Chapter 3 Surgery

- **Introduction**

Malignant tumors are removed by surgical treatments such as liver resection and liver transplantation, which are the most reliable treatments for local control. In the Report of the 18th Follow-Up Survey of Primary Liver Cancer in Japan (2004–2005) (L3H00004[1)]), it was reported that operative mortality was 0.7%, with a safety comparable with that of other gastrointestinal surgeries. For this revised edition of the guidelines, English-language documents published between 2008 and 2011 were searched using the key words "hepatocellular carcinoma" and "surgery," and 2,898 original articles served as the basis of CQs and discussions. Table 1 shows the changes in CQs for Chapter 3.

Preoperative liver function evaluation plays the unrivaled role in determining indication of surgery, and new evidences have emerged that guarantees the safety of liver resection from liver damage. A new CQ was created for liver resection procedures with a comprehensive view of standard hepatectomies. Herein we describe the various aspects of evidence related to liver resection in Japan.

Prognostic factors have not been corrected in the CQs of any previous edition, and new evidence is now introduced for the long-term outcomes of liver resection. However, because both recommendations are no better than Grade B, it is anticipated that more prospective studies will be conducted in Japan.

A new CQ was established for perioperative care. In this new CQ, the pros and cons of abdominal drainage are addressed in addition to those of blood transfusion and hemorrhage control. Many of the adopted RCTs were non-Japanese and were conducted under conditions different from those in Japan in some aspect. Therefore, it is hoped that studies more suited to our clinical environment will be conducted in Japan.

Chapter 8 on is a new addition to this version, in which we discuss the post-treatment prevention of recurrence. In this chapter, adjuvant therapies are narrowed down to neoadjuvant chemotherapy and discussed. Prospective studies on postoperative adjuvant chemotherapies, with primary focus on molecular target drugs, are currently in progress, and the results are highly anticipated.

Liver transplantation was discussed in two carefully selected CQs on tumor downstaging and indications for transplantation. Conventional prognostic factors and comparisons with liver resection have been consolidated into one section concerning indications for liver transplantation (CQ31). Details can be found in the "Introduction" from Section 5 (p. 103).

These guidelines are not meant to limit or force clinical decisions; rather, it is hoped that each CQ will be used as a reference for selecting appropriate treatment methods. In addition, only a few prospective studies with a high level of evidence have been conducted in Japan. Therefore, it is anticipated that new findings pertaining to surgeries will be released in the future.

- **Document Selection**

English articles published between 2008 and 2011 were searched using the key words "hepatocellular carcinoma" and "surgery." The search resulted in 2,898 original reports, which served as the basis for formulating guidelines. For newly set CQs, the search was repeated, and documents were selected using the same methods used for the 2005 and 2009 editions.

- **References**

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Table 1 Changes in CQs for Chapter 3: Surgery

	2005	2009	2013
Indications for Surgery/Surgical Procedures			
Preoperative liver function evaluation	●	●	●

	2005	2009	2013
Small liver cancer treatment	●		
Extensive resection	●		
Resection range		●	
Treatment for recurrence	●	●	
Standard liver resection			●
Preoperative tumor evaluation			●
Prognostic factors			
Postroperative prognostic factors	●	●	●
Surgical margin	●	●	●
Anatomical resection	●	●	●
Perioperative care			
Blood transfusion	●	●	●
Blood loss	●	●	●
Surgical drainage			●
Adjuvant therapy			
Neoadjuvant therapy	●	●	
Postoperative adjuvant therapy	●	●	
Neoadjuvant chemotherapy			●
Postoperative adjuvant chemotherapy			●
Liver transplantation			
Pretransplant TAE	●		
Pretransplant treatment		●	
Downstaging			●
Indications for transplantation			●
Post-transplant prognostic factors	●	●	
Comparison with liver resection	●	●	
Treatment of recurrence	●		
Background disease and transplantation		●	

Section 1 Indications for Surgery/Surgical Procedures

CQ19 What assessment modalities are appropriate for evaluating liver function prior to liver resection? What are the indications for surgery from the perspective of liver function?

Recommendation

Preoperative assessment of liver function should include measurement of the indocyanine green retention rate at 15 min (ICG-15) as well as general liver function tests. Surgery is indicated depending on the balance between these values and the planned extent of liver resection **(Grade B)**.

- **Scientific Statement**

The Child classification* and its modified version, the Child–Pugh classification*, have been used worldwide to classify hepatic functional reserve for preoperative evaluation of liver function. Although this classification was originally designed to determine whether surgery is indicated for patients with gastroesophageal varices, it is an excellent semiquantitative method for assessing and classifying hepatic functional reserve. Scoring involves a point system with five parameters derived from basic clinical symptoms and blood test results. Of these five parameters, ascites is particularly considered to be an indicator of portal hypertension, and if not controlled well, surgery is contraindicated. Platelet counts have also long served as an indicator of portal hypertension, and it has been reported that a low preoperative platelet count (less than 150,000/μL) is a risk factor for postoperative complications, hepatic failure, and postoperative death (L3F01385[1)] Level 3). In addition, Bruix et al. studied 29 patients with Child–Pugh class A cirrhosis who underwent resection for HCC. Preoperative portal venous pressures were measured using the hepatic venous pressure gradient (HVPG), and the results of multivariate analysis showed that HVPG was the only factor that contributed to postoperative liver failure (LF00514[2)] Level 3). In western countries, patients with Child–Pugh class B and C disease are generally contraindicated for surgery; however, in light of these latest findings, they are now advocating criteria that rule out liver resection for patients with Child–Pugh class A disease and coexisting portal hypertension. These criteria have, in fact, been adopted in liver cancer treatment guidelines in western countries (L3H00018[3]). To the contrary, Cucchetti et al. conducted a study comparing outcomes after liver resection between patients with and without portal hypertension, and their results showed no significant difference in postoperative mortality rate or complication rate. In addition, they demonstrated that h liver resection of two or more segments (Couinaud classification) is not contraindicated in patients with portal hypertension (L3F01321[4] Level 2b). Japanese reports also argue that there is no increase in postoperative complications if less invasive resection procedures are selected even in patients with portal hypertension; therefore, liver resection is not contraindicated, even in HCC patients with portal hypertension (L3F02174[5] Level 2b).

