li X, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *J Hepatol* 2012; 57: 794-802. PMID: 22634125

10) Liu H, Wang ZG, Fu SY, et al. Randomized clinical trial of chemoembolization plus radiofrequency ablation versus partial hepatectomy for hepatocellular carcinoma within the Milan criteria. *Br J Surg* 2016; 103: 348-56. PMID: 26780107

*SURF-RCT, Surgery vs. RFA for Hepatocellular Carcinoma: A Randomized Controlled Trial (official name: Efficacy of Surgery vs. Radiofrequency Ablation on Primary Hepatocellular Carcinoma: A Multicenter Randomized Control Trial).

CQ12 What treatment modalities are recommended for 2 or 3 HCCs?

Recommendation

Strong recommendation: Hepatectomy or percutaneous ablation is recommended for HCCs ≤ 3 cm. For HCCs > 3 cm, hepatectomy is recommended as first-line therapy and embolization as second-line therapy.

■ Background

Several algorithms recommend treatment modalities for 2 or 3 HCCs. Here, we investigated the efficacy of treatment modalities by reviewing previous evidence.

■ Scientific Statement

A literature search conducted with a publication date between January 1, 1982 and June 30, 2016 and the keywords “hepatectomy”, “surgical resection”, “RFA”, “treatment algorithm”, “tumor number and size”, “Child-Pugh classification”, and “liver damage grade” extracted 532 articles reporting the outcome of treatment for 2 or 3 HCCs. This was narrowed down to 13 articles in the first screening, from which 8 articles with ambiguous conclusions were excluded in the second screening. Four articles that do not include the key words but reflect actual hepatology treatment strategies in Japan were extracted in manual searches and are cited for CQ12 along with the 5 articles selected in the

second screening.

As in CQ11, patients with Child-Pugh A (and partly B) liver function with no vascular invasion or extrahepatic metastasis are eligible for curative therapy.

Hepatectomy for HCC ≥ 10 cm has a 5-year survival rate of 20-30%, suggesting that tumor size does not limit the indications[1–3]. A study comparing the outcomes of hepatectomy for solitary and 2 or more HCCs showed that the former has a better long-term prognosis, but the study did not find any contraindication for hepatectomy for multiple HCCs[4].

Many studies have used "up to 3 HCCs ≤ 3 cm" as an indication for RFA. Murakami et al. showed that RFA had a significantly higher local recurrence-free rate in patients with solitary HCC ≤ 5 cm or up to 3 HCCs ≤ 3 cm compared with TACE[5]. Based on these findings, "up to 3 HCCs ≤ 3 cm" was used as an indication for RFA. Hasegawa et al. analyzed prognosis in patients who underwent hepatectomy, RFA, and PEI for 2 or 3 HCCs measuring < 2 cm or 2-3 cm in patients with Child-Pugh A/B liver function) and found that hepatectomy had a significantly higher recurrence-free survival only in patients with HCCs 2-3 cm and Child-Pugh A liver function, with no other intergroup differences[6]. Based on the above evidence, the Guidelines recommend hepatectomy or RFA for HCCs ≤ 3 cm.

In an RCT of hepatectomy and RFA for HCC within the Milan criteria, Huang et al. showed that hepatectomy had a significantly better prognosis and may be indicated as first-line therapy for 2 or 3 HCCs, even for lesions ≥ 3 cm, in patients with good liver function[7]. On the other hand, in an RCT, Llovet et al. showed the validity of TACE for multiple HCCs in patients with Child-Pugh A/B liver function[8]. Therefore, TACE is recommended in patients with HCCs difficult to resect.

■ Explanation

Hepatectomy is excellent for the local management of up to 3 HCCs and may be used as first-line therapy when liver function permits. However, RFA is also excellent for the local management of small HCCs (≤ 3 cm), with no clear difference in long-term prognosis between hepatectomy and RFA. In a meta-analysis of hepatectomy and RFA, overall survival rates were significantly higher in the hepatectomy group[9], but patient background and healthcare situations in the study do not reflect those in Japan, so further studies are needed. The SURF-RCT is currently underway to establish evidence for the treatment modalities for primary HCC, by comparing the outcomes of hepatectomy and RFA for up to 3 primary HCCs ≤ 3 cm in 308 patients with good liver function (Child-Pugh score 7). The patients have been undergoing follow up since study registration was completed in August 2015.

Based on the evidence currently available, hepatectomy or RFA is recommended for HCCs ≤ 3 cm, and hepatectomy and embolization are recommended as first-line and second-line therapy, respectively, for HCCs > 3 cm. These recommendations are supported by the findings of large-scale

studies and have been adopted widely in clinical settings. Therefore, they are rated strong in the current Guidelines.

