Chapter 4:

Surgery

● Introduction

Hepatectomy is a curative treatment for liver cancer, and the safety of this procedure has improved dramatically in recent years. However, statistics from the National Clinical Database in Japan show that surgery-related mortality is 2.4% in all cases of hepatectomy, suggesting that the safety of this procedure must be improved further. To achieve this, the stage of liver cancer and liver function and hepatic functional reserve, all of which are indications for hepatectomy, should be evaluated and used accurately to select a safe and practical surgical procedure.

Some notable changes related to hepatectomy in recent years are advancements made in surgical devices and techniques and the introduction of laparoscopic hepatectomy. In Japan, laparoscopic hepatectomy was approved as a highly sophisticated medical procedure in 2005. In 2010, partial hepatectomy and lateral segmentectomy were approved for coverage by the National Health Insurance system in Japan, followed in 2016 with the approval of all types of hepatectomy, except those involving revascularization and biliary tract reconstruction. Since then, the number of patients undergoing laparoscopic hepatectomy has increased rapidly. However, laparoscopic hepatectomy is not a well-established surgical procedure, especially for extended resection, and it is always associated with some risks.

The description of laparoscopic hepatectomy in the Guidelines prompted several discussions, mainly due to safety-related concerns reported in the last few years. However, the Revision Committee has decided to establish a CQ about indications for laparoscopic hepatectomy in the current Guidelines because of the reported evidence on the short- and long-term benefits of laparoscopic hepatectomy and because the procedure was proposed at the International Consensus Conference. Nevertheless, instead of simply recommending the procedure, the recommendation and its explanation are intended to emphasize the importance of careful incorporation, accurate implementation, and proper postoperative management of laparoscopic hepatectomy.

Previous CQs remain in use to emphasize the importance of identifying prognostic factors to improve the efficacy and safety of hepatectomy, determining resection margins, reducing blood loss during hepatectomy by occluding hepatic blood inflow or lowering the central venous pressure, and performing abdominal drainage. Also, this chapter includes a description of neoadjuvant therapy for hepatectomy, but not adjuvant therapy after hepatectomy, which is described in Chapter 9, “Post-treatment Surveillance and Prevention and Treatment of Recurrent HCC”.

Liver transplantation is a treatment modality for HCC as well as cirrhosis, the primary cause of HCC, but as always, the eligibility criteria and downstaging therapy are described.

A literature search for pre-established CQs was conducted by setting a publication date between January 1, 2012 and June 30, 2016, whereas a literature search for newly established CQs was conducted by targeting all articles published before June 30, 2016.

CQ20 Which patients are eligible for hepatectomy?

Recommendation

Strong recommendation: 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 (right and left portal veins) may be an indication for surgery.

■ Background

The CQ "What are the indications for liver resection in terms of tumor condition?" was used up until the third edition (2013 version). In the current Guidelines, the wording was changed to "Which patients are eligible for hepatectomy?" to reflect patients in different age groups and with different PS levels.

■ Scientific Statement

A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 556 articles. This was narrowed down to 146 in the first screening, from which 14 articles with high-quality evidence and clinical importance were extracted in the second screening. The indications for hepatectomy were reviewed from the perspective of tumor conditions, but the staging of HCC is performed based on tumor number and size and the severity of vascular invasion described in the General Rules for the Clinical and Pathological Study of Primary Liver Cancer issued by the Liver Cancer Study Group of Japan.

The 5-year survival rate after hepatectomy is approximately 20-30% in patients with a tumor ≥ 10 cm. Although no study has compared 5-year survival rates between hepatectomy and other treatment modalities such as percutaneous treatments and chemotherapy, because the results are clearly better than the presumed natural course, tumor size is unlikely to limit the indication. However, liver cancer recurs soon after hepatectomy in some patients. 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 ≥ 10 cm, suggesting the importance of carefully selecting patients[1].