On the other hand, quantitative evaluation of preoperative liver function can be performed using galactose tolerance tests, 99mTc-GSA liver scintigraphy, ICG-15, amino acid clearance, and the aminopyrine breath test. Galactose tolerance testing was performed for 258 patients who underwent liver resection (6 postoperative deaths, 2%), of which 78 had HCC. The galactose elimination capacity (GEC) served as a useful prognostic factor for postoperative complications and death, and similar results have been confirmed in HCC patients (LF12084[6] Level 2b). It has been reported that 99mTc-GSA liver scintigraphy is superior for evaluating histological liver damage compared with ICG-15 (LF00457[7] Level 4). An increasing number of studies investigating the ability of ICG clearance have demonstrated its usefulness as a predictor of postoperative death. A study examining 127 HCC-resected patients revealed that ICG-15 is a better predictor of postoperative death compared with amino acid clearance or aminopyrine breath testing (LF00441[8] Level 2a). Furthermore, a study examining the safety of extensive liver resection of two or more segments showed that, in patients with cirrhosis, an ICG-15 of 14% was a useful cut-off value for predicting in-hospital mortality (LF00568[9] Level 2b). In fact, ICG-15 has been adopted by the Liver Cancer Study Group of Japan as a factor for evaluating liver damage (LF12088[10] Level 5) and is a standard test for assessing preoperative liver function. Yamanaka et al. devised a prediction score for liver failure to be used as a criterion for surgery. Scores were based on ICG-15, the extent of liver resection, and patient age (L3H00034[11)] Level 4). These criteria were further verified in 376 patients with HCC and 58 patients with metastatic liver cancer in their study, and it was reported that the fulfillment of these criteria accurately predicted postoperative death (LF00632[12] Level 2b). Takasaki et al. have also proposed different criteria that set, tolerable extents of liver resection according to individual ICG clearance values (L3H00037[13] Level 4). These criteria were also confirmed in 98 patients who underwent liver resection, and it was demonstrated that incidences of liver failure after liver resection and death were 2% and 0%, respectively, in patients who met the criteria and 23% and 1%, respectively, in those who did not (L3F01300[14] Level 2b). Makuuchi's criteria is widely applied in Japan (LF01858[15] Level 4) and uses ascites, total serum bilirubin levels, and ICG-15 to determine whether liver resection is indicated or contraindicated as well as the tolerable extent of resection. Liver resection was performed in 1,056 patients who met the criteria, and the reported operative mortality was 0% (L3H00036[16] Level 4).

- **Explanation**

Liver resection requires an even stricter assessment of hepatic functional reserve. Emphasis has been placed on the importance of conducting quantitative tests such as load tests in addition to qualitative evaluations such as general clinical tests. Nevertheless, no method for the quantitative evaluation of liver function can accurately determine liver function if used alone. The use of a single method enalbes the evaluation of only a single aspect of the liver, which has a wide range of functions. Ultimately, a comprehensive assessment of liver function, including blood test and imaging findings, is essential in addition to other tests.

There are many studies on ICG-15 as a quantitative test used in combination with blood tests and regular clinical data for preoperative liver function assessment. When performing liver resection, it is recommended that operability be determined on the basis of the balance between the estimated degree of liver damage and the extent of liver resection. Therefore, criteria that indicate the relationship between hepatic functional reserve and the permissible extent of liver resection are being proposed, mostly in Japan. Although these criteria have been verified according to reports of patients treated first-hand, their external validation is pending, which will be a future issue to be resolved. According to a follow-up study performed by the Liver Cancer Study Group of Japan, the operative mortality rate associated with liver resection in liver cancer patients in Japan was 0.8% (LF12089[17) Level 2a). However, an analysis of 54,145 liver cancer patients in the Diagnosis Procedure Combination (DPC) database revealed an in-hospital mortality rate of 2.6% (L3H00039[18) Level 2b). From a criteria evaluation standpoint, if one assumes the operative mortality rate to be ≤3% for liver cancer resection in Japan, and if the end-point is postoperative death, evaluation and verification of these criteria are not practical, ethical, or realistic in terms of liver function. The aforementioned reports also indicated a difference in in-hospital mortality associated with hospital volume. Futhermore, it was reported that the mortality rate in high-volume hospitals was 1.55%, whereas that in low-volume hospitals was higher at 4.04%. Therefore, hospital volume must also be taken into consideration when determining the indications for surgery (L3H00039[18) Level 2b).

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(Footnote)

*: The Child classification was originally termed the Child–Turcotte classification. The revised version by Pugh was the Child–Turcotte–Pugh classification (CTP classification). However, the term Child–Pugh classification is used in these guidelines to maintain consistency with the General Rules for the Clinical and Pathological Study of Primary Liver Cancer.

CQ20 What is the standard surgical procedure for liver resection?

Recommendation

Anatomical liver resection over a small area or partial resection as limited resection (particularly in patients with poor liver function) is chosen for the treatment of a small HCC lesion (maximum diameter ≤ 5 cm). Extended resection (including right or left lobectomy) of two or more segments is chosen for large HCC lesions **(Grade C1)**.

- **Scientific Statement**

The majority of HCCs develop against a background of chronic liver disease and initially appear as cirrhosis. The resulting liver damage inevitably decreases the permissible extent of resection compared with that for normal livers, and extensive liver resection such as left/right lobectomy often cannot be performed. Therefore, resection methods for HCC, such as partial liver resection (including tumor enucleation), were proposed (LF00992[1) Level 2b). In addition, because the liver is hard in patients with cirrhosis, tumors often cannot be identified by palpating the surface of the liver. Therefore, liver resection is often more difficult for HCC than for metastatic liver cancer. This issue has been addressed with the use of intraoperative ultrasound, which can identify the location of the tumor in the liver during resection (LF03339[2) Level 4).

HCC is known to metastasize to the liver via the portal vein, and from a theoretical and curative standpoint, it is recommended to anatomically perform resection of the relevant area associated with the portal vein. A procedure was developed for anatomical resection of small areas of the liver in patients with chronic liver injury. This method involves the injection of a dye via ultrasound-guided puncture into portal vein branches in the tumor-bearing region, which enables identification of the surface of the relevant hepatic segment and facilitates resection (LF00988[3) Level 4). Furthermore, in the event that puncture and staining of the tumor-bearing segment via the portal vein is not possible because of an arterioportal (AP) shunt or portal venous tumor thrombus, another method that involved the counterstaining of neighboring segments to identify the tumor-bearing segment was devised (LF06786[4] Level 5). On the other hand, a method that involves treatment of the portal vein and arteries and Glisson's capsule with the associated biliary duct branches in the tumor-bearing segment and identification of the segment, followed by anatomical liver resection, has been implemented (LF00859[5] Level 4). Moreover, other surgical procedures that maximize conservation of the liver parenchyma, such as liver resection that treats the root of the right hepatic vein and conserves the segment if the branch of the hepatic vein from S6 (right inferior hepatic vein) that flows directly into the inferior vena cava is present, have been reported (LF01861[6] Level 4). Alternatively, S2 can be conserved and S3/4 can be resected (LF01860[7] Level 4).

The caudate lobe of the liver is located on the dorsal side of the hilar plate, and until now, tumors in this area have usually been treated with extensive liver resection that included liver parenchyma on the abdominal side. However, because the majority of HCC patients also have liver disease, this method cannot be adopted. High dorsal resection has been proposed in response to this issue, which involves counterstaining from the dorsal side and single resection of the caudate lobe (LF01856[8] Level 5). Another resection method that uses an anterior transhepatic approach with isolated resection of the liver has been developed, wherein the liver is transected anteriorly along the middle hepatic vein (LF00334[9] Level 4).

With an improvement in liver resection procedures because of developments such as anatomical resection using intraoperative ultrasound and parenchyma-sparing surgical methods, conventionally applied surgeries such as segmentectomy and others have also become more refined in practice. As many as 10–20 reports on central bisegmentectomy (LF00916[10] Level 4) and anterior segmentectomy (LF01859[11] Level 4) have been published.