■ References

1) Lee NH, Chau GY, Lui WY, King KL, Tsay SH, Wu CW. Surgical treatment and outcome in patients with a hepatocellular carcinoma greater than 10 cm in diameter. *Br J Surg* 1998; 85:1654-7. PMID: 9876069

2) Poon RT, Fan ST, Wong J. Selection criteria for hepatic resection in patients with large hepatocellular carcinoma larger than 10 cm in diameter. *J Am Coll Surg* 2002; 194: 592-602. PMID:12022599

3) Liau KH, Ruo L, Shia J, et al. Outcome of partial hepatectomy for large (>10 cm) hepatocellular carcinoma. *Cancer* 2005; 104: 1948-55. PMID: 16196045

4) Ishizawa T, Hasegawa K, Aoki T, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology* 2008; 134: 1908-16. PMID: 18549877

5) Murakami T, Ishimaru H, Sakamoto I, et al. Percutaneous radiofrequency ablation and transcatheter arterial chemoembolization for hypervascular hepatocellular carcinoma: rate and risk factors for local recurrence. *Cardiovasc Intervent Radiol* 2007; 30: 696-704. PMID: 17497071

6) Hasegawa K, Kokudo N, Makuuchi M, et al. Comparison of resection and ablation for hepatocellular carcinoma: a cohort study based on a Japanese nationwide survey. *J Hepatol* 2013; 58:724-9. PMID: 23178708

7) Huang J, Yan L, Cheng Z, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann Surg* 2010; 252: 903-12. PMID:21107100

8) Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; 359: 1734-9. PMID: 12049862

9) Ni JY, Xu LF, Sun HL, Zhou JX, Chen YT, Luo JH. Percutaneous ablation therapy versus surgical resection in the treatment for early-stage hepatocellular carcinoma: a meta-analysis of 21,494 patients. *J Cancer Res Clin Oncol* 2013; 139: 2021-33. PMID: 24072235

CQ13 What treatment modalities are recommended for 4 or more HCCs?

Recommendation

Strong recommendation: Embolization is recommended as first-line therapy. TAI or molecular-targeted therapy is recommended as second-line therapy.

■ Background

Several algorithms recommend treatment modalities for multiple HCCs. Novel findings were also reported after the publication of the 2013 version of the Guidelines. Here, we investigated the

efficacy of treatment modalities by reviewing previous evidence.

■ Scientific Statement

A literature search conducted with a publication date between January 1, 1982 and June 30, 2016 and the keywords “TAE”, “TACE”, “TAI”, “sorafenib”, “treatment algorithm”, and “treatment allocation” extracted 497 articles that reported the outcome of treatment for multiple HCCs. This was narrowed down to 10 articles in the first screening, from which 7 with ambiguous conclusions were excluded. Two articles that do not include the keywords but reflect actual treatment strategies for HCC in Japan were extracted in manual searches and are cited for CQ13 along with the 3 articles selected in the second screening.

A study that investigated an association between tumor number and the outcome of hepatectomy showed poor long-term prognosis for multiple HCCs, but hepatectomy could be performed safely with proper assessment of hepatic functional reserve and adequate resectional volume[1]. Because there is lack of clear evidence for limiting resection by tumor number, however, “up to 3 HCCs”, a conventional recommendation for locoregional therapy, is applied as an indication for hepatectomy. Therefore, the Guidelines recommend treatment modalities other than hepatectomy and RFA for 4 or more HCCs.

Llovet et al. compared the prognosis of 112 patients with multiple HCCs and Child-Pugh A/B liver function after allocating them to either TAE (n = 37), TACE (n = 40), or symptomatic therapy (n = 35) and found significantly better prognosis in the TACE group[2]. The validity of the indications in the third edition of the Guidelines has been shown in a study by Takayasu et al., in which 4,966 patients treated with TACE were stratified by tumor number, tumor size, and liver function[3]. Nouso et al. investigated the validity of TAI with 5-FU and cisplatin in patients with advanced HCC and found that survival rate was significantly better in the TAI group compared with no-treatment controls matched by propensity score[4]. The Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) study, a double-blind RCT, showed the validity of sorafenib in HCCs that are unresectable and unresponsive to TACE, compared with the placebo group[5]. Based on these studies, the Guidelines recommend TACE or TAE as first-line therapy for 4 or more HCCs and TAI or molecular-targeted therapy as second-line therapy for HCC unresponsive to TACE or TAE.

■ Explanation

Previous studies have reported the validity of hepatectomy, combination therapy with hepatectomy and chemotherapy, and TACE in patients with multiple HCCs, but these were case reports of a small number of patients or had undefined control groups. To date, no studies have shown high-quality evidence for limiting treatment by tumor number. In general, “up to 3 HCCs” is considered the limit in hepatectomy and RFA. As in the stratification study[3], it is appropriate to perform TACE/TAE as

first-line therapy in patients with 4 or more HCCs. In the case of TACE/TAE failure, TAI and molecular-targeted therapy are good options. Based on the evidence presented above, the Guidelines recommend TACE/TAE as first-line therapy for 4 or more HCCs and TAI or molecular-targeted therapy as second-line therapy. All these treatment modalities are commonly used in clinical practice and are supported by sufficient consensus. Therefore, the recommendation is rated as "strong". However, the validity of these treatment modalities has not been proven for HCC accompanied by extrahepatic metastasis or portal vein tumor thrombus (see other CQs).

■ References

1) Ishizawa T, Hasegawa K, Aoki T, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology* 2008; 134: 1908-16. PMID: 18549877

2) Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; 359: 1734-9. PMID: 12049862

3) Takayasu K, Arii S, Kudo M, et al. Superselective transarterial chemoembolization for hepatocellular carcinoma. Validation of treatment algorithm proposed by Japanese guidelines. *J Hepatol* 2012; 56: 886-92. PMID: 22173160

4) Nouso K, Miyahara K, Uchida D, et al. Effect of hepatic arterial infusion chemotherapy of 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma in the Nationwide Survey of Primary Liver Cancer in Japan. *Br J Cancer* 2013; 109: 1904-7. PMID: 24008659

5) Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; 359: 378-90. PMID: 18650514

CQ14 What treatment modalities are recommended for HCC in patients with liver damage grade C (Child-Pugh C liver function)?

