

## Chapter 2

### Treatment Algorithm

- Introduction

The “Treatment algorithm” has been the most cited aspect of the Guidelines. 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 3 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, evidence has been added with each revision of the Guidelines.

In the past, the “Treatment algorithm” compiled in the Guidelines, and the “consensus-based treatment algorithm”, which more closely reflected actual hepatology treatment strategies, published by incorporating the opinions of experts in Japan were compiled on the “Clinical Practice Manual for Hepatocellular Carcinoma” edited by the Japan Society of Hepatology in 2007. The algorithm has been revised up to the 3rd edition of the “Clinical Practice Manual for Hepatocellular Carcinoma” published in 2015. The biggest changes in the 2017 version (fourth edition), which is the previous version of the Guidelines, were the merger of the evidence-based “treatment algorithm” of the Guidelines with the “consensus-based treatment algorithm”, and the establishment of the CQ system, which serves as the basis for each treatment recommendation of the algorithm. In addition, by incorporating the concept and methods of the GRADE system, which is an international standard for grading the quality of evidence and the strength of recommendations, it was decided to reflect the contents of discussions at the Revision Committee meetings in the text.

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. From the fourth edition, the presence or absence of extrahepatic metastasis and vascular invasion were added as factors for treatment selection of the algorithm, and it was described as being within the Milan criteria as an indication for liver transplantation. Also, in accordance with the principle that important evidence would be incorporated as needed in the Guidelines,

the 5-5-500 rule has been included in the eligibility criteria for liver transplantation in patients with HCC in the 2017 revised version (4th revised edition) published in 2020. In the latest revision of the current Guidelines, the principles of algorithm development incorporated literature-based evidence, consensus reached through clinical practice, and their grading system, according to the fourth edition. As a result, the recommendations for CQ10 to 15 were determined. Based on the recommendation for each CQ, recommended treatment up to the second choice was described in the algorithm according to the principle from the first edition. Evidence literature was searched for articles with a publication date between July 1, 2016 and January 31, 2020, following the search period of the fourth edition, including articles published after the search period. Important evidence was added by hand-searching as appropriate. The treatment algorithm in this 2021 version (fifth edition) recommends treatments based on the combination of 5 core factors: hepatic functional reserve, extrahepatic metastasis, vascular invasion, tumor number, and tumor size. It is desirable that this treatment algorithm is refined through the use of large numbers of clinicians, while incorporating new important evidence as needed.

#### Explanation of the treatment algorithm for HCC

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 indocyanine green (ICG) test results. Extrahepatic metastasis, vascular invasion, tumor number, and tumor size are assessed based on pre-treatment diagnostic imaging findings.

Three treatments shown below 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 tumors  $\leq 3$  cm (see CQ10). (2)

Hepatectomy is recommended as first-line therapy and TACE as second-line therapy for up to 3 HCCs  $> 3$  cm (see CQ10 and 11). (3) TACE is recommended as first-line therapy and hepatic arterial infusion chemotherapy (HAIC) or drug therapy as second-line therapy for  $\geq 4$  tumors (see CQ12).

Drug therapy is recommended for HCC patients with Child-Pugh A liver function and extrahepatic metastasis (see CQ14). In HCC patients with vascular invasion and no extrahepatic metastasis, hepatectomy is recommended for resectable cases, and drug therapy is recommended for unresectable cases. In addition, after hepatectomy and drug

therapy, TACE and HAIC are also recommended. However, in accordance with the principle of the treatment algorithm, requiring the specification of treatment up to the second-line, it was decided not to specify this information in the present algorithm (see CQ15).

Liver transplantation is recommended for HCC within the Milan criteria (solitary HCC lesion  $\leq 5$  cm or up to 3 HCCs  $\leq 3$  cm), or HCC within the 5-5-500 rule [tumor diameter  $\leq 5$  cm,  $\leq 5$  tumors and alpha fetoprotein (AFP)  $\leq 500$  ng/mL, with no distant metastasis or vascular invasion], in Child-Pugh C patients aged  $\leq 65$  years (see CQ13). 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.

- 48. Treatment algorithm    HCC
- 49. Hepatic functional reserve    Child-Pugh A/B\*<sup>1</sup>    Child-Pugh C
- 50. Extrahepatic metastasis    No    Yes
- 51. Vascular invasion    No    Yes
- 52. Tumor number (n)    1-3     $\geq 4$
- 53. Tumor size  $\leq 3$  cm     $> 3$  cm
- 54. Within Millan Criteria or within 5-5-500 rule\*<sup>4</sup>    Not transplantable
- 55. Treatment
- Resection / RFA    Resection TA(C)E    TA(C)E HAIC / DT\*<sup>2</sup>
- Resection / DT\*<sup>2</sup>    DT\*<sup>2</sup>    Transplantation\*<sup>3</sup>    Palliative care

Abbreviations; RFA: radiofrequency ablation, TA(C)E: transcatheter arterial (chemo) embolization, HAIC: hepatic arterial infusion chemo therapy, DT: drug therapy

For treatment modalities of the upper and lower layers, the upper one should be prioritized. Treatment modalities separated by slashes are equally recommended.

\*1: Assessment based on liver damage is recommended in the case of hepatectomy.

\*2: Patients with Child-Pugh A only.

\*3: Patients age  $\leq 65$  years.

\*4: Tumor diameter  $\leq 5$  cm,  $\leq 5$  tumors and AFP  $\leq 500$  ng/mL, with no distant metastasis or vascular invasion.

CQ10 What treatment modalities are recommended for solitary HCC?

## Recommendation

For HCC  $\leq$  3 cm, hepatectomy or RFA is recommended. For HCC  $>$  3 cm, hepatectomy is recommended as first-line therapy. (Strong Recommendation, Evidence Level A).

### ■ Background

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

### ■ Scientific Statement

A literature search conducted with a publication date between July 1, 2016 (after the search for the fourth edition) and January 31, 2020 and the keywords “hepatectomy”, “RFA”, “transcatheter arterial chemoembolization (TACE)”, “radiation therapy,” “tumor number and size”, and “prognosis” extracted 1,149 articles about HCC. This was narrowed down to 49 articles in the first screening. Then, in the second screening, the contents of these articles were reviewed. Since there were a great number of reports on the treatment of HCC to select high-evidence articles, focus was placed on randomized controlled trials (RCTs) and meta-analyses, including multicenter studies and articles that have important implications for each treatment. As a result, 10 articles were selected in the second screening.

From the 10 articles cited for the fourth edition, 4 articles were excluded, and 1 article with updated information was included. In addition, 5 new hand-searched articles containing important information although published after January 31, 2020, were included. Thus, a total of 22 articles are cited for CQ10.

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. 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<sup>1</sup>; the BCLC staging system recommends treatment other than hepatectomy<sup>2</sup>. In Japan, Ishizawa et al. have performed small liver resections safely in patients with portal hypertension<sup>3</sup>.

Regarding HCC treatment, 8 RCTs<sup>4-12</sup> have compared the outcomes of hepatectomy and radiofrequency ablation (RFA). Previous studies reviewed had problems associated with study design or background factors, and therefore were not adopted as evidence up to the fourth edition. However, in the current revision, an RCT conducted in Hong Kong and a Japanese RCT (SURF trial) have been newly included, demonstrating there is no difference in prognosis after treatment between hepatectomy and RFA. Ng et al.

conducted an RCT designed to show the superiority of RFA to hepatectomy in patients with HCC within the Milan criteria. They compared the prognosis after hepatectomy (109 patients) and RFA (109 patients). The results showed no statistically significant difference in the prognosis after hepatectomy and RFA, in either overall survival ( $p = 0.531$ ) or recurrence-free survival ( $p = 0.072$ ). Thus, no superiority of RFA over hepatectomy was demonstrated<sup>9</sup>. On the other hand, Izumi, Kudo, et al. conducted RCTs in Japan, designed to show the superiority of RFA to hepatectomy in patients with  $\leq 3$  HCC  $\leq 3$  cm. They compared the prognosis after hepatectomy (150 patients) and RFA (152 patients). The results showed no statistically significant difference in either overall survival ( $p = 0.838$ ) or recurrence-free survival ( $p = 0.793$ ). Thus, no superiority of RFA over hepatectomy was demonstrated<sup>11,12</sup>.

In the current revision, articles on radiation therapy were newly cited for CQ10. Bush et al. conducted an RCT comparing the prognosis after proton beam therapy (33 patients) and TACE (36 patients). Their interim analysis reported that there was no difference in short-term survival between proton beam therapy and radiation therapy, but the incidence rates of local recurrence and adverse events were lower with proton beam therapy<sup>13</sup>. Kim et al. conducted an RCT comparing the prognosis between proton beam therapy (72 patients) and RFA (72 patients), and reported non-inferiority of proton beam therapy over RFA<sup>14</sup>. In addition, 2 studies compared stereotactic body radiation therapy (SBRT) and RFA using a propensity score matching for factors including liver function. These studies reported that there was no difference in prognosis, and that local control rate was superior with SBRT<sup>15,16</sup>.

#### ■ 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  $\leq 10 \times 10^4/\mu\text{L}$ ) vary between Japan and the United States/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<sup>17</sup>. In Japan, hepatectomy is performed safely by combining pre-hepatectomy endoscopic treatment of esophageal varices and systematic segmentectomy, etc.

Eight RCTs comparing hepatectomy and RFA<sup>4-12</sup> and one meta-analysis<sup>18</sup> of RCTs were cited for CQ10, and their contents were reviewed. The previous studies reviewed in the fourth edition had problems associated with study design or background factors, did not reflect actual clinical situations in Japan, and therefore were not adopted as evidence. An RCT meta-analysis by Yu et al. cited newly for CQ 10 in the current edition reported that the long-term recurrence-free survival favored hepatectomy. However, the majority of the articles analyzed by Yu et al. were those not selected in the review for the fourth edition, and therefore were not reflected on the recommendations<sup>18</sup>. Of the newly adopted three RCT articles published in 2016 onwards, one study conducted by Lee et al. reported that recurrence-free survival favored hepatectomy. However, the number of patients enrolled in the study was 68, far below the target sample size of 217 patients. Therefore, the article was not adopted as the evidence for treatment recommendations<sup>10</sup>. Ng et al. conducted an RCT which was designed to show a 20% superiority of RFA to hepatectomy in 3-year recurrence free survival rate in patients with HCC within the Milan criteria. The study was conducted on 109 patients for each of the hepatectomy and RFA groups. However, the 3-year recurrence free survival rate was 50.9% with hepatectomy and 46.6% with RFA ( $p = 0.072$ ), showing no statistically significant difference between the two groups<sup>9</sup>. The results from the SURF trial, which was an RCT comparing hepatectomy and RFA in Japan, were presented at the Annual Meeting of the American Society of Clinical Oncology (ASCO) by Izumi et al. in 2019<sup>11</sup>, followed by Kudo et al. in 2021<sup>12</sup>. The SURF trial was designed to show a 10% superiority of hepatectomy to RFA in either overall survival rate or recurrence-free survival rate. However, the 3-year recurrence-free survival rate was 49.8% with hepatectomy and 47.7% with RFA ( $p = 0.793$ ), and the 5-year recurrence-free survival rate was 74.6% with hepatectomy and 70.4% with RFA ( $p = 0.838$ ), showing no significant differences. Based on these results, it has been concluded for CQ10 that hepatectomy and RFA are equally effective. On the other hand, hepatectomy requires general anesthesia, a long hospitalization period, and may cause many complications. Therefore, it was discussed whether RFA should be recommended as first-line therapy, in consideration of its non-invasiveness. However, in consideration of the facts that there is no difference between the two treatment modalities and that the SURF trial is an important Japanese RCT, but conducted with a sample size, only a half of the target sample size of 600 patients, evidence has not been established to overturn the recommendation from the fourth edition: hepatectomy as first-line therapy and RFA as second-line therapy. Thus, it was agreed to recommend that hepatectomy and RFA are equally effective.

Articles comparing hepatectomy and RFA in non-RCT settings included a Korean registry study by Lee et al. They analyzed solitary HCCs of 3 to 5 cm in size in patients with matched background factors, and reported that RFA demonstrated better prognosis than TACE and was comparable to hepatectomy<sup>19</sup>. Cucchetti et al. suggested the possibility that prognosis was better with hepatectomy than with RFA and TACE in an observational study using a method estimating the average treatment effect. However, there was little difference between hepatectomy and RFA in patients with tumors  $\leq 2$  cm<sup>20</sup>. Takayasu et al. retrospectively evaluated data from the National Follow-up Survey Report on Primary Hepatic Cancer of the Liver Cancer Study Group of Japan. They reported that there were no differences in overall survival rate among hepatectomy, RFA and percutaneous ethanol injection (PEI) in the treatment of solitary hypovascular HCC  $\leq 2$  cm in patients with matched background factors. In addition, they reported the recurrence-free survival rate to be better with hepatectomy than in other two groups<sup>21</sup>. None of these studies reached the RCTs in term of the level of evidence and therefore were included as evidence for the preparation of recommendations.

Radiation therapy was also newly investigated in the current revision. Radiation therapy is a minimally invasive treatment that allows patients to be treated in an outpatient setting for a short period of time, and may often be indicated for patients with tumors in areas where percutaneous ablation is not feasible or patients ineligible for surgical treatment. In studies conducted by Hara et al.<sup>15</sup> and Kim et al.<sup>16</sup> in patients with matched background factors, SBRT compared with RFA was reported to be comparable in prognosis and to show a higher local control rate. Shiba et al. conducted a study comparing heavy-ion (carbon-ion) radiotherapy and TACE in patients with matched background factors. They reported that heavy-ion radiotherapy was superior both in survival rate and local control rate<sup>22</sup>. Bush et al. conducted an RCT comparing prognosis between proton beam therapy (33 patients) and TACE (36 patients). Their interim analysis results showed that there was no difference in short-term survival between proton beam therapy and TACE, and that the incidence rates of local recurrence and adverse events were low<sup>13</sup>. In addition, Kim et al. conducted an RCT comparing prognosis between proton beam therapy (72 patients) and RFA (72 patients), and showed non-inferiority of proton beam therapy over RFA<sup>14</sup>. However, the number of high-evidence articles reporting direct comparison with other treatment modalities is limited for particle radiotherapy, compared with hepatectomy and RFA. Therefore, it has been concluded that the evidence is insufficient to recommend radiation therapy. However, radiation therapy can be an option for patients ineligible for other locoregional therapies.

Voting results:

- Ⓒ Regarding the statement of recommendation “For HCC  $\leq$  3 cm, hepatectomy or RFA is recommended. For HCC  $>$  3 cm, hepatectomy is recommended as first-line therapy”, its adoption was strongly recommended by voting of committee members.

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

Total voters: 18 members (abstention because of COI: 4 members)

#### ■ References

CQ11 What treatment modalities are recommended for 2 or 3 HCCs?

#### Recommendation

Hepatectomy or percutaneous ablation is recommended for HCCs  $\leq$  3 cm. For HCCs  $>$  3 cm, hepatectomy is recommended as first-line therapy and embolization as second-line therapy (Strong Recommendation, Evidence Level A).

#### ■ Background

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

#### ■ Scientific Statement

A literature search conducted with a publication date between July 1, 2016 (i.e., after the search for the fourth edition) and January 31, 2020 and the same keywords used for CQ10 (hepatectomy, RFA, TACE, radiation therapy, tumor number and size, and prognosis) extracted 1,149 articles. This was narrowed down to 49 articles in the first screening. Then, in the second screening, the contents of these articles were reviewed to select mainly high-evidence articles, such as RCTs and meta-analyses, including multicenter studies and articles that have important implications for each treatment. As a result, 5 articles were selected in the second screening.



From the 9 articles cited for the fourth edition, 2 articles were excluded. In addition, 3 new hand-searched articles which were not selected with the search words or which contained important information although published after January 31, 2020, were included. Thus, a total of 15 articles were cited for CQ11.

As in CQ10, 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  $\geq 10$  cm has a 5-year survival rate of 20-30%, suggesting that tumor size does not limit the indications<sup>1-3</sup>. 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<sup>4</sup>.

Many studies have used “up to 3 HCCs  $\leq 3$  cm” as an indication for RFA. Murakami et al. showed that RFA had a significantly lower local recurrence rate in patients with solitary HCC  $\leq 5$  cm or up to 3 HCCs  $\leq 3$  cm compared with TACE<sup>5</sup>.

In RCTs<sup>6-9</sup> comparing hepatectomy and RFA in  $\leq 2$  HCCs or  $\leq 3$  HCCs, as reviewed also in CQ10, there was no difference between hepatectomy and RFA<sup>7-9</sup>, excluding studies that had problems associated with study design or background factors, although some articles reported different results (see CQ10). In most of these RCTs, no sub-analysis of patients with 2 or 3 HCCs was performed. Only the Japanese SURF trial carried out sub-analyses of patients with multiple tumors. It has been reported that, in 2 or 3 HCCs  $\leq 3$  cm, as seen for solitary HCC, there are no differences between hepatectomy and RFA in either recurrence-free survival or overall survival<sup>8,9</sup>.

Llovet et al. showed the efficacy of TACE in an RCT in patients who had multiple HCCs with Child-Pugh A/B liver function<sup>10</sup>.

Also for CQ11, newly selected articles included those reporting radiation therapy. As in the comparison between hepatectomy and RFA, there are no studies where the number of HCCs was limited to 2 or 3, and no prospective or retrospective comparative studies performing sub-analysis of 2 or 3 HCCs. However, a study<sup>11</sup> comparing proton therapy and TACE by limiting the indication to patients with  $\leq 2$  HCCs or  $\leq 3$  HCCs, and a study<sup>12</sup> comparing proton therapy and RFA reported non-inferiority of proton therapy and a low incidence rate of local recurrence. In addition, studies<sup>13,14</sup> comparing stereotactic body radiation therapy (SBRT) and RFA reported that there was no difference in prognosis between SBRT and RFA, and that SBRT showed a higher local control rate (see CQ10).

#### ■ Explanation

Regarding treatment of small HCC ( $\leq 3$  cm), multiple RCTs have reported that there is no difference in the outcomes of hepatectomy and RFA. Most of these RCTs included many cases of solitary HCC, and therefore no sub-analysis for 2 to 3 HCCs was performed. Only the Japanese SURF trial carried out sub-analyses of patients with multiple tumors. It has been reported that, in 2 or 3 HCCs  $\leq 3$  cm, as seen for solitary HCC, there are no differences between hepatectomy and RFA in either recurrence-free survival or overall survival<sup>8,9</sup>. Also based on extrapolation of RCT results, including solitary HCC, and sub-analysis results in the SURF trial, it has been concluded that hepatectomy and RFA are equivalent for treatment of 2 or 3 HCCs  $\leq 3$  cm. Of articles reporting non-RCT studies, an observational study by Cucchetti et al. suggested the possibility that prognosis was better with hepatectomy than with RFA and TACE, using a method estimating the average treatment effect. They have reported that there is little difference between hepatectomy and RFA in patients with HCC  $\leq 2$  cm, and that hepatectomy can improve prognosis more than TACE in patients with HCC  $> 2$  cm or with multiple tumors within the Milan criteria. On the other hand, it has been reported that, although TACE is commonly performed in many cases of multiple tumors ( $\geq 2$  HCCs), patients with successful resection have better prognosis in comparison with TACE<sup>15</sup>.

Many studies have used “up to 3 HCCs  $\leq 3$  cm” as an indication for RFA. Murakami et al. showed that RFA had a significantly lower local recurrence rate in patients with solitary HCC  $\leq 5$  cm or up to 3 HCCs  $\leq 3$  cm compared with TACE. However, although RFA was significantly superior for HCC  $\leq 2$  cm, but there was no difference for HCC  $> 2$  cm<sup>5</sup>. The majority of studies have reported “up to 3 HCCs  $\leq 3$  cm” as an indication for percutaneous ablation since the time when percutaneous ethanol injection (PEI) was regarded as the mainstay of percutaneous ablation. In addition, the area of ablation with the electrode of most RFA systems is set at around 3 cm in diameter. Taking also into account this, “up to 3 HCCs  $\leq 3$  cm” is specified for RFA, as the same indication from the fourth edition (see CQ28).

On the other hand, an excellent treatment for local management of relatively large HCCs  $> 3$  cm is hepatectomy. Since it has been used for a long period of time in clinical practice as an effective treatment, there is no study directly comparing it with other treatment modalities. In an RCT comparing hepatectomy and RFA, an indication was set to be HCCs up to 5 cm, which is the Milan criteria. However, in reality, the number of patients with HCCs  $> 3$  cm is limited. Taken together, as mentioned above, hepatectomy is indicated as first-line therapy for HCCs  $> 3$  cm.

Based on the evidence from the RCT conducted by Llovet et al.<sup>10</sup> using TACE in patients who had multiple HCCs with Child-Pugh A/B liver function, TACE is recommended in patients with HCCs difficult to resect.

Regarding the radiation therapy also reviewed in CQ10, there are no studies where study patients were limited to those with 2 or 3 HCCs, but there are studies where patients with  $\leq 3$  HCCs were included. Based on these articles, radiation therapy can be an option for patients ineligible for other locoregional therapies (see CQ10).

Thus, based on the evidence obtained at present, it has been decided to recommend the same treatment modalities from the fourth edition for 2 to 3 HCCs: that is, the first-line therapy to be recommended is hepatectomy or percutaneous ablation for HCCs  $\leq 3$  cm and hepatectomy for HCCs  $> 3$  cm, and the second-line therapy to be recommended is embolization. This recommendation for CQ11, supported by multiple RCTs and meta-analyses, is concluded to have high-quality evidence.