As a result of these improvements in safety and overall surgical procedures, extensive resection is becoming increasingly effective for advanced HCC. If necessary, patients with cancer invasion in the inferior vena cava can reportedly be treated with combined liver and inferior vena cava resection with reconstruction by vascular grafting (L3F04355[12] Level 4, L3F06074[13] Level 4). On the other hand, the right lobe of the liver is usually displaced before liver resection in right hepatectomy, and mobilization is often difficult if the tumor is large. In such situations, leading liver resection from the anterior (abdominal side) side (anterior approach) has also been proposed, and both short- and long-term outcomes have been better than those with methods using regular liver mobilization (LF11149[14] Level 1b). Although it is difficult to control bleeding from the hepatic vein deep in the liver, a method where the liver is lifted during resection has been designed. In this method, a tape is passed along the anterior face of the inferior vena cava and the back of the liver to lift the liver during resection (L3H00009[15] Level 4). This method is used widely and it has been considered an effective procedure when combined with right hepactectomy using the anterior approach (L3F05006[16] Level 2b).

As HCC progresses, it often forms tumor thrombi in the main branches of the portal vein. In such situations, a portal vein tumor thrombus is generally resected concurrently with the targeted liver segment (LF00136[17] Level 2b). However, because this method requires extensive liver resection or total liver resection (in theory), it is often difficult to perform in patients with liver damage. Reports of a liver resection method that removes only the tumor thrombus from the inner wall of the portal vein also exist; this method is considered efficacious because there is no difference in long-term outcome when compared with that of conventional methods (L3F01800[18] Level 2b).

- **Explanation**

Liver resection has been documented and sporadically performed since the 1950s. However, in a time when computed tomography (CT) and ultrasonography were not available, it was realistically impossible to understand the intrahepatic vascular structure of each individual patient. Although segmentectomies and more extensive liver resections have been performed once identifiable veins are treated in the hepatic portal area, in reality, the majority of procedures were lateral segmentectomies, left/right lobectomies, and wedge resections of the liver margin. It was after the late 1970s that CT and ultrasonography were developed and became available for clinical use. Furthermore, technology in liver resection drastically advanced during the early 1980s, once intraoperative ultrasound and its application during liver resection made it possible to grasp real-time positional relationships between hepatic tumors and vascular structures during surgery. In addition, the liver is damaged in the majority of HCC patients; therefore, tumors that cannot be visually examined or palpated on the liver surface require limited yet anatomical resection, and this need has driven technological advancements in liver resection further. One must keep in mind that there is a vast amount of surgical literature in Japan regarding the development and advancement of these various liver resection procedures.

Compared with surgery in other organs, there is a variety of liver resection techniques that depend on the segment to be resected and its size. Furthermore, the majority of surgeries require advanced technology during resection, such as intraoperative ultrasound of the parenchyma, given that internal structures cannot be observed directly. Despite the fact that highly advanced techniques are required, blood loss and mortality rates associated with liver resection have decreased dramatically over the past 20–30 years, indicating the establishment and increasing safety of surgical techniques. On the other hand, the evidence level of documents referenced for this CQ is mostly Level 4; therefore, additional evidence must be collected hereafter to determine the pros and cons of each surgical procedure for various tumor conditions.

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CQ21 What are the indications for liver resection in terms of tumor condition?

Recommendation

Liver resection is indicated for HCC if there are three or fewer tumors and all are limited to the liver. There is no restriction on tumor size. It is suggested that patients with tumor invasion to the portal vein be indicated for surgery if the tumor has not progressed beyond the first-order branches **(Grade B)**.

- **Scientific Statement**

Classification of HCC progression incorporates treatment regulations proposed by the Liver Cancer Study Group of Japan and includes factors such as tumor size, tumor number, presence or absence of vascular invasion, and degree of invasion, which will be described herein.

There are multiple reports on the long-term outcome of resection for liver tumors measuring 10 cm or larger, and the 5-year survival rate is reportedly 20%–30% (LF00354[1]) Level 2b, L3F06268[2]) Level 2b, LF11836[3]) Level 2b). Although no studies have compared this therapy with other therapies or non-treatment, these results are clearly preferable to those of non-treatment (L3H00008[4]) Level 1a); therefore, operability is not limited by tumor size.

In terms of tumor number, the outcomes of resection in patients with two or more tumors were compared with those in patients with single tumors, and in another study, the outcomes were compared with those of other treatment methods (L3F02174[5]) Level 2b, L3F00035[6]) Level 2b). Although the long-term outcome for multiple tumors is poorer than that for single tumors, resection is not necessarily contraindicated, with results better than those of other noncurative or maintenance therapies. Therefore, resection is not contraindicated in patients with multiple liver tumors. In these reports, the majority of patients with multiple lesions had two tumors. There are no reports with a high level of evidence on the maximum number of tumors permissible for resection; the limit was set at three tumors or lesser, similar to the criteria for percutaneous ablation therapies.

Portal vein invasion is consistently reported as the most powerful prognostic factor for HCC. There are many reports describing resection outcomes in patients with portal vein invasion (LF00136[7]) Level 2b, L3F06087[8]) Level 2b, L3F01800[9]) Level 2b). The prognosis is poor when tumor thrombus has advanced into the portal vein. However, if tumor invasion does not progress beyond the first-order branches, the postoperative 5-year survival rate is 10%–40% and surgery is indicated, considering that other treatment methods are contraindicated and that nontreatment is a poor choice in comparison. If the tumor thrombus has progressed to the portal vein trunk, the prognosis is poor and surgery is contraindicated. However, if the condition is mild, the outcome after resection is reportedly the same as that when the thrombus has not reached the first-order branches; therefore, surgery is indicated (L3F01800[9)] Level 2b).

- **Explanation**

In this CQ, we described the maximum progression of HCC permissible for liver resection. For HCC cases that follow the typical multi-stage development of cancer, it is important to have a CQ that discusses the stage (precancerous conditions or early stage) at which patients become candidates for treatment interventions, including resection. This issue, however, will be discussed in other sections. If a tumor meets the criteria for other treatment methods, a CQ discussing whether to select liver resection or another treatment(s) would be important, particularly when choosing between surgery and percutaneous ablation therapy or between surgery and transplantation. This, however, will be discussed in other sections.

Among the factors of tumor size, tumor number, and vascular invasion, tumor size and vascular invasion are indicators of cancer progression, and the issue of determining the point of cancer progression at which resection is indicated remains. Generally, there is no alternative therapy for patients with advanced tumor determined by these factors. Therefore, this comes down to the issue of comparing improved survival benefits with treatment to those without treatment and finding the optimum balance at which benefits outweigh risks (complications, operative mortality, etc.). Liver resection in such advanced cases of HCC often demands a highly complicated surgery; therefore, indications may vary with the level of proficiency at each institution. In contrast, the number of tumors generally indicates the potential severity of carcinogenesis in the background of the entire liver (it is also an indicator of intrahepatic metastases). The CQ that discusses the number of tumors that qualifies for liver resection is synonymous with the CQ that discusses the extent to which local surgery can still be performed, which, in that sense, is considered equivalent to the debate of tumor count and radiofrequency ablation criteria. The question now is, what is the maximum number of tumors acceptable for percutaneous ablation therapies compared with that acceptable for treatments that involve the entire liver, such as transplantation and TACE? As the number of tumors increases, a gradual transition to TACE is appropriate; however, setting a threshold number of tumors can be a delicate matter. There are no reports backed with strong evidence that compare resection of four or more tumors with other treatment methods; this CQ was written on the basis of existing standards stating that liver resection is indicated for three or fewer tumors.