Recommendation

Strong recommendation: Liver transplantation is recommended for HCC in patients with liver damage grade C (Child-Pugh C liver function), provided that the pathological condition is within the Milan criteria.

■ Background

Cirrhosis with liver damage grade C (Child-Pugh C liver function) is end-stage liver disease with poor prognosis and a low tolerability to treatment. For these reasons, regardless of comorbidity with HCC, only liver transplantation is thought to contribute to prognosis. However, in actual clinical situations, minimally invasive modalities that have advanced rapidly in recent years are often used to

treat HCC in patients with liver damage grade C (Child-Pugh C liver function). Here, we investigated treatment modalities that can be recommended for patients with HCC and liver damage grade C (Child-Pugh C liver function).

■ Scientific Statement

A literature search conducted with a publication date between January 1, 1982 and June 30, 2016 extracted 409 articles that reported the outcome of treatment for HCC in patients with liver damage grade C (Child-Pugh C liver function) or end-stage cirrhosis. This was narrowed down to 47 in the first screening. After extracting articles with a small number of patients, 4 articles that clearly describe treatment targets and indications are cited for CQ14.

Mazzaferro et al. performed liver transplantation in patients with HCC within the Milan criteria (solitary HCC ≤ 5 cm or up to 3 HCCs ≤ 3 cm with no vascular invasion or extrahepatic metastasis)[1]. After transplantation, 15 patients with Child-Pugh C liver function had a 1-year, 3-year, and 4-year survival rate of 93%, 93%, and 80%, respectively, and a 1-year, 3-year, and 4-year recurrence-free survival rate of 93%, 86%, and 86%, respectively, but these rates were comparable to those of patients with Child-Pugh A/B liver function. Similarly, in a review of living donor liver transplantation performed at multiple institutions in Japan, the post-transplantation survival rates of 156 patients with Child-Pugh C liver function were 75.1% and 68.7% after 1 and 3 years, respectively, and the recurrence rates were 9.9% and 16.1% after 1 and 3 years, respectively[2]. Again, these rates were comparable to those obtained in patients with Child-Pugh A/B liver function. However, in a prospective multicenter study of PEI and liver transplantation for HCC within the Milan criteria, the mean survival period in patients with Child-Pugh C liver function were 95.3 months after liver transplantation and 31.5 months after PEI; recurrence-free survival was 139.0 months after liver transplantation and 34.8 months after PEI, indicating that treatment outcomes were better with liver transplantation[3]. Also, in a retrospective study of 443 patients with HCC, the risk of mortality or emergency liver transplantation and the incidence of irreversible liver damage within 6 weeks of embolization were 5.4 times and 59 times higher, respectively, in patients with Child-Pugh C liver function than in patients with Child-Pugh A liver function[4].

■ Explanation

Patients with HCC are expected to have good prognosis after liver transplantation when HCC is within the Milan criteria. In the United States and Europe, liver transplantation is indicated for HCC regardless of the background liver, and therefore studies there include a certain proportion of patients with compensated cirrhosis. However, outcomes for liver transplantation for HCC accompanied by decompensated cirrhosis in Japan are as good as those for liver transplantation in the United States and Europe, suggesting that it is reasonable to recommend liver transplantation as a good choice for

patients with liver damage grade C (Child-Pugh C liver function), provided that HCC is within the Milan criteria.

The question associated with other existing treatment modalities for HCC is whether they are performed safely and contribute to prognosis in patients with liver damage grade C (Child-Pugh C liver function). Very few studies have investigated the validity of hepatectomy for HCC in patients with liver damage grade C (Child-Pugh C liver function), suggesting that hepatectomy is normally not indicated for this group of patients. In terms of locoregional therapy, PEI had a slightly better short-term survival curve but poorer prognosis compared with liver transplantation. This suggests that the long-term treatment outcome of PEI is poor despite the robust short-term safety of the treatment. The most recent literature search did not extract a comprehensive report on percutaneous ablation, which is currently the mainstay of locoregional therapy. Also, there were no reports on long-term survival following embolization for HCC. However, it was concluded from findings of studies extracted in the literature search that embolization is associated with a high risk of complications in patients with liver damage grade C (Child-Pugh C liver function). In addition, the most recent literature search extracted only a limited number of reports on molecular-targeted therapy. Consequently, there is insufficient evidence to recommend treatment other than liver transplantation for patients with HCC and liver damage grade C (Child-Pugh C liver function). There were comments suggesting that, in addition to liver transplantation, other treatment options be included in the Guidelines because some studies reported improved prognosis in patients with liver damage grade C (Child-Pugh C liver function) with treatments other than liver transplantation, compared with untreated patients. After careful consideration, the Revision Committee has concluded that these studies are associated with selection bias, and the evidence is insufficient to recommend other treatment options, especially when considering the risks associated with liver failure and complications. Therefore, careful attention should be given to individual patients and treatment modalities when selecting treatment for patients with Child-Pugh C liver function.