Voting results:

- ⊙ Regarding the statement of recommendation “Hepatectomy or percutaneous ablation is recommended for HCCs  $\leq 3$  cm. For HCCs  $> 3$  cm, hepatectomy is recommended as first-line therapy and embolization as second-line therapy”, its adoption was strongly recommended by voting of committee members.

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

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

## ■ References

CQ12 What treatment modalities are recommended for 4 or more HCCs?

### Recommendation

Embolization is recommended as first-line therapy. HAIC or systemic drug therapy is recommended as second-line therapy. (Strong Recommendation, Evidence Level B)

## ■ Background

Several algorithms recommend treatment modalities for multiple HCCs. Novel findings were also reported after the publication of the fourth edition of the Guidelines. Here, we investigated the efficacy of treatment modalities by reviewing previous evidence.

#### ■ Scientific Statement

This CQ was established as a continuation of CQ13 in the fourth edition. A literature search conducted with a publication date between July 1, 2016 (after the search for the fourth edition) and January 31, 2020 extracted 654 articles about treatment outcomes for multiple HCCs. The search was based on the following inclusion criteria: limited to prospective studies, except for retrospective studies with at least multicenter trial to receive an upper level of evidence, where comparison is made with treatment recommended by existing algorithms. The 654 articles were narrowed down to 22 in the first screening. Then, in the second screening, 2 articles reporting analyses or sub-analyses of BCLC Stage B were newly selected. As a result, a total of 7 articles, including the 5 articles from the fourth edition, are cited for CQ12.

BCLC Stage B is defined as multiple HCCs (4 or more HCCs of any size; or multiple HCCs  $\geq 3$  cm) with no vascular invasion or distant metastasis. Therefore, it should be noted that, strictly speaking, even if the number of tumors is less than 4, large HCCs of  $\geq 3$  cm are classified as BCLC Stage B. In addition, since 4 or more HCCs with vascular invasion and with extrahepatic metastasis are presented in CQ15 and CQ14, respectively, this CQ reviewed the treatment modalities for multiple intrahepatic HCCs (4 or more HCCs) with no vascular invasion or extrahepatic metastasis.

A study that investigated an association between tumor number and the outcome of hepatectomy showed poor long-term prognosis for the resection of multiple HCCs. However, hepatectomy could be performed safely with proper assessment of hepatic functional reserve and adequate resectional volume<sup>1</sup>. 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. As described in the fourth edition, studies by Llovet et al.<sup>2</sup>, Takayasu et al.<sup>3</sup> and Nouso et al.<sup>4</sup> and the SHAPP study<sup>5</sup> have demonstrated the efficacy of TACE, HAIC and sorafenib in comparison with each symptomatic treatment or untreated groups. By limiting the study patients to those with 4 or more HCCs, as specified in CQ12, no studies were found where these treatment modalities were strictly compared.

Kudo et al. conducted a multicenter study<sup>6</sup> with the objective of assessing clinical benefit by adding sorafenib to TACE in patients with unresectable HCC<sup>6</sup>. In the study, 156 patients with unresectable HCC were randomly allocated to either a TACE plus sorafenib group (80 patients) or a TACE alone group (76 patients), and progression-free survival and overall survival were compared between the groups. This study revealed a significant prolongation of progression-free survival in the TACE plus sorafenib group. However, also the sub-analysis [TACE plus sorafenib group (44 patients) vs. TACE alone group (34 patients)] showed a hazard ratio of 0.45 [95% confidence interval (CI): 0.26 - 0.78], demonstrating the clinical benefit of add-on sorafenib therapy.

#### ■ Explanation

Previous studies have reported the validity of hepatectomy, combination therapy with hepatectomy and chemotherapy, and TACE in patients with multiple HCCs. However, these were either 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 the current revision, an article reporting analyses or sub-analyses of BCLC Stage B was newly selected. BCLC Stage B is defined as multiple HCCs (4 or more HCCs of any size; or multiple HCCs  $\geq 3$  cm) with no vascular invasion or distant metastasis. Therefore, it should be noted that, even if the number of tumors is less than 4, large HCCs of  $\geq 3$  cm are classified as BCLC Stage B, which is not necessarily consistent with the classification in this CQ.

In general, “up to 3 HCCs” is considered the limit in hepatectomy and RFA. However, in 2018, Hyun et al. conducted a meta-analysis of 18 articles that compared hepatectomy and TACE in usefulness in BCLC Stage B or C HCC patients. They showed the superiority of hepatectomy over TACE in 5-year survival rate<sup>7</sup>. However, in the meta-analysis, the majority of BCLC Stage B HCCs were  $< 4$  HCCs. Therefore, the evidence from this article is insufficient to conclude that hepatectomy is appropriate for 4 or more HCCs.

Based on the results from the stratification study with a large sample size, as adopted in the fourth edition, it is appropriate to perform TACE/ transcatheter arterial embolization (TAE) as first-line therapy in patients with 4 or more HCCs. In the case of TACE/TAE failure, systemic drug therapy and HAIC as local drug therapy are good options.

Regarding the usefulness of combination therapy with TACE/TAE and molecular-targeted therapy, further study is needed to accumulate more evidence.

Based on these findings, for 4 or more HCCs, TACE/TAE is recommended as first-line therapy, and HAIC or systemic drug therapy is recommended as second-line therapy. All

these treatment modalities have been clinically widely used and gained sufficient consensus and therefore have been decided to be strongly recommended. On the other hand, for HCCs with extrahepatic metastasis or portal vein tumor thrombus, these treatment modalities cannot be considered appropriate. Therefore, those who seek information on such cases should refer to other CQs.

Voting results:

- ◎ Regarding the statement of recommendation “Embolization is recommended as first-line therapy. HAIC or systemic drug therapy is recommended as second-line therapy”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
94.7% (18 members)	5.3% (1 member)	0% (0 members)	0% (0 members)

Total voters: 19 members

## ■ References

CQ13 What treatment modalities are recommended for HCC in patients with liver damage grade C (Child-Pugh C liver function)?

### 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 or within the 5-5-500 rule\*. (Strong Recommendation, Evidence Level B).

\*Tumor diameter  $\leq$  5 cm,  $\leq$  5 tumors and AFP  $\leq$  500 ng/mL, with no distant metastasis or vascular invasion.

## ■ 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 July 1, 2016 and January 31, 2020 extracted 580 articles about 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 1 article in the first screening. This article was eventually selected also in the second screening. As a result, a total of 6 articles, including the 5 articles from the fourth revised edition, are cited for CQ13.

Mazzaferro et al. performed liver transplantation in patients with HCC within the Milan criteria (solitary HCC  $\leq 5$  cm or up to 3 HCCs  $\leq 3$  cm with no vascular invasion or extrahepatic metastasis)<sup>1</sup>. After transplantation, 15 patients with Child-Pugh C liver function had 1-year, 3-year, and 4-year survival rates of 93%, 93%, and 80%, respectively, and 1-year, 3-year, and 4-year recurrence-free survival rates of 93%, 86%, and 86%, respectively. 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<sup>2</sup>. Again, these rates were comparable to those obtained in patients with Child-Pugh A/B liver function. However, in a prospective multicenter study of percutaneous ethanol injection (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<sup>3</sup>. 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<sup>4</sup>. In addition, in 2019, a study conducted in patients who underwent living-donor liver transplantation (LDLT) for

HCC in Japan reported criteria enabling the maximal enrollment of LDLT candidates in patients within the 5-5-500 rule (tumor diameter  $\leq 5$  cm,  $\leq 5$  tumors and AFP  $\leq 500$  ng/mL, with no distant metastasis or vascular invasion), while securing the low recurrence rate and high survival rate comparable to those in patients within the Milan criteria<sup>5</sup>.

#### ■ 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.

For liver transplantation, because the number of donor livers is limited, the upper age limit for recipients is generally set up from the social and ethical point of view. The upper age limit for deceased donor liver transplantation in Japan is 65 years.

Regarding the eligibility criteria for liver transplantation, it has been discussed whether biomarkers should be included. In a study conducted by the Japanese Liver Transplantation Society in 965 patients who underwent LDLT for HCC in Japan, the criteria enabling the maximal enrollment of LDLT candidates while securing the outcomes (5-year recurrence rate of  $< 10\%$  and 5-year survival rate of  $\geq 70\%$ ) achieved with patients within the Milan criteria were investigated. In this investigation, various combinations of tumor numbers and AFP/PIVKA-II levels were examined, while the maximal tumor diameter was maintained at 5 cm<sup>1</sup>. As a result, the 5-5-500 rule (tumor diameter  $\leq 5$  cm,  $\leq 5$  tumors and AFP  $\leq 500$  ng/mL, with no distant metastasis or vascular invasion) was proposed as expanded LDLT criteria<sup>5</sup> (see CQ26).

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 percutaneous ablation, 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 percutaneous ablation. 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). In addition, a retrospective cohort study in patients with Child-Pugh C liver function, registered in the National Follow-up Survey Report on Primary Hepatic Cancer in Japan, reported a higher survival rate in patients receiving percutaneous ablation or TACE than in those receiving palliative care. The higher survival rate was observed in both the entire cohort and in propensity score-matched patients with Child-Pugh  $\leq 12$ <sup>6</sup>.

Thus, 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 have not provided sufficient data on safety, such as the frequency of treatment-related complications and treatment-related mortality, and the evidence is insufficient to recommend other treatment options than transplantation. Therefore, careful attention should be given to individual patients and treatment modalities when selecting treatment other than transplantation for patients with liver damage grade C (Child-Pugh C liver function).

Voting results:

- ◎ Regarding the statement of 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 or within the 5-5-500 rule\*”, its adoption was strongly recommended by voting of committee members.

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

Total voters: 24 members (abstention because of COI: 1 member)

## ■ References

CQ14 What treatment modalities are recommended against extrahepatic metastasis from HCC?

### Recommendation

Drug therapy is recommended for advanced HCC accompanied by extrahepatic metastasis. (Strong Recommendation, Evidence Level A).

## ■ 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 CQ38, 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 CQ14.

## ■ Scientific Statement

A literature search conducted with a publication date between July 1, 2016 and January 31, 2020 extracted 111 English articles that reported extrahepatic metastasis from HCC, and lung, lymph node or adrenal metastasis and dissemination and contained the following in the title: radiation therapy, interventional radiology (IVR), chemotherapy, resection, embolization, TACE, RFA, cryotherapy, or high-intensity focused ultrasound (HIFU). This was narrowed down to 12 articles in the first screening to extract case reports, studies with a sample size of  $\leq 5$  patients, and reviews that were not systematic reviews. The contents of the 12 articles were reviewed, and the following 5 articles were selected in the second screening: a sample size of  $\geq 30$  patients for studies on the resection of lung or lymph node metastasis and dissemination, or a sample size of 20 patients for studies on adrenal metastasis, which occurs a relatively small number of

patients, ensuring that data are sufficiently large to be handled in the Guidelines. Excluded were articles about systemic drug therapy in patients with advanced HCC accompanied by extrahepatic lesions, and articles not clearly specifying treatment for extrahepatic lesions. As a result, in this revision, 12 articles were newly selected, including 7 hand-searched articles reporting the results from the Phase III study of drug therapy. Eventually, a total of 29 articles, including the 17 articles cited in the fourth edition, are cited for CQ14.

Drug therapy is the standard treatment for advanced HCC accompanied by extrahepatic metastasis, as described in CQ38. The first-line drug therapy for HCC at present is reported to be atezolizumab plus bevacizumab combination therapy, sorafenib and lenvatinib. As the second-line drug therapy after sorafenib, evidence has been reported for the use of regorafenib, ramucirumab and cabozantinib. These studies included the presence of extrahepatic metastasis in the patient inclusion criteria, and showed consistent efficacy of drug therapy by sub-analyses also in subgroups of patients with extrahepatic metastasis<sup>1-7</sup>.

Therefore, this CQ14 focuses on locoregional therapy for extrahepatic metastasis, as a continuation of CQ15-2 in the fourth version.

The most commonly reported extrahepatic metastasis was lung metastasis, in 10 articles, all of which were retrospectively conducted. Except for one article reporting RFA, the remaining articles reported surgical resection of the lung lesions<sup>8-18</sup>. Excluding one study that examined patients who underwent treatment for lung metastasis after liver transplantation, the 5-year survival rate of the patients was reported to be 27.5% to 66.9%<sup>8-12,14-18</sup>. Better prognosis was reported for the resection group by a study where patients who underwent and did not undergo resection of lung metastasis after hepatectomy were compared between groups of 7 patients each matched based on propensity scores<sup>17</sup>. In addition, pulmonary metastasis after liver transplantation was reported. The 2-year survival rate was reported to be poor (30.6%) in patients who underwent pulmonary metastasectomy and 0% in patients who did not undergo it, suggesting that resection improves long-term prognosis<sup>13</sup>. Another study that involved RFA (which is not a common treatment like lung resection) for lung metastasis from HCC in 32 patients with lung metastasis from HCC reported a median survival of 37.7 months and a rate of complications, such as pneumothorax, of 25%<sup>14</sup>.

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<sup>19</sup>. In addition, the possible improvement of

long-term prognosis by adrenalectomy was shown in 26 patients with metachronous adrenal metastases, including recurrence after liver transplantation<sup>20</sup>.

In patients with lymph node metastasis from HCC, prognosis was better with metastasectomy than without metastasectomy<sup>21</sup>, and with TACE for not only lymph node metastasis but also intrahepatic lesions than with TACE for intrahepatic lesions only<sup>22</sup>. In the National Follow-up Survey Report on Primary Hepatic Cancer conducted by the Liver Cancer Study Group of Japan, 112 patients who underwent lymph node metastasectomy had a 5-year survival rate of 29.5%<sup>23</sup>. Another study comparing CT-guided RFA and non-RFA groups in 46 patients each reported that 6-month and 1-year survival rates were higher in the RFA group<sup>24</sup>.

Two articles about the treatment of dissemination are cited for CQ14, one of which reports that prognosis is better with resection than without resection in patients with preserved liver function<sup>25</sup>. 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<sup>26</sup>.

Among other locoregional therapies, helical tomotherapy (a form of intensity-modulated radiation therapy for multiple lung, adrenal, or lymph node metastases) provides palliative benefit<sup>27</sup>.

Many studies that involved the use of locoregional therapy for extrahepatic metastasis have shown the importance of managing intrahepatic lesions<sup>10,19,26</sup>, and in another study, performance status (PS) and vascular invasion (for intrahepatic lesions) were prognostic factors among 342 patients with HCC and extrahepatic metastasis<sup>28</sup>. A study in 85 patients who underwent resection of extrahepatic lesions demonstrated long-term overall survival (27.2 months), and also reported poor prognosis by multivariate analysis in patients who underwent resection of  $\geq 3$  tumors<sup>29</sup>.

#### ■ 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 CQ14 included only retrospective studies with relatively low evidence levels, and no RCTs or meta-analyses for extrahepatic lesions only. In recent years, articles presenting evidence that drug therapy improves survival in patients with advanced HCC have been accumulating. In these reports demonstrating prolonged survival, consistent prolonged survival has been shown by sub-analysis of patients with extrahepatic metastasis. Based on these findings, it has been decided to recommend drug therapy for advanced HCC accompanied by extrahepatic metastasis.

In the fourth edition, based on the results of several retrospective studies, locoregional therapies (including resection) are recommended, although weakly, as treatment options for extrahepatic metastasis from HCC (lung, adrenal, and lymph node metastasis and dissemination). The recommendation states that “locoregional therapies (including resection) may be selected for lung, adrenal, and lymph node metastasis and dissemination, provided that intrahepatic lesions are absent or well controlled.” Since the issuance of the fourth edition, new evidence for the use of atezolizumab plus bevacizumab combination therapy, lenvatinib, ramucirumab and cabozantinib has been added to the drug therapy with sorafenib or regorafenib. Thus, it has become possible to select multiple drug therapies. On the other hand, for locoregional therapies for extrahepatic lesions, as described above, which have been evaluated only in retrospective studies, there has been no high-level evidence. Based on these findings, the Revision Committee discussed about the deletion of locoregional treatment from the recommendation for extrahepatic lesions in this revision. Opinions at the committee meeting included that the recommendation in the fourth edition was made when there were not many effective drug therapies, that some procedures (including RFA) have not been performed for extrahepatic lesions in Japan, and that locoregional therapies have become common treatment for patients in whom the only problem lies in the local area, regardless of cancer type. The Committee members voted on whether to delete it. As a result, with the consent of the majority, it was finally decided not to list it. In this revision, it has been decided not to include the locoregional therapies for the treatment of extrahepatic lesions. However, it does not intend to rule out locoregional therapies, including resection, from the treatment modalities for extrahepatic lesions. As described in the Scientific Statement section, there are studies, although retrospective, reporting the effectiveness of locoregional therapies for extrahepatic lesions.

Voting results:

- ◎ Regarding the statement of recommendation “Drug therapy is recommended for advanced HCC accompanied by extrahepatic metastasis”, its adoption was strongly recommended by voting of committee members.

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

Total voters: 19 members (abstention because of COI: 2 members)

## ■ References

CQ15 What treatment modalities are recommended for HCC accompanied by vascular invasion?

### Recommendations

1. If resectable, hepatectomy is recommended (Strong Recommendation, Evidence Level B)
2. If unresectable, systemic drug therapy is recommended. (Strong Recommendation, Evidence Level B)
3. If not eligible for hepatectomy and systemic drug therapy, HAIC and embolization may be performed. (Weak Recommendation, Evidence Level B)

## ■ Background

This CQ was newly established in the fourth edition, to investigate effective treatment modalities for HCC with vascular invasion, especially focusing on patients with portal vein tumor thrombus, which has a particularly high incidence.

## ■ Scientific Statement

In the fourth edition, the literature search conducted with a publication date between January 1982 and July 2016 and the keywords “portal vein tumor thrombus”, “surgical resection”, “chemotherapy”, “treatment algorithm”, and “treatment allocation” extracted 12 articles about the treatment of HCC accompanied by vascular invasion.

In the current revision, a literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 87 articles. This was narrowed down to 26 articles in the first screening. In the second screening, articles with unclear results and with a small sample size were excluded, and 3 articles that reflect the current state of medical care in Japan were newly selected. Eventually, a total of 25 articles are cited for CQ15, consisting of 12 articles from the fourth edition and 13 newly selected articles, ten of which are new hand-searched articles that were not detected by the search query but are cited for another CQ about the treatment modalities of CQ15.

The treatment outcomes of hepatic resection, systemic drug therapy, HAIC, TACE, and radiation therapy in patients with HCC accompanied by vascular invasion are described below in this order.

The 5-year survival of patients with portal vein tumor thrombus who underwent hepatectomy were reported to be 10-38%, indicating that surgery prolongs life to some extent<sup>1,2</sup>. In a retrospective study using data from the National Follow-up Survey Report on Primary Hepatic Cancer conducted by the Liver Cancer Study Group of Japan, patients with HCC accompanied by portal vein tumor thrombus were divided into the hepatectomy group (2,093 patients) and other treatment group (4,381 patients). Compared in patients matched for background based on propensity scores (1,058 patients), 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)<sup>3</sup>. In another study, combination therapy of hepatectomy and hepatic perfusion therapy with doxorubicin was attempted<sup>4</sup>. However, the results were inconclusive. A large-scale cohort study of patients with HCC accompanied by hepatic vein tumor thrombus was conducted using the data from the National Follow-up Survey Report on Primary Hepatic Cancer conducted by the Liver Cancer Study Group of Japan<sup>5</sup>. The published results 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 (1,021 patients) was significantly longer in the resection group (4.47 years, 540 patients) than in the other treatment group (1.58 years, 481 patients). The difference remained significant in an analysis performed in patients matched for background based on propensity scores.

The treatment outcomes have been reported from Phase III studies of systemic drug therapy using molecular-targeted drugs and immune checkpoint inhibitors, mostly from sub-analyses of patients with HCC accompanied by vascular invasion. According to sub-analyses of the SHARP trial of sorafenib, which is a first-line therapy drug, sorafenib (108 patients) compared with placebo (123 patients) improved survival by 3.2 months in patients with HCC accompanied by vascular invasion (hazard ratio: 0.68, 95% CI: 0.49-0.93)<sup>6</sup>. The sub-analyses of a Phase III study (IMbrave150 trial) of atezolizumab plus bevacizumab combination therapy<sup>7</sup> demonstrated that the combination therapy compared with sorafenib improved prognosis (hazard ratio: 0.53, 95% CI: 0.37-0.76). On the other hand, the sub-analyses of a Phase III study (REFLECT trial) of lenvatinib<sup>8</sup> showed that the hazard ratio for survival remained at 0.908 (95% CI: 0.783-1.054) with lenvatinib compared with sorafenib. The sub-

analyses of patients with HCC accompanied by vascular invasion in a Phase III study (RESORCE trial) of regorafenib, which is second-line therapy,<sup>9</sup> showed that regorafenib improved survival with a hazard ratio of 0.67(95% CI: 0.46-0.98). On the other hand, the sub-analyses of the Phase III studies of ramucirumab<sup>10</sup> and cabozantinib<sup>11</sup> showed no improvement in survival.