In this edition, it is not mentioned whether surgical treatment with liver resection is recommended to treat a limited number of HCC metastases (lungs, adrenal glands, lymph nodes, etc.) because only a few scattered reports are available in this regard.

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Section 2 Prognostic Factors

CQ22 What are the prognostic factors after liver resection?

Recommendation

Major prognostic factors after liver resection are stage classification, vascular invasion, liver function, and tumor number **(Grade B)**.

- **Scientific Statement**

A study of the post-resection survival rate showed a favorable prognosis for patients with single, pTNM stage I/II tumors measuring smaller than 5 cm with capsule formation, no vascular invasion, and serum albumin levels less than 40 g/L, and of these factors, pTNM stage was found to be the most reliable prognostic factor (LF00073[1)] Level 2a). Furthermore, a study of relapse-free survival found that stage classification, tumor diameter, vascular invasion, tumor number, and capsule formation were significant prognostic factors, similar to those found in the previous study. Of these factors, vascular invasion was associated with prognosis for survival during the entire postoperative period (LF00777[2]) Level 2b). Less than 2 years after surgery, the factors for early-stage recurrence were nonanatomical resection, pathological vascular invasion, and an AFP level of 32 ng/mL or higher (LF11429[3]) Level 2b). On the other hand, there are reports that tumor diameter does not affect prognosis (LF00623[4]) Level 2b, LF00853[5]) Level 4, L3F01869[6]) Level 2b); therefore, it cannot be assumed that the prognosis for giant HCC will necessarily be poor. In addition, the survival rate is good for early-stage HCC tumors measuring 2 cm or smaller (LF00378[7]) Level 2a). Furthermoe, positive prognostic factors for patients who undergo HCC resection and have tumor thrombus in the main trunk or first-order branches of the portal vein include the absence of ascites, a prothrombin activity of 75% or higher, and a tumor diameter of 5 cm or lesser (LF10619[8]) Level 2b). Prognosis can also be improved in patients with limited hepatic functional reserve by performing liver resection with portal vein tumor thrombus removal by extraction, similar to extensive liver resection (L3F01800[9]) Level 2b).

- **Explanation**

Thirty-seven articles related to prognostic factors were selected for this 2009 edition of the guidelines, and vascular invasion, liver function, tumor number, tumor stage classification, and tumor diameter were found to be significant prognostic factors. In this revised edition, 2,898 original articles published between 2008 and 2011 in English were found in a search using the key words “hepatocellular carcinoma” and “surgery”. Fifty-four of these documents were relevant to prognostic factors, of which 38 were found to be highly reliable. Some of these articles included studies on hepatitis virus markers and genetic markers in addition to the previously reported factors. Furthermore, of these factors, vascular invasion was reported most often (34%) as a significant factor, followed by liver function (18%), tumor number (16%), tumor diameter (16%), and stage classification (11%). Other factors included levels of tumor markers (24%), genetic markers (18%), and hepatitis virus markers (11%). The Child–Pugh classification and serum albumin levels were often found to be significant factors for liver function. Tumor diameter did not always affect prognosis; therefore, a consensus has yet to be reached. Of the different stage classifications, stage 0 or early-stage HCC carried a favorable prognosis; therefore, early-stage HCC may also be considered as a prognostic factor (LF00378[7] Level 2a). There has been an increase in molecular biological studies, such as reports that PIVKA-II and AFP-L3 fraction are predictors of recurrence and that the cytochrome P450 1A2 (CYP1A2) gene is linked to recurrence (L3F01429[10] Level 2b). In addition, several documents reported that significant prognostic factors pertaining to surgical procedures include decreased blood loss and anatomical resection. The majority of documents, however, state that the surgical margin is not a significant factor.

- **References**

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CQ23 Does the size of the resection margin affect prognosis?

Recommendation

A minimum surgical margin is sufficient for liver resection **(Grade B)**.

- **Scientific Statement**

No significant difference in postoperative recurrence rate was observed between two groups, one with liver resection margins of 1 cm or wider and another with margins smaller than 1 cm (LF00128[1)] Level 2a, LF00777[2)] Level 2b). A comparative study divided patients according to liver resection margins of 5 mm or greater or less than 5 mm and found no significant difference in postoperative recurrence (LF00623[3]) Level 2b, LF00728[4]) Level 2b). Even if the tumor was adjacent to a major vessel and a resection margin could hardly be secured for liver resection, there was no significant difference in relapse-free survival or the cumulative survival rate (L3F01389[5]) Level 2b). No significant difference in survival was reported when lobectomy and more extensive resections were compared to limited surgery (LF00033[6]) Level 2b). Although an RCT has shown that securing a 2-cm margin carries a better prognosis than securing a 1-cm margin (LF11766[7]) Level 1b), the optimum width of surgical margins remains unclear, and it is unlikely that the size of the resection margin contributes to prognosis.

- **Explanation**

In this 2009 edition of the guidelines, "hepatocellular carcinoma" and "surgery" were used as key words to search 1,117 articles written in English and published from 1980 to 2007. The search found266 original articles pertaining to prognostic factors, of which 74 highly credible articles were selected and reviewed. However, only 2 articles were found to be relevant to the surgical margin within this revision period. It is therefore believed that surgical margins measuring 5 mm to 1 cm do not contribute to prognosis. In addition, if a tumor located adjacent to vessels is removed and liver resection is performed, there is no significant difference in relapse-free survival and cumulative survival, even if almost no surgical margin has been secured (L3F01389[5]) Level 2b). On the other hand, Shi et al. conducted an RCT in Hong Kong that separated patients with solitary HCCs without vascular invasion into 1- and 2-cm resection margin groups, it was found that prognosis was better in the latter group (LF11766[7]) Level 1b). However, the characteristics of patients were very different from those of patients in Japan, as the mean age of patients in both groups was 51 years or lesser, ICG-15 was less than 10%, and more than 80% patients had hepatitis B. In general, resection margins are limited by hepatic function, tumor location, and tumor size, and securing a margin of 2 cm or larger is realistically difficult in many patients. Therefore, it is recommended that liver resection for HCC be performed at a width of 5–10 mm from the tumor edge, and if there is an adjacent vessel, then resection at 0 mm is sufficient.

- **References**

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CQ24 Does anatomical liver resection affect prognosis?

Recommendation

Anatomical resection is recommended for liver resection **(Grade B)**.

- **Scientific Statement**

In a retrospective study of HCC lesions measuring 5 cm or smaller, the survival rates were better with anatomical resection than with partial resection, and the differences were particularly significant in patients with extranodal metastases (LF00102[1)] Level 2b). A study of relapse-free survival also showed that anatomical resection is superior to partial resection (LF00253[2)] Level 2b). Furthermore, in solitary HCCs, survival rates and relapse-free survival were significantly better with anatomical resection and subsegmentectomy than with partial resection (LF11148[3)] Level 2b). Moreover, a national follow-up study conducted in 5,781 patients by the Liver Cancer Study Group of Japan similarly reported that anatomical subsegmentectomy is superior (L3F01974[4)] Level 2a). Reports have also stated that relapse-free survival differs only for tumors with no cirrhosis or invasion (LF00728[5)] Level 2b). On the basis of the abovementioned findings, it is highly possible that anatomical resection improves prognosis.