■ References

1) Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; 14; 334: 693-9. PMID: 8594428

2) Todo S, Furukawa H; Japanese Study Group on Organ Transplantation. Living donor liver transplantation for adult patients with hepatocellular carcinoma: experience in Japan. *Ann Surg* 2004; 240: 451-9. PMID: 15319716

3) Andriulli A, de Sio I, Solmi L, et al. Survival of cirrhotic patients with early hepatocellular carcinoma treated by percutaneous ethanol injection or liver transplantation. *Liver Transpl* 2004; 10: 1355-63. PMID: 15497162

4) Garwood ER, Fidelman N, Hoch SE, Kerlan RK Jr, Yao FY. Morbidity and mortality following transarterial liver chemoembolization in patients with hepatocellular carcinoma and synthetic hepatic dysfunction. *Liver Transpl* 2013; 19: 164-73. PMID: 23008091

CQ15-1 Is radiation therapy effective against bone and brain metastasis from HCC?

Recommendations

Strong recommendation: Radiation therapy is recommended for the management of painful bone metastasis.

Strong recommendation: Whole brain radiotherapy, stereotactic radiotherapy, or the combination therapy is recommended for brain metastasis.

■ Background

There are many reports of RCTs where radiation therapy was administered for bone or brain metastasis of unknown primary, suggesting that radiation therapy is the standard treatment. As far as solid tumors are concerned, there is no evidence that it is beneficial to change the strategy of radiation therapy based on 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 CQ51 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 168 articles. This was narrowed down to 52 based on the article titles and abstracts in the first screening. Then, in the second screening, the content of the 168 articles was reviewed carefully to select studies, including retrospective studies, that evaluated radiation therapy for bone and brain metastasis from HCC as well as RCTs, systematic reviews, and meta-analyses of bone and brain metastasis of unknown primary. In total, 19 articles are cited for CQ15-1: 12 that were extracted in the literature search and 7 articles from the third version.

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[1–3], although they included very few HCC cases. Whereas some retrospective studies have shown the beneficial effect of radiation therapy on pain management in bone metastasis from HCC[4–7], others have reported lower treatment efficacy and the need for higher radiation doses compared with radiation therapy for bone metastasis from other organs[8–11]. This suggests that instead of radiation therapy for ordinary bone metastasis, dose fractionation is appropriate for bone metastasis from HCC.

Similarly, no clinical studies have reported high-quality evidence for performing radiation therapy for brain metastasis solely from HCC. However, the 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 from the primary cancer originating in the organs[12–16]. 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[17–19].

■ 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 of unknown primary. Generally, there is insufficient evidence to recommend changing the indications for radiation therapy or the dose-fractionation method based on the organs of primary involvement 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 do not apply 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 importance 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 to date.

Based on these findings, radiation therapy is recommended for managing the pain associated with bone metastasis. For brain metastasis, whole brain radiotherapy, stereotactic radiotherapy, or both are recommended as treatment. The General Affairs Committee for the current Guidelines has unanimously decided to strongly recommend these treatments based on their clinical validity and merits, despite the lack of high-quality evidence.

■ References

1) Chow E, Zeng L, Salvo N, Dennis K, Tsao M, Lutz S. Update on the systematic review of palliative radiotherapy trials for bone metastases. *Clin Oncol (R Coll Radiol)* 2012; 24: 112-24. PMID: 22130630

2) McQuay HJ, Collins SL, Carroll D, Moore RA. Radiotherapy for the palliation of painful bone metastases. *Cochrane Database Syst Rev* 2000: CD001793. PMID: 10796822

3) Wu JS, Wong R, Johnston M, Bezjak A, Whelan T; Cancer Care Ontario Practice Guidelines Initiative Supportive

Care Group. Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases. *Int J Radiat Oncol Biol Phys* 2003; 55: 594-605. PMID: 12573746

4) Choi C, Seong J. Predictive factors of palliative radiotherapy response and survival in patients with spinal metastases from hepatocellular carcinoma. *Gut Liver* 2015; 9: 94-102. PMID: 25071067

5) Habermehl D, Haase K, Rieken S, Debus J, Combs SE. Defining the role of palliative radiotherapy in bone metastasis from primary liver cancer: an analysis of survival and treatment efficacy. *Tumori* 2011; 97: 609-13. PMID: 22158492

6) Hayashi S, Tanaka H, Hoshi H. External beam radiotherapy for painful bone metastases from hepatocellular carcinoma: multiple fractions compared with an 8-Gy single fraction. *Nagoya J Med Sci* 2014; 76: 91-9. PMID: 25129995

7) Sakaguchi M, Maebayashi T, Aizawa T, Ishibashi N, Fukushima S, Saito T. Radiation therapy and palliative care prolongs the survival of hepatocellular carcinoma patients with bone metastases. *Intern Med* 2016; 55: 1077-83. PMID: 27150858

8) Choi SH, Chang JS, Jeong YH, Lee Y, Yun M, Seong J. FDG-PET predicts outcomes of treated bone metastasis following palliative radiotherapy in patients with hepatocellular carcinoma. *Liver Int* 2014; 34: 1118-25. PMID: 24528941

9) Choi Y, Kim J, Lee I, Seong J. Dose escalation using helical tomotherapy improves local control in spine metastases from primary hepatic malignancies. *Liver Int* 2014; 34: 462-8. PMID: 23859251

10) Kaizu T, Karasawa K, Tanaka Y, et al. Radiotherapy for osseous metastases from hepatocellular carcinoma: a retrospective study of 57 patients. *Am J Gastroenterol* 1998; 93: 2167-71. PMID: 9820391

11) Nakamura N, Igaki H, Yamashita H, et al. A retrospective study of radiotherapy for spinal bone metastases from hepatocellular carcinoma (HCC). *Jpn J Clin Oncol* 2007; 37: 38-43. PMID: 17142252