In a retrospective study<sup>12</sup> of HAIC in portal vein tumor thrombus patients matched for background based on propensity scores<sup>12</sup>, HAIC using 5-FU and cisplatin improved survival compared with the symptomatic treatment (median survival: 7.9 months with HAIC and 3.1 months with symptomatic treatment). Regarding the use of interferon  $\alpha$  in combination with HAIC using 5-FU and cisplatin<sup>13</sup>, results have been inconclusive. In a retrospective study of treatment outcomes of HAIC (110 patients) and sorafenib (39 patients) in patients with HCC accompanied by vascular invasion<sup>14</sup>, the median survival in patients who had not developed unresponsiveness to TACE was 13.4 months in the HAIC group, showing a significant improvement in prognosis compared with the sorafenib group (6.0 months). In two retrospective multicenter studies<sup>15,16</sup> in Japan that were conducted in more than 1,000 patients and published after 2020, the overall survival was significantly improved in the HAIC group (10.1-15.0 months) compared with the sorafenib group (7.9-9.1 months) in the cohort of patients with HCC accompanied by vascular invasion without extrahepatic lesions who were matched for background based on propensity scores. In addition, in a Phase III study assessing clinical benefit by adding sorafenib to HAIC<sup>17</sup>, FOLFOX combined with HAIC, compared with sorafenib alone, improved prognosis (median survival: 13.37 months for HAIC, 7.13 months for sorafenib alone; hazard ratio: 0.35 [95% CI: 0.26-0.48,  $p < 0.001$ ]).

For TACE, a prospective study (non-randomized) reported long-term outcomes of TACE (84 patients) and symptomatic treatment (80 patients) in patients with HCC accompanied by vascular invasion<sup>18</sup>. The study reported the effectiveness of TACE in one-year survival rate (30.9% vs. 9.2%).

Treatment outcomes of radiation therapy in patients with portal vein tumor thrombus are reported by a meta-analysis of 37 studies in 2,513 patients. The meta-analysis compared treatment modalities: three-dimensional conformal radiotherapy (3D-CRT), stereotactic body radiotherapy (SBRT) and selective internal radiotherapy (SIRT)<sup>19</sup>. The meta-analysis reported that, although there was no significant difference in survival among 3D-CRT, SBRT and SIRT, the response rate to SBRT was significantly higher. In a Phase III study where SIRT using Yttrium-90 was compared with sorafenib, sub-analysis of patients with HCC accompanied by vascular invasion receiving SIRT (149



patients) and sorafenib (128 patients) showed no significant difference in survival between the two treatment modalities (hazard ratio: 1.19, 95% CI: 0.92-1.54,  $p = 0.49$ )<sup>20</sup>. Also in a meta-analysis of 6 studies comparing SIRT and sorafenib showed no significant difference in survival between the two treatment modalities in patients with portal vein tumor thrombus (hazard ratio: 1.00, 95% CI: 0.83-1.19,  $p = 0.96$ )<sup>21</sup>. However, according to an RCT in patients with HCC accompanied by vascular invasion (portal vein tumor thrombus and/ or hepatic vein tumor thrombus), conventional external beam radiotherapy plus TACE, compared with sorafenib alone, yielded a higher progression-free survival rate at 12 weeks after treatment (86.7% vs. 34.3%,  $p < 0.001$ ), and higher response rate and median survival at 24 weeks after treatment (33.2% vs. 2.2%,  $p < 0.001$ ) (55.0 vs. 43.0 weeks,  $p = 0.04$ )<sup>22</sup>.

#### ■ 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 Vp2, Vp3, and Vp4. 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. There has been no study that comprehensively compared all treatment modalities. Therefore, it is considered appropriate to recommend treatment modalities that are applicable in Japan and supported by high levels of evidence, such as data from studies using symptomatic therapy and sorafenib as controls, among the treatment modalities reported in recent articles.

Under CQ15, 4 types of treatment modalities are recommended. These treatments should be contraindicated depending on the extent of progression of vascular invasion. For example, embolization (one of the recommended treatment options) for Vp3 and Vp4 tumor thrombus should be performed carefully because of the risk of liver abscess and hepatic infarction. Solitary HCC with Vp2 tumor thrombus is a good indication for surgery, because compared with other treatment modalities, surgery yields superior outcomes in HCC patients with Vp3 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 in some cases. HAIC and systemic drug therapy may be considered for patients with multiple HCCs and extensive vascular

invasion who are not therefore eligible for resection. Multiple well-designed studies evaluating systemic drug therapy have been reported. Therefore, systemic drug therapy can be recommended as a treatment modality for patients with HCC accompanied by vascular invasion who are not eligible for hepatectomy. Although most studies of HAIC were conducted retrospectively, a large-scale cohort study in patients matched based on propensity scores showed an improvement in prognosis with HAIC, compared with symptomatic therapy<sup>12</sup> and sorafenib<sup>15,16</sup>.

There have been an increasing number of studies on radiation therapy conducted overseas mostly, showing such as the utility of radiation therapy using Yttrium-90<sup>23</sup>, the life-prolonging effect of 3D-CRT<sup>24</sup> and the utility of embolization using Yttrium-90<sup>25</sup>. However, the real issue is that therapies using Yttrium-90 are currently not practiced in Japan. In addition, the superiority of the therapies using Yttrium-90 over sorafenib has not been proven. Therefore, it was determined that the evidence was scant to recommend SIRT for Vp-positive patients. 3D-CRT and SBRT are also available in Japan, and can be a treatment option for patients with HCC accompanied by vascular invasion. However, these treatment modalities are poorly supported by evidence from comparison with non-radiation therapies. Although new evidence has shown that prognosis is better with combined use of radiation therapy than with sorafenib<sup>22</sup>, the TACE performed in the study was mainly HAIC with cisplatin. In addition, the protocol is less used in clinical practice in Japan. Based on these findings, we examined whether radiation therapy should be newly adopted as the recommended treatment for CQ 15. However, the majority of voters agreed not to newly include radiation therapy in this revision. Therefore, it has been decided to provide the information about radiation therapy in the Explanation section, and this will be discussed after obtaining the results of RCTs currently ongoing.

In the meetings for finalizing recommendations for CQ 15, committee members had differing opinions and therefore longer time was needed for in-depth discussion than for other CQs. The recommendation in the fourth edition listed all treatment modalities, stating that “Embolization, hepatectomy, HAIC, and molecular-targeted therapy are recommended” under Strong Recommendation. However, in the current revision, the recommendation of each treatment modality was evaluated. Based on the evidence described in the Scientific Statement section, voting was performed.

Voting results:

◎ Regarding the statement of recommendation 1 “If resectable, hepatectomy is

recommended”, its adoption was strongly recommended by voting of committee members.

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

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

- ⊙ Regarding the statement of recommendation 2 “If unresectable, systemic drug therapy is recommended”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
100% (21 members)	0% (0 members)	0% (0 members)	0% (0 members)

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

- ⊙ Regarding the statement of recommendation 3 “If not eligible for hepatectomy and systemic drug therapy, HAIC and embolization may be performed”, its adoption was weakly recommended by voting of committee members.

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

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

Vascular invasion generally implies portal vein tumor thrombus. The literature search extracted a very limited number of articles on treatment outcomes only for hepatic vein tumor thrombus or bile duct tumor thrombus. However, 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 are still unable to make recommendations specific to hepatic vein tumor thrombus.

## ■ References



## Chapter 3

### Prevention

#### Introduction

HCC rarely occurs in the otherwise healthy liver but occurs frequently in the presence of chronic liver disease. In Japan, since 2015, the incidence of new-onset HCC associated with hepatitis C virus (HCV) has been reduced to less than 50%, whereas the incidence of non-B non-C (nonviral) HCC has increased to 30-40%. As the mechanism of HCC development, it has been suggested that hepatitis virus-associated carcinogenesis is caused by the persistence of immunity-mediated inflammation, relevant gene mutations and changes in intracellular signal transduction, and, in hepatitis B virus (HBV), the involvement of the virus itself. In non-B non-C HCC, carcinogenesis is considered to involve the activation of inflammatory cytokines (e.g., TNF- $\alpha$  and IL-6) and of the signal transduction system associated with insulin resistance and hyperinsulinemia.

Interventions for hepatitis virus-related HCC include antiviral therapy. The most notable recent advance is the development of antiviral therapy against HCV. Sustained virologic response (SVR) is achieved in almost all patients after 8- to 12-week administration of direct acting antivirals (DAA). Many studies have demonstrated that SVR is an important factor not only involved in the development of HCC, but also in overall survival for patients with chronic type C liver disease.

Regarding HBV infection, a significant effect of nucleos(t)ide analogue treatment on the prevention of HCC has been shown in comparison with untreated patients. However, there has been no clear evidence on the effect of each drug on the prevention of HCC development. Therefore, in the future, studies are needed to follow up patients over a long period of time. In addition, there is no evidence for strongly recommending nucleos(t)ide analogues, aiming to prevent HCC and prolong overall survival, for hepatitis B patients in the immune-tolerance phase. In the future, if drugs that can achieve seroclearance of hepatitis B virus surface antigen (HBs antigen) are introduced, a new era with new antiviral treatment aiming to prevent HBV-associated HCC is expected to come.

For non-B non-C HCC for which interventions are most difficult to find, identification of population in which HCC development can become an alternative indicator of death is required. On the other hand, because many studies include patients with viral liver disease, we discussed CQ18 from the standpoint of preventive measures for developing HCC from chronic liver disease, either viral or nonviral, as in the 2017 version (fourth

edition). Interventions were examined by various methods, including medications, diet and lifestyle habits. The results from studies conducted in special populations are described in the Explanation section, but not included in recommendations.

Regarding the development of HCC after HCV-SVR, risk factors have been proved by multiple studies supported by high levels of evidence. These factors include being elderly and male, presence of advanced liver fibrosis, low platelet counts and low albumin levels. Regular surveillance according to the level of risk is important also after achievement of SVR.

CQ16 What treatment modalities are recommended as preventive measures against liver cancer associated with chronic hepatitis B liver disease?

#### Recommendation

Nucleos(t)ide analogues are recommended as a preventive measure against liver cancer in patients with HBV-DNA positive chronic hepatitis type B and cirrhosis. (Strong Recommendation, Evidence Level B)

#### ■ Background

Treatment with nucleos(t)ide analogues and interferon suppresses the growth of HBV and reduces liver inflammation in patients with chronic hepatitis B liver disease. Here, we investigated the validity of antiviral therapy to be recommended as a preventive measure against liver cancer.

#### ■ Scientific Statement

This CQ was established based on CQ17 in the fourth edition. A literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 267 articles. This was narrowed down to 46 articles in the first screening and to 25 articles in the second screening based on the following inclusion criteria: randomized comparative studies (RCTs) or non-randomized, comparative, controlled studies, using the development of HCC as the primary endpoint. A total of 42 articles, including 17 articles from the fourth edition, are cited for CQ16.

A meta-analysis showed that nucleos(t)ide analogues reduce the risk of developing HCC by 78% in patients with chronic hepatitis B and cirrhosis (risk ratio: 0.22, 95% CI: 0.10-0.50)<sup>1</sup>. A retrospective cohort study found that oral administration of nucleos(t)ide

analogues (lamivudine, entecavir, and tenofovir) reduced the cumulative incidence of HCC among patients with hepatitis B compared with controls<sup>2-13</sup>. The most recent literature search extracted all the tenofovir-related articles as evidence for tenofovir disoproxil fumarate (TDF), not for tenofovir alafenamide (TAF).

Entecavir and tenofovir are currently first-choice nucleos(t)ide analogues in Japan. Yokosuka et al. reported the incidence of resistant virus was 3.3% during 3-year administration of entecavir, and at week 96 of treatment, the level of HBV-DNA was < 400 copies/mL in 83% of the patients, demonstrating that entecavir effectively suppresses viral growth<sup>14</sup>.

To date, only one RCT that involved the use of lamivudine has shown that nucleos(t)ide analogues prevent HCC<sup>15</sup>. Similarly, only one meta-analysis evaluated the effect of lamivudine<sup>1</sup>, and this article is cited in the current Guidelines, as it was in the fourth edition. However, due to the issue of drug resistance, lamivudine is currently not a drug of first choice in Japan. Regarding entecavir, Wong et al. conducted a retrospective cohort study in 1,870 patients, and reported that entecavir suppressed the incidence of HCC only in patients with cirrhosis (risk ratio: 0.55, 95% CI: 0.31-0.99)<sup>5</sup>. Also a study detected by the literature search for the 2021 version (fifth edition) demonstrated the effect of entecavir on the prevention of HCC in 1, 818 patients with cirrhosis (risk ratio: 0.40, 95% CI: 0.28-0.57)<sup>11</sup>. In contrast, a propensity score matching study by Hosaka et al. showed that nucleos(t)ide analogue treatment prevented HCC in both patient groups with and without cirrhosis (hazard ratio: 0.37, 95% CI: 0.09-0.55,  $p = 0.03$ )<sup>3</sup>.

Comparison in hepatitis B patients with cirrhosis between 797 tenofovir-treated patients and 291 untreated patients showed that tenofovir significantly prevented the development of HCC (adjusted hazard ratio: 0.46, 95% CI: 0.29-0.75,  $p < 0.01$ )<sup>13</sup>. In addition, another propensity score matching study showed a significant decrease in the incidence of HCC in both cirrhosis patients and chronic hepatitis patients<sup>12</sup>. The JSH Clinical Practice Guidelines for Chronic Hepatitis B currently recommends anti-therapy with nucleos(t)ide analogues depending on (1) histological stage, (2) ALT level, and (3) HBV-DNA level. This suggests that nucleos(t)ide analogues are not always administered to hepatitis B patients only for the purpose of preventing HCC. However, it is recommended to use nucleos(t)ide analogues in accordance with the above criteria, also from the standpoint of HCC prevention.

Also for hepatitis B patients in the immune-tolerance phase, multiple studies were conducted from the viewpoint of whether nucleos(t)ide analogues can prevent HCC. Studies showing positive results for the use of nucleos(t)ide analogues include: a study reporting that nucleos(t)ide analogue treatment prevented HCC even in patients with

ALT < 40 in the immune-tolerance phase<sup>16</sup>; a study reporting that patients with normal ALT in the immune-tolerance phase had a higher incidence of HCC than chronic hepatitis B achieving a sustained virologic response (SVR) with nucleos(t)ide analogues (10 years: 12.7% vs. 6.1%,  $p = 0.001$ <sup>17</sup>; 5 years: 2.7% vs. 1.1%,  $p < 0.001$ <sup>18</sup>). On the other hand, there were studies denying the use of nucleos(t)ide analogues in patients in the immune-tolerance phase. These studies reported that there was no difference in the risk of HCC development between active hepatitis patients led to SVR and hepatitis B patients in the immune-tolerance phase<sup>19</sup>; the incidence of HCC was higher in patients receiving nucleos(t)ide analogues than in patients in the immune-tolerance phase (hazard ratio: 3.44, 95% CI: 1.82-6.52,  $p < 0.017$ )<sup>20</sup>. These studies were conducted retrospectively. Therefore, it can be said that there is no strong evidence at present for recommending the use of nucleos(t)ide analogues for hepatitis B patients in the immune-tolerance phase.

Comparison in the effect of nucleos(t)ide analogues on the prevention of HCC was reported by retrospective cohort studies<sup>21-23</sup>. They reported that there was no significant difference between entecavir and lamivudine. The most recent literature search detected an RCT reporting no significant differences in the risk of HCC development between entecavir and other nucleos(t)ide analogues (adefovir, lamivudine and emtricitabine)<sup>24</sup>. However, it should be noted that this study involved a cross-over design and combined use of 2 nucleos(t)ide analogues. Among studies comparing between entecavir and tenofovir, 1 meta-analysis<sup>25</sup> and 4 retrospective cohort studies<sup>26-29</sup> showed that: the incidence of HCC was lower in patients receiving tenofovir than in those receiving entecavir. On the other hand, 5 retrospective cohort studies showed that the incidence of HCC was comparable between patients receiving tenofovir and those receiving entecavir<sup>30-34</sup>.

As indicated above, nucleos(t)ide analogue treatment effectively prevented the development of HCC. However, because HCC does occur despite this therapy, it is important to perform surveillance for HCC even in patients undergoing nucleos(t)ide analogue treatment. Seroclearance of HBs antigen<sup>35,36</sup> was reported as a risk of HCC development in patients undergoing nucleos(t)ide analogue treatment. Good treatment adherence is reported as a factor contributing to lower the risk of HCC development<sup>37</sup>.

#### ■ Explanation

Four meta-analyses of the effect of interferon therapy have been reported. The most recent literature search extracted a matching study showing a significant decrease in the incidence of HCC in patients receiving interferon therapy than in those receiving



nucleos(t)ide analogue treatment<sup>38</sup>. However, interferon therapy was not included in the recommendation due to the lack of definite HCC preventive effect. Miyake et al. have reported that interferon therapy prevents HCC in patients with chronic hepatitis B (risk difference: -5.0%, 95% CI: -9.4 to 0.5; p = 0.028), but response to interferon therapy varies by race or HBe-Ag status. For example, the response to interferon therapy is particularly high among Asians with HBe-Ag-positive chronic hepatitis B<sup>39</sup>. Sung et al. (risk ratio: 0.66, 95% CI: 0.48-0.89)<sup>1</sup> and Yang et al. (risk ratio: 0.59, 95% CI: 0.43-0.81)<sup>40</sup> have also reported meta-analysis results, showing that interferon therapy significantly prevents HCC. The most recent literature search extracted a prospective cohort study<sup>41</sup> and a retrospective cohort study<sup>42</sup>. The former reported no significant difference in the effects of peginterferon and entecavir on the prevention of HCC. The latter reported a significant effect of interferon compared with entecavir on the prevention of HCC. It should be noted that cirrhosis is not an indication for interferon therapy and that there is currently insufficient evidence to support the effect of interferon therapy on the prevention of HCC.

Regarding antiviral therapy in chronic hepatitis B, since the publication of the fourth edition, more evidence has been accumulated for HCC prevention by nucleos(t)ide analogues in chronic hepatitis B patients, mainly from the standpoint of the risk of HCC development by adherence to long-term medications and by HBs antigen seroclearance status.

#### Voting results

- ⊙ Regarding the statement of recommendation “Nucleos(t)ide analogues are recommended as a preventive measure against liver cancer in patients with type B hepatitis positive for hepatitis B virus DNA and cirrhosis”, its adoption was strongly recommended by voting of committee members.

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

Total voters: 23 members

#### References

CQ17 What treatment modalities are recommended as preventive measures against liver

cancer associated with chronic hepatitis C liver disease?

## Recommendation

Antiviral therapy for the eradication of hepatitis C virus (HCV) is recommended as a preventive measure against liver cancer in patients with chronic hepatitis C and compensated cirrhosis type C. (Strong Recommendation, Evidence Level B)

### ■ Background

Patients with chronic hepatitis C and cirrhosis are at the highest risk of HCC in Japan. Here, we investigated whether the eradication of HCV reduces the development of HCC in patients with chronic hepatitis C liver disease.

### ■ Scientific Statement

This CQ was established based on CQ18 in the fourth edition. A literature search conducted with a publication date between July 1, 2016 and January 31, 2020 extracted 462 articles. This was narrowed down to 26 articles in the first screening and 15 articles in the second screening based on the following inclusion criterion: studies with the incidence of HCC or survival as the primary endpoint. Currently, interferon (IFN)-free DAA is recommended for treatment of type C liver disease in Japanese and overseas guidelines. Of the articles selected in the second screening, 4 articles were about IFN-based treatment, 5 articles about IFN-based or DAA therapy, and 6 articles about DAA therapy. A total of 29 articles, including the 14 articles from the fourth edition, are cited for CQ17.

Interferon therapy significantly decreases the risk of HCC in patients with chronic hepatitis C and compensated cirrhosis type C. Three meta-analyses reported that interferon therapy in patients with chronic hepatitis C and compensated cirrhosis type C significantly reduced the risk of HCC development<sup>1-3</sup>. All the studies comparing patients who achieved sustained virologic response (SVR) after antiviral therapy and non-SVR patients have reported that the incidence of HCC is significantly lower in SVR patients<sup>4-18</sup>. Darvishian et al. investigated the risk of HCC development in 46,666 patients in a cohort study. They reported that, compared with patients with spontaneous HCV clearance, the hazard ratio was 14.52 (95% CI: 9.83-21.47) in patients unresponsive to INF, 5.85 (95% CI: 4.07-8.41) in patients not treated with IFN, and 2.49 (95% CI: 1.52-4.06) in patients achieving SVR after IFN therapy.

DAA therapy decreases the risk of HCC in patients with chronic hepatitis C and compensated cirrhosis type C. Carrat et al. conducted a multicenter prospective study in

9,895 patients (7,344 treated with DAA and 2,551 untreated patients). In the final results, when adjusting for age, sex, extent of liver fibrosis, etc., they showed that DAA therapy significantly decreased the risk of HCC development (hazard ratio: 0.66, 95% CI: 0.46-0.93) and the risk of all-cause mortality (hazard ratio: 0.48, 95% CI: 0.33-0.70)<sup>19</sup>. Singer et al.<sup>20</sup> compared 30,183 DAA-treated patients, 12,948 IFN-treated patients, and 137,502 untreated patients. When adjusting for factors, such as age, sex, and the extent of liver fibrosis, the risk of HCC development reduced significantly in DAA-treated patients compared with untreated and IFN-treated patients (adjusted hazard ratio: 0.84 [95% CI: 0.73-0.96] vs. 0.69 [95% CI: 0.59-0.81]). In addition, other 3 articles<sup>21-23</sup> also showed a decrease in the incidence of HCC in DAA-treated patients after achieving SVR. Cheung et al.<sup>24</sup> conducted a prospective study in patients with decompensated cirrhosis type C to compare 406 DAA-treated patients and 261 untreated patients. They reported that the incidence of HCC after 6 months was 4.2% in both DAA-treated and untreated groups, showing no difference.