With regard to tumor number, studies have compared treatment outcomes between hepatectomy for 2 or more HCCs and solitary HCC and between hepatectomy for 2 or more HCCs and other treatment modalities for 2 or more HCCs. Compared with solitary HCC, long-term prognosis is worse in patients with multiple HCCs, but similar resection outcomes were reported between multiple patients with multicentric cancer and those with single cancer[2]. Because the treatment outcomes of hepatectomy and sorafenib therapy for multiple HCCs are currently unknown, multiple HCCs is not a contraindication for resection. In terms of the upper limit of tumor number, some

studies reported a lower risk of recurrence in patients with up to 2 HCCs in the same liver segment than in patients with 3 or more HCCs in different segments or patients with microscopic vascular invasion[3,4], while another study has reported that even 4 or more HCCs is an indication for hepatectomy when the patient has good hepatic functional reserve and no portal venous invasion[5]. 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, 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_3 tumor thrombus). Sorafenib is the first-line therapy for HCC accompanied by portal vein tumor thrombus. However, surgery may be indicated because the long-term outcomes of sorafenib therapy for HCC with Vp_3 tumor thrombus are currently unknown. In patients with tumor thrombus in the main portal vein (Vp_4 tumor thrombus), surgery is contraindicated because of its association with poor prognosis. However, surgery may be indicated for mild tumor thrombosis because the outcomes of resection are reportedly similar between mild Vp4 and ordinary Vp_3 tumor thrombus[6].

In addition to the portal vein, HCC occasionally invades the hepatic veins and bile duct, forming tumor thrombus and resulting in poor prognosis. However, hepatectomy improved prognosis of patients with HCC and tumor thrombus in 2 studies[7,8], one where hepatectomy was performed safely in many patients with HCC accompanied by inferior vena cava tumor thrombus and another where median survival was 18 months after curative resection.

Hepatectomy for HCC accompanied by bile duct tumor thrombus is often reported negatively due to its frequent association with vascular invasion and poorly differentiated HCC as well as a high rate of recurrence soon after the procedure[9]. Still, hepatectomy for HCC without portal vein invasion or in patients for whom curative resection is indicated sometimes yields long-term survivors[10]. Due to inconsistent study results, further study is needed to clarify the outcomes of hepatectomy.

■ Explanation

The indications for hepatectomy were described from the perspective of HCC stage. Patients with multiple HCCs may have primary HCC and 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 (e.g., RFA) are used. However, the indication is thought to shift toward 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[11].

Overall survival rates and recurrence-free survival rates did not differ significantly between elderly patients aged < 80 years and those aged ≥ 80 years[12]. In patients aged ≥ 70 years undergoing hepatectomy, intraoperative blood loss and pre-existing comorbidity were associated with a high incidence of postoperative complications[13]. The indications for surgery are difficult to elucidate in elderly patients because their background factors are generally different from those of controls. Therefore, the indications for surgery should be determined in individual cases. In patients with small HCCs and PS0, prognosis was better after hepatectomy than after RFA, but prognosis did not differ significantly in patients with ≥ PS1[14]. In patients with HCC beyond the Milan criteria, regardless of PS, long-term treatment outcome was better after hepatectomy than after TACE[15]. Despite these findings, no definitive recommendation is made due to the lack of high-quality evidence. Therefore, the indications for surgery should be investigated further from the perspective of age as well as PS in the future.

Again, the most recent literature search did not generate recommendations for elderly patients or for PS. After comprehensive discussion, the Revision Committee has decided to strongly recommend hepatectomy for patients with up to 3 tumors located solely in the liver. There are no limitations with regard to tumor size. Tumor thrombus involving up to the first branches of the portal vein (i.e., the right and left portal vein) may be an indication for surgery.

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CQ21 What tests effectively evaluate liver function prior to hepatectomy?

Recommendation

Strong 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.

■ Background

This CQ was established as a continuation of CQ19 “What are the indications for surgery from the

perspective of liver function?" in the third edition, after a literature search for novel indications with high-quality evidence.

■ Scientific Statement

A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 284 articles. This was narrowed down to 25 in the first screening and to 6 based on the following inclusion criterion of studies showing the utility of assessing liver function prior to hepatectomy. A total of 23 articles, including 17 of the 18 articled in the third edition, are cited for CQ21.

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 indication 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[1]. Despite the criteria, portal hypertension was not considered a contraindication for hepatectomy involving 2 or more segments in a study conducted in Europe[2]. 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[3].