12) Chang UK, Kim MS, Han CJ, Lee DH. Clinical result of stereotactic radiosurgery for spinal metastasis from hepatocellular carcinoma: comparison with conventional radiation therapy. *J Neurooncol* 2014; 119: 141-8. PMID: 24803002

13) Horton J, Baxter DH, Olson KB. The management of metastases to the brain by irradiation and corticosteroids. *Am J Roentgenol Radium Ther Nucl Med* 1971; 111: 334-6. PMID: 5541678

14) Patil CG, Pricola K, Garg SK, Bryant A, Black KL. Whole brain radiation therapy (WBRT) alone versus WBRT and radiosurgery for the treatment of brain metastases. *Cochrane Database Syst Rev* 2010: CD006121. PMID: 20556764

15) Sahgal A, Aoyama H, Kocher M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys* 2015; 91: 710-7. PMID: 25752382

16) Tsao M, Xu W, Sahgal A. A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. *Cancer* 2012; 118: 2486-93. PMID: 21887683

17) Choi HJ, Cho BC, Sohn JH, et al. Brain metastases from hepatocellular carcinoma: prognostic factors and

outcome: brain metastasis from HCC. *J Neurooncol* 2009; 91: 307-13. PMID: 18949445

18) Park TY, Na YC, Lee WH, et al. Treatment options of metastatic brain tumors from hepatocellular carcinoma: surgical resection vs. gamma knife radiosurgery vs. whole brain radiation therapy. *Brain Tumor Res Treat* 2013; 1: 78-84. PMID: 24904896

19) Yamakawa Y, Moriguchi M, Aramaki T, et al. Brain metastasis from hepatocellular carcinoma: the impact of radiotherapy on control of intracranial hemorrhage. *Hepatol Res* 2015; 45: 1071-5. PMID: 25470452

CQ15-2 What treatment modalities are effective against extrahepatic metastasis (e.g., lung, adrenal, and lymph node metastasis and dissemination) from HCC?

Recommendations

Strong recommendation: Molecular-targeted therapy is the standard treatment for advanced HCC accompanied by extrahepatic metastasis.

Weak recommendation: Locoregional therapies, including resection, may be selected for lung, adrenal, and lymph node metastasis and dissemination in HCC patients with no other intrahepatic lesions or well-managed intrahepatic lesions.

■ Background

HCC accompanied by extrahepatic metastasis is often associated with intrahepatic lesions in the advanced stage. The treatment strategy for this group of patients will be reviewed under CQ43, but we often encounter situations where it is possible to suppress intrahepatic lesions and administer locoregional therapy for extrahepatic metastasis. Considering locoregional therapy under such circumstances, treatment strategies that are effective for extrahepatic metastasis (e.g., lung, adrenal, and lymph node metastasis and dissemination) were reviewed for CQ15-2.

■ Scientific Statement

A literature search conducted with a publication date between January 1, 1982 and June 30, 2016 extracted 473 English articles that reported treatment of HCC accompanied by extrahepatic metastasis (e.g., lung, adrenal, and lymph node metastasis and dissemination) and contained radiation therapy, interventional radiology, chemotherapy, resection, embolization, TACE, RFA, cryotherapy, or high-intensity focused ultrasound (HIFU) in the title. This was narrowed down to 68 articles in the first screening to extract case reports, studies with ≤ 5 patients, and reviews that were not systematic reviews. The content of the 68 articles was further reviewed and 17 studies including ≥ 30 cases of resection for lung and lymph node metastasis and dissemination or ≥ 20 cases of

resection for adrenal metastasis were extracted. After excluding articles with insufficient data for use in guidelines, articles about systemic chemotherapy for advanced HCC with extrahepatic lesions, and articles with ambiguous description of treatment for extrahepatic lesions, 17 articles are cited for this CQ.

Molecular-targeted therapy is the standard treatment for advanced HCC accompanied by extrahepatic metastasis, as described in CQ43. Therefore, this CQ15-2 focuses on locoregional therapy for extrahepatic metastasis.

A relatively large number of studies (7 studies involving ≥ 30 patients[1–7]) have examined resection for lung metastasis from HCC. Excluding one study that examined patients who underwent liver transplantation, the 5-year survival rate of the patients in the remaining 6 studies ranged from 27.5% to 66.9%[1–6]. On the other hand, the 2-year survival rate after liver transplantation was 30.6% in patients who underwent pulmonary metastasectomy and 0% in patients who did not unergo it, suggesting that resection improves long-term prognosis[7]. Another study that involved RFA (which is not a common treatment like lung resection) for lung metastasis from HCC in 32 patients reported a median survival of 37.7 months and a rate of complications such as pneumothorax of 25%[8].

Although the number of studies on adrenal metastasis from HCC is small, better prognosis was reported with resection than with other treatment modalities when intrahepatic lesions had been controlled[9], and the possible improvement of long-term prognosis by adrenalectomy was shown in 26 patients with metachronous adrenal metastases, including recurrence after liver[10].

In patients with lymph node metastasis from HCC, prognosis was better after resection than in the no-treatment group[11] and after TACE for lymph node metastasis and intrahepatic lesions than after TACE for intrahepatic lesions only[12]. In a nationwide survey conducted by the Liver Cancer Study Group of Japan, 112 patients who underwent resection for lymph node metastasis from HCC had a 5-year survival rate of 29.5%[13].