There were 5 articles evaluating patients receiving IFN-based therapy or DAA therapy. Li et al.<sup>25</sup> evaluated 3,534 IFN-treated patients and 5,834 DAA-treated patients, in comparison with 8,468 untreated patients. They reported that, in treated patients, the incidence of HCC was similar between the IFN and DAA groups (hazard ratio: 1.07, 95% CI: 0.55-2.08), and that the incidence of HCC development was significantly lower in treated patients (with DAA or IFN) than in untreated patients. A Japanese study by Nagata et al. showed that there was no significant difference in the incidence of HCC between 752 patients receiving DAA therapy and 1,145 patients receiving IFN-based therapy<sup>26</sup>. Toyoda et al. compared 1,086 DAA-treated patients who achieved SVR and 1,533 IFN-treated patients. They reported that the incidence of HCC was 6.23% in the DAA-SVR group and 3.01% in the IFN-SVR group, and that the IFN-SVR group had significantly greater number of patients with low HCC risk scores calculated from the age, platelet counts, AFP and the extent of liver fibrosis (F3-4) before antiviral therapy (84.1% vs. 55.6%  $p < 0.0001$ )<sup>27</sup>. Remaining 2 articles<sup>28,29</sup> also showed that the incidence of HCC was lower in patients who achieved SVR after antiviral therapy (with DAA or IFN), and that the extent of liver fibrosis, age, albumin level, platelet count, etc., are associated with the development of HCC, being independent of SVR status.

#### ■ Explanation

The current Guidelines strongly recommends antiviral therapy for the eradication of HCV, as in the fourth edition. The fourth edition stated that there is no sufficient evidence to confirm the effect of DAA therapy on the prevention of HCC development.

However, thereafter, a large-scale cohort study has shown that the eradication of HCV by DAA therapy prevents the development of HCC in patients with chronic hepatitis C/ decompensated cirrhosis type C. On the other hand, although SVR is achieved in  $\geq 90\%$  of DAA-treated patients, the majority of DAA-treated patients are more elderly and have more advanced liver fibrosis than patients receiving IFN-based therapy. Therefore, it is necessary to pay sufficient attention to the development of HCC after SVR. In the majority of articles cited for CQ 17 in the current edition recommended the continuation of regular HCC surveillance also in patients who achieved SVR, if they are elderly and male, have advanced liver fibrosis (F3 or F4), low platelet counts and low albumin levels, etc. In addition, it is important to achieve SVR for patients receiving DAA therapy. For patients unresponsive to DAA therapy, more careful HCC surveillance and treatment rechallenge aiming at SVR needs to be considered. For decompensated cirrhosis type C, there is no evidence at present that DAA therapy prevents the development of HCC.

#### Voting results

- ⊙ Regarding the statement of recommendation “Antiviral therapy for the eradication of hepatitis C virus is recommended as a preventive measure against liver cancer in patients with chronic hepatitis C and compensated cirrhosis type C”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
100% (23 members)	0% (0 members)	0% (0 members)	0% (0 members)

Total voters: 23 members

#### References

CQ18 What preventive measures are recommended for liver cancer associated with viral or nonviral chronic liver disease?

#### Recommendation

Coffee consumption may decrease the risk of liver cancer. (Weak Recommendation, Evidence Level C)

## ■ Background

This CQ was established based on CQ19 in the fourth edition. In recent years, the incidence of HCC has been increasing in patients with non-B and non-C hepatitis, drawing attention to the prevention of HCC associated with nonviral hepatitis. However, because many studies include patients with viral liver disease, we investigated preventive measures for the development of HCC for both viral and nonviral chronic liver disease in this CQ.

## ■ Scientific Statement

A literature search conducted with a publication date between July 1, 2016 and January 31, 2020 extracted 246 articles. This was narrowed down to 18 articles in the first screening and to 13 articles in the second screening, using the keyword “prevention of HCC”. A total of 23 articles, including the 10 articles from the fourth edition, are cited for CQ18.

A cross-sectional study has shown the association between daily intake of  $\geq 600$  mL coffee and a lower risk of HCC development (risk ratio, 0.25; 95% CI, 0.011-0.62)<sup>1</sup>. Moreover, 2 meta-analyses cited newly for CQ18 in the current edition also suggested a decrease in the risk of HCC development<sup>2,3</sup>. These meta-analyses have reported that the risk ratio for HCC development is 0.85 (95% CI: 0.81-0.90) with the consumption of 1 cup of coffee per day by Bravi et al., and 0.65 (95% CI: 0.59-0.72) with the consumption of 2 cups of coffee per day by Kennedy et al.

In a large-scale study, intake of polyunsaturated fatty acids (PUFAs) reduced the incidence of HCC in a dose-dependent manner<sup>4</sup>. The study, which divided participants into 5 groups based on administration of different amounts of PUFAs (the lowest, 9.6 g/day, which was set at 1 in analysis; the highest, 70.6 g/day), demonstrated dose-dependent prevention of HCC by PUFAs (highest group: hazard ratio: 0.64, 95% CI: 0.42-0.96,  $p = 0.03$ ). In the same study, when the participants were divided into 5 groups according to the intake of eicosapentaenoic acid (EPA), similar results were obtained (highest group: hazard ratio: 0.56, 95% CI, 0.36-0.85). These results shows the significance of EPA compared with different PUFAs. However, when adjusting for HBV/HCV infection, there was no significant difference between EPA and other PUFAs, although a similar trend was obtained. Another study of dietary habit (in this case, the Mediterranean diet) was published in Europe and showed an association between higher adherence scores and lower incidence of HCC<sup>5</sup>.

## ■ Explanation

Several epidemiological studies have reported the association between coffee intake and a lower incidence of HCC as well as other cancers. A cross-sectional study and meta analyses that reported an association between coffee intake and risk of HCC are included in the current edition.

Also, multiple studies have reported the utility of metformin<sup>6-10</sup> for the treatment of diabetes and statins<sup>11-14</sup> for the treatment of dyslipidemia as preventive measures for HCC. Five of these articles were epidemiological studies that used the Taiwan National Health Insurance Research Database. The results of all these studies of metformin and statins showed a reduction in the risk of HCC development. There are meta-analyses reporting similar results<sup>15,16</sup>. Although application is limited to patients with diabetes or dyslipidemia, the administration of metformin and statins is likely to decrease the risk of HCC development. Furthermore, Kawaguchi et al. performed a prospective multicenter study of branched-chain amino acids (BCAA) to compare BCAA and no-BCAA groups<sup>17</sup>. Significant differences were observed between the BCAA and no-BCAA groups in the levels of albumin, ammonium, molar ratio of total branched-chain amino acids to tyrosine (BTR), Child-Pugh score, and ferritin. However, multivariate Cox regression analysis and Fine-Gray model analysis revealed that BCAA intake was significantly correlated with the incidence of HCC (risk ratio: 0.45, 95% CI: 0.24-0.88,  $p = 0.019$ ) and all deaths (risk ratio: 0.009, 95% CI: 0.0002-0.365,  $p = 0.015$ ). One article reporting a cohort study about physical activity is cited for CQ18 in the current edition. The study suggested a decrease in the risk of HCC development in people with sustained physical activity of at least moderate intensity from teenage years. However, no effects of physical activity were found in people at certain ages. Therefore, at present, the effects of physical activity are considered limited<sup>18</sup>. For aspirin, there are several reports suggesting its effect on the reduction of the risk of HCC development<sup>19-21</sup>. In addition, there are also reports about tricyclic antidepressants<sup>22</sup> and angiotensin-converting enzyme inhibitors/ receptor antagonists<sup>23</sup>, their effects on the reduction of the risk of HCC development have not been demonstrated.

In patients with nonviral HCC, unlike viral HCC, interventions for background liver disease conditions are not clearly defined. In the future, prospective studies are needed to investigate whether treatment modalities for nonalcoholic steatohepatitis (NASH), the major cause of nonviral liver disease, can prevent the development of HCC. After careful consideration, the Revision Committee decided to recommend the consumption of coffee for CQ18, which was a CQ about the prevention of HCC development in any individuals. The evidence level was rated as C (weak) because the

evidence was gathered from epidemiological studies, but not from comparative or controlled studies. For the consumption of coffee, evidence from two meta-analyses has been newly added to the CQ18 in the current edition, whereas there is no additional evidence to the consumption of PUFAs, which was recommended in the fourth edition. Thus, with the evidence still limited to one article from an epidemiological study, PUFAs was not recommended in the current edition. Metformin, statin, BCAA, and aspirin are not recommended for CQ18 in the current edition, as in the previous edition. Also physical activity is not recommended as described above, because its effects are considered limited.

#### Voting results

- © Regarding the statement of recommendation “Coffee consumption may decrease the risk of liver cancer”, its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
0% (0 members)	100% (23 members)	0% (0 members)	0% (0 members)

Total voters: 23 members

#### References

## Chapter 4

### Surgery

#### ● Introduction

Hepatectomy is the most curative treatment for liver cancer. The topics in this field include an increase in the number of elderly patients with liver cancer undergoing hepatectomy, improved safety and spread of laparoscopic hepatectomy, and an increase in the scientific evidence for perioperative management methods.

In recent years, numerous reports were published concerning the outcome of hepatectomy in elderly patients with liver cancer, and age was adopted as an additional factor for the CQ related to indications for hepatectomy. Furthermore, following accumulation of treatment outcome data on ruptured liver cancer, the features of ruptured liver cancer were also adopted as factors for such CQ.

Since 2016, all procedures of hepatectomy not accompanied by revascularization or biliary tract reconstruction have been deemed indicated for laparoscopic hepatectomy. However, it is known that the incidence of postoperative complications and the mortality rate rise as the technical difficulty in operation gets higher and that the number of medical facilities providing high-difficulty operations is limited. With these borne in mind, the present revision adds a statement emphasizing the importance of carefulness in performing high-difficulty operations to the conventional recommendations.

For a reason of increase in the evidence available concerning hepatectomy procedures and perioperative management, the conventional CQs about blood loss-reducing measures and abdominal drainage are replaced with CQs about operative procedures for hepatectomy and perioperative management. In this connection, the hanging maneuver and prophylactic antimicrobial agents are added to the new CQs. Meanwhile, the CQ about prognosis-predicting factors has been deleted because such factors themselves are not recommendable clinical practices and are hence not suitable as CQ.

The scope of HCC indicated for hepatectomy in Japan has been expanded from cases within the Milan criteria accompanied by decompensated cirrhosis to cases within Milan criteria accompanied by decompensated cirrhosis or cases outside Milan criteria but up to 5 HCCs  $\leq$  5 cm and alpha-fetoprotein (AFT) 500 ng/mL (5-5-500 rule). In Japan, however, there is insufficient scientific evidence to support that HCC treatment prior to liver transplantation improves the prognosis after liver transplantation, because the number of patients undergoing such treatment is quite limited.

A literature search for pre-established CQs was conducted by setting a publication date between July 1, 2016 and January 31, 2020, whereas a literature search for newly



established CQs was conducted by targeting all articles published by January 31, 2020.

CQ19 Which patients are eligible for hepatectomy?

#### Recommendation

1. It is desirable to perform hepatectomy in patients with up to 3 tumors located solely in the liver, regardless of tumor size. Tumor invasion up to the first branches of the portal vein may be an indication for surgery. (Strong Recommendation, Evidence Level B)
2. Advanced age is not a limiting factor for hepatectomy. (Strong Recommendation, Evidence Level B)
3. Ruptured HCC having overcome the acute stage may be indicated for hepatectomy. (Weak Recommendation, Evidence Level B)

#### ■ Background

The CQ “What are the indications for liver resection in terms of tumor condition?” was used up until the third edition (2013 version). Since the fourth edition (2017 version), the wording of this CQ has been changed into the current one to incorporate viewpoints such as advanced age, liver function and performance status.

#### ■ Scientific Statement

A literature search conducted after the previous revision, covering the period from July 1, 2016 to January 31, 2020 in terms of the publication date, extracted 892 articles. This was narrowed down to 19 in the first screening, from which 13 articles with high-quality evidence and clinical importance were extracted in the second screening. With the addition of 11 clinically important articles selected from the 15 articles adopted during the previous revision and 2 other articles extracted by means of hand search, a total of 26 articles are cited for CQ19 in the current edition.

In arguing about the indications for hepatectomy, the staging of HCC is performed based on the tumor number and size, presence/absence of vascular invasion and its severity described in the General Rules for the Clinical and Pathological Study of Primary Liver Cancer (hereinafter simply called “the General Rules”) issued by the Liver Cancer Study Group of Japan.

The 5-year survival rate after hepatectomy has been reported to be approximately 20-30% in patients with a tumor  $\geq 10$  cm. Although no study has compared 5-year survival rates between hepatectomy and other treatment modalities (such as percutaneous treatments and chemotherapy) or the natural course, tumor size is unlikely to limit the indication for

hepatectomy because the results are clearly better than the presumed natural course. However, it is not uncommon that liver cancer recurs soon after hepatectomy. Lim et al. have proposed the high preoperative levels of total bilirubin, low platelet counts, and portal vein tumor thrombus as the risk factors for recurrence within 1 year of the resection of liver cancer  $\geq 10$  cm, suggesting the importance of carefully selecting patients<sup>1</sup>.

With regard to tumor number, resection outcomes are better for 2 or more HCCs (multiple HCCs) than for solitary HCC, and there are also reports that among cases of multiple HCCs the outcomes are better for multicentric multiple HCCs<sup>2</sup>, 2 HCCs affecting the same segment<sup>3,4</sup> and 4 or more HCCs without portal invasion<sup>5,6</sup>. However, because high-quality evidence about the upper limit of tumor number is lacking, up to 3 HCCs, which is a well-accepted indication for RFA and some other procedures, may also be a good indication for hepatectomy when hepatectomy is defined as locoregional therapy.

Many studies have clearly shown that portal venous invasion is the most influential prognostic factor for HCC. In general, prognosis worsens as tumor thrombus advances within the portal vein, but 5-year survival rates are approximately 10-40% in patients with remnant tumor thrombus within the first branches of the portal vein (i.e., up to Vp<sub>3</sub> tumor thrombus). Also in the nationwide follow-up survey of primary liver cancer by the Liver Cancer Study Group of Japan, the hepatectomy outcomes were better for up to Vp<sub>3</sub> tumor thrombus as compared to unoperated cases<sup>7</sup>. Drug therapy is one of the alternatives for HCC accompanied by portal vein tumor thrombus. However, surgery may be indicated because the long-term outcomes of drug therapy for HCC with Vp<sub>3</sub> tumor thrombus are currently unknown. In patients with tumor thrombus in the main portal vein (Vp<sub>4</sub> tumor thrombus), surgery is contraindicated because of its association with poor prognosis. However, there is a report that surgery may be indicated for mild tumor thrombosis because the outcomes of resection in cases of mild Vp<sub>4</sub> tumor thrombus differ little from those in Vp<sub>3</sub> cases<sup>8</sup>. It has been additionally reported that the survival was longer in patients having undergone intrahepatic arterial infusion chemotherapy after curative resection<sup>9</sup>.

In addition to the portal vein, HCC occasionally invades the hepatic veins and bile duct, forming tumor thrombus and usually resulting in poor prognosis. However, even in patients with HCC accompanied by inferior vena cava tumor thrombus, hepatectomy could be often performed safely, with the median survival being 18 months after curative resection<sup>10,11</sup>.

The indication for hepatectomy is often reported negatively in cases of HCC accompanied by bile duct tumor thrombus due to its frequent association with vascular invasion and poorly differentiated HCC as well as a high rate of recurrence soon after the procedure<sup>12</sup>.

Still, hepatectomy for HCC without portal vein invasion or in patients indicated for curative resection sometimes yields long-term survivors<sup>13,14</sup>. Due to inconsistent study results, further study is needed to clarify the outcomes of hepatectomy.

Many reports demonstrate that the incidence of complications following hepatectomy is generally higher in elderly patients than in younger patients. According to a large-scale cohort study in Japan, complications following hepatectomy and in-hospital deaths after hepatectomy increased with age until 79, while there was no difference in complications or in-hospital deaths between patients in their 70s and those in their 80s<sup>15</sup>. According to the analysis given in the report from the nationwide follow-up survey of primary liver cancer, elderly patients were poor in terms of prognosis after hepatectomy, characterized by a high death rate from other illnesses, as compared to younger patients<sup>16</sup>. However, the recurrence-free survival rate and the overall survival rate after hepatectomy were higher than those following treatment with the other methods<sup>17</sup>.

Stabilization of the systemic condition by means of hemostasis is essential in the management of ruptured HCC. Transcatheter arterial embolization (TAE) has a high effect in achieving hemostasis (53-100%). The 30-day death rate and the in-hospital death rate are lower following post-TAE two-stage operation than following one-stage operation<sup>18,19</sup>. Furthermore, the survival rate is higher for patients undergoing hepatectomy than for those undergoing TAE alone. Although the long-term prognosis is poorer for ruptured HCC than for non-ruptured HCC, there is a report that the long-term prognosis was affected by tumor factors other than rupture-related factors, as is the case with non-ruptured HCC<sup>20</sup>. The “General Rules for the Clinical and Pathological Study of Primary Liver Cancer, the 6<sup>th</sup> Edition, Revised Version”<sup>21</sup> also states that the T factor is not altered by rupture of HCC. However, care needs to be taken in Child-Pugh B cases<sup>19</sup>.

#### ■ Explanation

Patients with multiple HCCs may have primary HCC plus intrahepatic metastasis, multicentric HCCs, or both. Depending on the combination, treatment outcome varies among patients with the same number of HCCs. Although hepatectomy is a locoregional therapy, the superiority of systemic hepatectomy over partial resection is associated with the route of invasion through the portal venous system in patients with HCC and intrahepatic metastasis. As for multicentric HCCs, in addition to considering the oncogenic potential of the background liver, the eligibility criteria for locoregional therapy are used. However, the indication is thought to shift toward transcatheter arterial chemoembolization (TACE) as the number of tumors increases. In terms of tumor number, Yang et al. developed a nomogram for the prediction of long-term survival after

hepatectomy for multiple HCCs, suggesting the importance of stratifying the indication for hepatectomy in patients with multiple HCCs<sup>22</sup>.

With regard to age, a large-scale cohort study using the database from the DPC (diagnosis procedure combination) system (13,908 cases aged 69 and under, 10,805 cases aged 70-79, 2,011 cases aged 80-84 and 370 cases aged 85 and over) revealed an increase of cerebrovascular disease, respiratory disease and dementia with aging as well as an increase of post-hepatectomy complications and in-hospital deaths with aging until 79, but there was no difference in terms of post-hepatectomy complications or in-hospital deaths between patients in their 70s and those aged 80 and over<sup>15</sup>. These results are considered to reflect that in Japan hepatectomy has been conducted safely based on consideration of indications of individual cases. According to the report from the nationwide follow-up survey of primary liver cancer by the Liver Cancer Study Group of Japan (patients aged  $\geq 75$ ; hepatectomy in 2,020 cases, RFA in 1,888 cases, microwave coagulation therapy in 193 cases, TACE in 2,389 cases), the 3-year recurrence-free survival rate (39.6%) and the 5-year overall survival rate (67.3%) after hepatectomy were higher than those after treatment with the other methods. The overall survival rate did not differ between the hepatectomy group and the RFA group, but it was higher in the hepatectomy group when analysis was confined to cases with the tumor size not exceeding 3 cm<sup>17</sup>. It seems therefore rational to say that age does not always limit the indications for hepatectomy and that hepatectomy deserves consideration also in elderly patients. It has, however, been reported that the post-hepatectomy complications and the capability of patients to lead daily living without assistance are affected by the aging-related reduction of ADL and physical/social/psychomental decline as well as by the so-called performance status, sarcopenia and frailty<sup>23-25</sup>, suggesting that comprehensive evaluation of functions during senility is essential when judging the indication of elderly patients for hepatectomy.

Emergency TAE is valid as a means of coping with intraperitoneal hemorrhage arising from rupture of HCC. Two-stage hepatectomy, by which hepatectomy is conducted after hemostasis and subsequent detailed evaluation of the systemic condition, cancer progression, etc., has been reported to have a higher success rate (21-56% vs. 13-31%) and a lower in-hospital death rate (0-9% vs. 17-100%) than one-stage hepatectomy<sup>18</sup>. A nationwide follow-up survey of primary liver cancer (1,160 ruptured cases and 48,548 non-ruptured cases)<sup>20</sup> designed to compare the prognosis according to the tumor stage of ruptured cases (stage defined in the General Rules, ignoring the rupture factors) and the stage of non-ruptured cases yielded the following findings: (1) the prognosis for the ruptured Stage II group was intermediate between the non-ruptured Stage III group and

the non-ruptured IVA group (a significant difference between the latter two groups); (2) the prognosis did not differ between the ruptured Stage III group and the non-ruptured Stage IVA group; (3) the prognosis for the ruptured Stage IVA group was intermediate between the non-ruptured Stage IVA group and the non-ruptured IVB group (a significant difference between the latter two groups); and (4) the prognosis for the ruptured Stage IVB group was poorer than that for the non-ruptured IVB group ( $p = 0.081$ ). Thus, long-term prognosis was poor for ruptured HCC as compared to non-ruptured HCC, but tumor factors (excluding rupture factors) were shown to affect the long-term prognosis for ruptured HCC, as is the case with non-ruptured HCC, and long survival can be expected also in cases of ruptured HCC if the tumor stage (ignoring the rupture factors) is low. Furthermore, in analysis of the outcome of hepatectomy in ruptured HCC cases, the 3-/5-year survival rates were 48.6%/33.9%, higher than those after TACE (14.1%/6.0%). Taken together, these results indicate that ruptured HCC, having overcome the acute stage by means of TAE, etc., may be indicated for hepatectomy. However, care needs to be taken of Child-Pugh B cases<sup>19</sup>.