The ICG test and hepatobiliary scintigraphy with technetium-99m galactosyl serum albumin (^{99m}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[4,5]. 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[6], 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[7] and accurately predicted postoperative mortality[8]. Takasaki et al. also proposed novel criteria that set different maximum allowable resection volumes for different ICG rates[9]. 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[10]. 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[11]. Mortality was 0% when hepatectomy was performed in 1,056 patients in accordance with

the criteria[12].

Previous studies have reported that hepatobiliary scintigraphy with ^{99m}Tc-GSA was superior to ICGR15 in the histological assessment of liver damage[13], and hepatic functional reserve calculated based on hepatobiliary scintigraphy with ^{99m}Tc-GSA was a useful predictor of postoperative complications and surgery-related deaths in patients with background liver disease, compared with simple postoperative assessments[14]. However, hepatobiliary scintigraphy with ^{99m}Tc-GSA is not a popular assessment tool in many institutions because of limitations on the use of the radionuclide generator ^{99m}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 were described up until the third edition but are not included in the current 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 factor predicting postoperative complications, liver failure, and death[15]. 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)[16].

Previous studies have reported that the preoperative measurement of hepatic venous pressure gradient (HVPG), the pressure gradient between the wedged hepatic venous pressure and free hepatic venous pressure, is a useful, albeit invasive, predictor of postoperative liver failure[17,18]. However, in reality, hardly any medical institutions measure HVPG in the preoerative 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[19–21]. Liver stiffness may be valuable in assessing preoperative liver function.

Because mortality from liver resection is ≤ 3% in Japan[22,23], it is not realistic practically or ethically to evaluate and verify eligibility criteria from the perspective of liver function with postoperative mortality 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[23].

Because the literature search did not extract any articles with high-quality evidence about novel indicators of liver function, the recommendation made in the third edition remains in use in the current Guidelines. After debating whether the ICGR15 is still the most common preoperative liver function test, the Revision Committee has decided to strongly recommend the test.

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CQ22 What procedures are considered safe and reasonable for liver resection?

Recommendation

Strong 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 (≤ 5 cm), and extended resection involving 2 or more segments (including hemi-hepatectomy) is recommended for large HCCs.

■ Background

One of the CQs related to hepatectomy in the third edition was CQ20 "What is the standard surgical procedure for liver resection?" However, because of uncertainty about whether the use of "standard" is appropriate, the CQ was changed to "What procedures are considered safe and reasonable for liver resection?" and a literature search was conducted to search for articles with high-quality evidence.

■ Scientific Statement

A literature search conducted with the search search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 556 articles. This was narrowed down to 40 articles in the first screening and to 12 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 26 articles, including 14 of the 18 articles in the third edition, are cited for CQ22.

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[1]. 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[2].

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[3]. 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[4]. 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[5,6].

Prognosis is thought to be better after anatomical resection than after non-anatomical resection, and this is supported by the findings of recent studies[7-11]. However, other studies have shown no significant difference in cumulative survival rates and recurrence-free survival rates when

anatomical and non-anatomical resection was compared in 2 groups of patients matched by propensity score[12-14]. Therefore, this point 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 also 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 while preserving the segment[15]. The other involves resecting S3/4 while preserving S2[16].

Conventionally, extended hepatectomy is performed for tumors in the caudate lobe located on the dorsal side of the hilar plate and the liver parenchyma on the ventral side. 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[17,18], 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[19].

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 produces better short- and long-term outcomes than right hepatectomy via the conventional approach (mobilization)[20]. 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[21]. 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[22].

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)[23,24], 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[25].

An increasing number of studies have reported the safety and utility of laparoscopic hepatectomy. In a study conducted by a high-volume center with cutting-edge technologies, patients matched by propensity score underwent open or laparoscopic hepatectomy. The results showed that short-term treatment outcomes were better in the laparoscopic group, with no significant differences in long-term treatment outcomes between the two groups[26]. Accordingly, a novel CQ was established in the current version of the Guidelines to ask the question "What are the indications for laparoscopic hepatectomy?" (see CQ23).

