REVIEW

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2018 Korean Liver Cancer Association–National Cancer Center Korea Practice Guidelines for the Management of Hepatocellular Carcinoma

Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC), Korea

Hepatocellular carcinoma (HCC) is the fifth most common cancer globally and the fourth most common cancer in men in Korea, where the prevalence of chronic hepatitis B infection is high in middle-aged and elderly patients. These practice guidelines will provide useful and constructive advice for the clinical management of patients with HCC. A total of 44 experts in hepatology, oncology, surgery, radiology and radiation oncology in the Korean Liver Cancer Association-National Cancer Center Korea Practice Guideline Revision Committee revised the 2014 Korean guidelines and developed new recommendations that integrate the most up-to-date research findings and expert opinions. **(Gut Liver 2019;13:227-299)**

Key Words: Diagnosis; Guidelines; Carcinoma, hepatocellular; Management

INTRODUCTION

1. Intent of revision

The Korean Liver Cancer Study Group (KLCSG)–National Cancer Center (NCC) Korea practice guidelines for the management of hepatocellular carcinoma (HCC) were first announced in 2003 and have been revised twice, first in 2009 and then in 2014. Since then, many new research findings and therapies for HCC have been presented and published in Korea and other countries. Many studies have been conducted and a substantial body of knowledge has been accumulated on diagnosis, staging, and treatment specific to Asia that shows different clinical behaviors of HCC from the West, especially in Korea; this has provided action plans and measures based on the new research findings. Accordingly, in the summer of 2017, the Korean Liver Cancer Association (KLCA, formerly KLCSG)–NCC Korea Practice Guideline Revision Committee (KPGRC) has initiated the revision of the guidelines to develop a new recommendation plan that integrates the most up-to-date research findings and expert opinions after the release of the 2014 guidelines.

2. Target population

The primary targets of these new guidelines are patients with suspicious or newly diagnosed HCC. The key to treatment according to these guidelines is the initial treatment of patients with newly diagnosed HCC; however, for the first time we extensively reviewed and discussed residual, progressive, or recurrent cancer after initial treatment and provided relevant recommendations. Moreover, these guidelines can be applied more usefully to actual clinical practice by also describing prevention methods, surveillance tests, a treatment overview, preemptive antiviral treatment of underlying chronic hepatitis and management of cancer pain, and an assessment of the tumor response after treatment.

3. Intended users

These guidelines are intended to provide useful clinical information and direction for all clinicians in charge of the diagnosis and treatment of HCC in Korea. It also provides specific and practical information for medical residents in training, special-

*Annotation: These guidelines are organized opinions for which specialists reviewed current medical literature so that they may actually be used as references for clinical practice, research, and education about hepatocellular carcinoma. These guidelines are intended to be flexible in contrast to "standards of care," which are mandatory policies to be followed in every case. These guidelines were prepared by a joint collaboration of the Korean Liver Cancer Association (KLCA) and the National Cancer Center (NCC), Korea. This may not be revised, changed, or assumed without prior consent from these two institutions.

Correspondence to: Korean Liver Cancer Association[a]-National Cancer Center, Korea[b], Practice Guideline Revision Committee
[a]Korean Liver Cancer Association, 1527 Gangnam Finance Plaza, 419 Teheran-ro, Gangnam-gu, Seoul 06160, Korea
Tel: +82-2-313-1900, Fax: +82-2-539-5410, E-mail: klca@livercancer.or.kr
[b]Center for Liver Cancer, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang 10408, Korea
Tel: +82-31-920-1605, Fax: +82-31-920-1520, E-mail: jwpark@ncc.re.kr
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ists, and their instructors.

4. Developers and funding source

The KLCA-NCC KPGRC organized by the consensus of the KLCA and NCC consists of hepatologists, oncologists, surgeons, radiologists, and radiation oncologists. All required funding was provided by the NCC (#1731510-1). Each member of the KPGRC collected and analyzed relevant evidence and wrote the manuscript. Conflicts of interests among the members are summarized in Appendix 1.

5. Literature search for evidence collection

The 2018 KPGRC (Appendix 2) collected and analyzed the Korean and international literature published on HCC since the announcement of the 2014 guidelines through a PubMed search for revisions of the guidelines based on latest updated evidence. Only English and Korean literature was searched, and the keywords included HCC and other keywords specific to related subtopics. The sub-topics encompassed a wide range of clinically important items such as epidemiology, prevention, diagnosis, staging, treatment, and response assessment of HCC.

6. Systematic literature review, levels of evidence, grading of recommendations

Literature collected for evidence was analyzed through systematic review, and levels of evidence were classified by the revised Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (Table 1).[1-4] The levels of evidence were categorized on the basis of the possibility of changes in the assessment through further research, and were defined as high (A) with lowest possibility, moderate (B) with certain possibility, and low (C) with highest possibility. For example, level A evidence is similar but not identical to that from one or more randomized controlled trials (RCTs). Even if there is no possibility of a change in the level of evidence because further RCTs are unlikely to be conducted, such evidence could be considered level A. In contrast, RCTs that have a small population of target patients and need further research or are published only in abstracts also have a lower level of evidence. The GRADE system was implemented for classifying grades of recommendation as strong (1) and weak (2), collectively considering not only the level of evidence but also the quality, patient-important outcome, and socioeconomic aspects of each study. Therefore, each recommendation was graded on the basis of the level of evidence (A–C) and grades of recommendation (1 or 2) as follows: A1, A2, B1, B2, C1, or C2 (Table 1). These guidelines avoided giving C2 grades as much as possible.

7. List of the clinical questions

The KPGRC selected sub-topics and clinical questions from four departments regarding the revision of the guidelines (Appendix 3), reviewed the evidence of each item, and suggested recommendations through discussion with each subcommittee and the KPGRC.

8. Manuscript review

Recommendation drafts were made through several intradepartmental meetings after the initial meeting of the KPGRC and three interdepartmental meetings attended by all members of the committee. The drafts were then thoroughly reviewed through several online discussions and three department head meetings. In addition to the integrity of the contents, methodological validity of the manuscript was also evaluated on the basis of the AGREE II (Appraisal of Guidelines for Research and Evaluation II).[5,6] The complete draft was then reviewed by the advisory board and through a public meeting and was modified further at the KPGRC department head meeting. The advisory board consists of nine clinical specialists in liver cancer. The guidelines made through this process were endorsed by the open meeting, board of directors of the KLCA, and the NCC (Appendix 4).

Table 1. Grading of Recommendations, Assessment, Development and Evaluation

Quality of evidence	Criteria
High (A)	Further research is unlikely to change confidence in the estimate of the clinical effect.
Moderate (B)	Further research may change confidence in the estimate of the clinical effect.
Low (C)	Further research is very likely to impact confidence on the estimate of clinical effect.
Strength of recommendation	**Criteria**
Strong (1)	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost.
Weak (2)	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, higher cost or resource consumption.

Regarding the quality of the evidence, we excluded "very low quality (D)" in our guidelines for convenience, which was originally included in the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system and indicates that any estimate of effect is very uncertain. Evidence levels were downgraded if there was only an abstract or there was poor quality or inconsistency between studies; levels were upgraded if there was a large effect size.

9. Release of guidelines

The revised guidelines were presented at Liver Week on June 15, 2018 held jointly by the Korean Association for the Study of the Liver, KLCSG, Korean Association of Hepato-Biliary-Pancreatic Surgery, and Korean Liver Transplantation Society. The Korean version is available on the KLCSG and NCC websites (http://livercancer.or.kr and http://ncc.re.kr).

10. Plan for updates

The KLCA and NCC Korea will update part or all of these guidelines when new test methods, drugs, or treatments regarding HCC are developed and new significant research findings are made, and thus revision of the guidelines is deemed necessary for promoting the national health of Korea. The schedule for this plan will be posted when necessary.

EPIDEMIOLOGY

1. Metrics of disease burden from liver cancer

The disease burden of a cancer is often expressed as cause-specific mortality due to the cancer and incidence of the cancer. Of these two indicators, the cause-specific mortality rate is used as the most important and fundamental measure of disease burden assessment. Mortality due to a specific disease and its trend for each country is critical for informed priority setting and for prioritizing policy and research for new health technologies. Trends in causes of death provide an important geographical summary of whether society is making progress in reducing the burden of premature (and especially avoidable) mortality and where renewed efforts are needed.[7,8]

Korea's cancer mortality rate is reported by the Korean Statistical Information Service (KOSIS) as both a crude rate and an age-standardized rate (adjusted for the 2005 mid-year population). In this guideline, Korea refers to South Korea. Cancer incidence is reported by the Korea Central Cancer Registry (KCCR) as both a crude rate and an age-standardized rate (adjusted for the 2000 mid-year population). There is no significant difference in the analysis result according to the standard population that is used in the age-standardized rate. However, the crude rates and the age-standardized rates may be inconsistent with each other. This is especially true when the whole population is aging rapidly, as in the case of Korea. The U.S. Center for Disease Control and Prevention recommends that the decision to use the crude rate or age-standardized rates depends on the purpose of the evaluation (https://www.cdc.gov/cancer/npcr/uscs/technical_notes/stat_methods/rates.htm). Age-standardized rates ensure that differences in incidence or deaths between geographical areas are not due to differences in the age distribution of the populations being compared. However, crude rates and the absolute number of deaths are more helpful in determining disease burden and the specific requirements for services for a given population.

In this context, this guideline considers that the crude death rate (and the absolute number of deaths) is the most important indicator of the disease burden from liver cancer or HCC. The crude incidence rate, age-standardized death rate, and age-standardized incidence rate are considered as auxiliary indicators.