- **Explanation**

HCC that advances via the portal vein is often concomitant with portal vein invasion or intrahepatic metastases, and from a curative standpoint, anatomical resection of the tumor-bearing segment is recommended. Nevertheless, because extensive resection in patients with chronic hepatitis and cirrhosis can lead to excessive invasion, anatomical subsegmentectomy was designed to resolve the conflict between curative treatment and preservation of liver function. Currently, all comparative studies conducted for partial resection and anatomical resection are retrospective ones. Hasegawa et al. classified hepatectomies performed for solitary liver cancer into an anatomical resection group (n = 156) and a nonanatomical resection group (n = 54) and studied the prognoses (LF11148[3)] Level 2b). Their results showed that the 5-year survival rate

(66% vs. 35%, p = 0.01) and relapse-free survival rate (34% vs. 16%, p = 0.006) were significantly favorable with anatomical resection. Furthermore, Eguchi et al. investigated the significance of anatomical resection according to tumor diameter and found that relapse-free survival was good in the anatomical resection group if tumor diameters were 2–5 cm (L3F01974[4] Level 2a). Sixteen compiled retrospective studies have similarly indicated the superiority of anatomical resection. However, 11 of these studies were Japanese, accounting for the majority of study data. The other studies included two each from France and Korea and one from the United States (L3F01988[6] Level 2b). In order to establish an optimized procedure for liver resection, we are awaiting reports of RCTs that have been designed to reflect the actual situation in Japan.

- **References**

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Section 3 Perioperative Management

CQ25 Is proactive, perioperative administration of blood products recommended?

Recommendation

Homologous red blood cell transfusion should be avoided if possible **(Grade B)**.

Administration of fresh frozen plasma is not always necessary **(Grade B)**.

- **Scientific Statement**

The majority of reports state that homologous red blood cell transfusion should be avoided as much as possible because it increases the risk of cancer recurrence and is likely to induce hyperbilirubinemia and liver failure and because lower hematocrit levels are desirable for microcirculation in the liver (L3F01363[1] Level 4, L3F01724[2] Level 3). Conversely, some reports state that the recurrence rate does not change, irrespective of blood transfusion (LF00031[3] Level 3).

It has been reported that autologous transfusion increases the synthetic ability of the liver without increasing the risk of cancer recurrence; therefore, it is a safe and efficient method to avoid homologous red blood cell transfusion.

In addition, administration of fresh frozen plasma reportedly has no effect on the postoperative course of hepatectomy, and patients with relatively good liver function, in particular, do not necessarily need frozen plasma unless they have lost a large amount of blood or the patient has hypoalbumineamia (L3F02461[5] Level 3, L3F02475[6] Level 2a).

- **Explanation**

In general, surgery without blood transfusion is recommended. Blood transfusion particularly presents a problem in cancer surgery because it may lead to immunosuppression. Differences in tumor recurrence rates associated with blood transfusion have been reported in a large variety of cancer surgeries, and the same can be said for HCC (L3F01363[1] Level 4, L3F01724[2] Level 3). However, some reports found no difference in recurrence rates, regardless of blood transfusion. Under these circumstances, autologous blood transfusion may be used to avoid homologous red blood cell transfusion without inducing adverse events.

In order to avoid blood transfusion throughout the perioperative period, a minimum hematocrit level of as low as 20% should be maintained as long as hemodynamics can be maintained (LF00917[7] Level 3). There is, however, no data with a high level of evidence to support this recommendation.

In the past, it has been recommended that fresh frozen plasma be administered for replenishing coagulation factors and maintaining effective plasma volume and plasma osmolality (LF00917[7] Level 3). Fresh frozen plasma has not always affected the postoperative course (L3F02461[5] Level 3), however, according to a cohort study examining Child–Pugh class A patients with an intraoperative blood loss of less than 1,000 mL. If serum albumin levels exceed 2.4 g/dL 2 days after surgery, fresh frozen plasma is unnecessary (L3F02475[6] Level 2a). Excessive administration also reportedly increased respiratory complications (L3F01724[2] Level 3). Furthermore, administration of plasma derivatives, in general, is not recommended unless there is heavy bleeding (L3H00015[8] Level 1a).

- **References**

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carcinoma. Ann Surg 2009;249(4):617-23.

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3) LF00031 Kwon AH, Matsui Y, Kamiyama Y. Perioperative blood transfusion in hepatocellular carcinomas:influence of immunologic profile and recurrence free survival. Cancer 2001;91(4):771-8.

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6) L3F02475 Yamazaki S, Takayama T, Kimura Y, Moriguchi M, Higaki T, Nakayama H, et al. Transfusion criteria for fresh frozen plasma in liver resection:a 3+3 cohort expansion study. Arch Surg 2011;146(11):1293-9.

7) LF00917 Makuuchi M, Takayama T, Gunven P, Kosuge T, Yamazaki S, Hasegawa H. Restrictive versus liberal blood transfusion policy for hepatectomies in cirrhotic patients. World J Surg 1989;13(5):644-8.

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CQ26 Does hepatic pedicle clamping and decreased central venous pressure decrease bleeding during liver resection?

Recommendation

Hepatic pedicle clamping is effective for decreasing the amount of blood loss during liver resection **(Grade A)**.

Decreasing central venous pressure (CVP) is also an effective means for decreasing the amount of blood loss during liver resection **(Grade C1)**.

- **Scientific Statement**

RCTs pertaining to hepatic pedicle clamping show that intermittent occlusion of blood flow to the liver (Pringle maneuver) decreases the amount of blood loss during liver resection without affecting liver function (LF00434[1)] Level 1b, L3F02530[2)] Level 1b). The effectiveness of hemihepatic vascular inflow occlusion has also been reported (LF01862[3)] Level 2b, L3F02488[4)] Level 1b), and there was no difference in liver function when a protease inhibitor was administered during intermittent occlusion of blood flow to the liver at 15- and 30-min intervals (L3F02504[5)] Level 1b).

RCTs have demonstrated that decreasing the CVP to 5 cm H_2O or lower by clamping the inferior vena cava below the liver during liver resection and/or by using drugs can decrease the amount of blood loss and stabilize hemodynamics (L3F02524[6)] Level 1b, L3F02528[7)] Level 1b). There are, however, reports in which decreased CVP did not result in decreased blood loss (L3F02503[8)] Level 1b). Furthermore, it has been reported that pulmonary embolism was caused by clamping of the inferior vena cava below the liver. Therefore, caution must be exercised (L3F02524[6)] Level 1b).

- **Explanation**

Intermittent occlusion of blood flow to the liver has been broadly implemented to decrease bleeding during hepatectomy, and the safety of this procedure has been confirmed. Hemihepatic vascular inflow occlusion is recommended when the resection range is limited to one lobe. Because the majority of blood loss during liver resection is from the hepatic veins, decreasing CVP seems appropriate and is reportedly useful; however, there are contradictory reports as well. Inferior vena cava occlusion and drugs can be used to decrease CVP; however, pulmonary embolism should be carefully considered when performing inferior vena cava occlusion and the safety of these procedures must be investigated in detail.

- **References**

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6) L3F02524 Rahbari NN, Koch M, Zimmermann JB, Elbers H, Bruckner T, Contin P, et al.