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 version of the Guidelines uses, with no modification, the corresponding CQ and recommendation in the third 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. Based on this, the Revision Committee strongly recommends anatomical resection of a small area or partial hepatectomy.

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CQ23 What are the indications for laparoscopic hepatectomy?

Recommendation

Strong recommendation: Solitary HCC measuring ≤ 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.

■ Background

The inclusion of laparoscopic hepatectomy in the current edition of the Guidelines was deliberated on due to safety concerns over the last few years. However, the Revision Committee has decided to establish a novel CQ for laparoscopic hepatectomy in the current edition after carefully considering the fact that the International Consensus Conference recommended a specific method for performing the surgical procedure. This recommendation was based on a rapid increase in the number of cases of laparoscopic hepatectomy after being approved for coverage by National Health Insurance system in Japan and an increase in the number of various evidence-based articles published.

■ Scientific Statement

The literature search extracted 560 articles about laparoscopic hepatectomy published before June 30, 2016, including the first report published in 1991. Of these 560 articles, 75 were extracted in the first screening and 15 articles with high-quality evidence or of clinical importance were extracted in the second screening to recommend the optimum indications for laparoscopic hepatectomy.

Compared with open hepatectomy, laparoscopic hepatectomy provides a magnifying effect and decreases bleeding from the hepatic vein due to intra-abdominal pressure, thereby suppressing intraoperative blood loss[1–3]. In addition, laparoscopic hepatectomy for HCC, which is often associated with chronic liver disease such as cirrhosis, is less frequently associated with postoperative complications such as ascites compared with open hepatectomy[4–6]. While the long-term prognosis of patients with HCC is often comparable between laparoscopic and open hepatectomy[7–10], laparoscopic hepatectomy is superior to RFA as a locoregional therapy for small superficial HCCs[11]. However, the technical difficulty of laparoscopic hepatectomy varies depending

on resection site, tumor size, and the presence of comorbidity such as cirrhosis. In other words, operative time, amount of blood loss, and the conversion rate to open surgery increase in laparoscopic hepatectomy for the right posterior superior and anterosuperior segments (S7 and 8) compared with the other segments of the liver (S2-6)[12], emphasizing the importance of establishing stricter indications than for open hepatectomy[13]. Based on these studies, it was decided at the International Consensus Conference on Laparoscopic Liver Resection held in Morioka, Japan, in 2014 that the most important indication for laparoscopic hepatectomy is hepatic functional reserve sufficient for open hepatectomy, and the most suitable surgical procedure is partial hepatectomy or lateral segmentectomy for solitary HCC ≤ 5 cm in S2-6[14].

■ Explanation

Since first reported by Reich et al. in 1991 laparoscopic hepatectomy is now widely performed across Japan. This is due to numerous technological advances made in surgical devices and approval of the procedure as an advanced medical treatment in 2005. The National Health Insurance system has covered partial hepatectomy and lateral segmentectomy since 2010 and all other hepatectomy procedures that do not involve revascularization or biliary tract reconstruction since 2016. However, laparoscopic hepatectomy is not a fully established surgical technique, especially when performed in extensive resection, and it is associated with particular risks. For these reasons, there were debates over the recommendation and the strength of recommendation at the meetings for finalizing the recommendations. Finally, after considering the decisions made in the consensus meetings and the results of recent meta-analyses, the Revision Committee has decided to strongly recommend laparoscopic hepatectomy for solitary HCC ≤ 5 cm located in the periphery of the S2, 3, 4, 5, and 6 segments where partial hepatectomy and lateral segmentectomy are applicable. Of course, only high-volume centers that have medical teams with sufficient experience in open hepatectomy and advanced endoscopic procedures should perform laparoscopic hepatectomy. Furthermore, it is important to incorporate supportive measures such as a preoperative difficulty scoring system[15] when performing laparoscopic hepatectomy that requires greater skills, more experience, and has a steeper learning curve than required in partial hepatectomy and lateral segmentectomy, both of which were approved under the National Health Insurance system in 2016. Surgeons planning to perform laparoscopic hepatectomy are also required to register preoperatively with the Endoscopic Liver Surgery Study Group and National Clinical Database.