2. Liver cancer mortality and economic burden

The most important cause of death of Korean people is malignant neoplasm, or cancer. According to statistics released by the KOSIS, the cancer mortality rate in 2016 was 153 per 100,000 population, ranking first, nearly three times higher than the second-highest cause of mortality, which is heart disease at a rate of 58.2 per 100,000 population. In 2016, the mortality rate for liver cancer was 21.5 per 100,000 population, the second highest cancer death rate after the lung cancer mortality rate of 35.1 per 100,000 population. The mortality rate for liver cancer among all age groups was second in men (31.5 per 100,000 population) and third in women (11.6 per 100,000 population). However, liver cancer mortality was the highest among the economically active working age group, who were aged 40 to 59 years old.

The annual economic burden caused by liver cancer in Korea was USD 3,114 million (about KRW 3.4 trillion) in 2010, making it the highest among all cancers, and showed a large increase on the burden of USD 2,065 million (about KRW 2.3 trillion) in 2000.[9] In other words, liver cancer has the greatest burden of all cancers in Korea.

3. Trends in liver cancer mortality and incidence

The crude annual rate of liver cancer mortality has increased over the last 30 years, which is why the disease burden of liver cancer is increasing. The annual rate of liver cancer per 100,000 population increased steadily from 16.2 persons in 1984 to 20.5 persons in 1999 and 22.9 persons in 2002, and then remains

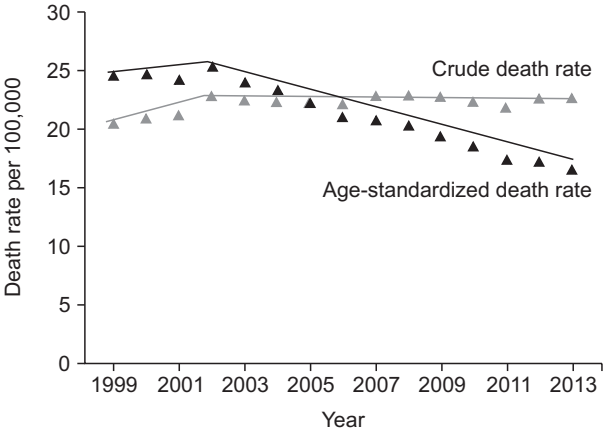


Fig. 1. Crude death rate and age-standardized death rate in the Korea in calendar years 1999 to 2013.

stable between 21 and 23 up to 2015 (Fig. 1). The absolute number of annual deaths from HCC has also increased by 17.8% over the past 20 years, from 9,682 in 1999 to 11,405 in 2013 (Fig. 2). The crude annual incidence of liver cancer has also increased over the past two decades. The annual incidence of HCC per 100,000 population has continuously increased from 28.2 in 1999 to 32.7 in 2010 and remains stable at 31–32 up to 2015.

In contrast to the increase in crude mortality and crude incidence of liver cancer, the age-standardized mortality and age-standardized incidence of liver cancer have declined over the past two decades. The age-standardized mortality rate of liver cancer per 100,000 people has greatly decreased from 24.7 in 1999 to 16.4 in 2014, and the age-standardized incidence rate from 33.8 in 1999 to 19.9 in 2014. The dissociation between crude and age-standardized rates of liver cancer mortality and incidence may be explained by rapidly aging population in Korea. The average age and distribution of elderly people in the whole Korean population have increased sharply between 1999 and 2014. The age-standardized rates of liver cancer seem to be further lowered because the mean age of the patients with liver cancer has increased more than that of the whole population.

4. Summary

In summary, in Korea, the mortality rate of liver cancer is the second highest across all age groups, but is highest in the economically-active age group, and thus the disease burden of liver cancer has been the highest among various cancers over the past 20 years. The age-standardized mortality and incidence rates of liver cancer appear to be declining; however, this is not because of a reduced burden of liver cancer, but because of the rapid aging of the entire Korean population. Crude rates, incidence rates, and the absolute number of patients associated with liver cancer mortality are still increasing. These data suggest that liver cancer is the most important cancer to overcome in Korea.

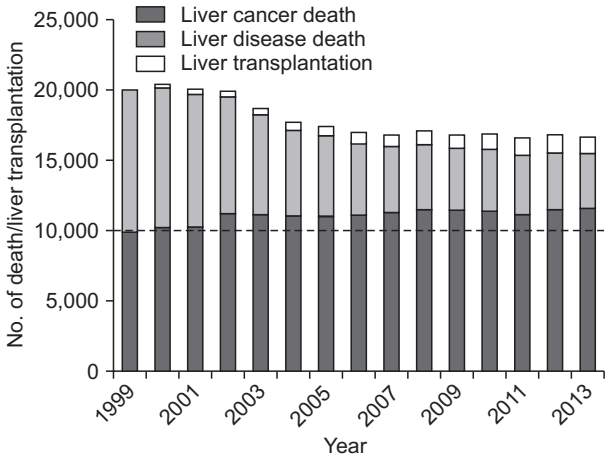


Fig. 2. Annual number of liver cancer deaths, liver disease deaths and liver transplantations in the Korea during calendar years 1999 to 2013.

PREVENTION

1. Causes and prevention of HCC

HCC occurs almost exclusively in patients with risk factors, such as chronic hepatitis B, chronic hepatitis C, or liver cirrhosis. The most important cause of HCC in Korea is chronic hepatitis B virus (HBV) infection. According to the results of a random selection registry study of the KLCA and the KCCR, 62.2% of patients diagnosed with HCC between 2008 and 2010 were infected with HBV and 10.4% with hepatitis C virus (HCV). Unknown causes accounted for the remaining 27.4%.[10] It is presumed that liver cirrhosis caused by alcoholic and/or nonalcoholic fatty liver disease would be the main underlying disease for the unknown causes. HBV rates are somewhat higher in cohorts of HCC patients visiting tertiary hospitals. Because about 90% of patients with HCC have cirrhosis or chronic hepatitis B at diagnosis, it is difficult to perform radical treatment, and the risk of recurrence continues even 5 years or 10 years after treatment, which worsens the prognosis of the patients. According to the National Cancer Registry released by the KCCR in 2017, the 5-year survival rate of patients with HCC is 33.6% and the 10-year survival rate is as low as 20%.[11] These data suggest that preventive measures against HCC are of utmost importance.

Primary prevention of HCC is to prevent the risk of HCC, including vaccination against HBV and abstinence from alcohol consumption. Secondary prevention is to reduce the risk of developing HCC in patients who already have a risk of HCC, including antiviral treatment for HBV and HCV to prevent progression of chronic inflammation and fibrosis of the liver. Tertiary prevention is to prevent the development of new HCC in the remaining liver after curative treatment in patients who have already developed HCC.[12]

2. Primary prevention of HCC

The most important preventive measure for HCC in Korea is the universal neonatal vaccination against HBV, since most HBV infection is caused by vertical transmission of the virus from mother to child in the neonatal period.[13] HBV vaccination should be given as early as possible within 24 hours after birth. The World Health Organization (WHO) recommends HBV vaccination for all newborns regardless of maternal HBV status.[14] In addition, adults who do not have antibodies to the HBV surface antigen (HBsAg) and who have never been exposed to the virus (negative for all HBsAg, HBV surface antibody [anti-HBs], and IgG HBV core antibody [anti-HBc]) should be vaccinated against HBV.[15,16] In particular, people at high risk of HBV infection (family members of chronic hepatitis B patients, health care workers, travelers traveling to areas with high HBV prevalence, injected drug abusers, and people with multiple sexual partners, etc.) should also be vaccinated against HBV.

No vaccine has yet been developed to prevent HCV infection. Because HCV is transmitted almost entirely through contaminated blood, infection must be prevented by avoiding unsanitary invasive procedures (such as multiple use of acupuncture needles, capping, tattooing, or needle sharing).

Excessive alcohol intake over an extended time is an independent cause of liver cirrhosis and HCC, and further increases the risk of liver cirrhosis and HCC in patients with preexisting chronic liver disease. In Korea, alcoholic liver cirrhosis is the third leading cause of HCC after chronic hepatitis B and C. Therefore, efforts should be made to lower the risk of developing HCC by limiting excessive alcohol consumption.

Metabolic syndrome and fatty liver disease are associated with obesity and diabetes mellitus, and are also known to increase the incidence of HCC.[17,18] Therefore, efforts to reduce obesity and metabolic syndrome are necessary to prevent the development of HCC. Statins for treating hyperlipidemia have been extensively studied for an association with the reduction of HCC risk. Large-scale meta-analyses have reported that statin use is associated with a reduction in the incidence of HCC by 37%;[19] however, most of the studies were retrospective analyses, and two RCTs did not show a reduction of HCC incidence with statin therapy. Therefore, statins do not yet have a sufficient evidence to lower the incidence of HCC, and caution is needed because the long-term safety of statins is not well documented in patients with cirrhosis at high-risk of HCC.[20] In addition, a study reported that metformin reduced HCC development in type 2 diabetes,[21] which needs further prospective study.