It is desirable to confine the indications for hepatectomy to patients with liver damage grade A or Child-Pugh A liver function. However, hepatectomy is sometimes needed also in cases with poor liver function because of difficulty in percutaneous therapy or TACE. In the past, there was no report of large-scale study on hepatectomy for Child-Pugh B cases. In 2020, however, the results of hepatectomy analyzed in 253 HCC cases at 9 facilities of Oriental countries and 5 facilities of Western countries were reported<sup>26</sup>. According to that report, 108 patients (42.7%) developed postoperative complications within 90 days of the operation and 11 patients (4.3%) died within 90 days, with the 5-year survival rate being as low as 47%. On the other hand, the incidence of complications was low in patients free of comorbidity and having undergone narrow hepatectomy with laparoscopic guide, and factors associated with favorable long-term prognosis of HCC were identified to be initial onset, solitary tumor and tumor size not exceeding 3 cm. Therefore, if indications of individual cases are judged appropriately, favorable prognosis by means of hepatectomy may be expected even in Child-Pugh B cases. However, since few studies have been published concerning hepatectomy for Child-Pugh B cases, no concrete statement of recommendation can be made in the current edition.

#### Voting results

- ◎ Regarding the statement of recommendation 1 “It is desirable to perform hepatectomy in patients with up to 3 tumors located solely in the liver, regardless of tumor size. Tumor invasion up to the first branches of the portal vein may be

an indication for surgery”, its adoption was strongly recommended by voting of committee members.

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

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

- ◎ Regarding the statement of recommendation 2 “Advanced age is not a limiting factor for hepatectomy”, its adoption was strongly recommended by voting of committee members.

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

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

- ◎ Regarding the statement of recommendation 3 “Ruptured HCC having overcome the acute stage may be indicated for hepatectomy”, its adoption was weakly recommended by voting of committee members.

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

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

#### ■ References

21) Liver Cancer Study Group of Japan (edt.). The General Rules for the Clinical and Pathological Study of Primary Liver Cancer, 6th Japanese edition, revised version, Tokyo, Kanehara-Shuppan, 2019, p26

CQ20 What tests effectively evaluate liver function prior to hepatectomy?

#### Recommendation

It is recommended that the indocyanine green retention rate at 15 minutes (ICGR15) be measured in addition to regular liver function tests. It is appropriate to decide the

indications for surgery based on the test results and estimated liver resection volume. (Strong Recommendation, Evidence Level B)

#### ■ Background

This CQ was established as a continuation of CQ21 “What tests effectively evaluate liver function prior to hepatectomy?” in the fourth edition, after a literature search for new indicators with high-quality evidence.

#### ■ Scientific Statement

A literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 162 articles. This was narrowed down to 6 in the first screening and to 3 in the second screening based on the inclusion criterion of studies showing the utility of assessing liver function prior to hepatectomy. A total of 26 articles, including the 23 articles in the fourth edition, are cited for CQ20.

The Child classification system\* and the modified version, the Child-Pugh classification system\*, are commonly used worldwide to classify hepatic functional reserve in the preoperative assessment of liver function. In particular, surgery is not indicated when ascites, which is an indicator for portal hypertension, is uncontrollable. In general, surgery is not indicated in patients with Child-Pugh B/C liver function in the United States or Europe. Even in patients with Child-Pugh A liver function, hepatectomy is contraindicated if portal hypertension is present. The criteria are described in the Clinical Practice Guidelines for Liver Cancer published in the United States and Europe<sup>1</sup>. Despite the criteria, portal hypertension was not considered a contraindication for hepatectomy involving 2 or more segments in a study conducted in Europe<sup>2</sup>. Similarly, a Japanese study showed that portal hypertension is not a contraindication for hepatectomy, because the risk of postoperative complications does not increase when relatively minimal hepatectomy is selected<sup>3</sup>.

The ICG test and hepatobiliary scintigraphy with technetium-99m galactosyl serum albumin (<sup>99m</sup>Tc-GSA) are the major quantification methods for assessing liver function prior to hepatectomy. Many studies have shown the ICG test is a useful predictive factor of postoperative mortality<sup>4,5</sup>. The ICGR15 is defined as a diagnostic factor for liver damage in the General Rules for the Clinical and Pathological Study of Primary Liver Cancer published by The Liver Cancer Study Group of Japan<sup>6</sup>, and the ICG test is a standard test for preoperative assessment of liver function.

Yamanaka et al. established eligibility criteria for surgery based on ICGR15, the extent

of hepatectomy, and age-based prediction scores for liver failure<sup>7</sup> and accurately predicted postoperative mortality<sup>8</sup>. Takasaki et al. also proposed novel criteria that set different maximum allowable resection volumes for different ICG rates<sup>9</sup>. They reported the incidence of postoperative liver failure and mortality after hepatectomy performed according to the criteria were 2% and 0%, respectively, but were 23% and 1% after hepatectomy performed without regard for the criteria, demonstrating the utility of the criteria<sup>10</sup>. Furthermore, criteria established by Makuuchi et al. and in common use in Japan clearly define the indications and contraindications for hepatectomy (determined based on ascites, total serum bilirubin values, and ICGR15) and acceptable resection volume<sup>11</sup>. Mortality was 0% when hepatectomy was performed in 1,056 patients in accordance with the criteria<sup>12</sup>.

Kokudo et al. reported the utility of the Albumin-Indocyanine Green Evaluation (ALICE) grade based on serum albumin values and ICGR15 in predicting the survival rate after hepatectomy and the onset of postoperative liver failure<sup>13</sup>. The ALICE grade is superior over the Child-Pugh classification system in terms of hepatectomy outcome predictability and, if combined with presence/absence of portal hypertension, may serve as a more useful means of liver function evaluation and classification<sup>14,15</sup>.

Previous studies have reported that hepatobiliary scintigraphy with <sup>99m</sup>Tc-GSA was superior to ICGR15 in the histological assessment of liver damage<sup>16</sup>, and hepatic functional reserve calculated based on hepatobiliary scintigraphy with <sup>99m</sup>Tc-GSA was a useful predictor of postoperative complications and surgery-related deaths in patients with background liver disease, compared with simple postoperative assessments<sup>17</sup>. However, hepatobiliary scintigraphy with <sup>99m</sup>Tc-GSA is not a popular assessment tool in many institutions because of limitations on the use of the radionuclide generator <sup>99m</sup>Tc.

The methods often used in studies to assess liver function before selecting surgery are routine clinical examination, hematological testing to calculate Child-Pugh scores, and the quantitative ICG test. When actually resecting the liver, it may be best to determine the indication for hepatectomy based on a balance between the area of hepatectomy (liver resection volume) and the severity of liver damage diagnosed based on findings from the above tests. Many studies have proposed criteria specifying the relationship between hepatic functional reserve and maximum allowable resection volume, especially those conducted in Japan.

\* The official name of the Child classification system is the Child-Turcotte classification system. The official name of the modified version by Pugh is the Child-Turcotte-Pugh (CTP) classification system. However, the “Child-Pugh classification system” is used in



the Guidelines to maintain consistency with the General Rules for the Clinical and Pathological Study of Primary Liver Cancer.

#### ■ Explanation

The utility of the galactose tolerance test, amino acid clearance test, and aminopyrine breath test was described up until the third edition but is not included in the fourth and current editions of the Guidelines because these tests are not usually used now.

Among other indicators, platelet count, a known indicator of portal hypertension, was shown to be a risk factor predicting postoperative complications, liver failure, and death<sup>18</sup>. Regardless of resection volume, platelet count effectively predicts postoperative liver failure. As shown by Tomimaru et al., platelet count is a better predictive factor than ICGR15, especially in small-scale liver resection (resection volume < 100 g)<sup>19</sup>.

Previous studies have reported that the preoperative measurement of hepatic venous pressure gradient (HVPG), i.e., the pressure gradient between the wedged hepatic venous pressure and free hepatic venous pressure is a useful, albeit invasive, predictor of postoperative liver failure<sup>20,21</sup>. However, in reality, hardly any medical institutions measure HVPG in the preoperative assessment of liver function.

Several recent studies measured liver stiffness before hepatectomy and investigated the relationship between liver stiffness and prognosis, mostly reporting that preoperative liver stiffness is a useful predictor of postoperative complications and liver failure<sup>22-24</sup>. Liver stiffness may be valuable in assessing preoperative liver function.

Because mortality from liver resection is  $\leq 3\%$  in Japan<sup>25,26</sup>, it is not realistic practically or ethically to evaluate and verify eligibility criteria from the perspective of liver function with postoperative mortality serving as an endpoint. Partly because of the difference in the number of deaths due to different hospital volumes, the in-hospital mortality rate is 1.55% in high-volume hospitals and as high as 4.04% in low-volume hospitals, which suggests that it is important to account for the institution's experience when determining the indication for surgery<sup>26</sup>.

Because the literature search did not extract any articles with high-quality evidence about novel indicators of liver function, the recommendation made in the fourth edition remains in use in the current Guidelines. At the Revision Committee, there was a debate over whether the ICGR15 is still the most common preoperative liver function test.

#### Voting results

- ◎ Regarding the statement of recommendation “It is recommended that the indocyanine green retention rate at 15 minutes (ICGR15) be measured in addition

to regular liver function tests. It is appropriate to decide the indications for surgery based on the test results and estimated liver resection volume”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
75.0% (15 members)	25.0% (5 members)	0% (0 members)	0% (0 members)

Total voters: 20 members (abstention because of COI: 1 member)

## ■ References

CQ21 What procedures are considered safe and reasonable for liver resection?

### Recommendation

Anatomical resection of a small area or partial hepatectomy as a cytoreductive surgery (especially in patients with poor liver function) is recommended for small HCCs ( $\leq 5$  cm), and extended resection involving 2 or more segments (including hemi-hepatectomy) is recommended for large HCCs. (Strong Recommendation, Evidence Level B)

## ■ Background

This CQ, similar to CQ22 in the fourth edition “What procedures are considered safe and reasonable for liver resection?”, has been adopted for the current edition through the steps including a literature search exploring new indicators with high-quality evidence.

## ■ Scientific Statement

A literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 661 articles. This was narrowed down to 13 articles in the first screening and to 5 articles in the second screening based on the following inclusion criteria: studies that showed the safety and rationale of surgical procedures and intraoperative maneuvers. A total of 30 articles, including 25 of the 26 articles in the fourth edition, are cited for CQ21.

Because many HCCs occur in association with chronic disease in the background liver, the maximum allowable volume of resection is often inevitably reduced, making it very difficult to perform extended hepatectomy. Because of this, partial liver resection (including tumor enucleation) was proposed for HCC resection<sup>1</sup>. Also, because liver

stiffness in patients with cirrhosis often makes identifying tumors on abdominal palpation difficult, a surgical procedure guided by intraoperative US was developed for hepatectomy that can identify the location of the tumors<sup>2</sup>.

HCC is known to spread to other areas of the liver via the portal vein. Therefore, in theory, to achieve a radical cure, it is desirable to dye the liver segments supplied by the corresponding branches of the portal vein and perform anatomical resection of HCC under US guidance<sup>3</sup>. When the injection of dye into the corresponding branches is prevented by pathological conditions such as AP shunt and portal vein tumor thrombus, the counterstaining method can be used to stain the area adjacent to the cancer so that the cancerous area can be identified and resected<sup>4</sup>. Methods known as the “Glissonean pedicle approach” have also been developed to perform anatomical resection of HCC after identifying and collectively handling the Glisson's sheath surrounding the portal vein, hepatic artery, and bile duct running through the area affected by cancer<sup>5,6</sup>.

Prognosis is thought to be better after anatomical resection than after non-anatomical resection, and this is supported by the findings of recent studies<sup>7-14</sup>. However, other studies have shown no significant difference in cumulative survival rates and recurrence-free survival rates when anatomical and non-anatomical resections were compared in 2 groups of patients matched by propensity score<sup>15-17</sup>. The prognosis after non-anatomical resection was more favorable in cases where the surgical margin was negative (surgical margin > 0 mm)<sup>18</sup>. Therefore, the difference in prognosis depending on operative procedure or resection stump is not mentioned in the current Guidelines.

#### ■ Explanation

Surgical procedures for resecting the liver vary widely compared with those for resecting other organs. In the liver, the procedure depends on which liver segments are to be resected and how large the resection area will be. Liver resection often requires sophisticated techniques such as intraoperative US-guided resection, where US is used to guide the resection procedure without actually looking at the structures within the liver parenchyma. Nonetheless, the surgical techniques appear to be fully established given that hepatectomy-related mortality and intraoperative blood loss have decreased dramatically over the last 20-30 years.

Two hepatectomy procedures have been developed to spare the liver parenchyma as much as possible. One entails resecting the root of the right hepatic vein, if the inferior right hepatic vein (the branch of the hepatic vein in S6 that directly flows into the inferior vena cava) is present, thereby preserving this segment<sup>19</sup>. The other involves resecting S3/4 while preserving S2<sup>20</sup>.

Conventionally, extended hepatectomy is performed for tumors in the caudate lobe located on the dorsal side of the hilar plate, thereby simultaneously resecting the liver parenchyma on the ventral side as a rule. However, extended hepatectomy is contraindicated for most patients with HCC because of liver damage. These patients undergo high dorsal resection, in conjunction with the counterstaining method, to identify and resect only the caudate lobe from the dorsal side<sup>21,22</sup>, or the anterior transhepatic approach is used to excise only the caudal lobe after transecting the liver from the anterior side along with the middle hepatic vein<sup>23</sup>.

The right hemi-liver is generally resected after mobilization of the liver, but large tumors often make hepatic mobilization difficult. In such cases, right hepatectomy via the anterior (ventral) approach (without prior mobilization) produces better short- and long-term outcomes than right hepatectomy via the conventional approach (with prior mobilization)<sup>24,25</sup>. Also, it is difficult to manage bleeding from the hepatic vein located deep inside the liver. In such cases, hepatectomy is performed while lifting the liver with a tape placed in the space between the posterior aspect of the liver and the inferior vena cava<sup>26</sup>. This procedure has recently become more common, but in one study it was combined with the anterior approach to improve the efficacy of right hepatectomy<sup>27</sup>.

HCC often causes tumor thrombosis in the major branches of the portal vein during its clinical course. In patients with HCC accompanied by tumor thrombus, HCC is resected along with the portal vein containing the tumor thrombus and the liver segment supplied by the corresponding portal vein, thus requiring extended hepatectomy or total hepatectomy (theoretically)<sup>28,29</sup>, but both are difficult to perform in patients with liver damage. In a special hepatectomy procedure developed as an alternative, only the tumor thrombus from the interior wall of the portal vein is excised. The long-term outcome was comparable to the outcome of the conventional procedure, demonstrating efficacy<sup>30</sup>.

A literature search was conducted to gain new insights into safe and practical surgical procedures, but it did not extract articles with high-quality evidence. Therefore, the current edition of the Guidelines uses, with no modification, the corresponding CQ and recommendation in the fourth edition. In patients with HCC, the clinical significance of extended resection is low, and when curative resection is possible in terms of liver function and tumor size, minimal resection is more practical in actual clinical settings. Voting at the Revision Committee was made on the basis of this view.

#### Voting results

- ◎ Regarding the statement of recommendation “Anatomical resection of a small area or partial hepatectomy as a cytoreductive surgery (especially in patients with

poor liver function) is recommended for small HCCs ( $\leq 5$  cm), and extended resection involving 2 or more segments (including hemi-hepatectomy) is recommended for large HCCs”, its adoption was strongly recommended by voting of committee members.

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

Total voters: 23 members (abstention because of COI: 2 members)

## ■ References

CQ22 What are the indications for laparoscopic hepatectomy?

### Recommendation

1. Solitary HCC measuring  $\leq 5$  cm at the periphery of the anterior section (S2, 3, 4, 5, 6), where it is possible to perform partial hepatectomy and lateral segmentectomy, is a good indication for laparoscopic hepatectomy. (Strong Recommendation, Evidence Level B)
2. The indication in highly difficult cases should be judged with consideration of difficulty in operation, institution’s experience, etc. (Strong Recommendation, Evidence Level B)

## ■ Background

In April 2010, the coverage of laparoscopic hepatectomy by the National Health Insurance system in Japan was approved for partial hepatectomy and lateral segmentectomy. In April 2016, all procedures of laparoscopic hepatectomy without being accompanied by revascularization or biliary tract reconstruction began to be covered by the same system. According to the prospective registry of the Endoscopic Liver Surgery Study Group (October 2015 to December 2017), the in-hospital mortality following extended hepatectomy under laparoscopic guide was low, 0.22% (2/891) at 30 days and 0.67% (6/891) at 90 days. Evidence for diverse procedures of laparoscopic hepatectomy has been reported to date. The current Guidelines thus revise the previous recommendation about indications for laparoscopic hepatectomy.

## ■ Scientific Statement

Of the 263 articles about laparoscopic hepatectomy published between July 1, 2016 and

January 31, 2020 identified by the literature search, 13 were extracted in the first screening. From these articles, 9 articles with high-quality evidence for the recently increasing extended hepatectomy, re-hepatectomy, etc. were extracted in the second screening. These 9 articles plus 12 clinically important articles adopted in the preceding revision and 1 article extracted by means of hand search (22 articles in total) are quoted in the current edition.

Compared with open hepatectomy, laparoscopic hepatectomy provides a magnifying effect and decreases bleeding from the hepatic vein thanks to the intra-abdominal pressure used for abdominal insufflation, thereby suppressing intraoperative blood loss<sup>1-3</sup>. In addition, laparoscopic hepatectomy for HCC, which is often associated with chronic liver disease such as cirrhosis, has been reported to result in less intraoperative blood loss, less need of blood transfusion, less frequent postoperative complications such as ascites, and earlier discharge from the hospital compared with open hepatectomy<sup>4-7</sup>. While the long-term prognosis of patients with HCC is often comparable between laparoscopic and open hepatectomy<sup>8-11</sup>, laparoscopic hepatectomy is superior to RFA as a locoregional therapy for small superficial HCCs<sup>12</sup>. In recent years, reports have been increasing about laparoscope-guided procedures for major hepatectomy<sup>13,14</sup>, re-hepatectomy<sup>15,16</sup> and resection of giant liver cancer<sup>17</sup>, all revealing less intraoperative blood loss, less frequent postoperative complications and earlier discharge from hospital with laparoscopic hepatectomy than with open hepatectomy. Meanwhile, there is a report that the technical difficulty of these procedures of laparoscopic hepatectomy determines the intraoperative parameters (conversion, operation time, volume of blood loss) and postoperative outcomes (severe complication, in-hospital mortality)<sup>18</sup>. Also in the analysis of the data from the National Clinical Database (BCD) Registry (2011-2017), laparoscopic hepatectomy has been spreading definitely, with the number of institutions applying this procedure to more than 10 cases per year having increased from 54 (2011) to 255 (2017) and the number of institutions applying it to more than 50 cases per year having increased from 1 (2011) to 14 (2017). The in-hospital mortality following segmentectomy or more difficult procedures under laparoscopic guide decreased from 3.6% in 2011 to 1.0% in 2017, although only a limited number of institutions applied these procedures frequently<sup>19</sup>.

#### ■ Explanation

Since first reported by Reich et al. in 1991 laparoscopic hepatectomy is now widely performed in the world under the influence from advances in surgical devices. In Japan, laparoscopic hepatectomy was authorized as an advanced medical treatment under the National Health Insurance (NHI) system in 2005. The NHI system began to cover partial

hepatectomy and lateral segmentectomy in 2010 and all procedures of laparoscopic hepatectomy not accompanied by revascularization or biliary tract reconstruction in 2016. However, laparoscopic hepatectomy is not a fully established surgical technique, especially when performed in extensive resection, and its risks cannot be fully ruled out. Although the in-hospital mortality following partial hepatectomy, lateral segmentectomy and subsegmental hepatectomy under laparoscopic guide is as low as 0.5% and the in-hospital mortality following segmental or more extensive hepatectomy under laparoscopic guide also decreased from 3.6% in 2011 to 1.0% in 2017, the number of institutions positively applying the laparoscopic procedure for segmental or more extensive hepatectomy is limited<sup>19</sup>. Therefore, only institutions having medical teams with sufficient experience in open hepatectomy and advanced endoscopic procedures should perform laparoscopic hepatectomy. The indications of laparoscopic procedure for partial hepatectomy or hepatectomy more extensive than lateral segmentectomy should be expanded with consideration of preoperative difficulty assesment<sup>20</sup>, etc. on the basis of sufficient experience with laparoscopic hepatectomy and the learning curve<sup>21,22</sup>. With these borne in mind, the Revision Committee has decided to strongly recommend that laparoscopic hepatectomy (partial hepatectomy and lateral segmentectomy) is indicated well for solitary HCC  $\leq 5$  cm located in the periphery of the anterior section (S2, 3, 4, 5, 6) and that the indication of highly difficult cases for laparoscopic hepatectomy be judged with consideration of technical difficulty, institution’s experience (case volume), etc. Surgeons planning to perform laparoscopic hepatectomy are required to register preoperatively with the National Clinical Database.

#### Voting results

- ◎ Regarding the statement of recommendation 1 “Solitary HCC measuring  $\leq 5$  cm at the periphery of the anterior section (S2, 3, 4, 5, 6), where it is possible to perform partial hepatectomy and lateral segmentectomy, is a good indication for laparoscopic hepatectomy”, its adoption was strongly recommended by voting of committee members.

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

Total voters: 18 members (abstention because of COI: 2 members)

- ◎ Regarding the statement of recommendation 2 “The indication in highly difficult

cases should be judged with consideration of difficulty in operation, institution’s experience, etc.”, its adoption was strongly recommended by voting of committee members.