Two articles about the treatment of dissemination are cited for CQ15-2, one of which reports that prognosis is better with resection than without resection in patients with preserved liver function[14]. The other article reports that resection has a 5-year survival rate of 39% and is clinically significant when intrahepatic lesions are absent or well controlled[15].

Among other locoregional therapies, helical tomotherapy (a form of intensity-modulated radiation therapy for multiple lung, adrenal, or lymph node metastasis) provides palliative benefit[16].

Many studies that involved the use of locoregional therapy for extrahepatic metastasis have shown the importance of managing intrahepatic lesions[3,9,15], and in another study, performance status (PS) and vascular invasion (for intrahepatic lesions) were prognostic factors among 342 patients with HCC and extrahepatic metastasis[17].

■ Explanation

Articles cited for this CQ focus on the treatment of extrahepatic lesions that accompany HCC. Largely due to the difficulty finding appropriate controls in this field, the literature search for CQ15-2 included only retrospective studies with relatively low evidence levels, and no RCTs or meta-analyses. In a subgroup analysis of articles presenting evidence that molecular-targeted therapy improves survival in patients with advanced HCC accompanied by extrahepatic metastasis, the improvement was found not to be statistically significant[18,19]. However, because the results of the subgroup analysis that did not concern the primary endpoint of the study are of little significance and because presumably the results would have been significant with a larger number of patients, molecular-targeted therapy is strongly recommended, as in CQ43, as the standard treatment for HCC accompanied by extrahepatic metastasis in patients with fair PS and Child-Pugh A liver function.

However, based on the results of several retrospective studies and considering that locoregional therapy will be selected for intrahepatic lesions as well as extrahepatic metastasis, locoregional therapies (including resection) are recommended, although weakly, as treatment options for extrahepatic metastasis from HCC (lung, adrenal, and lymph node metastasis and dissemination), provided that intrahepatic lesions are well controlled.

■ References

1) Kuo SW, Chang YL, Huang PM, et al. Prognostic factors for pulmonary metastasectomy in hepatocellular carcinoma. *Ann Surg Oncol* 2007; 14: 992-7. PMID: 17151787

2) Han KN, Kim YT, Yoon JH, et al. Role of surgical resection for pulmonary metastasis of hepatocellular carcinoma. *Lung Cancer* 2010; 70: 295-300. PMID: 20353879

3) Lee CY, Bae MK, Park IK, et al. Surgical resection for pulmonary metastasis from hepatocellular carcinoma: analysis of prognosis in relation to primary control. *J Surg Oncol* 2010; 101: 239-43. PMID: 20127898

4) Yoon YS, Kim HK, Kim J, et al. Long-term survival and prognostic factors after pulmonary metastasectomy in hepatocellular carcinoma. *Ann Surg Oncol* 2010; 17: 2795-801. PMID: 20517683

5) Kitano K, Murayama T, Sakamoto M, et al. Outcome and survival analysis of pulmonary metastasectomy for hepatocellular carcinoma. *Eur J Cardiothorac Surg* 2012; 41: 376-82. PMID: 21727012

6) Kow AW, Kwon CH, Song S, Kim JM, Joh JW. Clinicopathological factors and long-term outcome comparing between lung and peritoneal metastasectomy after hepatectomy for hepatocellular carcinoma in a tertiary institution. *Surgery* 2015; 157: 645-53. PMID: 25794626

7) Hwang S, Kim YH, Kim DK, et al. Resection of pulmonary metastases from hepatocellular carcinoma following liver transplantation. *World J Surg* 2012; 36: 1592-602. PMID: 22411088

8) Hiraki T, Yamakado K, Ikeda O, et al. Percutaneous radiofrequency ablation for pulmonary metastases from hepatocellular carcinoma: results of a multicenter study in Japan. *J Vasc Interv Radiol* 2011; 22: 741-8. PMID: 21531575

9) Park JS, Yoon DS, Kim KS, et al. What is the best treatment modality for adrenal metastasis from hepatocellular

carcinoma? *J Surg Oncol* 2007; 96: 32-6. PMID: 17345596

10) Ha TY, Hwang S, Ahn CS, et al. Resection of metachronous adrenal metastasis after liver resection and transplantation for hepatocellular carcinoma. *Dig Surg* 2014; 31: 428-35. PMID: 25573138

11) Tomimaru Y, Wada H, Eguchi H, et al. Clinical significance of surgical resection of metastatic lymph nodes from hepatocellular carcinoma. *Surg Today* 2015; 45: 1112-20. PMID: 25205550

12) Wu H, Liu S, Zheng J, Ji G, Han J, Xie Y. Transcatheter arterial chemoembolization (TACE) for lymph node metastases in patients with hepatocellular carcinoma. *J Surg Oncol* 2015; 112: 372-76. PMID: 26368066

13) Hasegawa K, Makuuchi M, Kokudo N, et al. Impact of histologically confirmed lymph node metastases on patient survival after surgical resection for hepatocellular carcinoma: report of a Japanese nationwide survey. *Ann Surg* 2014; 259: 166-70. PMID: 23532111

14) Lin CC, Liang HP, Lee HS, et al. Clinical manifestations and survival of hepatocellular carcinoma patients with peritoneal metastasis. *J Gastroenterol Hepatol* 2009; 24: 815-20. PMID: 19655437

15) Takemura N, Hasegawa K, Aoki T, et al. Surgical resection of peritoneal or thoracoabdominal wall implants from hepatocellular carcinoma. *Br J Surg* 2014; 101: 1017-22. PMID: 24828028

16) Jang JW, Kay CS, You CR, et al. Simultaneous multitarget irradiation using helical tomotherapy for advanced hepatocellular carcinoma with multiple extrahepatic metastases. *Int J Radiat Oncol Biol Phys* 2009; 74: 412-8. PMID: 18963538

17) Uchino K, Tateishi R, Shiina S, et al. Hepatocellular carcinoma with extrahepatic metastasis: clinical features and prognostic factors. *Cancer* 2011; 117: 4475-83. PMID: 21437884

18) Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; 359: 378-90. PMID: 18650514

19) Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; 10: 25-34. PMID: 19095497

CQ16 What treatment modalities are effective against HCC accompanied by vascular invasion?