Infrahepatic inferior vena cava clamping for reduction of central venous pressure and blood loss during hepatic resection:a randomized controlled trial. Ann Surg 2011;253(6):1102-10.

7) L3F02528 Ryu HG, Nahm FS, Sohn HM, Jeong EJ, Jung CW. Low central venous pressure with milrinone during living donor hepatectomy. Am J Transplant 2010;10(4):877-82.

8) L3F02503 Kato M, Kubota K, Kita J, Shimoda M, Rokkaku K, Sawada T. Effect of infra-hepatic inferior vena cava clamping on bleeding during hepatic dissection:a prospective, randomized, controlled study. World J Surg 2008;32(6):1082-7.

CQ27 Is abdominal drain placement necessary for liver resection?

Recommendation

Intra-abdominal drainage is not always necessary for elective liver resection **(Grade B)**.

- **Scientific Statement**

According to RCTs pertaining to abdominal drain placement during elective liver resection, routine drain placement is reported to be unnecessary or contraindicated because of increased wound complications, sepsis, and accumulation of infectious fluid, resulting in a significant increase in hospital days (L3F02693[1]) Level 1b, L3F02777[2]) Level 1b, L3F02563[3]) Level 1b). On the other hand, abdominal drainage is recommended for cirrhotic patients with portal hypertension, as there are fewer complications related to postoperative ascites and because hospital stay is shortened (L3F02634[4]) Level 1b). Because drain placement is therapeutically useful for treating bile leakage and abdominal fluid retention (L3F02680[5]) Level 4) and for monitoring bilirubin levels in drainage fluid to predict possible bile leakage (L3F02781[6]) Level 4), it has also been recommended for patients at high risk of developing bile leakage, such as those with biliary tract reconstruction, exposure of major Glisson's sheath, and intraoperative bile leakage (L3F02656[7])

Level 3). However, intra-abdominal drainage is reportedly unnecessary during liver resection for living donor liver transplantation (L3F02692[8)] Level 4).

A few reports have recommended that the drain be removed in the early stages (L3F02656[7)] Level 3). However, none of these studies are backed with strong evidence.

- **Explanation**

The Center for Disease Control and Prevention (CDC) Guidelines for the Prevention of Surgical Site Infection recommend that “if drainage is necessary, closed suction drainage should be used and the drain should be removed as early as possible” (L3H00014[9)]). Hepatectomy is unlike other abdominal surgeries and is often concomitant with chronic liver disease; therefore, one must be aware of bile leakage and refractory ascites. Although an RCT pertaining to drain placement for elective liver resection has been implementd since 1990, patient numbers were low and problems with evaluation methods were reported.A study that examines the degree of coexisting liver damage and resection procedures is required. Furthermore, drain placement should be performed with more care during living donor liver transplantation in healthy adults. Additional studies are also required to examine drain placement for laparoscopic liver resection, which has been increasingly performed in recent years.

- **References**

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al. Abdominal drainage after liver resection for hepatocellular carcinoma in cirrhotic patients:a randomized controlled study. Hepatogastroenterology 2004;51(56):536-40.

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6) L3F02781 Torzilli G, Olivari N, Del Fabbro D, Gambetti A, Leoni P, Gendarini A, et al. Bilirubin level fluctuation in drain discharge after hepatectomies justifies long-term drain maintenance. Hepatogastroenterology 2005;52(64):1206-10.

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8) L3F02692 Liu CL, Fan ST, Lo CM, Chan SC, Yong BH, Wong J. Safety of donor right hepatectomy without abdominal drainage:a prospective evaluation in 100 consecutive liver donors. Liver Transpl 2005;11(3):314-9.

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Section 4 Adjuvant Therapy

CQ28 Does neoadjuvant chemotherapy improve prognosis after liver resection?

Recommendation

There is no recommended neoadjuvant chemotherapy aimed at improving prognosis after liver resection for HCC **(Grade C2)**.

- **Scientific Statement**

There are few studies with a high level of evidence supporting the use of systemic chemotherapy as neoadjuvant chemotherapy. When transcatheter arterial embolization (TAE)/transcatheter arterial chemoembolization (TACE) is performed a single time as neoadjuvant chemotherapy, liver function is only slightly impaired and the prevalence of complications is low. Tumor necrosis and shrinkage by TAE or TACE may increase the rate of resection for advanced HCC, but no consensus pertaining to prognosis improvement has been reached (LF00018[1)] Level 4, L3F00931[2)] Level 4, LF00142[3)] Level 3, LF00373[4)] Level 2b: effective, L3F02802[5)] Level 3, LF00350[6)] Level 2b, LF00497[7)] Level 2b, LF12028[8)] Level 2b, LF00537[9)] Level 1b, L3F02806[10)] Level 1b, L3F02805[11)] Level 1a: ineffective). Furthermore, it has yet to be confirmed whether preoperative hepatic arterial infusion chemotherapy effectively inhibits recurrence or improves survival rates (LF10065[12)] Level 1a).

- **Explanation**

Nearly all the documentation supporting TAE/TACE as an effective neoadjuvant chemotherapy was published around the year 2000. However, only a few articles were backed by strong evidence for this therapy. On the other hand, articles that determined TAE/TACE as ineffective included RCTs and meta-analyses supported by evidence from 2000 onward Although a consensus has not been reached, neoadjuvant chemotherapy with TAE/TACE is not recommended.

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CQ29 Does adjuvant chemotherapy improve prognosis after liver resection?

Recommendation

There is no recommended adjuvant chemotherapy for improving prognosis after liver resection for HCC **(Grade C2)**.

- **Scientific Statement**

There are reports claiming that systemic chemotherapy is a useful postoperative adjuvant chemotherapy in patients with good liver function, yet there are reports in which liver function was exacerbated with systemic chemotherapy, resulting in a poor prognosis. Therefore, a consensus has not been reached (LF00502[1)] Level 1b, L3F00645[2)] Level 1b: effective, LF00032[3)] Level 1a, LF00351[4)] Level 1b, LF10555[5)] Level 1b: ineffective). Transcatheter hepatic arterial therapies such as hepatic arterial infusion chemotherapy, TAE, and TACE have also been performed as adjuvant chemotherapy; however, the majority of these reports showed no difference in cumulative survival, despite significant differences in relapse-free survival (in terms of cumulative survival, L3H00017[6)] Level 1b: effective; LF02670[7)] Level 1b, LF00522[8)]Level 1b, LF00351[4)] Level 1b: ineffective). In a meta-analysis that included four RCTs, transcatheter hepatic arterial therapy reeduced the recurrence rate and improved the survival rate (LF10065[9)] Level 1a). However, completely different drugs and methods were used; therefore, the outcomes must be carefully evaluated. In special cases, there are reports confirming that postoperative therapy via the portal vein and TACE are effective in patients with HCC and portal vein tumor thrombus (L3F00497[10] Level 3, L3F02820[11] Level 1b). Furthermore, short-term prognosis was reportedly improved with intra-arterial injection of [131-I] Lipiodol (LF00316[12] Level 1b); however, these effects were not observed for long-term prognosis in a follow-up report (L3F00717[13] Level 1b).