Aspirin and other antiplatelet agents have also been suggested to reduce the risk of developing HCC in large prospective population-based observational studies (relative risk [RR], 0.59; 95% confidence interval [CI], 0.45 to 0.77).[22,23] However, caution is needed in the interpretation of the study results because the use of antiplatelet agents is generally limited in patients with cirrhosis who are at high risk of developing HCC, which might have caused selection bias in studies including low-risk patients in the anti-platelet therapy group.[24]

Coffee is the only food or drink that has evidence for reducing the risk of HCC. In recent meta-analyses and large-scale cohort studies, coffee consumption significantly reduced the risk of developing HCC, regardless of the consumption amount, as well as the severity and cause of underlying liver disease.[25-28]

3. Secondary prevention of HCC

Continued high-level viremia in patients with chronic hepatitis B or C is an independent risk factor for the development of HCC. Therefore, inhibition of HBV or HCV proliferation by antiviral therapy is expected to reduce the incidence of HCC. For antiviral therapy of chronic hepatitis B and chronic hepatitis C, we recommend following the clinical practice guidelines of the Korean Association for the Study of Liver (KASL).[29,30]

Oral antiviral agents, such as tenofovir and entecavir, are preferred as the first-line treatment for chronic HBV infection. There is no RCT to determine whether interferon therapy reduces the incidence of HCC in chronic hepatitis B patients. Lamivudine, the first oral antiviral agent in patients with chronic hepatitis B, has been shown to reduce the incidence of HCC in patients with advanced hepatic fibrosis in an RCT (32 months follow-up: lamivudine vs control, 3.9% vs 7.4%; p=0.047).[31] Large-scale observational studies have consistently shown that long-term therapy with entecavir and tenofovir, potent antiviral agents that have a strong inhibitory effect on HBV proliferation, significantly reduce the incidence of HCC compared with the untreated control group.[32-34] However, it is not clear whether the effect of tenofovir or entecavir on HCC risk reduction is greater than that of lamivudine. It is clear that the risk of HCC does not completely disappear even with long-term potent antiviral medication.[35-38] In conclusion, the preventive effect of long-term oral antiviral therapy on HCC in patients with chronic hepatitis B has been proved, but is not complete.[39]

The primary aim of chronic hepatitis C treatment is to achieve a sustained virologic response (SVR) that is defined as undetectable HCV RNA using polymerase chain reaction (PCR) at 12 or 24 weeks after the end of treatment. The HCV recurrence rate after an SVR is only about 1% in the long term, so it is regarded as a virological cure. The achievement of an SVR can prevent progression to cirrhosis and the development of HCC. However, in patients with preexisting hepatic fibrosis, there is a continuing risk of developing HCC even after achieving an SVR.[34]

Interferon therapy has been consistently reported to reduce the incidence of HCC in chronic hepatitis C patients compared with untreated controls. In a meta-analysis of 20 studies (4,700 patients), the HCC risk was significantly reduced in the interferon treatment group (RR, 0.43; 95% CI, 0.33 to 0.56) and to a greater extent in patients with an SVR (RR, 0.35; 95% CI, 0.26 to 0.46) compared with those in the control group.[40] Another meta-analysis of 30 studies (approximately 25,000 patients) reported a 76% reduction in the incidence of HCC in patients with an SVR compared with those without an SVR.[41] These results were consistent regardless of the degree of hepatic fibrosis or the presence of cirrhosis.

Direct-acting antivirals (DAAs) against HCV have been introduced successively, leading to an SVR achievement rate as high as 98% to 100%. In a large-scale retrospective study of 22,500 patients in U.S. Veterans Health Administration Hospitals, the risk of developing HCC was significantly lower than that of patients without an SVR with DAA treatment, which was a 0.28-fold reduction.[42] However, among patients with an SVR, those with cirrhosis had a 4.73-fold higher risk of developing HCC compared with those without cirrhosis. In another retrospective study of 62,354 patients in the U.S. Veterans Health Administration Hospitals database, the incidence of HCC was reduced by 71% when an SVR was achieved with DAA therapy.[43] In a meta-analysis comparing the risk of developing HCC between DAA

treatment and interferon therapy, the incidence and recurrence rates of HCC were not different between the two treatments after adjusting the follow-up period and patient age.[44] In summary, although there are limitations of a short observation period and retrospective nature in most of the studies, the achievement of an SVR with DAA treatment was consistently associated with a reduced incidence of HCC. However, long-term prospective follow-up studies are needed.

4. Tertiary prevention of HCC

HCC is associated with a high rate of recurrence even after curative treatment; the 5-year recurrence rate is as high as 50% to 70%; thus, tertiary prevention is very important. Recurrence within 2 years after curative treatment is highly likely to be metastasis of the primary tumor, and thus adjuvant cytotoxic chemotherapy has been tried without proving recurrence reduction or prolongation of survival.[34]

There has been no RCT to determine whether antiviral treatment could reduce the incidence of HCC after hepatectomy in patients with chronic HBV or HCV infection. However, many observational studies have reported that oral antiviral therapy after curative treatment of HBV-associated HCC can significantly reduce recurrence of HCC by up to 50% (hazard ratio [HR], 0.48).[45] A meta-analysis showed that antiviral treatment for HBV after curative treatments (i.e., surgical resection, radiofrequency ablation, and percutaneous ethanol injection) reduced the recurrence of HCC (55% vs 58%: odds ratio [OR], 0.59; 95% CI, 0.35 to 0.97; p=0.04), liver-related mortality (0% vs 8%: OR, 0.13; 95% CI, 0.02 to 0.69, p=0.02), and overall mortality (38% vs 42%: OR, 0.27; 95% CI, 0.14 to 0.50; p<0.001).[46,47]

In a meta-analysis of interferon therapy after curative treatment for HCV-associated HCC that observed 665 patients for 2 to 7 years, the achievement of an SVR was associated with a 74% reduction in the HCC recurrence rate and a 60% reduction in the mortality rate.[48] In another meta-analysis, HCC recurrence was significantly lower in the interferon-treated group than in the non-treated group after surgical resection.[47]

A case series reported that the DAA treatment seems to increase the recurrence of HCC. In this study, 58 patients who received DAA therapy after treatment for HCV-associated HCC showed a 27.6% HCC recurrence rate at a median of 5.7 months.[49] It was suggested that the mechanism of high HCC recurrence in the patients would be DAA-induced immunologic derangements.[50-53] A short-term Italian study reported that DAA treatment failed to reduce the incidence or recurrence of HCC.[54] However, in a large prospective cohort study of French Agency for AIDS and Viral hepatitis Research, after the curative treatment of HCC, the recurrence rate was not significantly different between the DAA-treated group and the no-treatment group; nevertheless, there was a significantly higher HCC recurrence rate in the no-treatment group in the presence of compensated cirrhosis.[55] In the prospective multicenter RESIST-HCV cohort study,[56] HCC recurred in 19% of the DAA-treated patients, which was not significantly higher than untreated historical control patients. In a small Japanese retrospective study of patients with HCC treated with radio-frequency ablation, the recurrence rate of HCC was the lowest in patients treated with DAA compared with interferon treatment and no treatment (30% vs 68% vs 64%, respectively), and DAA treatment was not associated with recurrence of HCC.[57] In another Japanese retrospective study of patients who underwent curative treatment of HCC,[58] the recurrence rate of HCC was significantly higher in untreated patients than in those treated with DAA (at year 2: 25.0% vs 46.5%, p=0.003). In this study, DAA treatment reduced the risk of recurrence of HCC by 65%. In summary, recurrence of HCC may occur during or after treatment with DAA; however, treatment with DAA does not appear to increase the recurrence rate of HCC.[44,59] Long-term comparative studies are needed to determine the relationship between DAA treatment and HCC recurrence.

Recommendations

1. All newborns (**A1**) and seronegative (negative for all of HBsAg, anti-HBs, and anti-HBc) children and adults should be vaccinated against HBV (**B1**) to prevent HCC.
2. General HCC preventive measures include the following: prevention of HBV/HCV transmission (**A1**); avoidance of alcohol abuse; and control of metabolic disorders, such as obesity and diabetes (**C1**).
3. Antiviral therapy as a secondary prevention of HCC may follow the KASL guidelines for the management of chronic hepatitis B (**A1**).
4. The risk of HCC can be reduced if HBV replication is completely suppressed in patients with chronic hepatitis B (**A1**), and if an SVR is achieved by interferon therapy (**A2**) or by DAA therapy (**C1**) in patients with chronic hepatitis C.
5. After curative treatment of HBV-associated HCC, anti-HBV therapy should be considered to reduce the risk of HCC recurrence in patients with detectable HBV DNA in serum (**B1**).
6. After curative treatment of HCV-associated HCC, the association of DAA therapy with risk or prevention of HCC recurrence is not yet clear (**C1**).
7. Coffee consumption in patients with chronic liver disease can lower the risk of HCC (**B1**).