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CQ24 What factors effectively predict prognosis after hepatectomy?

Recommendation

No recommendation: The main prognostic factors after hepatectomy are tumor size and number, vascular invasion, and liver function.

■ Background

In the third edition (2013 version), the answer to CQ22 "What are the prognostic factors after liver resection?" was stage classification, vascular invasion, liver function, and tumor number. The content of that recommendation was unchanged from the second edition (2009 version). For the current Guidelines, we conducted a literature search to extract articles with high-quality evidence for prognostic factors.

■ Scientific Statement

A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 301 articles. This was narrowed down to 42 in the first screening and to 9 in the second screening to extract studies that elucidated factors affecting and predicting prognosis in patients with HCC after hepatectomy. A total of 20 articles, including 1 article that had been hand-searched during the second screening and the 10 articles from the third edition, are cited for CQ24.

In a study that investigated post-hepatectomy survival rates, factors predictive of prognosis were multiple HCCs ≥ 5 cm with vascular invasion, non-encapsulated tumor, < 40 g/L serum albumin (liver function), TNM stage III/IV, and ≥ 32 ng/mL AFP[1–3]. However, a few studies have shown that tumor size does not affect prognosis[4–6], suggesting that larger size does not necessarily mean poor prognosis. Also, patients with early-stage HCC ≤ 2 cm have good survival rates[7], and Shindoh et al. showed that the presence or absence of histological vascular invasion makes no difference in terms of prognosis in patients with early-stage HCC ≤ 2 cm[8].

■ Explanation

Among various molecular biological markers, PIVKA-II, AFP, AFP-L3 fraction, and alpha-1-fucosidase were shown to predict recurrence[9], the CYP1A2 gene encoding cytochrome P450 1A2 was identified as being associated with recurrence[10], and the levels of and changes in circulating tumor cells may be a useful predictor of recurrence[11].

Patients with tumor thrombus in the main portal vein or the first branch are known to have poor prognosis, but prognosis has been shown to improve in some patients after resection[12,13].

From the perspective of cumulative survival, the Glasgow Prognostic Score is an important predictor of prognosis after surgery for HCC and more clearly stratifies patients with HCC rated 0-1 on the Cancer of the Italian Program (CLIP) scale[14]. Also, the preoperative neutrophil-to-lymphocyte

ratio in peripheral blood was an independent predictor of poor prognosis after surgery for HCC[15].

The number of studies investigating the relationship between sarcopenia and cancer has been increasing in recent years. In HCC, sarcopenia was revealed to be an independent risk factor for poor prognosis[16,17].

A nationwide study in Japan reported that compared with HCC associated with HBV or HCV, non-HBV- and non-HCV-associated HCC shows better prognosis in terms of cumulative survival rate by stage and a significantly lower incidence of recurrence[18].

To reveal the relationship between post-hepatectomy prognosis and time to recurrence, Cheng et al. examined patients with solitary HCC and found that late recurrence (after 2 years) and curative therapy for recurrent HCC were the best predictors of survival after recurrence[19].

As for surgical skills, non-anatomical resection, blood loss, and blood transfusion were significant prognostic predictors[20].

No change was made in the content of recommendation between the third and second editions. However, because stage classification depends on tumor number and size and vascular invasion, these three factors and liver function, instead of stage classification, have been chosen as the major predictors of prognosis after hepatectomy. Although prognostic factors are clinically important, the Revision Committee agrees that no recommendation is appropriate at the present time.

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CQ25 Do resection margins affect prognosis?

Recommendation

Strong recommendation: In hepatectomy for HCC, resection margins may be kept at a minimum.

■ Background

This CQ concerns the effect of resection margins in hepatectomy on prognosis, and the recommendation has not changed since the second edition. For the current Guidelines, we conducted a literature search to extract articles with better evidence.

■ Scientific Statement

A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 269 articles. This was narrowed down to 29 in the first screening, from which 2 articles with high-quality evidence and clinical importance were extracted in the second screening. A total of 9 articles, including 1 hand-searched article and 6 relevant articles (out of 7) from the third edition, are cited for CQ25.