- **Explanation**

Tegafur, carmofur, and capecitabine have been used as postoperative adjuvant chemotherapies, and doxorubicin, cisplatin, and 5-FU have been used as transcatheter hepatic arterial therapy. Unlike neoadjuvant chemotherapy, some reports have provided evidence for postoperative adjuvant chemotherapy. Regardless of the administration route or method, a standard protocol for adjuvant chemotherapy has yet to be established, and further investigations are needed to design an effective protocol. Sorafenib, an oral molecular targeted drug, is a promising adjuvant therapy. At present, a multinational cooperative study called “Sorafenib as adjuvant treatment in the prevention of recurrence of hepatocellular carcinoma (STORM)” is in progress worldwide, the results of which are strongly anticipated.

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Section 5 Liver Transplantation

- **Introduction**

In the 1980s, liver transplantation was introduced for HCC patients with unresectable tumors, and nearly all patients died from recurrence within a few years. As a result of these experiences, HCC patients were no longer accepted as candidates for liver transplantation in most liver transplant facilities. In the early 1990s, tumor criteria for liver transplantation in HCC patients (such as the Milan criteria, etc.) were established, and it became clear that the outcome of liver transplantation for HCC was not inferior to that for benign, end-stage liver disease. As a result, HCC patients have come to be acceptable candidates for liver transplantation.

On the other hand, the majority of HCC patients also present persistent infection with hepatitis B virus (HBV) or hepatits C virus (HCV). Cancer treatment alone is insufficient for HCC transplantation; the suitability of antiviral therapy must also be considered. Indications and treatment policies for liver transplantation requiring antiviral therapy have rapidly changed over the past 20 years. Transplant outcomes for hepatitis B patients in particular have dramatically improved with the introduction of antiviral drugs and neutralizing antibodies.

New therapies generally begin at an experimental stage, and as the number of patients accumulates, a general consensus is normally reached. Evidence based on RCT results is established at the final stage after the treatment method has become established to some extent over a considerable amount of time. In that context, liver transplantation is a relatively new therapy for HCC, and there are no Level 1b studies. In addition, because of the unique characteristics of liver transplantation, it is difficult to implement RCTs in order to compare liver transplantation with other therapies or with different transplant criteria. In this sense, it should be noted first that regular procedures for creating guidelines, in which recommendations are generated from CQs based on documents with a high level of evidence, do not completely apply in this field.

In this revised edition, the content of CQs was significantly altered from that in the previous edition (2009 edition). In the 2009 edition, the following four CQs were included: CQ27, “Does treatment for hepatocellular carcinoma before liver transplantation improve prognosis?”; CQ28, “What are the prognostic factors after liver transplantation? With what tumor criteria can liver transplantation be recommended? (What eligibility criteria are appropriate for hepatocellular carcinoma patients to be candidates for transplantation?)”; CQ29, “How many HCC patients are candidates for surgery or transplantation, or both? In addition, in patients who are eligible for both treatments, which may achieve better results, surgery or transplantation?”; and CQ30, “Are there any differences in results after transplantation according to differences in background liver diseases (HBV, HCV, alcohol, primary biliary cirrhosis, and cryptogenic)? Do indications change?” In this revised edition, these questions were simplified into two CQs: CQ30, “Does pretransplantation tumor downstaging improve prognosis of liver transplantation?” and CQ31, “What are the criteria for liver transplantation in hepatocellular carcinoma patients?”

CQ30 Does pretransplantation tumor downstaging improve the prognosis of liver transplantation?

Recommendation

There is insufficient scientific evidence to support that tumor downstaging prior to liver transplantation improves HCC prognosis **(Grade C1)**.

- **Background**

The most influential factor affecting prognosis in HCC patients with complications of cirrhosis and liver failure is whether the patient has undergone liver transplantation. Because of the serious shortage of deceased donors and risks associated with living donor transplantation, however, tumor stage, a major risk factor for post-transplant recurrence, imposes restrictions on liver transplantation for HCC. The statement below is a discussion of whether downstaging of HCC using pretransplantation therapy improves post-transplantation prognosis.

- **Scientific Statement**

Mazzaferro et al., who proposed the Milan criteria, treated 28 out of 48 patients while they were on a transplant wait list [26 cases of TACE, 1 case of percutaneous ethanol injection (PEI), and 1 case of liver resection] and found there was no significant difference in the 4-year survival rate, which was 79% for the treatment group and 69% for the non-treatment group (LF00540[1)] Level 2a). The response rate, however, is not mentioned in their report. A multicenter, co-operative, retrospective case–control study was performed in France by Decaens et al., in which 100 patients pretreated with TACE before liver transplantation were compared with 100 untreated patients (LF10869[2)] Level 2b). According to this study, the 5-year survival rates for the TACE treatment group and non-treatment group were 59.4% and 59.3%, respectively. Relapse-free survival rates were also analyzed in patients who survived at least 3 months after transplantation, and the rates were not significantly different after 5 years, at 67.5% and 64.1%, respectively. Among patients who met the Milan criteria, there was no significant difference in 5-year survival rates between 74 patients treated with TACE and 68 untreated patients, at 68.8% and 67.1%, respectively. The explanted livers of 30 patients in the TACE group were confirmed to be 80% necrotic, and the 5-year survival rate was 63.2%. Although the result was slightly better than that (54.2%) observed in the control group, there was no significant difference.

In terms of meeting the Milan criteria, out of 68 patients who were treated with TACE, 62 responded favorably and had a 5-year survival rate of 73.3%. In comparison, patients experiencing no change or disease progression had a 2-year survival rate of 40%, and none of the patients survived for 5 years (LF12091[3)] Level 4). In this report, there was a large amount of disparity in the number of patients between comparison groups, and no significant differences were observed between patients who exhibited complete necrosis (24 patients) and those with partial necrosis (38 patients). A multicenter, co-operative, case–control study examined the effects of supraselective TACE before partial transplantation in 30 patients and conventional TACE in 3 patients whose tumor criteria were matched from among 479 patients. Complete tumor necrosis was observed more frequently in the supraselective TACE group, and the 5-year relapse-free survival tended to be favorable; however, no significant difference was observed between groups (87% for supraselective TACE group vs. 64% for conventional TACE group) (LF10876[4)] Level 3).

In addition, results of a prospective study in which adjuvant therapy was administered to patients who were excluded from surgery on the basis of tumor staging but underwent transplantation after tumors were downstaged to meet criteria levels, have been published (L3F01870[5)] Level 4).

Futhermore, 35 patients who satisfied set tumor criteria were treated with TACE or radiofrequency ablation (RFA), and tumors were downstaged to meet the Milan criteria before transplantation. The 4-year survival rate was favorable at 92.1%. However, a comparison has not been performed with a control group. Based on the American MELD score, the HCC-adjusted MELD organ allocation scheme assigns exception points and decreases the wait list time. Compared with the Milan criteria, a decreased wait time is more beneficial to HCC patients than treatment response (LF10872[6] Level 3). Therefore, one must consider the organ allocation system and wait list time when interpreting report data for deceased donor liver transplantation.

Living donor liver transplantation is the main type of transplantation performed in Japan and does not involve wait lists. There is insufficient evidence to support the use of pretransplantation treatment to improve prognosis within the scope of the search performed for this set of guidelines.

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CQ31 What are the indications of liver transplantation for HCC?