SURVEILLANCE

The major rationale for intensive surveillance for cancer is to reduce disease-related mortality. There are only two RCTs on the efficacy of surveillance programs in reducing HCC-related mortality among individuals at risk of HCC. In a Chinese study of 5,581 chronic hepatitis B patients recruited in the early 1990s, surveillance for HCC using only 6-monthly alpha-fetoprotein

(AFP) assays resulted in earlier diagnosis of HCC; however, the gain in lead time did not result in a significant reduction in overall mortality because of ineffective treatments for HCC.[60] In contrast, a large-scale trial involving 18,816 Chinese patients with chronic hepatitis B demonstrated that, despite poor study adherence (58.2%), a strategy of surveillance with ultrasonography (US) and AFP measurement every 6 months significantly reduced HCC-related mortality by 37% compared with no surveillance. In addition, the surveillance strategy was associated with a higher rate of detection of small HCC and surgically amenable HCC, as well as better overall survival (OS) after the diagnosis of HCC.[61] Several non-randomized cohort studies and meta-analyses have also found that surveillance has detected more cases of early-stage HCC, provided a higher rate of curative treatments, and led to significantly better OS than that found in the control group, indicating the compelling justification for HCC surveillance in at-risk patients.[62-66]

Unlike other malignancies, HCC has well-established risk factors that allow the identification of an at-risk patient group. Since approximately 90% of HCC cases are associated with a well-known risk factor, most of the international guidelines have been adapted to perform HCC surveillance in the population at risk of HCC development.[63] Patients with cirrhosis derived from any etiology are regarded as the most important targets to perform a surveillance program, since more than 80% of patients diagnosed with HCC have underlying cirrhosis. Viral hepatitis is also one of the most important causal risk factors for HCC. Chronic HBV infection is responsible for around 70% of all patients diagnosed with HCC in East Asia, including Korea, whereas chronic HCV infection accounts for around 30% of HCC patients in Western countries, with most of the HCV-associated HCC patients having either cirrhosis or advanced fibrosis at diagnosis. However, one Korean study involving patients undergoing hepatectomy has shown that 32.5% of HCV-related HCCs were not associated with underlying cirrhosis, indicating a lower rate of HCV-related HCC accompanying cirrhosis than that reported in Western countries.[67] In addition, the risk of HCC also increases with patient age, excessive alcohol drinking, male sex, and diabetes mellitus, and is higher among Asian HBV carriers with high viral activity and family history of the disease, and chronic hepatitis B patients with cirrhosis or advanced fibrosis.[68,69] Based on a cost-effectiveness study, it is generally accepted that an annual incidence of HCC surpassing 1.5% would warrant a surveillance scheme of HCC in cirrhosis patients.[70] However, patients with chronic HBV infection can develop HCC in the absence of underlying cirrhosis. Thus, expert opinion indicates that HCC surveillance for chronic HBV carriers is deemed to be cost-effective if the annual incidence is at least 0.2%.[71] Given this definition, patients with liver cirrhosis of all etiologies, chronic HBV infection, or chronic HCV infection with cirrhosis or advanced fibrosis are the major target population for surveillance as a high risk group for HCC. From a pooled analysis of previously published studies on the natural history of various liver diseases, patients with liver cirrhosis are at the highest risk of developing HCC, irrespective of etiology. Patients with chronic HBV infection and those with HCV-related cirrhosis or advanced fibrosis are also at a high risk of HCC, of which annual incidences exceed 0.2% and 1.5%, respectively.[63,71] The major drawbacks that remain are the difficulties in accurately defining cirrhosis in alcoholic or all other liver diseases, as well as differentiating F3 from F2 disease in hepatitis C. The role of HCC surveillance is unclear among patients with non-viral liver disease and there is uncertainty regarding underlying cirrhosis. Although age is an important risk factor for HCC, there is no clear evidence to guide the target population according to age strata. With the exception of cirrhosis patients with alcoholic or nonalcoholic fatty liver disease, there are few data available on the actual HCC risk and surveillance and thus, a solid recommendation cannot be made for those with fatty liver disease.

In general, US with or without AFP is widely used as a tool for HCC surveillance. However, there is some discrepancy regarding the recommended surveillance methods. Among tumor markers relevant to HCC, no factors have actually been proven to be better in detecting HCC than AFP. Consequently, information on tumor markers for HCC surveillance is limited to AFP, since almost all studies looking at the effectiveness of a surveillance program have implemented only AFP as a tumor marker for HCC. The sensitivity of detecting early stage HCC in high-risk patients is reportedly approximately 60% when performing surveillance using US with and without serum AFP measurement.[72-74] The sensitivity and specificity of US as a surveillance tool for HCC in patients with chronic HBV infection were reported to be 65%–80% and over 90%, respectively, with a higher sensitivity for detecting liver cancer than that of serum markers such as AFP.[66,75] While AFP measurement and US are imperfect tools, they appear to be mutually complementary.[69] From a meta-analysis of 16 relevant studies, combined use of US and AFP measurement yielded a higher sensitivity for HCC detection than US alone (0.79 [95% CI, 0.57 to 0.91) vs 0.69 [95% CI, 0.46 to 0.85]), although it was not statistically significant.[62] In another meta-analysis of 13 selected studies, the pooled sensitivity for detecting early-stage HCC increased from 63% with US alone to 70% with US plus AFP measurement.[62] A pooled analysis of seven studies of patients with cirrhosis showed that US with versus without AFP measurement detected early-stage HCC with 63% sensitivity (95% CI, 48% to 75%) and 45% sensitivity (95% CI, 30% to 62%), respectively, indicating a higher sensitivity with US plus AFP measurement than US only.[76] The performance of surveillance varies depending on the cutoff levels of biomarkers and the prevalence of HCC among the general population in a certain region. In the United States and Europe where the prevalence of HCC is relatively low, only US examination is often recommended as a surveillance method, whereas in Korea and Japan where its prevalence is high, it is recom-

mended to perform US with serum AFP measurement for HCC surveillance in the high-risk population.[77-79]

The interval of cancer surveillance should be determined based on tumor doubling time, stage migration amenable for curative treatments at diagnosis, cost-effectiveness, and patient survival. Although the optimal surveillance intervals in at-risk patients for HCC have not yet been clearly determined, the intervals of HCC surveillance recommended by most of the regional guidelines range from 3 to 12 months.[71,77-80] An Italian study comparing 6-month versus 12-month surveillance failed to increase the chances of detection of single nodular tumors with 6-month surveillance compared with 12-month surveillance.[81] An RCT evaluating more intense surveillance of 3-month versus 6-month intervals also only provided similar results in detecting small HCCs.[82] In contrast, another Italian study looking at the performance for the early detection of HCC showed that semiannual surveillance increases the detection rate of early-stage HCC and patient survival compared with an annual program.[65] Another randomized trial that evaluated US as a surveillance tool in Taiwanese patients with viral hepatitis demonstrated that a 4-month interval scheme performed better in detecting very early stage HCC compared with that of a 12-month interval, although it did not provide a survival benefit.[83] Moreover, the pooled sensitivity of detecting HCC increased from 50% with the annual scheme to 70% with the semiannual surveillance.[62] In a cost-effective study, a semiannual US surveillance program in cirrhotic patients provided an incremental cost-effectiveness ratio and improved clinical outcomes at a reasonable cost.[84] The mean tumor doubling time of small HCCs (<5 cm) was estimated to be around 4 to 7 months, ranging between 136 and 204 days.[85,86] Lastly, semiannual surveillance is the interval employed in the only RCT that showed survival benefits with an HCC surveillance scheme.[61] Thus, taken together, a 6-month interval for an HCC surveillance program would be considered a preferable and reasonable strategy.

Given that the incidence of HCC varies according to the cause of liver disease and the degree of cirrhosis even in the high-risk group, there may be groups at higher risk of HCC than others. Under circumstances in which HCC is highly suspected, contrast-enhanced US, liver dynamic computed tomography (CT), or contrast-enhanced magnetic resonance imaging (MRI) can be performed as an alternative to US when a US examination fails to detect nodules or is incomplete due to poor visualization. With the advantage of assessing blood supply and vascular invasion of tumors, contrast-enhanced US has been found more cost-effective in surveillance for HCC than US alone.[87]

A recent randomized trial comparing biannual US with yearly contrast CT has shown the former to be marginally more sensitive and less costly for the detection of early HCC in patients with compensated cirrhosis.[88] More recently, MRI with liver-specific contrast in a surveillance setting of cirrhotic patients has resulted in a higher detection rate of HCC and lower false-positive findings than US.[89] However, the information on the alternative surveillance imaging strategies is very limited and should be interpreted with caution. Study results regarding the diagnostic performance of CT or MRI for HCC cannot be directly extrapolated to the setting of cancer surveillance. In addition, the risks, accessibility, and cost-effectiveness of these alternative imaging methods should be meticulously evaluated. Therefore, accuracy, costs, and potential harms regarding these new radiological modalities need to be further studied before the wide implementation of the alternative surveillance imaging strategies.

Recommendations

1. Surveillance for HCC should be performed in high-risk groups; patients with chronic hepatitis B (**A1**), chronic hepatitis C (**B1**), and liver cirrhosis (**A1**).
2. Surveillance test for HCC should be performed with liver US plus serum AFP measurement every 6 months (**A1**).
3. If liver US cannot be performed properly, liver dynamic CT or dynamic contrast-enhanced MRI can be performed as an alternative (**C1**).

DIAGNOSIS

HCC can be diagnosed either pathologically with a biopsy or with noninvasive imaging in high-risk groups with chronic hepatitis B, chronic hepatitis C, or cirrhosis. In at-risk patients with a nodule ≥1 cm in size on surveillance tests, a first-line imaging test should be performed, such as multiphase CT or multiphase MRI with extracellular contrast agents or hepatobiliary contrast agents like gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA). Diagnostic imaging tests are used to diagnose HCC and determine its extent. As imaging-based diagnosis relies on the typical findings of multiphase CT or MRI; single-phase CT or MRI cannot be used as a diagnostic tool for HCC.