Recommendation

Strong recommendation: Embolization, hepatectomy, TAI, and molecular-targeted therapy are recommended. Optimal treatment is selected considering each patient's condition (see below for a detailed explanation).

■ Background

The previous 2013 version of the Guidelines did not contain any CQ on HCC accompanied by

vascular invasion. Therefore, we established a new CQ for HCC with vascular invasion for the current version and investigated treatment modalities that are particularly effective for portal vein tumor thrombus.

■ Scientific Statement

A literature search conducted with a publication date between January 1, 1982 and June 30, 2016 and the keywords “portal vein tumor thrombus”, “surgical resection”, “chemotherapy”, “treatment algorithm”, and “treatment allocation” extracted 578 articles about the treatment of HCC accompanied by vascular invasion. This was narrowed down to 35 articles in the first screening, from which 26 with ambiguous conclusions were excluded. Three articles that did not include the keywords but reflect actual hepatology treatment strategies in Japan were extracted in manual searches and are cited for CQ16 along with the 9 articles selected in the second screening.

A prospective (non-randomized) study has reported the 1-year survival rate of patients with HCC accompanied by vascular invasion as 30.9% in the TACE group (n = 84) and 9.2% in the symptomatic therapy group (n = 80), indicating the effectiveness of TACE[1].

The 5-year survival of patients with HCC with portal vein tumor thrombus who underwent hepatectomy were reported to be 10-38%, indicating that surgery prolongs life to some extent[2,3]. In a study conducted by Kokudo et al., patients with HCC accompanied by portal vein tumor thrombus were divided into the hepatectomy group (n = 2,093) and other treatment group (n = 4,381). Compared with the background-matched control group (n = 1,058), prognosis was significantly better in patients with Child-Pugh A liver function in the hepatectomy group, suggesting that hepatectomy is an effective therapeutic procedure when the locations of tumor thrombi are limited to the right and left portal veins (first branches of the portal vein)[4]. In another study, Ku et al. evaluated combination therapy of hepatectomy and hepatic perfusion therapy with doxorubicin, but the results were inconclusive[5].

Nouso et al. evaluated the utility of TAI with 5-FU and cisplatin in patients with advanced HCC accompanied by portal vein tumor thrombus and found that median survival was longer in patients who underwent TAI (7.9 months) than in background-matched control patients with associated portal vein tumor thrombus (3.1 months)[6].

The efficacy of molecular-targeted therapy was evaluated in the subgroup analysis of the SHARP study that investigated the effect of sorafenib (n = 108) and placebo (n = 123) in patients with HCC accompanied by vascular invasion (n = 231 in total). Compared with placebo, sorafenib improved cumulative survival to 3.2 months, thus demonstrating the life-extending effect of the drug[7].

A large-scale cohort study of patients with HCC accompanied by hepatic vein tumor thrombus was conducted using the database of the Liver Cancer Study Group of Japan, which contains patient data from hospitals across Japan. Results published after the public hearing about the Guidelines

have shown that the median survival of Child-Pugh A patients with HCC accompanied by hepatic vein tumor thrombus without inferior vena cava tumor thrombus (n = 1,021) was significantly longer in the resection group (4.47 years, n = 540) than in the no-resection group (1.58 years, n = 481)[8]. The difference remained significant when adjusting for background factors.

■ Explanation

Because advanced HCC tends to invade the portal vein, the most critical prognostic factor is portal vein tumor thrombus. The portal vein tumor thrombi that are normally detectable on preoperative diagnostic imaging are the portal vein invasion categories Vp_2, Vp_3, and Vp_4. However, a small number of cases or experimental treatments have been studied so far regarding HCC accompanied by Vp2, Vp3, or Vp4 tumor thrombus, and thus high-quality evidence about the efficacy of treatment modalities for HCC accompanied by Vp2, Vp3, or Vp4 tumor thrombus is scant. This means that, at present, treatment strategy is individualized based on liver function, tumor condition, and severity of vascular invasion. The General Rules for the Clinical and Pathological Study of Primary Liver Cancer (sixth edition) state that patients with tumor thrombus in large vessels (such as Vp_3 and Vp_4) should be treated as curability C even when macroscopic residual tumor is absent after resection. Therefore, it makes sense to choose treatment modalities that are frequently reported in recent years, have high evidence levels, and are easy to apply in Japan.