Recommendation

Liver transplantation can be considered for HCC patients with decompensated cirrhosis if disease control is not possible using other treatment methods. Tumor diameter, tumor number, tumor marker levels, extent of vascular invasion, and degree of tumor differentiation are strong predictors of recurrence. Factors that can be evaluated before surgery include tumor diameter, tumor number, and tumor marker levels. Although it has been widely proposed that the Milan criteria be extended, these criteria are currently valid **(Grade B)**.

- **Background**

Liver resection, percutaneous ablation therapies, and TACE are well advanced in Japan. However, nearly all patients undergo liver transplantation as a result of uncontrollable HCC or background liver damage such as decompensated cirrhosis, and this precludes other therapies.

Liver transplantation for HCC not only removes all tumors from the liver but also serves to be an ideal treatment method for resolving metachronous multicentric recurrence (secondary de novo cancer) after surgery. Nevertheless, perioperative mortality is high compared with that associated with other therapies, and there are issues of risk and the need for donors. Therefore, a low recurrence rate is desired as an indication for operability, and it is important to be familiar with the post-transplantation prognostic factors for HCC. In addition, prognostic factors that can be evaluated before surgery, such as blood testing and diagnostic imaging, must be the criteria for transplantation.

- **Scientific Statement**

Tumor number and tumor diameter are factors that affect recurrence after transplantation for HCC (LF00739[1)] Level 4). At present, these factors are linked to widely used selection criteria (Milan criteria: solitary tumor with a diameter of 5 cm or less, 2–3 tumors with a diameter of 3 cm or less)

(LF00540[2] Level 2a). In addition to these factors, histopathological factors in the explanted liver, such as vascular invasion and degree of tumor differentiation, have been reported to be independent prognostic factors (LF00017[3] Level 4, LF00065[4] Level 4, LF00342[5] Level 4, LF00026[6] Level 4). Recurrence of HCC immediately after transplantation is theoretically metastasis, and vascular invasion has been a consistent, medically verified prognostic factor. Other factors (number, size, degree of differentiation) can be thought of as alternative factors.

Moreover, AFP and PIVKA-II (equal to DCP) levels reflect the biological malignancy of tumors and are reported to be independent prognostic factors for HCC recurrence after transplantation. In addition to past reports (LF00094[7] Level 4, LF11144[8] Level 2b, LF11602[9] Level 4), Todo et al. analyzed 653 cases of liver transplantation in Japan and reported that AFP and PIVKA-II were independent prognostic factors (LF12128[10] Level 2b). Takada et al. also demonstrated that tumor number, tumor diameter, and PIVKA-II were independent factors (L3F02143[11] Level 2b). Fujiki et al. reported that patients with elevated PIVKA-II levels often exhibit significant vascular invasion and poorly differentiated HCC and that PIVKA-II is also an alternative prognostic factor for liver transplantation (L3F02049[12] Level 2b). Toso et al. reported AFP and total tumor volume (sum of tumor volumes) as independent prognostic factors (L3F01433[13] Level 2b, L3F02148[14] Level 2b), and DuBay et al. also independently reported AFP as an independent prognostic factor (L3F01328[15] Level 2b). When determining whether transplantation is possible, factors that can be measured before surgery, such as tumor number, tumor size, and tumor marker levels, are of great clinical significance.

Similarly, from the standpoint of preoperative evaluation, outcomes were favorable in patients who responded to TACE and local therapy before transplantation (LF10873[16] Level 4, L3F02032[17] Level 2b). It has also been reported that positive FDG-PET prior to transplantation is an independent prognostic factor (L3F01378[18] Level 2b, L3F04286[19] Level 2b).

After the Milan criteria were released, they were expanded in terms of tumor number and tumor size. Many facilities have reported no significant difference in outcome when the original criteria are used and that when the revised criteria are used (L3F02165[20]) Level 2a, L3F02055[21]) Level 2a, L3F02141[22]) Level 2b, L3F01453[23]) Level 2b). Mazzaferro et al., who proposed the Milan criteria, reported that if the up-to-seven criteria (sum of tumor number and maximum tumor diameter is 7 or less) were met, there was no significant difference in outcome; however, this was a retrospective study conducted in patients without pathological vascular invasion (L3F02100[24]) Level 2b). Furthermore, by incorporating the aforementioned tumor markers into the criteria, it became possible to exclude highly malignant HCC patients before surgery, even when the criteria were extended in terms of tumor number and tumor size. Therefore, the expanded criteria were also found to be useful (L3F02143[25]) Level 2b, L3F01433[26]) Level 2b, L3F02080[27]) Level 2b). The relationship between transplant outcome and recurrence after HCC therapy was examined in a study in which three groups were compared for post-transplantation survival rate and recurrence rate. The groups included patients who underwent transplantation because of post-resection recurrence, those who underwent transplantation because of recurrence after pretreatment without liver resection, and those who did not undergo pretreatment. No significant differences were observed in outcomes among the three groups (L3F01671[28]) Level 2b). Background liver characteristics such as post-transplantation survival rates and relapse-free survival rates were compared between hepatitis C-positive and -negative patients; both were poorer for the hepatitis C-positive patients than for the hepatitis C-negative patients (LF11508[29]) Level 2b).

- **Explanation**

Pathological vascular invasion and degree of tumor differentiation are consistently strong prognostic factors, yet it is not realistically feasible to evaluate these factors before surgery. In terms of selection criteria for transplantation candidates, tumor diameter and tumor number are significant factors. In addition, AFP, PIVKA-II, and response to pretransplantation TACE may be factors worth investigating. On the basis of patient outcomes, further extension of the Milan criteria to include transplantation has been emphasized upon of late. However, these criteria also depend on the alternative factors of tumor number, tumor size, and tumor marker levels. In order to verify expanded criteria, they must be compared to the original Milan criteria in a large-scale, prospective, noninferiority study. Therefore, the Milan criteria are currently appropriate selection criteria for liver transplantation candidates among HCC patients.

It is difficult to perform such prospective noninferiority studies in the field of liver transplantation. In Japan, where there are few liver donors, such a study seems nearly impossible. First, determining the point of disease progression at which a patient becomes eligible for transplantation is complex, and determining the tolerable survival and recurrence rates is not so much a medical issue as it is a social issue. In Japan, where liver resection, percutaneous ablation therapies, and TACE are well advanced, transplantation is almost always performed when HCC has become uncontrollable or when background liver damage such as decompensated cirrhosis precludes other treatments. Consequently, in the present situation, liver transplantation is performed when all other treatment options are deemed impossible. Unlike the situation in western countries, where deceased liver donation is most common, deceased donor liver transplantation for HCC are rarely performed in Japan, even with the recent increase in its applicability. Therefore, there is no need to consider a fair distribution of deceased donor organs. Selection criteria for living donor liver transplantation for HCC are therefore determined by balancing curability and the risk of using living donors. In these guidelines, it is recommended that if the Milan criteria are fulfilled and if the safety of living donor transplantation and a low recurrence rate can be secured, transplantation should be allowed in each facility.

Of the reports that examined liver transplantation outcomes for HCC, few studies analyzed the differences between patients with recurrence after pretreatment and those with background liver damage. Therefore, it is necessary to accumulate more cases and conduct comparative studies with long-term follow-up durations.

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