A recent meta-analysis regarding the diagnostic performances showed a per-lesion sensitivity of 76% (95% CI, 72% to 80%) for multiphase CT and 83% (95% CI, 80% to 86%) for multiphase MRI, respectively.[72] Per-patient specificities were 91% (95% CI, 84% to 95%) for multiphase CT and 89% (95% CI, 82% to 93%) for multiphase MRI, respectively.[72] In addition, several meta-analyses reported that MRI using hepatobiliary contrast agents was associated with higher sensitivity (hepatobiliary contrast agents, 85.6%; 95% CI, 81.1% to 87.7% vs extracellular contrast agents, 77.5%; 95% CI, 73.1% to 79.3%) and a higher positive predictive value (hepatobiliary contrast agents, 94.2%; 95% CI, 90.9% to 96.3% vs extracellular contrast agents, 83.6%; 95% CI, 77.2% to 87.5%) than those using extracellular contrast agents.[90,91]

When an imaging diagnosis of HCC cannot be made with confidence on a first-line examination, a second-line examina-

tion with an alternative modality or contrast agent can be applied to enhance the sensitivity to diagnose HCC.[92,93] Imaging modalities for second-line examinations include multiphase CT, multiphase MRI with extracellular contrast agents or hepatobiliary contrast agents, and contrast-enhanced US with blood pool contrast agents. Contrary to the previous concern regarding its potential risk of misdiagnosing cholangiocarcinoma as HCC, contrast-enhanced US with blood pool contrast agents had a high specificity for HCC in a recent large retrospective study.[94] A meta-analysis found that contrast-enhanced US was comparable to multiphase CT and MRI with extracellular contrast agents in terms of sensitivity, which was 84.4% (95% CI, 79.4% to 86.7%) and positive predictive value, which was 89.3% (95% CI, 85.7% to 92.5%).[91] A prospective multicenter trial revealed that contrast-enhanced US had very high specificity for HCC diagnosis as a second imaging technique after a first inconclusive CT or MRI.[95] Because contrast-enhanced US is limited in evaluating the tumor extent in the whole liver (i.e., radiologic staging), it is not recommended as a first-line imaging modality. Instead, contrast-enhanced US is recommended as a second-line imaging technique if first-line imaging is inconclusive. In patients with early HCC, addition of MRI with Gd-EOB-DTPA to multiphase CT led to the detection of additional small nodules in 16.4% of patients and stage migration in 13.3%, which decreased the risk of HCC recurrence and lowered the mortality rate by 28% and 35%, respectively.[96]

Noninvasive diagnosis of "definite" HCC is based on the typical imaging hallmarks of HCC on multiphase CT or multiphase MRI with extracellular contrast agents or hepatobiliary contrast agents for a nodule ≥1 cm detected in at-risk patients. The major imaging features for a "definite" diagnosis of HCC are defined as arterial phase hyperenhancement with washout in the portal venous, delayed, or hepatobiliary phases (Table 2, Figs 3 and 4). If the size of newly detected nodule(s) during surveillance tests is smaller than 1 cm, follow-up US in 6 months or less is recommended.

On multiphase MRI with a hepatobiliary phase agent, washout can be considered present if a nodule shows hypoenhancement relative to the surrounding hepatic parenchyma not only during the portal or delayed phases but also during the hepatobiliary phase. The classic imaging hallmarks of HCC, which were adopted in previous guidelines, include arterial phase hyperenhancement and washout confined to the portal or delayed phases. Based on these diagnostic criteria, prospective studies demonstrated that multiphase CT or MRI with extracellular contrast agents had a sensitivity of 65% to 89% and a specificity of 91% to 100%.[92,93] In spite of the high specificity, the sensitivity of HCC diagnosis under these criteria is limited, which is even worse in nodules smaller than 2 cm where it only shows a sensitivity of 41% to 62%.[97,98] When hypointensity in the hepatobiliary phase is considered as washout, the sensitivity is increased.[99-101] Given the medical environments in Korea characterized by the wide use of MRI with hepatobiliary contrast agents and an emphasis on early detection and treatment, the diagnostic criteria for HCC should aim for high sensitivity. Thus, this guideline defines washout in the portal, delayed, and hepatobiliary phases. However, the usefulness of this approach can be offset by misdiagnosis of hemangioma and cholangiocarcinoma as HCC.[101] The diagnostic criteria for HCC should not be applied in lesions showing marked T2 hyperintensity or

Table 2. Diagnosis of Hepatocellular Carcinoma

1. Imaging diagnosis: In at-risk patients (chronic hepatitis B, chronic hepatitis C, and liver cirrhosis) having a lesion ≥1 cm on surveillance tests
   (1) Non-invasive diagnosis of "definite" HCC is based on the typical imaging hallmarks of HCC on multiphase CT or multiphase MRI with extracellular contrast agents or hepatobiliary contrast agents.
   If a first-line imaging is inconclusive, a second line examination can be applied. The imaging modalities for the second line examinations include multiphase CT, multiphase MRI with extracellular contrast agents or hepatobiliary contrast agents, and contrast-enhanced US with blood pool contrast agents.
   (2) The major imaging features for "definite" diagnosis of HCC are defined as arterial phase hyperenhancement with washout in the portal venous, delayed or hepatobiliary phases. These criteria should be applied only to a lesion which does not show either marked T2 hyperintensity or targetoid appearance on diffusion-weighted images or contrast-enhanced sequence.
   (3) The typical hallmark for "definite" HCC diagnosis at contrast-enhanced US is defined as arterial phase hyperenhancement followed by late (>60 seconds) washout of mild degree.
   (4) In nodule(s) with some but not all the aforementioned major imaging features of HCC, the category of "probable" HCC can be assigned by applying ancillary imaging features.* This category should be applied only to lesion(s) which does not show either marked T2 hyperintensity or targetoid appearance on diffusion-weighted images or contrast-enhanced sequence.
2. Pathologic diagnosis
   When the imaging-based diagnosis inconclusive or lesion(s) shows atypical imaging features, biopsy is indicated.

HCC, hepatocellular carcinoma; CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasound.
*Ancillary imaging features are summarized in Table 3.

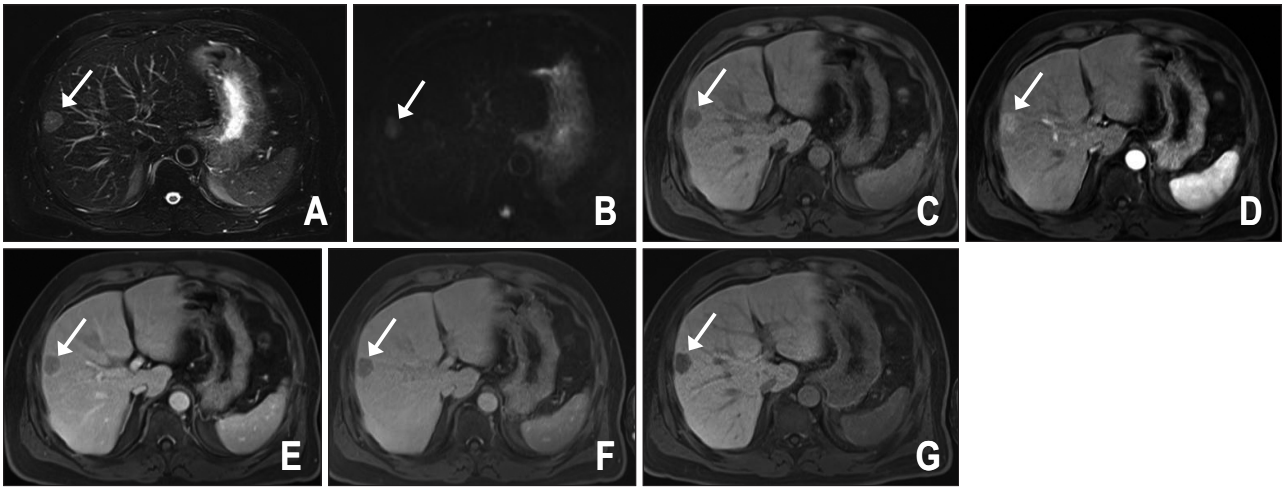


Fig. 3. Typical hallmarks of hepatocellular carcinoma (arrow) on Gd-EOB-DTPA (gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid) magnetic resonance imaging. (A) T2-weighted image, (B) diffusion-weighted image, (C) non-contrast image, (D) arterial phase image, (E) portal phase image, (F) delayed phase image, and (G) hepatobiliary phase image.

Table 3. Ancillary Imaging Features

Favoring malignancy in general	Mild-to-moderate T2 hyperintensity, restricted diffusion, hepatobiliary phase hypointensity, threshold growth*
Favoring HCC in particular	Non-enhancing capsule, mosaic architecture, nodule-in-nodule appearance, fat or blood products in mass
Ancillary features favoring benignity	Size stable ≥2 years*, marked T2 hyperintensity, no mass effect

*Threshold growth is now defined as an increase in the size of a nodule by at least 5 mm and at a sufficient rate: either ≥50% increase in size in ≤6 months or ≥100% increase in size in >6 months.[90]

targetoid appearance on diffusion-weighted images or contrast-enhanced sequences, which are typical imaging features of hemangioma or cholangiocarcinoma. Eosinophilic infiltration in the liver, which is common in Korean patients, can also mimic HCC.[102] In order to avoid this pitfall, the peripheral eosinophil count needs to be determined before making a diagnosis of HCC. The typical hallmark for "definite" HCC diagnosis on contrast-enhanced US is defined as arterial phase hyperenhancement followed by late (>60 seconds) washout of a mild degree.[90]

In a nodule with some but not all of the aforementioned major imaging features of HCC, a diagnosis of "probable" HCC can be made by applying ancillary imaging features (Table 3, Fig. 4). This category should be applied only to a lesion which does not show either marked T2 hyperintensity or a targetoid appearance on diffusion-weighted images or contrast-enhanced sequence. "Probable" HCC in this guideline corresponds to LR-4 (probable HCC) according to the Liver Imaging Reporting and Data System proposed by the American College of Radiology.[90] For "probable" HCC, a follow-up imaging study with an interval of less than 6 months or biopsy needs to be considered to establish the diagnosis.