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

Total voters: 18 members (abstention because of COI: 2 members)

■ References

CQ23 What procedures are considered safe for hepatectomy?

Recommendation

1. Hepatic vascular occlusion minimizes blood loss during hepatectomy. (Strong Recommendation, Evidence Level B)
2. Lowering of the central venous pressure (CVP) minimizes blood loss during hepatectomy. (Strong Recommendation, Evidence Level A)
3. Hanging maneuver minimizes blood loss during open hemi-hepatectomy. (Weak Recommendation, Evidence Level A)

■ Background

In the preceding edition, the CQ “Does hepatic vascular occlusion or lowering of the central venous pressure reduce blood loss during hepatectomy?” concerned only the suppression of blood loss. The recommendation based on such a CQ stated that hepatic vascular occlusion and lowering of the CVP minimize blood loss during hepatectomy. During the current revision, the statements about the operative procedure for hepatectomy were modified extensively, and the above-cited CQ has been changed into “What procedures are considered safe for hepatectomy?”.

■ Scientific Statement

A literature search conducted with a publication date between January 1, 2000 and January 31, 2020 extracted 541 articles. This was narrowed down to 34 in the first screening, from which 6 articles with high-quality evidence and clinical importance were extracted in the second screening. A total of 18 articles, including 10 articles with high-



quality evidence from the fourth edition and 2 additional articles extracted by hand search for explanation about the hanging maneuver, are cited in the current edition.

An RCT on hepatic vascular occlusion showed that intermittent hepatic vascular occlusion, known as the Pringle maneuver, reduced blood loss in hepatectomy without affecting liver function<sup>1,2</sup>. Other studies also reported the efficacy of hemi-hepatic vascular occlusion<sup>3,4</sup> and no difference in adverse effects of the Pringle maneuver on liver function between the maneuver lasting for 15 minutes and that lasting for 30 minutes, when used in combination with protease inhibitors<sup>5</sup>. Following recent advances in operative procedures and devices, it has also been reported that the intraoperative blood loss does not differ between the procedure using the Pringle maneuver and the procedure without it<sup>6</sup>.

Also, several meta-analyses, including RCTs, have reported that blood loss is minimized when the central venous pressure is lowered by clamping the inferior vena cava (IVC) below the liver or administering drugs during hepatectomy<sup>7-9</sup>. The optimum range of central venous pressure was 2.1-3 mmHg<sup>10</sup>, and clamping of the IVC was more effective than drug-induced lowering of the central venous pressure<sup>11</sup>. However, lowering central venous pressure does not always reduce blood loss<sup>12</sup>. Also, caution must be exercised when clamping the IVC because of the possibility of pulmonary embolism.

The hanging maneuver, by which the liver is hung by a tape applied onto the anterior plane of inferior vena cava during hepatectomy, has been often used for resection of giant tumors, hemi-hepatectomy, etc.<sup>13</sup>. The current meta-analysis (15 articles: open hemi-hepatectomy, 1 article: open caudate lobectomy) identified an article reporting reduction of the operation time, the volume blood loss and the incidence of postoperative complications with this maneuver<sup>14</sup>.

#### ■ Explanation

The Pringle maneuver is commonly used to minimize blood loss during hepatectomy, and its safety has been verified. Because of the substantial reduction in blood loss achieved in recent years due to advances in surgical skills and devices, the volume of intraoperative blood loss did not differ depending on application of the Pringle maneuver, and some reports were not in favor of routinely using the Pringle maneuver<sup>6</sup>. However, because these reports suggesting that the Pringle maneuver is thus not indispensable for hepatectomy lacked evidence for the safety and utility of this maneuver, the Revision Committee has decided to recommend it for hepatic vascular occlusion as strongly as before. Hemi-hepatic vascular occlusion is also recommended for unilateral hepatectomy. In hepatectomy with the Pringle maneuver, bleeding mostly originates from the hepatic

veins. For this reason, lowering the central venous pressure has been shown to be useful in minimizing the blood loss as well as the risk of requiring blood transfusion, without greatly affecting postoperative liver function or short-term prognosis. Therefore, based on these reports, the Revision Committee strongly recommends lowering the central venous pressure. However, because no previous studies have reported long-term outcomes of the procedure, further study is needed to determine the indications of CVP lowering based on the site of hepatectomy and other factors.

The hanging maneuver is a technique employed during hepatectomy reported in 2001 by Belghiti et al.<sup>13</sup>. With this technique, the right lobe is not mobilized during right hepatectomy for treatment of a giant tumor having invaded the diaphragm. Instead, a tape is passed from the anterior plane of inferior vena cava below the liver into the middle and right hepatic vein entry points. The tape thus exposed on the liver surface is lifted during hepatectomy. After arrival at the inferior vena cava, manipulation is made on the right hepatic vein and the short hepatic vein, followed by dissection between the right hepatic lobe parenchyma and the coronary and right triangular ligaments. This maneuver is aimed at minimizing the risk for injury of vessels near the tumor. This maneuver has spread for use during donor right hepatectomy or resection of giant HCC. A recent meta-analysis<sup>14</sup> covered 2 RCTs and 14 retrospective studies (evidence level 1b in 2 articles, 2a in 5 articles, 2b in 8 articles and 3a in 1 article). The Revision Committee has decided to recommend this maneuver weakly because some articles included cases of metastatic liver cancer and donor surgery although the evidence level was high on the whole. Also concerning this maneuver during laparoscopic hepatectomy, one systematic review was extracted<sup>15</sup>, but its sample size was small and no control group (without hanging maneuver) had been incorporated, thus making sufficient evaluation difficult. For this reason, the current edition recommends this maneuver only for open hemi-hepatectomy. There is an RCT reporting that the blood loss during hepatectomy in cases of liver tumors located at the hepatic vein junction or having invaded the hepatic vein was smaller with the Pringle maneuver + hepatic vein occlusion than with the Pringle maneuver alone (80 cases vs. 80 cases)<sup>16</sup>. Further discussion is needed about the indications for this procedure. Another RCT<sup>17</sup> demonstrated absence of utility in the bile leak test designed to check for bile leakage by injection a dye through a catheter inserted from the cystic duct to the common bile duct after hepatectomy for the purpose of preventing postoperative bile leakage. However, it cannot be ruled out that the study included some cases of bile leakage due to bile duct division having no communication with the common bile duct. In 21 (41%) of the 51 cases having received this test, the bile leakage was repaired soon after detection by the test and only 3 cases (6%) had postoperative bile leakage. Meanwhile,

there is a prospective observational study<sup>18</sup> demonstrating that the number of cases with postoperative bile leakage decreased to 10 cases as a result of repair (+ decompression tube insertion) of the bile leakage detected by the bile leak test in 42 cases during central hepatectomy with a high risk for bile leakage (resection of central two segments, anterior segments, medial segments or the like). This suggests that there are cases where postoperative bile leakage can be prevented by the bile leak test and the countermeasures based on the test findings. Although the bile leak test deserves to be tried during operative procedures causing the hepatic hilus to be exposed, care is needed about its ineffectiveness as a means of detecting bile leakage without communication with the common bile duct.

#### Voting results

- ◎ Regarding the statement of recommendation 1 “Hepatic vascular occlusion minimizes blood loss during hepatectomy”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
95.0% (19 members)	5.0% (1 member)	0% (0 members)	0% (0 members)

Total voters: 20 members (abstention because of COI: 1 member)

- ◎ Regarding the statement of recommendation 2 “Lowering of the central venous pressure (CVP) minimizes blood loss during hepatectomy”, its adoption was strongly recommended by voting of committee members.

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

Total voters: 20 members (abstention because of COI: 1 member)

- ◎ Regarding the statement of recommendation 3 “Hanging maneuver minimizes blood loss during open hemi-hepatectomy”, its adoption was weakly recommended by voting of committee members.

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

	members)		
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Total voters: 20 members (abstention because of COI: 1 member)

## ■ References

CQ24 What are useful in perioperative management for hepatectomy?

### Recommendation

1. Whether or not to perform abdominal drainage for elective hepatectomy is decided with consideration of the risk factors such as hemorrhage and bile leakage. (Strong Recommendation, Evidence Level A)
2. Prophylactic use of antimicrobial agents for prevention of surgical site infection after hepatectomy is recommended to be continued until 24 hours after surgery. (Strong Recommendation, Evidence Level A)

## ■ Background

The CQ “Is routine abdominal drainage necessary after hepatectomy?” in the fourth and earlier editions has been replaced in the current edition with a CQ concerning not only abdominal drainage but also methods useful for perioperative management.

## ■ Scientific Statement

A literature search conducted with a publication date between January 1, 2000 and January 31, 2020 extracted 624 articles. This was narrowed down to 16 in the first screening, from which 10 articles including perioperative management and influences on postoperative complications with high-quality evidence and clinical importance were extracted in the second screening. A total of 23 articles, including 12 articles from the fourth edition with high-quality evidence and 1 hand-searched article, are cited for CQ24. An RCT that evaluated the utility of abdominal drains after elective hepatectomy showed that routine drain placement is unnecessary or contraindicated. This is largely because drain placement increases the incidence of drain- and surgical wound-related complications, sepsis, or fluid retention caused by infection, which significantly extends hospital stay<sup>1-4</sup>. In contrast, a study that involved patients with HCC associated with cirrhosis and portal hypertension showed that abdominal drain placement decreases the incidence of postoperative complications related to ascites and shortens hospital stay, and thus recommends abdominal drainage<sup>5</sup>. It has also been reported that abdominal drain

placement should be avoided unless the risk for hemorrhage or bile leakage is high<sup>6</sup>. Some investigators reported a case without drain placement having developed delayed bile leakage, having the potential of following a serious course<sup>7</sup>. Other studies have also reported the clinical utility of drain placement in the treatment of bile leakage and intraperitoneal fluid pooling<sup>8,9</sup>, the possible prediction of bile leakage by monitoring bilirubin levels in drain effluent<sup>9,10</sup>, and the recommended use of drains only in patients at high risk of bile leakage, such as patients undergoing biliary tract reconstruction and those with exposed major Glisson's sheath or with intraoperative detection of bile leakage<sup>11</sup>. On the other hand, abdominal drainage is reported not to be essential in hepatectomy for living donor liver transplantation<sup>12</sup>.

Regarding the duration of prophylactic use of antimicrobial agents for prevention of surgical site infection (SSI), no difference in the incidence of SSI was noted in an RCT comparing the group treated before and during surgery (without postoperative treatment) with the group treated from a preoperative day to the third postoperative day or in another RCT comparing the group treated from a preoperative hour to the sixth postoperative hour (one-day treatment) with the group treated from a preoperative day to the second postoperative day (3-day treatment)<sup>13,14</sup>. When these comparisons were made also in patients undergoing open hepatectomy and those receiving laparoscopic hepatectomy, there was no difference in the incidence of SSI or distant site infection depending on the duration of prophylactic medication, allowing a statement that the optimal duration of prophylactic use of antimicrobial agents is up to 24 hours<sup>15</sup>.

#### ■ Explanation

Unlike surgery on other intraperitoneal organs, hepatectomy is often performed on cases complicated by chronic liver disease, thus requiring adequate care of hemorrhage, bile leakage and intractable ascites. RCTs have been conducted since the 1990s to examine the appropriateness of drainage for elective hepatectomy, but when interpreting the results from those studies, it is essential to consider the extent of accompanying liver disease and the procedure used for resection because some of these RCTs involved problems with adequacy of sample size and evaluation methods. More carefulness is required for donor surgery which is performed on healthy individuals serving as the living donors for liver transplantation. Appropriateness of drainage needs to be discussed also for laparoscopic hepatectomy which has been performed on an increasing number of patients recently. With these borne in mind, the current edition strongly recommends that a decision as to abdominal drainage for elective hepatectomy be made with consideration of the risk factors such as hemorrhage and bile leakage.

The Guidelines for the Prevention of Surgical Site Infection published by the Centers for Disease Control and Prevention (CDC) in the United States recommends, if necessary, using closed suction drains and removing them as early as possible<sup>16</sup>. Regarding the timing for drain withdrawal, there are reports stating that withdrawal is desirable within 2 or 3 days of surgery unless any problem is found in the property of drain effluent, etc.<sup>9,17,18</sup>.

In an RCT on prophylactic use of antimicrobial agents, the incidence of SSI was 7.5% vs. 13.8% ( $p = 0.235$ ) and that of distant site infection was 2.1% vs. 8.5% ( $p = 0.100$ ) when the group treated with flomoxef 1 g before and during surgery (without postoperative treatment;  $n = 95$ ) was compared with the group treated with the same drug from a preoperative day to the third postoperative day ( $n = 95$ )<sup>13</sup>. In another study (non-inferiority study) comparing the group treated with flomoxef 1 g until 6 hours after surgery (one-day treatment,  $n = 232$ ) with the group treated with the same drug until 6 hours plus 2 days after surgery (3-day treatment,  $n = 235$ ), the incidence of SSI was 9.5% vs. 9.8% (non-inferiority  $p = 0.001$ ) and the incidence of distant site infection was 6.9% vs. 9.4% (non-inferiority  $p < 0.001$ )<sup>14</sup>. There was no difference in the incidence of SSI or distant site infection also in a retrospective study by means of trend score matching for comparison and evaluation of the group treated until the 24th postoperative hour and the group treated until the third postoperative day subdivided by the approach (open or laparoscopic)<sup>15</sup>. On the basis of these results, the current edition strongly recommends continuation of prophylactic use of antimicrobial agents for prevention of surgical site infection until 24 hours after hepatectomy.

The ERAS (enhanced recovery after surgery) was recently introduced for patients undergoing hepatectomy, and success in achieving early recovery after surgery as well as reduction in the incidence of complications has been shown by RCTs and meta-analyses<sup>19-22</sup>. In this connection, pain control is a critical factor, and there is a report showing non-inferiority of IV-PCA (intravenous patient-controlled analgesia) to epidural anesthesia<sup>23</sup>. ERAS can reduce medical expenses and is expected to spread from now on also in Japan, but the current edition does not adopt it as a recommendation because linkage and cooperation to/of anesthesiologists and affiliated healthcare professionals are needed for implementation of ERA and because the design of ERAS varies among institutions at present.

#### Voting results

- ◎ Regarding the statement of recommendation 1 “Whether or not to perform abdominal drainage for elective hepatectomy is decided with consideration of the

risk factors such as hemorrhage and bile leakage”, its adoption was strongly recommended by voting of committee members.

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

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

© Regarding the statement of recommendation 2 “Prophylactic use of antimicrobial agents for prevention of surgical site infection after hepatectomy is recommended to be continued until 24 hours after surgery”, its adoption was strongly recommended by voting of committee members.

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

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

## ■ References

CQ25 Is preoperative therapy useful in hepatectomy?

### Recommendations

Preoperative therapy aimed at improving the prognosis of HCC is not recommended. (Weak Recommendation, Evidence Level C)

## ■ Background

CQ28 “Is neoadjuvant therapy necessary in hepatectomy?” in the fourth edition has been changed into this CQ. The fourth edition did not recommend any preoperative adjuvant chemotherapy aimed at improving the prognosis after hepatectomy.

## ■ Scientific Statement

A literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 262 articles. This was narrowed down to 4 in the first screening, from which 1 article was extracted in the

second screening based on the criterion of studies that reviewed the utility of neoadjuvant therapy for hepatectomy. A total of 17 articles, including the 16 from the fourth edition, are cited for CQ25 in the current edition.

Very few studies that evaluated the efficacy of systemic chemotherapy as neoadjuvant therapy have provided high-quality evidence. The resection rate after single TACE or TAE improves when either procedure is performed as neoadjuvant chemotherapy for advanced HCC, because TACE or TAE leads to tumor necrosis and shrinkage, without severely affecting liver function or precipitating many complications. However, no consensus has been reached on whether TACE or TAE has a beneficial effect on prognosis (References 1-4, beneficial; References 5-15, not beneficial)<sup>1-15</sup>. It is also unclear whether preoperative TAI effectively suppresses recurrence and improves survival<sup>16</sup>.

Also, Li et al. investigated the efficacy of preoperative radiation therapy in patients with HCC and tumor thrombus in the main portal vein and found that preoperative radiation therapy decreased the incidence of recurrence and the number of HCC-related deaths after hepatectomy. This suggests the utility of radiation therapy + hepatectomy in patients with advanced HCC and portal vein tumor thrombus<sup>17</sup>.

■ Explanation

Most studies that reported utility of TACE/TAE as neoadjuvant chemotherapy were published in or around the early 2000s, and only a few offered high-quality evidence. Reports providing negative views about the effectiveness of TACE/TAE include those based on RCTs and meta-analyses offering the evidence in and after 2000. Although there is no consensus over the utility of TACE or TAE, neither is recommended as neoadjuvant chemotherapy here.

Voting results

- ◎ Regarding the statement of recommendation “Preoperative therapy aimed at improving the prognosis of HCC is not recommended”, its adoption was weakly recommended by voting of committee members.

Such therapy is strongly recommended	Such therapy is weakly recommended	The statement is weakly recommended	The statement is strongly recommended
0% (0 members)	0% (0 members)	100% (24 members)	0% (0 members)

Total voters: 24 members

■ References



CQ26 What are the eligibility criteria for liver transplantation in patients with HCC?

#### Recommendation

Hepatectomy is considered for HCC within the Milan criteria accompanied by decompensated cirrhosis or HCC outside Milan criteria but up to 5 HCCs  $\leq$  5 cm and alpha-fetoprotein (AFT) 500 ng/mL (5-5-500 rule). (Strong Recommendation, Evidence Level B)

#### ■ Background

Theoretically, liver transplantation is an excellent treatment modality for patients with HCC and cirrhosis because it simultaneously eliminates HCC and cirrhosis, a major cause of HCC. However, historically, HCC was excluded from the indications for liver transplantation because of frequent recurrence and poor prognosis after transplantation. In 1996, Mazzaferro et al. demonstrated improved outcomes of liver transplantation in patients with HCC comparable to those observed in patients without HCC, achieved using criteria they developed based on the relationship between size and number of tumors seen on preoperative imaging: a solitary tumor  $\leq$  5 cm or up to 3 tumors  $\leq$  3 cm without vascular invasion or extrahepatic metastasis<sup>1</sup>. Today, these so-called Milan criteria are the accepted gold standard for liver transplantation in patients with HCC. In Japan, the National Health Insurance system covers liver transplantation only for those patients with HCC within the Milan criteria and decompensated cirrhosis. The clinical significance of the Milan criteria is that the biological malignancy of HCCs is analogized through the evaluation of simple elements, namely, the size and number of HCC. However, whether these criteria developed in the 1990s should continue to be used today in the face of technological advances in diagnostic imaging modalities and contrast agents for liver lesions, whether the Milan criteria, which are designed to be used for brain-dead donor liver transplantation, can be applied, and whether the addition of other factors would provide eligibility criteria with greater prognostic accuracy are the questions that need to be addressed. To this end, studies are currently underway to establish novel eligibility criteria for liver transplantation in patients with HCC.

#### ■ Scientific Statement

A literature search conducted with the existing search query and a publication date between July 1, 2016 and January 31, 2020 extracted 646 articles. This was narrowed

down to 11 articles in the first screening by extracting studies that included preoperatively assessed factors in the criteria for liver transplantation and studies that reported outcomes relative to those based on the Milan criteria. This was further reduced to 3 articles in the second screening. After selecting 15 articles from the 17 articles used in the 2017 revised version (revised version of the fourth edition), a total of 17 articles are cited for CQ26 (one article overlapping with the revised fourth edition).

As with the Milan criteria, many criteria for liver transplantation are based on tumor size and number and have outcomes comparable to those using the Milan criteria: the University of California San Francisco (UCSF) criteria (solitary tumor  $\leq 6.5$  cm or up to 3 tumors  $\leq 3$  cm each and  $\leq 8$  cm in total)<sup>2</sup>; the Tokyo criteria (up to 5 tumors  $\leq 5$  cm each)<sup>3</sup>; the up-to-seven criteria (up to 7 tumors  $\leq 7$  cm each)<sup>4</sup>; and an expansion of the Milan criteria that consists of a solitary tumor  $\leq 6$  cm or up to 3 tumors  $\leq 5$  cm each and  $\leq 9$  cm in total<sup>5</sup>. Besides tumor size and number, serum AFP and PIVKA-II values are also predictors of post-transplantation prognosis<sup>6-10</sup>. Accordingly, novel eligibility criteria for liver transplantation have been established by combining tumor size and number with AFP or PIVKA-II values. Many reports are available particularly on the eligibility criteria incorporating AFP, primarily from overseas, demonstrating higher capabilities of predicting the transplantation outcome as compared to the Milan criteria<sup>11-16</sup>. In a study of HCC patients having undergone living donor liver transplantation in Japan, reported in 2019, application of the eligibility criteria consisting of absence of distant metastasis and vascular invasion, up to 5 tumors  $\leq 5$  cm each and AFP  $\leq 500$  ng/mL (5-5-500 rule) allowed maximization of eligible patients while preserving low recurrence rate and high survival rate comparable to those with the Milan criteria<sup>17</sup>.