Postoperative recurrence rates did not differ significantly among patients who underwent hepatectomy for HCC with resection margins set at ≥ 1 cm or < 1 cm[1–3]. Also, there were no significant differences in postoperative cumulative survival rates or recurrence-free survival rates between hepatectomy with resection margins set at < 5 mm and ≥ 5 mm[4–6]. When the effect on recurrence-free survival of three different resection margins (≤ 1 mm, 1-9 mm, and ≥ 10 mm) was investigated after dividing patients based on the Milan criteria (within or beyond), recurrence-free survival rates improved as resection margins increased in patients with HCC within the Milan criteria. However, in patients with HCC beyond the Milan criteria, while recurrence-free survival rates were better when resection margins were 1-9 mm than at ≤ 1 mm, no significant difference was observed between 1-9 mm and ≥ 10 mm[7]. Furthermore, no significant difference was observed in recurrence-free survival rates or cumulative survival rates when hepatectomy was performed with hardly any resection margin because of the close proximity between HCC and the major vessels[8]. On the contrary, an RCT showed that prognosis was better in patients with 2-cm resection margins than in those with 1-cm resection margins[9]. Irrespective of these studies, the optimal resection margins in hepatectomy currently remain undecided.

■ Explanation

Many studies have reported that prognosis does not vary significantly when resection margins are between 5 mm and 1 cm. Prognosis was not affected even when liver resection was performed with hardly any resection margins due to the close proximity between HCC and the major vessels. In contrast, one RCT showed superior prognosis for patients with solitary HCC without vascular invasion when resection margins were 2 cm compared with 1 cm. However, in the RCT, the mean age of the patients was ≤ 51 years, ICGR15 was < 10%, and the proportion of patients with hepatitis B was ≥ 80%. These patient characteristics are noticeably different from those seen in Japan.

Furthermore, it is often difficult to ensure ≥ 2-cm resection margins due to factors such as liver function and tumor location and size. In a recent study in which HCC was categorized based on the Milan criteria, treatment outcomes improved with increasing resection margins in patients with HCC within the Milan criteria. These findings suggest that even though it is desirable to have wide resection margins for relatively early-stage HCC, it is fundamentally unlikely that prognosis is affected by resection margins, and therefore resection margins may be kept at a minimum. The outcome of the most recent literature search is comparable to the content of the recommendation in the second edition. Accordingly, the Revision Committee has decided to strongly recommend the acceptability that resection margins for HCC can be kept at a minimum in hepatectomy.

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CQ26 Does hepatic vascular occlusion or lowering of the central venous pressure reduce blood loss during hepatectomy?

Recommendations

Strong recommendation: Hepatic vascular occlusion minimizes blood loss during hepatectomy.

Strong recommendation: Lowering of the central venous pressure minimizes blood loss during hepatectomy.

■ Background

This CQ concerns the suppression of blood loss in hepatectomy by occluding hepatic blood inflow and lowering the central venous pressure. The content of the recommendation has remained the same since the second edition. For the current Guidelines, we conducted a literature search to extract high-quality evidence.

■ Scientific Statement

A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 103 articles. This was narrowed down to 39 in the first screening, from which 5 articles with high-quality evidence and clinical importance were extracted in the second screening. A total of 12 articles, including 7 (of the 8) articles with high-quality evidence in the third edition, are cited for CQ26.

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[1,2]. Other studies also reported the efficacy of hemihepatic vascular occlusion[3,4] and the safety of intermittent hepatic vascular occlusion for up to 30 min, with no adverse effects on liver function, when used in combination with protease inhibitors[5]. Also, several studies including meta-analyses and RCTs 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[6–9]. The optimum range of central venous pressure was 2.1-3 mmHg[10], and clamping of the IVC was more effective than drug-induced lowering of the central venous pressure[11]. However, lowering central venous pressure does not always reduce blood loss[12]. Also, caution must be exercised when clamping the IVC because of the possibility of pulmonary embolism.