Recent advances in imaging techniques have provided more opportunities to detect subcentimeter-sized lesions. Some HCC guidelines from Asian countries allow the diagnosis of subcentimeter-sized HCCs.[79,103,104] However, the diagnostic performances of imaging studies for subcentimeter-sized HCCs are worse than those for HCCs ≥1 cm (<1 cm vs ≥1 cm: 31% vs 82%, p<0.001 for CT; 48% vs 88%, p=0.02 for MRI).[90] Even MRI with hepatobiliary contrast agents showed significantly lower per-lesion sensitivity (46%) and positive predictive value (48%) for subcentimeter-sized HCCs than those for HCCs ≥1 cm (sensitivity, 95%; positive predictive value, 78%).[105] Recent studies found that adding the ancillary imaging features (Table 3, Fig. 4) improved diagnostic performances for subcentimeter-sized HCCs.[105-109] A subcentimeter-sized lesion should not immediately initiate the recall process. Instead, a conservative approach should be preferred, with close monitoring of interval growths or changes in follow-up imaging studies at an interval of less than 6 months.

When the imaging diagnosis using the first- and second-line examinations remains inconclusive for a nodule detected during surveillance tests in at-risk patients, the lesion is defined as "indeterminate." A study including more than 90 cases of 1 to 2 cm-sized indeterminate nodules found on surveillance revealed that the prevalence of malignancy was 14% to 23%, while the remaining lesions were diagnosed as arterioportal shunt, regenerative nodules, and dysplastic nodules.[110] Thus, for indetermi-

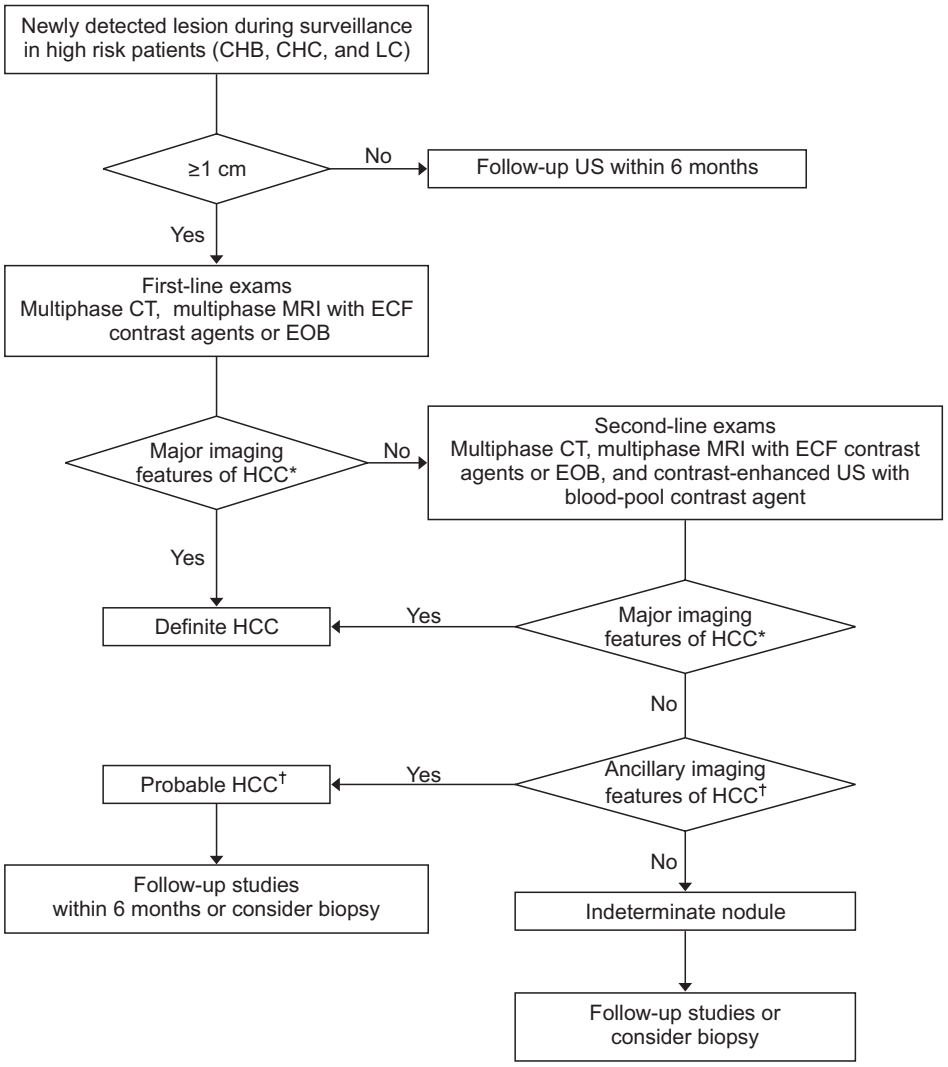


Fig. 4. Diagnostic algorithm and recall policy in patients with a high risk of hepatocellular carcinoma (HCC).
CHB, chronic hepatitis B; CHC, chronic hepatitis C; LC, liver cirrhosis; US, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; ECF, extracellular fluid; EOB, gadolinium ethoxybenzyl diethylenetriamine pentaacetate. *The major imaging features for "definite" diagnosis of HCC are defined as arterial phase hyperenhancement with washout in the portal venous, delayed or hepatobiliary phases. These criteria should be applied only to a lesion which does not show either marked T2 hyperintensity or targetoid appearance on diffusion-weighted images or contrast-enhanced sequence on contrast-enhanced US as second line exams, major imaging features include arterial hyperenhancement and mild wash-out with late onset (≥60 seconds); †In nodule(s) with some but not all of the aforementioned major imaging features of HCC, the category of "probable" HCC can be assigned only when the lesion fulfills at least one item from each of the following two categories of ancillary imaging features. The two categories which make up ancillary imaging features are findings favoring malignancy in general (mild-to-moderate T2 hyperintensity, restricted diffusion, hepatobiliary phase hypointensity, interval growth) and those favoring HCC in particular (non-enhancing capsule, mosaic architecture, nodule-in-nodule appearance, fat or blood products in the mass). These criteria should be applied only to a lesion which shows neither marked T2 hyperintensity nor a targetoid appearance on diffusion-weighted images or contrast-enhanced sequences.

nate lesions in at-risk patients, any changes in imaging patterns or serum tumor markers should be closely monitored, or biopsy can be considered for pathologic diagnosis.

For pathologic diagnosis of HCC, biopsy is considered a relatively safe procedure. However, in clinical practice, it is often difficult to perform due to the presence of ascites, a high risk of bleeding associated with poor hepatic function, concerns for needle track seeding, and challenges in tumor targeting. Among the techniques used to obtain a tissue, core needle biopsy should be preferred instead of fine needle aspiration cytology or fine needle aspiration biopsy. Sensitivity of pathologic diagnosis for HCC is reported as approximately 72%, although it varies according to the location, size and degree of differentiation.[111,112] The pathological diagnosis is more challenging for small HCCs less than 2 cm.[111,112] Sensitivity can be even worse, considering that the adequate biopsy sampling of such small lesions is challenging.[111] Cytologic examination methods, such as fine needle aspiration cytology and fine needle aspiration biopsy, may be helpful for the diagnosis of advanced HCC (≥grade 2). As the risk of tumor seeding was 0.6% to 5.1%, its rationale in patients

who have a chance for complete treatment after surgery or liver transplantation has been questioned.[113,114] The presence of stromal invasion, which is a criterion to differentiate between early HCC and dysplastic nodule, cannot be determined competently using liver biopsy.[111,112] In addition, liver tumor biopsy is associated with a 33% risk of false positive results.[111,112] Thus, the majority of diagnoses in clinical practice are made on the basis of noninvasive imaging studies. However, imaging sometimes fails to differentiate infrequent subtypes of primary hepatic tumors, including combined HCC and cholangiocarcinoma (combined HCC-CC) and cholangiocellular carcinoma, from HCC. Therefore, biopsy is required when a definite diagnosis cannot be made using the imaging criteria or atypical hepatic tumors do not follow an expected clinical course. Histologic markers, including heat shock protein 70, glypican 3, and glutamine synthetase, can be assessed to distinguish HCC from dysplastic nodules.[115] Unresponsiveness to treatment can also be an indication for liver biopsy.

The role of tumor markers is limited in the diagnosis of HCC due to their high false positive and false negative rates.[116] AFP levels stay within the normal range in 35% of patients with small HCCs, whereas AFP levels can be elevated not only in HCC but also in nonspecific conditions, such as aggravation of hepatitis activity or active regeneration of hepatocytes.[74,117,118] Therefore, AFP measurement alone is not sufficient to make a diagnosis of HCC.

Little is known about the imaging diagnosis criteria for recurrent hepatic tumors. However, given the high pre-test probability of recurrence in patients with a history of previous HCC, high sensitivity can be pursued in this setting. A diagnosis of HCC for newly detected or growing nodules in follow-up imaging studies can be more easily achieved using ancillary features in patients who have a history of HCC, even when the lesions are smaller than 1 cm or do not show the typical characteristics.