Under CQ16, 4 types of treatment modalities are recommended, without any data to suggest the strength of recommendation for each. These treatments should be contraindicated for patients with certain clinical conditions such as Vp. For example, embolization (one of the recommended treatment options) for Vp_3 and Vp_4 tumor thrombus should be performed carefully because of the risk of liver abscess and hepatic infarction. Solitary HCC with Vp_2 tumor thrombus is a good indication for surgery, because compared with other treatment modalities, surgery yields superior outcomes in HCC patients with Vp_3 tumor thrombus and relatively good liver function (Child-Pugh A) provided that macroscopically complete resection is achieved; thus, hepatectomy may be considered as first-line therapy. However, as in References 6 and 7, TAI and molecular-targeted therapy are also recommended for patients with multiple HCCs and extensive vascular invasion who are not therefore eligible for TACE and resection.

Some studies conducted overseas have shown the utility and life-prolonging effect of radiation therapy, such as with the use of yttrium-90[9], three-dimensional conformal radiotherapy (3D-CRT)[10], and embolization with yttrium-90 resin microspheres[11], but the effect is not certain and these therapies are currently not practiced in Japan. A study of systemic chemotherapy has been reported, but the efficacy was inconsistent[12].

Vascular invasion generally implies portal vein tumor thrombus. The literature search did not extract any articles on hepatic vein tumor thrombus or bile duct tumor thrombus. However, based on

the evidence reported in Reference 8, hepatectomy may be indicated for HCC accompanied by hepatic vein tumor thrombus in patients with relatively good liver function and macroscopically resectable lesions, as in portal vein tumor thrombus. Due to the lack of other treatment modalities with high-quality evidence, the current Guidelines make no recommendation specific to hepatic vein tumor thrombus.

In the meetings for finalizing recommendations for the CQ, committee members had differing opinions and therefore longer time was needed for in-depth discussion than for other CQs. Subsequently, based on the expected treatment response, embolization or hepatectomy was selected as first-line therapy and TAI or molecular-targeted therapy as second-line therapy, and these were presented in the public hearing and public comment sessions. However, several hepatologists had genuine concerns about selecting TACE as first-line therapy because of the risk associated with Vp_3/Vp4 tumor thrombus. They also pointed out the gap between the recommendation of TAI/molecular-targeted therapy as second-line therapy in the Guidelines and the frequent use of these treatment modalities in actual clinical practice in Japan. For these reasons, the Revision Committee revisited this issue but did not reach a consensus because of the observation that the references cited for CQ16, which are the foundation for evidence-based recommendation, are individually bound by specific selection criteria and do not provide sufficient scientific evidence to cover all cases of vascular invasion. Because it is difficult to provide universal ranking for the four treatment modalities at this point, the Committee Chair decided to recommend the four modalities in parallel. It is hoped that many studies with high-quality evidence will be published in the near future, enabling us to make a more specific and clearer recommendation for CQ16.

In summary, embolization, hepatectomy, TAI, and molecular-targeted therapy are recommended for HCC accompanied by vascular invasion. However, careful attention must be paid to various factors, including liver function and tumor characteristics, before selecting the most appropriate treatment for individual patients.

■ References

1) Luo J, Guo RP, Lai EC, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma with portal vein tumor thrombosis: a prospective comparative study. *Ann Surg Oncol* 2011; 18: 413-20. PMID: 20839057

2) Pawlik TM, Poon RT, Abdalla EK, et al. Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: results of a multicenter study. *Surgery* 2005; 137: 403-10. PMID: 15800485

3) Torzilli G, Belghiti J, Kokudo N, et al. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations? An observational study of the HCC East-West study group. *Ann Surg* 2013; 257: 929-37. PMID: 23426336

4) Kokudo T, Hasegawa K, Matsuyama Y, et al. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. *J Hepatol* 2016; 65: 938-43. PMID: 27266618

5) Ku Y, Iwasaki T, Tominaga M, et al. Reductive surgery plus percutaneous isolated hepatic perfusion for multiple advanced hepatocellular carcinoma. *Ann Surg* 2004; 239: 53-60. PMID: 14685100

6) Nouso K, Miyahara K, Uchida D, et al. Effect of hepatic arterial infusion chemotherapy of 5-fluorouracil and cisplatin for advanced hepatocellular carcinoma in the Nationwide Survey of Primary Liver Cancer in Japan. *Br J Cancer* 2013; 109: 1904-7. PMID: 24008659

7) Bruix J, Raoul JL, Sherman M, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. *J Hepatol* 2012; 57: 821-9. PMID: 22727733

8) Kokudo T, Hasegawa K, Matsuyama Y, et al. Liver resection for hepatocellular carcinoma associated with hepatic vein invasion: a Japanese nationwide survey. *Hepatology* 2017; 66: 510-7. PMID: 28437844

9) Kokabi N, Camacho JC, Xing M, et al. Open-label prospective study of the safety and efficacy of glass-based yttrium 90 radioembolization for infiltrative hepatocellular carcinoma with portal vein thrombosis. *Cancer* 2015; 121: 2164-74. PMID: 25847227

10) Nakazawa T, Adachi S, Kitano M, et al. Potential prognostic benefits of radiotherapy as an initial treatment for patients with unresectable advanced hepatocellular carcinoma with invasion to intrahepatic large vessels. *Oncology* 2007; 73: 90-7. PMID: 18337620

11) Sangro B, Carpanese L, Cianni R, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology* 2011; 54: 868-78. PMID: 21618574

12) Obi S, Yoshida H, Toune R, et al. Combination therapy of intraarterial 5-fluorouracil and systemic interferon-alpha for advanced hepatocellular carcinoma with portal venous invasion. *Cancer* 2006; 106: 1990-7. PMID: 16565970