■ Explanation

The Pringle maneuver is commonly used to minimize blood loss during hepatectomy, and its safety has been verified. Some reports were not in favor of routinely using the Pringle maneuver because of the substantial reduction in blood loss achieved in recent years due to advances in surgical skills and technological devices. However, because these reports 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. Hemihepatic 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 minimizes blood loss as well as the risk of requiring blood transfusion, without greatly affecting postoperative liver function or short-term prognosis. Therefore, 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 based on the site of hepatectomy.

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CQ27 Is routine abdominal drainage necessary after hepatectomy?

Recommendation

Strong recommendation: Abdominal drainage is not always necessary after elective hepatectomy.

■ Background

This CQ is a continuation of the corresponding CQ in the third edition.

■ Scientific Statement

A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 144 articles. This was narrowed down to 5 in the first screening, from which 2 articles with high-quality evidence and clinical importance were extracted in the second screening. A total of 12 articles, including 1 hand-searched article and 9 articles with high-quality evidence from the third edition, are cited for CQ27.

An RCT that evaluated the utility of abdominal drains after elective hepatectomy showed that routine drain placement is unnecessary and should not be indicated. 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[1-4]. 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[5]. Other studies have also reported the clinical utility of drain placement for bile leakage and ascites[6,7], the possible prediction of bile leakage by monitoring bilirubin levels in drain effluent[7,8], 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[9]. On the other hand, abdominal drainage is reported not to be essential in hepatectomy for living donor liver transplantation[10]. Some investigators have recommended that drains be removed within 2-3 days of surgery when drain effluent appears normal[7,11].

■ Explanation

The Guidelines for the Prevention of Surgical Site Infection published by the Centers for Disease Control and Prevention in the United States recommends, if necessary, using closed suction drains and removing them as early as possible[12]. However, unlike surgery involving other abdominal

organs, hepatectomy is performed in patients with chronic liver disease and often requires careful monitoring of bile leakage and intractable ascites. As for elective hepatectomy, RCTs have been performed since the 1990s to justify drain placement, but because of the small number of patients and problems associated with assessment methods, further study is needed that considers the effects of surgical procedures and the severity of comorbid liver disease. More careful treatments are needed for living donor liver transplantation performed in healthy individuals. Further investigation is needed to evaluate the efficacy of abdominal drainage in laparoscopic hepatectomy, which is becoming common.

Despite some concerns, the Revision Committee reasons, based on the results of several RCTs, that elective hepatectomy does not require routine drain placement and thus strongly recommends against its routine use.

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CQ28 Is neoadjuvant therapy necessary in hepatectomy?

Recommendation

Weak recommendation: No therapy is recommended as neoadjuvant therapy aimed at improving prognosis after hepatectomy for HCC.

■ Background

This CQ is a continuation of CQ28 “Does neoadjuvant chemotherapy improve prognosis after liver resection?” in the third edition (neoadjuvant therapy in the second edition). No neoadjuvant chemotherapy was recommended in the third edition as a treatment for improving prognosis after hepatectomy.

■ Scientific Statement

A literature search conducted with the search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 105 articles. This was narrowed down to 22 in the first screening and to 4 in the second screening based on the criterion of studies that reviewed the utility of neoadjuvant therapy for hepatectomy. A total of 16 articles, including the 12 from the third edition, are cited for CQ28.

Very few studies that evaluated the efficacy of systemic chemotherapy as neoadjuvant therapy have provided a high level of 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 5-14, not beneficial)[1-14]. It is also unclear whether preoperative TAI effectively suppresses recurrence and improves survival[15].

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[16].

■ 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. More recently, however, many studies with contradictory findings about TACE/TAE have been published and include RCTs and meta-analyses offering high-quality evidence. Due to the lack of consensus about the utility of TACE or TAE, neither is recommended as neoadjuvant chemotherapy here.

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CQ29 What are the eligibility criteria for liver transplantation in patients with HCC?

Recommendation

Strong recommendation: Liver transplantation should be considered for patients with HCC within the Milan criteria accompanied by decompensated cirrhosis.

■ 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 ≤ 5 cm or up to 3 tumors ≤ 3 cm without vascular invasion or extrahepatic metastasis[1]. 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 and whether the addition of other factors would provide eligibility criteria with greater prognostic accuracy are both 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 search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 462 articles. This was narrowed down to 4 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 13 articles based on the same criteria from the 29 articles used in the third edition, a total of 16 articles are cited for CQ29.