RISK OF RADIATION EXPOSURE DOSE OF CT EXAMINATION IN HCC PATIENTS

A study of low-dose radiation in atomic bomb survivors indicates a significant increase in cancer risk even from acute exposure to 10–50 mSv radiation.[119] In addition, studies of occupational radiation exposure suggest that protracted exposure to 50–100 mSv can increase cancer risk in humans.[120-122] The International Commission on Radiological Protection (ICRP) reports that the cancer risk after radiation exposure exhibits a linear-nonthreshold dose-response relationship.[123,124] However, there is no report on direct diagnostic X-ray radiation exposure-related cancer risk. The dose of radiation exposure of 4-phase liver dynamic CT is approximately 20–30 mSv. According to the BEIR VII phase 2 trial by the Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, the additional lifetime attributable solid cancer and leukemia incidence and mortality rates are 0.148% and 0.09%, respectively, in 50-year-old men with 25 mSv X-ray radiation exposure after a 4-phase liver dynamic CT.[125,126] The ICRP 2007 recommendations are as follows: "The limitation of the dose to the individual patient is not recommended because it may, by reducing the effectiveness of the patient's diagnosis or treatment, do more harm than good. The emphasis is then on the justification of the medical procedures and on the optimization of protection."[127] In addition, the radiation-associated cancer risk is considered less significant in patients with decreased life expectancy, such as elderly or severely ill patients.[128] Thus, strict limitation of the radiation dose of CT is not recommended for the diagnosis and follow-up evaluation of HCC. However, unnecessary radiation exposure from CT should be avoided and alternative imaging studies should be considered, particularly in patients with long life expectancy. Recently, CT techniques with a reduced radiation dose using iterative reconstruction and low voltage have been developed, without compromising image quality.[129,130] Thus, these low-dose techniques or alternative imaging methods, such as MRI, need to be considered in order to optimize radiation exposure.

Recommendations

1. A diagnosis of HCC can be made with either pathology or noninvasive imaging in high-risk groups (chronic hepatitis B, chronic hepatitis C, or cirrhosis) (**A1**).
2. In at-risk patients with a lesion ≥1 cm in size on surveillance tests, multiphase CT or multiphase MRI with extracellular contrast agents or hepatobiliary contrast agents should be performed as a first-line examination (**A1**). If first-line imaging is inconclusive, second-line imaging examination can be applied. The second-line imaging examinations include multiphase CT, multiphase MRI with extracellular contrast agents or hepatobiliary contrast agents, and contrast-enhanced US with blood pool contrast agents (**B1**).
3. An imaging diagnosis can be applied to a nodule ≥1 cm detected in at-risk patients during surveillance on the basis of the following radiologic hallmarks:
   (1) On multiphase CT or MRI with extracellular contrast agents, the major imaging features for a "definite" diagnosis of HCC are defined as arterial phase hyperenhancement with washout in the portal venous or delayed phases (**A1**).
   (2) On multiphase MRI with hepatobiliary contrast agents, the major imaging features for a "definite" diagnosis of HCC are defined as arterial phase hyperenhancement with washout in the portal venous, delayed, or hepatobiliary phases. These criteria should be applied only to a lesion which does not show either marked T2 hyperintensity or a targetoid appearance on diffusion-weighted images or contrast-enhanced sequences (**B1**).

4. In nodule(s) with some but not all of the aforementioned major imaging features of HCC, the category of "probable" HCC can be assigned only when the lesion fulfills at least one item from each of the following two categories of ancillary imaging features (**B1**). The two categories which make up ancillary imaging features are findings favoring malignancy in general (mild-to-moderate T2 hyperintensity, restricted diffusion, hepatobiliary phase hypointensity, interval growth) and those favoring HCC in particular (nonenhancing capsule, mosaic architecture, nodule-in-nodule appearance, fat or blood products in the mass). These criteria should be applied only to a lesion which shows neither marked T2 hyperintensity nor a targetoid appearance on diffusion-weighted images or contrast-enhanced sequences.
5. For "probable" HCC, follow-up imaging studies in less than 6 months or biopsy need to be considered to establish the diagnosis (**C1**). For indeterminate lesions, any changes in imaging patterns or serum tumor markers should be closely monitored, or biopsy can be considered for pathologic diagnosis (**B1**).
6. In patients with subcentimeter-sized nodules, follow-up with an interval of less than 6 months is recommended while closely monitoring interval growths or changes in imaging patterns (**C1**).
7. A new or a growing nodule which does not show typical imaging hallmarks of HCC found in the follow-up of a patient diagnosed with HCC could be diagnosed as HCC based on ancillary imaging features (**C1**).
8. Although strict limitation of the radiation dose from CT for diagnosis and follow-up evaluation of HCC is not recommended, unnecessary radiation exposure from CT should be avoided. Techniques with a reduced radiation dose and alternative imaging studies should be considered (**C1**).

STAGING

Cancer staging plays a pivotal role in predicting prognosis as well as in selecting the therapy to maximize survival potential. It also facilitates exchange of information and trial design. Prediction of the prognosis in HCC patients is complex because underlying liver function also affects prognosis.[131,132] Although several staging systems for patients with HCC have been devised, there is no global consensus.[133]

The American Joint Committee on Cancer (AJCC) has led a collaborative effort with the Union for International Cancer Control (UICC) to maintain a cancer staging system since 1959. This system classifies the extent of disease mostly on the basis of anatomic information on the extent of the primary tumor, regional lymph nodes, and distant metastases (i.e., the tumor-node-metastasis [TNM] staging system) and has been modified repeatedly. The eighth edition was proposed in 2017. The guidelines from the KLCA (ex-KLCSG) and the NCC Korea adopted the fifth version of the modified UICC (mUICC) staging system as a primary staging system for HCC in 2003.[134,135] Thus, the continuing use of this staging system may facilitate consistency in the analyses of registry data (Table 4).[79] However, the mUICC staging system lacks international validation and has limitations, such as the difficulty of extensive international information exchange because it differs from the AJCC/UICC TNM staging system. In addition, the revised mUICC staging system[135] has been applied to the same stage of biliary tract invasion and vascular involvement. The reason for this is unclear, and biliary tract invasion differs in terms of the indication of surgery and the prognosis after treatment compared with vascular invasion; therefore, research to verify this guideline is necessary. In addition to dynamic CT or MRI of the primary liver tumor, chest CT, bone, and positron emission tomography (PET)-CT scans may be required to stage HCC. The risk of distant metastasis is low for patients with early-stage HCC; therefore, tests for the evaluation of extrahepatic metastasis should be carefully selected. Gastroscopic examination is necessary to confirm the presence of portal hypertension, which is important in making the treatment decision.

The Barcelona Clinic Liver Cancer (BCLC) staging system includes factors for tumor stage, degree of liver function, and performance status of the patient. It suggests the most recommendable treatment modality for each stage and is endorsed by the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the European Organization for Research and Treatment of Cancer.[77,136] However, the use of the BCLC staging system is limited because it contains a subjective component (i.e., performance status), crude evaluation of liver function (i.e., Child-Pugh class), and unduly simplified recommendations for the treatment modality. The Hong Kong Liver Cancer (HKLC) staging system was developed for Asian patients, most of whom were hepatitis B patients. Patients with intermediate or advanced stage disease according to the BCLC staging system were more likely to have more active treatment than the BCLC staging system and the survival rate was increased when they followed HKLC staging system. However, validation is required for non-Asian populations and other causes of liver cancer.[137]

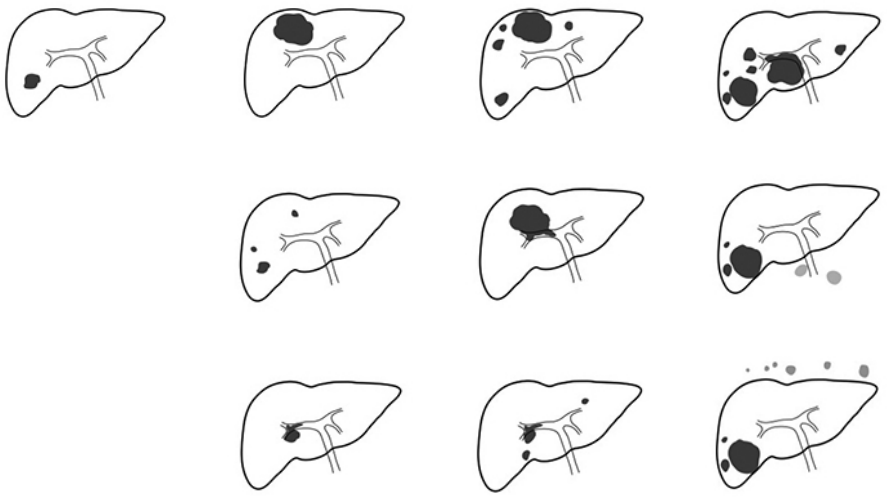
Evaluation of tumor extension is critical for determining the cancer stage and treatment strategy. Common sites of HCC metastasis include the lung, lymph nodes, bone, adrenal gland, and peritoneum.[138] Although the indications and methods to detect these metastatic lesions have not yet been established, the recent National Comprehensive Cancer Network guidelines recommend chest CT, complete imaging of the pelvis with contrast-enhanced CT, and bone scan as staging workups in patients with HCC.[139] Several meta-analyses and retrospective studies found that fluorodeoxyglucose F18 (^{18}F-FDG)-PET CT appeared to be useful in detecting extrahepatic metastasis in patients with HCC.[140-142] In a prospective Korean study including 35 metastatic

Table 4. Modified Union for International Cancer Control Stage*

Stage	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
IV A	T4	N0	M0
	T1, T2, T3, T4	N1	M0
IV B	T1, T2, T3, T4	N0, N1	M1

*Adapted from Liver Cancer Study Group of Japan.[134,135]

Criteria	T1	T2	T3	T4
(1) Number of tumors: solitary (2) Diameter of the largest tumor ≤2 cm (3) No vascular or bile duct invasion: Vp0, Vv0, B0	All three criteria are fulfilled	Two of the three criteria are fulfilled	One of the three criteria is fulfilled	None of the three criteria are fulfilled



HCC patients, the sensitivity of ^{18}F-FDG-PET CT for extrahepatic HCC lesions was reported to be up to 85.7%.[140] In particular, the detection rates of lung and bone metastases, which were the most common types of HCC metastases, were 80% and 100%, respectively. Another Korean study also demonstrated that 5% of BCLC stage A (6 of 119) and 1.4% of BCLC stage B (1 of 71) HCC patients were shifted to BCLC stage C after identifying extrahepatic lesions using ^{18}F-FDG-PET CT.[143] Hence, ^{18}F-FDG-PET CT can be selectively considered for patients with HCC prior to curative surgical treatments, such as hepatectomy and liver transplantation.