#### ■ Explanation

The factor that most influences prognosis after liver transplantation for HCC is recurrence. Therefore, it is necessary to exclude patients at high risk of recurrence in the indications for liver transplantation. The clinical significance of the Milan criteria, the current gold standard, is that they ensure good liver transplantation outcomes by selecting patients with a certain size and number of HCCs more amenable to the procedure. However, the application of the criteria established 20 years ago to today's diagnostic imaging may result in excluding patients who are actually eligible for liver transplantation. For this reason, several studies have reported expansion of the Milan criteria in terms of the size and number of tumors, generating outcomes comparable to those of liver transplantation performed according to the original criteria. Together, the findings of these studies suggest that moderate expansion of the Milan criteria (a solitary HCC  $\leq 5$  cm or up to 3

HCCs  $\leq 3$  cm) does not make a significant difference to liver transplantation outcomes. However, no consensus has been reached in terms of how far tumor size and number can be expanded. On the contrary, the utility of the Milan criteria has been confirmed because of good transplantation outcomes in many studies that used the criteria as controls. From these findings, it is recommended that tumor size and number specified in the Milan serve as the eligibility criteria for liver transplantation for now.

Many studies have reported preoperative AFP and PIVKA-II values as prognostic factors in liver transplantation. Therefore, by combining these tumor markers with tumor size and number, studies that are currently underway are seeking to establish novel eligibility criteria with greater accuracy. In particular, several studies including prospective studies reported that AFP values combined with tumor size and number improved prognostic accuracy over that with the Milan criteria, although the utility has yet to be verified. It should be noted that these studies used various methods to determine the AFP cutoff value, and there is no consensus about standard cutoff values. As for PIVKA-II values, most reports are from Japan presumably because PIVKA-II measurement is not common in the United States and Europe. Consequently, there are slightly less reports on PIVKA-II than on AFP. Based on these findings, the Revision Committee has decided that it is premature to include AFP and PIVKA-II in the current Guidelines even though the addition of AFP and PIVKA-II can improve the accuracy of eligibility criteria for liver transplantation. However, the Japanese Liver Transplantation Society carried out a study of 965 HCC patients having undergone living donor liver transplantation in Japan, exploring criteria which could maximize the number of eligible patients while assuring the 5-year recurrence rate  $< 10\%$  and the 5-year survival rate  $\geq 70\%$  achieved with the Milan criteria<sup>1</sup>. On the basis of the results from that study, the 5-5-500 rule (absence of distant metastasis and vascular invasion, up to 5 tumors  $\leq 5$  cm each and AFP  $\leq 500$  ng/mL) was proposed<sup>17</sup>. During that study, adoption of PIVKA-II was also considered, but AFP was finally adopted instead of PIVKA-II because the number of eligible patients was increased by its adoption. There are a small number of patients who satisfy the Milan criteria but do not satisfy the 5-5-500 rule. Because excluding these patients from the indications is not realistic, patients either satisfying the Milan criteria or the 5-5-500 rule were deemed eligible. This set of criteria was added to the recipient selection criteria for brain-dead donor liver transplantation.

In the United States and Europe, the indications for liver transplantation in patients with HCC are decided based on the disease stage regardless of the pathological condition of the background liver. In Japan, despite the frequent use of locoregional treatments such as hepatectomy, percutaneous ablation, and embolization for HCC, the number of brain-

dead donors remains low and liver transplantation is performed using living donors. When this clinical reality in Japan is taken into consideration, it makes sense to define patients with decompensated cirrhosis for whom liver transplantation is the only valid treatment choice as eligible for liver transplantation. Accordingly, decompensated cirrhosis is incorporated into the recommendation in the current edition, as in the revised fourth edition.

#### Voting results

- ◎ Regarding the statement of recommendation “Hepatectomy is considered for HCC within the Milan criteria accompanied by decompensated cirrhosis or HCC outside Milan criteria but up to 5 HCCs  $\leq$  5 cm and alpha-fetoprotein (AFT) 500 ng/mL (5-5-500 rule)”, its adoption was strongly recommended by voting of committee members.

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

Total voters: 24 members (abstention because of COI: 1 member)

#### ■ References

CQ27 Does treatment of HCC prior to liver transplantation improve prognosis after transplantation?

#### Recommendation

No prior treatment is recommended for HCC planned for liver transplantation. (Weak Recommendation, Evidence Level C)

#### ■ Background

Applying some treatment other than transplantation to HCC before liver transplantation is expected to manifest two effects (suppressing the dropout from the waiting list due to tumor progression and lowering of the post-transplant recurrence rate), possibly leading to better prognosis. Furthermore, the indications for liver transplantation could be expanded if it is possible to obtain comparable transplantation outcomes after HCC is downstaged to the point where transplantation is normally indicated, by first using other

methods to treat HCC that is beyond the eligibility criteria.

#### ■ Scientific Statement

A literature search conducted with the existing search query and a publication date between July 1, 2016 and January 31, 2020 extracted 240 articles. This was narrowed down to 7 in the first screening and then to 1 in the second screening. This article and 2 articles from the fourth edition (3 articles in total) are cited for CQ27 in the current edition. Reports have been made about multiple attempts of applying pre-transplant treatment (e.g., puncture-based locoregional therapy and TACE/TAE) to HCC at eligible stages, but there is no report with high-quality evidence having succeeded in demonstrating a lower waiting list dropout rate or post-transplant recurrence rate as compared to patients without pre-transplant treatment. Meanwhile, Yao et al. conducted a study designed to prospectively evaluate downstaging of HCC at stages beyond the eligible range<sup>1,2</sup>, reporting that HCCs were downstaged to within the Milan criteria in 65.3% of patients with a solitary nodule  $\leq 8$  cm, 2-3 nodules  $\leq 5$  cm each, or 4-5 nodules  $\leq 3$  cm each and  $\leq 8$  cm in total. No significant difference in liver transplantation outcomes was observed between patients having undergone liver transplantation after downstaging and those within the Milan criteria having undergone the transplantation during the same period. There was also no significant difference in transplantation wait-list survival rate between patients planned to undergo downstaging and those within the Milan criteria. Also in the retrospective analysis of the United Network for Organ Sharing (UNOS) database, the outcome of transplantation applied in accordance with such a downstaging protocol did not differ from the transplantation outcome in patients within the Milan criteria. Meanwhile, the transplantation outcome has been reported to be less favorable in patients having successfully undergone downstaging without using any eligibility criteria than in patients within the Milan criteria<sup>3</sup>.

#### ■ Explanation

No definite conclusion has yet been reached as to whether or not pre-transplant treatment of HCC at eligible stages can lower the wait-list dropout rate and the post-transplant recurrence rate, eventually improving the survival of patients. Regarding downstaging of HCC from beyond the eligible stages, a prospective study reported on indications for downstaging, success rates, and survival rates. The survival rate comparable to the control group was recorded not only in patients having completed the planned treatment until liver transplantation (per protocol analysis) but also in the entire group of patients for whom downstaging had been planned (intention-to-treat analysis). These findings suggest

that: (1) it is possible to downstage a certain number of HCCs from beyond to within the Milan criteria with an existing treatment method if they are within a limited range of stage; (2) comparable transplantation outcomes can be expected between successfully downstaged HCCs and HCCs within the Milan criteria; and (3) the downstaging plan itself does not adversely affect prognosis. In other words, downstaging prior to liver transplantation can be regarded as a treatment strategy for HCC. The validity of the outcomes of transplantation applied with such a downstaging protocol has been endorsed also in retrospective analysis of data from across the USA. However, when these reports are interpreted, it should be noted that the characteristics of the patients in these studies differ from those of patients encountered in daily clinical practice in Japan. In the United States where the studies were conducted, liver transplantation primarily uses the brain-dead donor liver, and the indications for liver transplantation in patients with HCC are decided solely on the basis of tumor stage, regardless of the condition of the background liver. Also in the reports cited above,  $\geq 50\%$  of the patients were Child-Pugh A cases with compensated cirrhosis or had Model for End-Stage Liver Disease (MELD) score  $\leq 15$ . In Japan, however, brain-dead donors for liver transplantation are scarce and liver transplantation primarily uses the living donor liver, with the indications of HCC for transplantation being confined to cases within Milan criteria or cases with decompensated cirrhosis satisfying the 5-5-500 rule. It is thus unclear at present whether pre-transplant treatment like the one mentioned above can be applied safely and effectively to HCC patients with decompensated cirrhosis in Japan. The number of cases where possible dropout from the waiting list raises a concern is also smaller in Japan. Accordingly, the Revision Committee has concluded that the evidence available is not sufficient enough to allow a definite statement that pre-transplant treatment can improve the prognosis of HCC after liver transplantation.

#### Voting results

- ◎ Regarding the statement of recommendation “No prior treatment is recommended for HCC planned for liver transplantation”, its adoption was weakly recommended by voting of committee members.

Such treatment is strongly recommended	Such treatment is weakly recommended	The statement is weakly recommended	The statement is strongly recommended
0% (0 members)	0% (0 members)	87.5% (21 members)	12.5% (3 members)

Total voters: 24 members

## ■ References

## Chapter 5

### Percutaneous Ablation

- Introduction

Percutaneous ablation (puncture-based locoregional therapy) for HCC is a treatment technique introduced following advances in the ultrasonic diagnostic devices, reportedly beginning with “percutaneous ethanol injection therapy” in 1983. Later, “percutaneous microwave coagulation therapy” was covered by the national health insurance (NHI) in Japan in 1996 and “percutaneous radiofrequency ablation” in 2004. These techniques now play a central role in percutaneous ablation in Japan. Percutaneous ablation can be characterized by its capability of curatively treating HCC, relatively low invasiveness and applicability to recently increasing elderly patients and patients with poor hepatic reserves difficult for surgical resection.

In the current edition, no new CQ regarding percutaneous ablation has been added to the CQs of the fourth edition (2017 version). CQ 36 in the fourth edition “What factors predict treatment response to percutaneous ablation?” has been deleted, and 5 CQs have been adopted for the current edition, including CQ28 “Which patients are eligible for percutaneous ablation?”, CQ29 “How should suitable ablation therapy be chosen?”, CQ30 “Can the combination of percutaneous ablation and TACE improve the survival of HCC patients?”, CQ31 “Is contrast-enhanced US or fusion imaging useful for image-guided percutaneous ablation?” and CQ32 “What imaging modalities are useful for assessing treatment response to percutaneous ablation?”.

With regard to CQ28, the indications for percutaneous ablation were discussed from the tumor features and background of individual cases using 12 articles in total (10 articles used in the fourth edition and 2 articles newly adopted), resulting in the recommendation similar to that in the fourth edition. With regard to CQ29, the treatment outcomes and complications following different ablation therapies were compared using 23 articles (6 newly adopted and the others used in the fourth edition), resulting a recommendation “RFA is recommended as percutaneous ablation”, while deleting the preceding edition’s recommendation “RFA and PI with artificial ascites are options for patients at higher risk of gastrointestinal perforation.” With regard to CQ30, the discussion using 17 articles (15 of the 16 articles used in the fourth edition and 2 newly adopted articles) resulted in a recommendation akin to that in the fourth edition. With regard to CQ31, the utility of guides used for treatment was discussed using 19 articles (11 articles used in the fourth edition and 8 newly adopted articles), resulting in a recommendation similar to the previous one. Also regarding CQ32, the discussion using 2 newly adopted articles



pertaining to comparison among contrast-enhanced CT/CRI/US and 9 articles used in the fourth edition resulted in a recommendation similar to the previous one.

Thus, the recommendations in the current edition differ little from those in the preceding edition. This may be interpreted as indicating that percutaneous ablation has been deeply adopted during clinical practice as an established treatment technique, although the accuracy of treatment with this technique is expected to be improved further following advances from now on in the apparatus for diagnostic imaging.

CQ28 Which patients are eligible for percutaneous ablation?

#### Recommendation

Percutaneous ablation is indicated for patients with Child–Pugh class A or B liver function, up to 3 tumors, and tumor diameter  $\leq 3$  cm. (Strong Recommendation, Evidence Level A)

#### ■ Background

Historically, percutaneous ablation began with percutaneous ethanol injection (PEI) introduced as an epoch-making treatment method simple, less invasive and thus easy in treating small HCCs. Percutaneous hot saline injection therapy (PHoT) and percutaneous acetic acid injection (PAI) are derivatives of PEI. Treatment with these techniques, however, involved a problem with insufficient responses from cases having a spectrum within the tumor or extracapsular invasion. For this reason, new techniques of percutaneous ablation enabling induction of homogeneous coagulation and necrosis were later introduced. Thus, percutaneous microwave coagulation therapy (PMCT) and radiofrequency ablation (RFA) began to be covered by the national health insurance (NHI) system in 1996 and 2004, respectively.

During the current revision, the indications for percutaneous ablation were discussed from the viewpoints of tumor's features and patient's background.

#### ■ Scientific Statement

This CQ is a continuation of CQ31 in the fourth edition. A literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 285 articles. This was narrowed down to 40 articles in the first screening based on the criteria: Adopting articles dealing with indications for treatment from the aspects of tumor size, tumor number, vascular invasion, extrahepatic

metastasis and patient's background (liver function, etc.) in studies setting the survival rate or the complication as an outcome. From these 40 articles, 20 were extracted by further evaluation of their content in the second screening. Then, 2 articles were finally adopted using the criteria: high-evidence level, large sample size, and high-quality study design. Complying with the "Policy of describing comparison among different treatment methods collectively in the Chapter of Treatment Algorithm" adopted from the current revision, these 2 articles plus 10 articles from the fourth edition (12 articles in total) are cited for CQ28<sup>1-12</sup>.

Using the database from the nationwide follow-up survey of primary liver cancer by the Liver Cancer Study Group of Japan, Hasegawa et al. compared the survival among 8 groups of patients with 2 or 3 HCCs divided by tumor size (< 2 cm or 2-3 cm) and liver function class (A or B), reporting that the recurrence-free survival rate following RFA did not differ between any two of these groups<sup>1</sup>. Another report demonstrated that the outcome of RFA was better (five-year survival rate: 60-74%) when analysis was confined to cases "Child-Pugh class A liver function and single tumor  $\leq$  2 cm)<sup>1,2</sup>.

Several reports demonstrated effectiveness of percutaneous ablation in the treatment of multiple HCCs (4 or more), but there is no published report with high-quality evidence analyzing the limit of treatment based on tumor number.

In a retrospective cohort study of HCC patients with Child-Pugh class C liver function (Child-Pugh score 10-11), the median overall survival differed significantly ( $p < 0.0001$ ) between the palliative care group (4.0 months, 95% confidence interval (CI): 2.9-5.1 months) and the percutaneous ablation group (26.0 months, 95% CI: 22.4-29.6 months)<sup>3</sup>.

#### ■ Explanation

As far as "tumor features" for indications are concerned, "up to 3 HCCs  $\leq$  3 cm" has been adopted as the feature eligible for percutaneous ablation in most of the articles published since the years when PEI served as a central role for this kind of therapy. It has additionally been reported that the local recurrence rate after PEI is high in cases of HCCs > 3 cm. With RFA, now serving as the standard technique, the area of ablation can be theoretically expanded by increasing the number of therapy sessions, but RFA is associated with complications when the number of therapy sessions is increased or the area of ablation is expanded. Combining RFA with TACE can expand the area of ablation, but sufficient evidence justifying the expansion of indications to "HCC > 3 cm" is not available. Also, because the area of ablation is about 3 cm with most RFA electrodes (although some electrodes are provided for use in ablation for more than 3 cm in terms of major axis), the Revision Committee has decided to continue using "up to 3 HCCs  $\leq$  3

cm” as the indication for percutaneous ablation including RFA.

As referred to also in CQ13 “What treatment modalities are recommended for HCC in patients with liver damage grade C (Child-Pugh C liver function)?”, percutaneous ablation and TACE were reported to have survival-improving effects in a retrospective cohort study of patients with Child-Pugh C liver function registered with the nationwide follow-up survey of primary liver cancer in Japan<sup>3</sup>. In view of such a report, the Revision Committee carefully considered whether or not to expand the range of treatment methods selected for patients with Child-Pugh C liver function, reaching a judgment that it is premature to recommend any method of treatment other than liver transplantation in the absence of sufficient data on safety (e.g., about the frequency of complications and treatment-related death).

“Invasiveness” is an additional factor possibly affecting the indications for treatment other than HCC size, number of HCCs, and liver function (hepatic reserve). Many studies comparing RFA with hepatectomy reported less complications and shorter hospital stay in the RFA group<sup>4-11</sup>. As far as “HCC-affected site” and “history of surgery (choledochojejunostomy and endoscopic papillotomy)” are concerned, the real-world data in Japan<sup>12</sup> suggest that these factors do not always suppress application of RFA.

In Japan, SURF Study\* was carried out to establish the evidence serving as the rationale for selection of treatment methods for primary HCC. It was a randomized controlled trial (RCT) designed to evaluate the efficacy of hepatectomy and RFA in initial-onset HCC patients satisfying the criteria: favorable liver function (Child-Pugh score  $\leq 7$ ), and up to 3 HCCs. The study finally analyzed 150 surgically resected cases and 151 cases treated by RFA at nationwide 49 facilities, demonstrating no significant difference in 3-year recurrence-free survival rate between the surgical resection group and the RFA group (49.8% vs. 47.7%,  $p = 0.793$ ) and no perioperative death in any of the two groups<sup>13</sup>. The overall survival in that study, still under follow-up and not yet been reported, is now being waited for. Both surgical resection and percutaneous ablation have the same goal of “achieving locoregional control.” With percutaneous ablation, however, ensuring a sufficient margin of ablation sometimes becomes more difficult as the HCC size increases, thus indicating the necessity of considering tumor features, patient background and surgeon’s skill when assessing the indications for percutaneous ablation.

\*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).

## Voting results

- ◎ Regarding the statement of recommendation “Percutaneous ablation is indicated for patients with Child–Pugh class A or B liver function, up to 3 tumors, and tumor diameter  $\leq 3$  cm”, its adoption was strongly recommended by voting of committee members.

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

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

## ■ References

CQ29 How should suitable ablation therapy be chosen?

### Recommendation

RFA is recommended as percutaneous ablation. (Strong Recommendation, Evidence Level A)

### ■ Background

The history of percutaneous ablation began with PEI in the 1980s. After the introduction of other types of locoregional therapy such as percutaneous acetic acid injection (PAI) and PMCT, percutaneous ablation is currently positioned as a representative technique of percutaneous ablation. To improve the outcome of RFA and the efficiency of treatment further, new devices such as bipolar RFA devices and electrodes with adjustable tip length have also been introduced for clinical use. Regarding next-generation microwave ablation, which was introduced as a new means of percutaneous ablation, the term “microwave ablation (MWA)” is now used frequently for distinction from the conventional microwave coagulation therapy (MCT). Treatment systems such as cryoablation and irreversible electroporation (IRE), both not yet approved for HCC in Japan, are also classified as percutaneous ablation.

### ■ Scientific Statement

This CQ is a continuation of CQ32 in the fourth edition. A literature search was conducted with the search query used in the fourth edition and a publication date between July 1,

2016 and January 31, 2020. As a result of discussion at the Revision Committee, a policy to include also “open and laparoscopic ablation” into this CQ was adopted. From the 136 articles thus extracted, 17 were adopted in the first screening. This was narrowed down to 6 in the second screening from the viewpoints of “evidence level” and “study design.” A total of 23 articles, including 17 of the 19 articles from the fourth edition (excluding the 2 articles on cryoablation), are cited for CQ29.

- Comparison of RFA and PEI

Five RCTs<sup>1-5</sup> and 6 meta-analyses covering these RCTs as well<sup>6-11</sup> have been reported. Here, the results of two meta-analyses reported recently are cited. Shen et al. reported better survival and local recurrence rates with RFA than with PEI<sup>10</sup>. Yang et al., in a review of 3 European studies, 4 Asian studies, and 1 African study, reported significantly better survival and local recurrence rates after RFA only in the Asian study<sup>11</sup>.

- Comparison of RFA and MCT

Two RCTs were newly adopted. In the RCT by Vietti et al., involving 152 patients, the 2-year recurrence rate was slightly higher in the RFA group than in the MCT group although the difference was not statistically significant (odds ratio, 1.62; 95% CI, 0.66-3.94;  $p = 0.27$ )<sup>12</sup>. Although the follow-up period was short, the 2-year survival rate did not differ significantly, and the incidence of complications did not differ between the two groups, either. Also in the RCT of 203 cases by Yu et al., there was no significant difference in terms of local recurrence, survival, or complications between the two therapies<sup>13</sup>. The meta-analysis conducted by Facciorusso et al. revealed no significant difference in the complete ablation rate between RFA and MCT (OR, 1.12; 95% CI, 0.67-1.88;  $p = 0.67$ ) or in the local recurrence rate (OR, 1.01; 95% CI, 0.53-1.87;  $p = 0.98$ )<sup>14</sup>. However, the local recurrence rate was significantly better after MCT than after RFA in patients with relatively large nodules (hazard ratio, 0.46; 95% CI, 0.24-0.89;  $p = 0.02$ ). Also, the 3-year survival rate did not differ significantly (OR, 0.95; 95% CI, 0.58-1.57;  $p = 0.85$ ) but tended to be higher after RFA. The number of major complications were slightly, but not significantly, higher after MCT (OR, 1.63; 95% CI, 0.88-3.03;  $p = 0.12$ ).

- Complications

In the meta-analysis by Bertot et al., the overall mortality after percutaneous ablation was 0.16% (95% CI: 0.10-0.24), and the mortality by treatment modality was 0.16% (0.10-0.24) for RFA, 0.15% (0.08-0.23) for MCT, and 0.23% (0.0-0.58) for PEI<sup>15</sup>. The incidence of severe complications after percutaneous ablation was 3.29% (95% CI, 2.43-4.28%), and the rate by treatment modality was 4.1% (3.3-5.1) for RFA, 4.6% (0.7-11.8) for MCT, and 2.7% (0.28-7.4) for PEI. The incidence of complications did not differ significantly between RFA and PEI in a meta-analysis by Germani et al. (OR, 1.21; 95% CI, 0.89-1.63;

$p = 0.22$ )<sup>9</sup>, but it tended to increase after RFA in a meta-analysis by Shen et al. (hazard ratio, 2.04; 95% CI, 0.81-5.15;  $p = 0.059$ )<sup>10</sup>.