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 ≤ 6.5 cm or up to 3 tumors ≤ 3 cm each and ≤ 8 cm in total)[2]; the Tokyo criteria (up to 5 tumors ≤ 5 cm each)[3]; the up-to-seven criteria (up to 7 tumors ≤ 7 cm each)[4]; and an expansion of the Milan criteria that consists of a solitary tumor ≤ 6 cm or up to 3 tumors ≤ 5 cm each and ≤ 9 cm in total[5]. Besides tumor size and number, serum AFP and PIVKA-II values are also predictors of post-transplantation prognosis[6–10]. Accordingly, novel eligibility criteria for liver transplantation have been established by combining tumor size and number with AFP or PIVKA-II values: the Kyoto criteria (up to 10 tumors ≤ 5 cm each and ≤ 400 mAU/mL PIVKA-II)[11,12]; the TTV/AFP criteria (total tumor volume 115 cm^3, ≤ 400 ng/mL AFP)[13–15]; and another criteria calculating a score by tumor size, tumor number, and AFP value separately[16]. Compared with the Milan criteria, these newer criteria better predict transplantation outcome.

■ 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 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 criteria (a solitary HCC ≤ 5 cm or up to 3 HCCs ≤ 3 cm) 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 criterian, 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 fewer 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.

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 deceased 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, as in the third edition, that liver transplantation should be considered for patients with HCC within the Milan criteria accompanied by decompensated cirrhosis.

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CQ30 Does downstaging of HCC prior to liver transplantation improve prognosis after transplantation?

Recommendation

Weak recommendation: There is insufficient scientific evidence to support that downstaging of HCC prior to liver transplantation improves the prognosis of transplantation.

■ Background

Indications for liver transplantation in patients with HCC are decided based on the stage of the HCC, because it is the major factor that denotes the risk of recurrence after transplantation. However, 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 search query used in the third edition and a publication date between January 1, 2012 and June 30, 2016 extracted 112 articles. This was narrowed down to 1 in the first and second screenings based on the following inclusion criteria: studies that clearly defined indications for downstaging as well as the success rate and transplantation outcomes after downstaging. One of the 6 articles in the third edition was selected using the same criteria, and therefore a total of 2 articles are cited for CQ30.

These 2 articles were published by the same institution[1,2]. After treatment such as embolization and percutaneous ablation, HCCs were downstaged to within the Milan criteria in 65.3% of patients with a solitary nodule ≤ 8 cm, 2-3 nodules ≤ 5 cm each, or 4-5 nodules ≤ 3 cm each and ≤ 8 cm in total. No significant differences in liver transplantation outcomes was observed between patients with HCC within the Milan criteria and those with HCC after downstaging. There as also no significant difference in transplantation wait-list survival rate between patients with HCCs undergoing downstaging and those with HCCs within the Milan criteria not undergoing downstaging.

■ Explanation

Although conducted at a single institution, the prospective studies reported on indications for downstaging, success rates, and survival rates. In these studies, there was no significant difference in posttransplantation survival rate between patients with and without downstaging (per protocol analysis). In addition, patients undergoing downstaging showed a similar overall survival rate to patients without downstaging (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 stage; (2) comparable transplantation outcomes can be expected between successfully downstaged HCCs and HCCs within the Milan criteria; and (3) downstaging itself does not adversely affect prognosis. In other words, downstaging prior to liver transplantation can be regarded as a treatment strategy for HCC. However, 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, the indications for liver transplantation are decided in patients with HCC regardless of the condition of the background liver: ≥ 50% of the patients had Child-Pugh A compensated cirrhosis in the studies. In Japan, however, where donors for liver transplantation are scarce, liver transplantation is indicated for patients with HCC within the Milan criteria accompanied by decompensated cirrhosis. It is currently unclear whether downstaging is being performed safely and effectively (as in the 2 Amercian studies) in Japanese patients with HCC accompanied by decompensated cirrhosis. Accordingly, the Revision Committee concluded that there is no scientific evidence to suggest that downstaging of HCC improves prognosis after liver transplantation.

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