#### ■ Explanation

During PEI, the fibrous capsule and septa inside HCC prevent ethanol from dispersing throughout the HCC and therefore the ability of PEI to achieve radical cure diminishes as the size of tumor increases. In contrast, one of the advantages of MCT and RFA is to induce necrosis in lesions as well as in surrounding tissues where satellite nodules are present. The literature search extracted many articles suggesting the superiority of RFA to PEI in terms of survival and local recurrence rates<sup>6-11</sup>. Also, subgroup analysis showed that treatment outcomes tend to differ more in patients with HCC  $\geq 2$  cm<sup>9,10</sup>. Because the most recent literature search did not extract any studies that compared treatment outcomes between different RFA devices, further study is needed to address this issue in the future. Regarding comparison between RFA and MCT, two new RCTs have been reported<sup>12,13</sup>, but there was no difference in outcome between them in none of these RCTs or the meta-analysis reported before<sup>14</sup>. With MWA, which began to be covered by the NHI in 2017, the heat sink effect is small and ablation in an approximately spherical form is expected with this technique in view of its design. MWA thus has the potential of achieving more extensive ablation, but no sufficient evidence is available concerning its efficacy in comparison to RFA. Considering these findings and the necessity of further evaluation, including long-term prognosis, about MWA, the current edition recommends RFA as the first-choice technique for percutaneous ablation.

Mono-center retrospective studies on open/laparoscopic RFA have been reported. Some of them demonstrated superiority of laparoscopic RFA over percutaneous RFA in terms of outcomes<sup>16</sup>, while many others revealed no significant difference in outcome between them<sup>17,18</sup>. Considering that a systematic review also revealed no difference in the incidence of complications among any of open, laparoscopic and percutaneous RFA<sup>19</sup>, open or laparoscopic RFA may be viewed as a valid alternative for cases where the percutaneous approach to ablation is difficult.

As for complications, no significant difference in the overall incidence of complications was observed between the different modalities of percutaneous ablations (RFA, MCT, and PEI)<sup>6,9,10</sup>. However, complications often occur in the vicinity of the porta hepatis and in areas of the liver adjacent to other organs<sup>20</sup>. In particular, gastrointestinal perforation occurs more often after RFA than after PEI<sup>17</sup>, and patients with postoperative adhesions are at high risk of gastrointestinal perforation<sup>21</sup>. Therefore, there are many retrospective studies in Japan reporting cases having followed favorable courses after RFA with

artificial ascites or PEI applied under these conditions<sup>20,22,23</sup>.

#### Voting results

© Regarding the statement of recommendation “RFA is recommended as percutaneous ablation”, its adoption was strongly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
100% (23 members)	0% (0 members)	0% (0 members)	0% (0 members)

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

#### ■ References

CQ30 Can the combination of percutaneous ablation and TACE improve the survival of HCC patients?

#### Recommendation

It is expected that combination therapy with percutaneous ablation and TACE can improve survival in patients with relatively large tumors. (Weak Recommendation, Evidence Level B)

#### ■ Background

The significance of performing TACE prior to ablation lies in that it can expand the area of ablation through diminishing the cooling effect of blood. Here, we investigated the possibility of improving survival by combining percutaneous ablation with TACE in HCC patients.

#### ■ Scientific Statement

This CQ is a continuation of CQ33 in the fourth edition. A literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 177 articles. This was narrowed down to 7 in the first screening, from which 2 studies reporting comparison of cutaneous ablation vs. TACE + percutaneous ablation (RCT, non-RCT) were extracted in the second screening. A total of 17 articles, which include 15 of the 16 articles from the fourth edition (excluding

one meta-analysis for a reason of “a study conducted relatively many years ago, involving comparison of miscellaneous treatment methods with a small sample size”) are cited for CQ30.

- Area of ablation

Kitamoto et al. showed a significantly larger area of ablation after combination therapy with TACE + RFA (maximum and minimum diameter 39.9 and 32.3 mm) than after RFA monotherapy (34.6 and 26.0 mm, respectively;  $p < 0.05$ )<sup>1</sup>.

Morimoto et al. also reported that the area of ablation was significantly larger after combination therapy with TACE + RFA (mean maximum and minimum diameter 50 and 41 mm) than after RFA monotherapy (58 and 50 mm, respectively;  $p = 0.012$ )<sup>2</sup>.

- Survival rate

Table 1 shows studies comparing the outcomes of combination therapy with TACE + RFA and RFA monotherapy<sup>3-10</sup>. Despite diverse patient characteristics, combination therapy with TACE + RFA showed a significantly higher survival rate in 6 studies and no significant difference in 2 studies, each compared to the RFA monotherapy. Seven meta-analyses also showed a significantly better survival rate after combination therapy with TACE + RFA<sup>11-17</sup>.

#### ■ Explanation

In previous studies, the timing of TACE varied widely from on the same day as ablation to within 2 months of ablation, but TACE performed within 1 month of ablation has been adopted most frequently in Japanese studies.

There is a general agreement in previous studies that the area of ablation increases when TACE is performed prior to RFA. Therefore, TACE is expected to decrease the number of treatments and the local recurrence rate through expansion of the ablation area. For example, the study by Morimoto et al. found significantly fewer therapy sessions were needed and the local recurrence rate was lower after combination therapy with TACE + RFA than after RFA monotherapy (TACE + RFA vs. RFA: 1.1 vs. 1.4 times,  $p < 0.01$ ; 6% vs. 39%,  $p = 0.012$ ; respectively)<sup>2</sup>.

Many of published papers support contribution of the combination TACE + RFA to longer survival when compared to RFA monotherapy. For example, the meta-analysis by Jiang et al. (involving 8 RCTs and 11 retrospective cohort studies) revealed marked superiority of TACE + RFA in terms of the odds ratio for one-year survival rate (2.14; 95%CI, 1.57-2.91;  $p < 0.001$ ), the odds ratio for 3-year survival rate (1.98; 95%CI, 1.28-3.07;  $p = 0.001$ ) and the odds ratio for 5-year survival rate (2.70; 95%CI, 1.42-5.14;  $p < 0.001$ )<sup>15</sup>. In addition, some subgroup analyses disclosed that contribution to longer survival was



greater in cases of larger HCC size. The current edition thus adopts the recommendation “It is expected that combination therapy with percutaneous ablation and TACE can improve survival in patients with relatively large tumors.”

Voting results

© Regarding the statement of recommendation “It is expected that combination therapy with percutaneous ablation and TACE can improve survival in patients with relatively large tumors”, its adoption was weakly recommended by voting of committee members.

Strongly recommended to adopt	Weakly recommended to adopt	Weakly recommended not to adopt	Strongly recommended not to adopt
4.3% (1 member)	91.3% (21 members)	4.3% (1 member)	0% (0 members)

Total voters: 23 members

(56)

Comparison of combination therapy with TACE + RFA and RFA monotherapy in patients with HCC

Author/Year of Publication Study Design No. of Cases (TRACE + RFA/RFA) Tumor Features 3-Year Survival Rate (%) 5-Year Survival Rate (%) p value

(57)

NRCT (trend score matching)

(58)

1-2 HCCs ≤ 3 cm

1 HCC ≤ 7 cm

2-3 HCCs ≤ 3cm

1 HCC 2-3 cm

Recurrence after TACE

1-3 HCCs ≤ 5 cm

1-3 HCCs < 7 cm

Within the Milan criteria

1 HCC ≤ 3 cm

1 HCC 3.1-5 cm

(59)

74.0 vs. 72.7 (4-year)

50 vs. 42

63 vs. 53

46 vs. 36

61.6 vs 45 (4-year)

(60)

NRCT: non-randomized controlled trial NA: not available

#### ■ References

CQ31 Is contrast-enhanced US or fusion imaging useful for image-guided percutaneous ablation?

#### Recommendation

Contrast-enhanced US and/or fusion imaging are useful for image-guided percutaneous ablation in patients with HCCs that are difficult to visualize on B-mode US. (Weak Recommendation, Evidence Level B)

#### ■ Background

Percutaneous ablation is performed under ultrasound guide. Therefore, achieving successful treatment requires clear visualization of the entire HCC in US-guided percutaneous ablation. Furthermore, to prevent local tumor recurrence, a sufficient area of ablation needs to be ensured, covering not only the tumor but also appropriate ablation margins. To this end, it is crucial to accurately define liver-tumor boundaries before setting ablation margins. However, it may be difficult to visualize or identify liver nodules on B-mode US when there is (1) a poorly defined liver-tumor boundary (due to poor encapsulation, etc.), (2) a small liver lesion hidden behind large regenerative nodules, and (3) a locally recurrent tumor isoechoic to the area necrotized in past ablative treatment. To visualize and treat tumors that are poorly defined on B mode, contrast-enhanced US guidance and fusion imaging guidance have been developed for percutaneous ablation. Here, we investigated the utility of these imaging guidance techniques.

#### ■ Scientific Statement

This CQ is a continuation of CQ34 in the fourth edition. A literature search conducted with the search query used in the fourth edition and a publication date between January 1, 2016 and January 31, 2020 extracted 68 articles. This was narrowed down to 20 articles in the first screening, from which 8 articles that compared the outcomes of treatment with US or fusion imaging guidance were extracted in the second screening. A total of 19 articles, which include 11 of the 12 articles from the fourth edition, are cited for CQ31.

- US guidance

Minami et al. performed RFA under the guidance of US in 108 patients with liver nodules that were poorly visualized on B-mode US and reported a mean number of therapy sessions of  $1.1 \pm 0.3$ <sup>1</sup>.

Masuzaki et al. also performed RFA under the guidance of US in 291 patients and found significantly fewer therapy sessions were needed compared with well-matched controls ( $n = 2,261$ ;  $1.33$  vs.  $1.49$ ;  $p = 0.0019$ )<sup>2</sup>.

- Fusion imaging guidance

Minami et al. have shown that HCCs poorly defined on B-mode US are treated more effectively in RFA guided by fusion imaging than in RFA guided by B-mode US (mean therapy sessions,  $1.1$  vs.  $1.3$  times;  $p = 0.021$ )<sup>3</sup>.

Lee et al. reported that the positive predictive value of CT/MRI fusion imaging ( $90.5\%$ ) was significantly higher than that of B-mode US ( $78.8\%$ ;  $p = 0.0003$ )<sup>4</sup>.

- Combination of contrast-enhanced US and fusion imaging

Min et al. successfully treated  $92.0\%$  of poorly defined HCCs on B-mode US by combining contrast-enhanced US and CT/MRI fusion imaging<sup>5</sup>.

Minami et al. observed no significant difference in the 3-year local recurrence rate after RFA guided by contrast-enhanced US, fusion imaging, or their combination ( $4.9\%$ ,  $7.2\%$ , and  $5.9\%$ , respectively)<sup>6</sup>.

Ma et al. reported significant improvement in all of treatment success rate, local recurrence rate, recurrence-free survival rate and overall survival following RFA guided by CT/MRI-CEUS fusion imaging than following RFA guided by B-mode US<sup>7</sup>. Ju et al. reported the guidance with this combination was particularly useful for HCCs with treatment-difficult features (size  $\geq 30$  mm, located near the vessels, etc.)<sup>8</sup>.

- New application of fusion imaging

US-US overlay fusion is a treatment supportive technique enabling real-time assessment of the area of ablation immediately after ablation<sup>9</sup>. The percentage of cases with a 5 mm or more safety margin secured was significantly higher and the local recurrence rate was significantly lower following US-US overlay fusion than following treatment with the

existing technique (89.3% vs. 47.0%,  $p < 0.01$ ; 0.8% vs. 6.0%,  $p = 0.022$ )<sup>10</sup>.

Huang et al. conducted an RCT with three guidance modalities (contrast-enhanced US, CT/MRI fusion imaging and 3-D US-CEUS fusion imaging), reporting a tendency for lower local recurrence rate in the fusion imaging groups (although no significant difference) and utility of fusion imaging particularly in cases of HCC located at highly difficult sites and cases of multiple HCCs<sup>11</sup>.

#### ■ Explanation

The US contrast agent perfluorobutane microbubbles (i) enables continuous observation and stable visualization of lesions throughout different phases, and (ii) improves recognition of lesions by targeting defects in the post-vascular phase (Kupffer imaging)<sup>12,13</sup>. Utilization of defect re-perfusion imaging improves localization and qualitative diagnosis of HCCs ill-defined on B-mode US and makes the US guidance more effective<sup>14</sup>. However, it may be still difficult to visualize lesions located deep in the liver or in the liver with advanced cirrhosis.

Fusion imaging technology displays multiplanar reconstruction images in real time similar to B-mode images, by synchronizing the coordinate system of pre-existing volume data from CT or MRI and the coordinate system of volume data generated by using a US probe mounted an electromagnetic tracking sensor<sup>15-18</sup>. One of the merits of fusion imaging is the ability to display reference images in contrast-enhanced US even under difficult conditions. Furthermore, technological advances in imaging devices (Active Tracker for automatic fusion between US and CT images, position sensor-built-in probes, etc.) have contributed to the improved accuracy in image adjustment and the reduced labor-intensiveness. However, it should be kept in mind that even fusion imaging does not always produce images that completely match the real image of the liver, because of displacement by respiratory excursion and liver contortions.

In the study of treatment using a combination of contrast-enhanced US and fusion imaging, the local recurrence rate after RFA guided by two imaging modalities was comparable with that for other treatments despite the much more challenging cases of HCCs, which were poorly defined on B-mode US and poorly identified on contrast-enhanced US or fusion imaging<sup>6</sup>. Contrast-enhanced US and fusion imaging should not be viewed as competing imaging systems<sup>19</sup>. What is important in the treatment of HCC is to achieve local control by using them in combination or selecting one that is appropriate to the tumor conditions or patient characteristics.

Although the guidance mentioned above is aimed at “targeting (the poorly identified HCCs),” “monitoring” of the area of ablation has recently been proposed as a new purpose

of applying fusion imaging. US-US overlay fusion is an imaging technique allowing visualization of the ablation margin by providing projection of the tumor image into the hyperechoic ablative area through overlapping of the images before/after ablation<sup>9,10</sup>. This technique allows ablation to be implemented while assessing the ablation margin, and application of US-US overlay fusion is expected to contribute to more precise ablation. Contrast-enhanced US and fusion imaging are thus judged to provide useful means of treatment guidance, as stated in the fourth edition. The literature search during the current revision identified another RCT to be cited, which reported absence of significant difference among any of three guidance techniques (CT/MRI-CEUS, 3D US-CEUS and CEUS). Many of the other pieces of evidence were based on the retrospective studies whose sample did not exceed a hundred and some dozens of cases. So, the evidence level of the recommendation for the current edition was set at B. It needs to be borne in mind that contrast-enhanced US and fusion imaging are techniques relying on ultrasound devices and that the contrast sensitivity and the way of fusion vary among different devices.

#### Voting results

- © Regarding the statement of recommendation “Contrast-enhanced US and/or fusion imaging are useful for image-guided percutaneous ablation in patients with HCCs that are difficult to visualize on B-mode US”, its adoption was weakly recommended by voting of committee members.

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

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

#### ■ References

CQ32 What imaging modalities are useful for assessing treatment response to percutaneous ablation?

#### Recommendation

Dynamic CT or dynamic MRI is recommended for assessing treatment response to percutaneous ablation. (Strong Recommendation, Evidence Level B)

## ■ Background

The Response Evaluation Criteria in Solid Tumors (RECIST)<sup>1</sup> is commonly used for the assessment of response in solid tumors. However, accurate assessment of response based on the RECIST is difficult in percutaneous ablation for HCC, due to the presence of residual tumor even after curative treatment. Therefore, to evaluate treatment outcomes in HCC, RECIST was modified in the United States and Europe to incorporate the effect of tumor necrosis into the evaluation (the modified version is designated mRECIST)<sup>2,3</sup>. In Japan, the Response Evaluation Criteria in Cancer of the Liver (2015 version)<sup>4</sup> was published as RECICL<sup>5</sup>. Here, we investigated diagnostic imaging modalities that are useful in assessing the treatment outcome of percutaneous ablation.

## ■ Scientific Statement

This CQ is a continuation of CQ35 in the fourth edition. A literature search conducted with the search query used in the fourth edition and a publication date between July 1, 2016 and January 31, 2020 extracted 310 articles. This was narrowed down to 5 in the first screening, from which 2 articles comparing CT with Gd-EOB-DTPA-enhanced MRI or contrast-enhanced US were extracted in the second screening. A total of 11 articles, including the 9 articles from the fourth edition, are cited for CQ32.

### • Simple MRI

Koda et al. reported that ablation margins were visualized as high-intensity rims on T1WI MRI in 86% of nodules after RFA<sup>6</sup>. Also, analysis of the ablation margins showed a good correlation between simple MRI and dynamic CT ( $\kappa$  coefficient = 0.716).

### • Gd-EOB-DTPA-enhanced MRI (EOB-MRI)

Granata et al. compared the diagnostic accuracy of EOB-MRI and dynamic CT against pathology-proven post-RFA residual tumors (n = 42)<sup>7</sup>. They found that at 1 month after RFA, EOB-MRI had a sensitivity of 92%, specificity of 97%, positive predictive value of 92%, and negative predictive value of 97%, showing the superiority of EOB-MRI over dynamic CT (p < 0.05).

In a surveillance of recurrent lesions after curative RFA (n = 97), Imai et al. compared the accuracy in detecting hypervascular recurrent lesions between contrast-enhanced CT and EOB-MRI each conducted at intervals of 3-4 months<sup>8</sup>. The median observation period was 385 (86-1,141) days. Of the 66 recurrent lesions found in 48 patients, 34 lesions (51.5%) in 26 patients (54.2%) were detected by contrast-enhanced CT, while 59 lesions (89.4%) in 44 patients (91.7%) were detected by EOB-MRI, thus indicating significant superiority of EOB-MRI over dynamic CT (p < 0.001).

- Contrast-enhanced US

According to Kudo et al., defect reperfusion imaging is capable of detecting residual HCC easily, allowing even the small nodules not detectable by contrast-enhanced CT to be diagnosed as HCC<sup>9</sup>.

Zhou et al. investigated chronological changes in post-RFA tumor margins on B-mode images and reported the detection rate of tumor margins was 65.2% at 1 day after RFA, 54.3% at 3 days, 43.5% at 4 days, and 39.1% at 5 days<sup>10</sup>.

Kong et al. evaluated the response to RFA using both contrast-enhanced CT and contrast-enhanced US (n = 60). At 1 month and 3 months after RFA, the area of ablation on contrast-enhanced CT did not differ from that on contrast-enhanced US, and a high correlation was noted between them ( $r^2 = 0.617$ )<sup>11</sup>.

- Explanation

Dynamic CT/MRI is recommended as the standard imaging modality for assessing treatment response to percutaneous ablation because objectivity is required when assessing imaging findings such as ablation margins and because it is necessary to examine many nodules. The recommendation level continues to be “strong” on the basis of the voting results at the recommendation deciding meeting because there has been no major change in the evidence available. Dynamic CT can be positioned as the standard imaging modality, considering its adoption as a gold standard in many past studies and its widespread distribution in Japan. Regarding the utility of EOB-MRI, Granata et al. reported the superiority of EOB-MRI over dynamic CT for detecting residual tumors<sup>7</sup>, and Imai et al. demonstrated, in a long-term surveillance of post-RFA recurrent lesions, superiority of EOB-MRI over dynamic CT<sup>8</sup>. However, since the sample size was small in these studies, further study is needed to accumulate more evidence.

Angiographic findings are absolutely necessary for the assessment of treatment response to percutaneous ablation. However, contrast-enhanced CT/MRI are contraindicated in patients with kidney failure and allergic disorder such as iodine allergy and asthma. Nephrogenic systemic fibrosis (NSF), a severe late-onset complication of Gd-based contrast agents used in MRI, is of particular importance in patients with kidney failure because renal dysfunction is a risk factor for NSF. In principle, an eGFR of < 30 mL/min/1.73 m<sup>2</sup> is a contraindication for medical examinations using contrast agents. Simple MRI and contrast-enhanced US may be viable alternatives. Simple MRI clearly visualizes many tumors and ablation margins owing to its high contrast resolution. Contrast-enhanced US has a low risk of complications associated with contrast agents and has excellent spatial, contrast, and time resolution. Accordingly, CT and MRI often

detect small lesions that are indistinguishable on contrast-enhanced US due to the partial volume effect. Furthermore, as reported by Zhou et al., ablation margins become unclear over time on B-mode US<sup>10</sup>. Approximately, one-third of tumor margins were ill-defined on the day after RFA, showing the limitation of B-mode US, even if combined with contrast-enhanced US, in the assessment of ablation margins. King et al., on the other hand, reported that the ablation margins did not differ between contrast-enhanced US and contrast-enhanced CT at 1 or 3 months after RFA<sup>11</sup>.

#### Voting results

- ◎ Regarding the statement of recommendation “Dynamic CT or dynamic MRI is recommended for assessing treatment response to percutaneous ablation”, its adoption was strongly recommended by voting of committee members.

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

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

#### ■ References

- 4) Kudo M, Ueshima K, Kubo S, Sakamoto M, Tanaka M, Ikai I, et al. Criteria for Assessing the Response of Liver Cancer to Treatment (2015 Revised Version). *Acta hepatologica Japonica* 2015; 56: 116-21.