Recommendations

1. This guideline adopts the mUICC stages as a primary staging system, with the BCLC staging system and the AJCC/UICC TNM staging system serving as complementary systems (**B1**).
2. The use of ^{18}F-FDG-PET CT is suggested to detect the presence of metastatic disease in the case of patients being considered for treatments with curative intent, such as hepatic resection and liver transplantation (**C1**).
3. Chest CT, pelvis CT, and bone scan can be used as part of the HCC staging workup if extrahepatic metastasis of HCC is suspected (**C1**).

MANAGEMENT OVERVIEW

The ultimate goal of treatment for HCC patients may vary depending on the patient's cancer stage, underlying liver function and performance status; however, generally the goal is to increase the survival time and rate and improve quality of life. This requires multidisciplinary treatment planning, including gastroenterology, hepatology, oncology, surgery, radiology, interventional radiology, radiation oncology, pathology, and many other departments.

Therapies should be selected on the basis of strong evidence, and the best evidence is from meta-analyses, RCTs, prospective controlled studies, and prospective large-scale cohort studies that verify the survival rate. Even though these studies are increasing, the best evidence like RCTs regarding HCC treatment is still insufficient, and thus a great part of treatment planning is based on moderate level evidence. Therefore, applying treat-

ments requires great understanding of the whole of HCC. It is difficult to establish a balanced and multidisciplinary treatment plan in actual clinical practice because treatment indications and results claimed by each department that directly performs treatment lack objectivity. Accordingly, more objective evaluation is necessary through group discussions of expert groups, such as the KPGRC.

The best treatments recommended in these guidelines are the results of evidence-based medicine. Prerequisites for the application of these recommendations include actual facilities and trained personnel to provide all possible treatments for the patients, as well as the financial conditions of patients and cooperation of patients and guardians. Therefore, these guidelines first provided both the best and alternative treatments for HCC according to mUICC staging in 2014 considering the various aforementioned requirements, and the same approach is taken in the revised guidelines (Fig. 5). However, as different treatments may be selected for HCC depending on underlying liver function and competency in addition to staging, not all possible cases could be listed and summarized in these guidelines. Recommendations for specific treatments are made on the basis of medical evidence and expert opinions for various HCC conditions, and are described in detail in each treatment section of these guidelines.

This overview summarizes the treatments for HCC patients with various mUICC disease stages with good liver function (Child-Pugh A level) and good performance status (Eastern Cooperative Oncology Group [ECOG] performance 0-1) without any complications of portal hypertension to promote understanding of treatments in general. These guidelines separately deal with second-line treatment for the first time, and this Management Overview provides information only on the initial treatment. Second-line treatments for residual, recurred, or progressed cancer after the initial treatment are described separately along with recommendations later.

HEPATIC RESECTION

Hepatic resection is not only a primary treatment modality for patients with solitary HCC unaccompanied by liver cirrhosis,[144] but also a preferentially considered option for cirrhosis patients with sufficient hepatic functional reserve.[145,146] The results of hepatic resection for HCC have markedly improved thanks to recent advances in preoperative tests and surgical skills, as well as accumulation of experience in postoperative management.[147] Recent studies show that postoperative mortality after HCC resection is less than 1% to 3%. In addition, the 5-year overall and disease-free survival rates are 46% to 69.5% and 23% to 56.3%, respectively.[148-151] The 5-year recurrence rate after hepatic resection of HCC ranges from 43.7% to 77%, and 80% to 95% of postoperative recurrences are intrahepatic.[152] Intrahepatic recurrences are divided into intrahepatic metastasis and *de novo* HCC by multicentric carcinogenesis. The two recurrence entities can be differentiated by means of genomic hybridization, DNA fingerprinting, DNA microarray, or HBV integration pattern.[153] However, no clinical definition of either entity has been established. In general, late recurrence more than 2 years after primary resection is considered *de novo* HCC.[154] Risk factors associated with recurrence after resection are classified as either tumor-related or underlying disease-related. Tumor-related factors, which are usually related to early recurrence, include tumor size and number, microvascular invasion, poor tumor differentiation, high serum AFP and prothrombin induced by vitamin K absence II (PIVKA-II) levels, and positivity of ^{18}F-FDG PET. Meanwhile, underlying disease-related risk factors, which influence late recurrence, include cirrhosis, high serum HBV DNA levels, and active hepatitis.[140,154-160] Nevertheless, no association between risk factors and recurrence time is evident in many cases because this time-dependent classification does not actually reflect the tumor-pathologic mechanism of HCC recurrence.

Imaging modalities, such as CT and MRI, as well as serum tumor markers are recommended surveillance tools during follow-up. Serum AFP, a traditional tumor marker of HCC, is also an effective marker for recurrence when liver function is normalized after resection in cases with preoperatively elevated AFP levels.[161] PIVKA-II is another HCC marker with increasing utility for diagnosis, follow-up, and prognostication of HCC.[155,162]

1. Preoperative evaluation

Child-Pugh classification is conventionally used to preoperatively assess the safety of hepatic resection (Table 5).[163] Hepatic resection is commonly performed in patients with Child-Pugh class A with ECOG performance status 0-2 (Table 6).[164] However, Child-Pugh classification is an insufficient preoperative indicator of operability because many patients' liver function can remain in Child-Pugh class A despite advanced cirrhosis.[165,166] Therefore, the indocyanine green 15-minute retention rate (ICG-R15), which was suggested for use in Japan, is evaluated at many Korean institutions as a preoperative test for the prediction of residual liver function.[167] Although major hepatic resection is recommended only for patients with ICG-R15 ≤10%, a study recently reported safe right hemihepatectomy even in patients with an ICG-R15 of up to 14%.[168] In contrast, portal hypertension and serum bilirubin level have been suggested to be criteria for resectability in Europe and the United States, in which portal hypertension is defined as a hepatic venous pressure gradient ≥10 mm Hg.[169] Esophageal varix and thrombocytopenia <100,000/mm^3 accompanied by splenomegaly are also indicators of portal hypertension, and thrombocytopenia is considered the most clinically relevant criterion.[77] The posthepatectomy complication rate is high and the long-term prognosis is poor in patients with portal hypertension.[169-171] However, some recent studies reported comparable outcomes even in patients

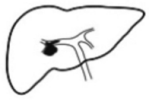
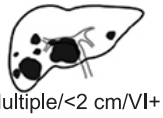
mUICC stage		Best option	Alternative option
I	 Single/≤2 cm/VI−	Resection RFA	TACE Other LRT EBRT
II	 Single/>2 cm/VI−	Resection LT (tumor size ≤5 cm) RFA (tumor size ≤3 cm)	TACE, TARE Other LRT (tumor size ≤3 cm) EBRT
II	 Multiple/≤2 cm/VI−	LT (within Milan criteria) TACE RFA (tumor number ≤3)	Resection (tumor number ≤2) Other LRT (tumor number ≤3) EBRT (tumor number ≤3)
II	 Single/≤2 cm/VI+	TACE EBRT Sorafenib Lenvatinib	Resection
III	 Multiple/>2 cm/VI−	TACE LT (within Milan criteria) RFA (tumor number ≤3 and size ≤3 cm)	Resection (tumor number ≤2) TACE EBRT (tumor number ≤3 and size ≤3 cm) Other LRT (tumor number ≤3 and size ≤3 cm)
III	 >Single/<2 cm/VI+	TACE+EBRT TACE Sorafenib Lenvatinib (tumor occupation <50%, Vp1−3)	Resection EBRT
III	 Multiple/≤2 cm/VI+	TACE+EBRT TACE Sorafenib, Lenvatinib	
IVa	 >Multiple/<2 cm/VI+	Sorafenib Lenvatinib (tumor occupation <50%, Vp1−3) TACE+EBRT	TACE
IVa	 Node+/no metastasis	Sorafenib Lenvatinib (tumor occupation <50%, Vp1−3)	TACE EBRT
IVb	 Metastasis+	Sorafenib Lenvatinib (tumor occupation <50%, Vp1−3)	TACE EBRT

Fig. 5. First-line treatment recommendations from the 2018 KLCA-NCC, Korea Practice Guidelines for Patients with hepatocellular carcinoma, Child-Pugh class A, no portal hypertension, and ECOG 0-1.
KLCA, Korean Liver Cancer Association; NCC, National Cancer Center; ECOG, Eastern Cooperative Oncology Group; mUICC, modified Union for International Cancer Control; VI, vascular or bile duct invasion; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; LRT, locoregional therapy; other LRT includes percutaneous ethanol injection, microwave ablation, and cryoablation; EBRT, external beam radiation therapy; LT, liver transplantation; TARE, transarterial embolization; Vp, portal vein invasion.

with portal hypertension.[172-175] Minor hepatic resection instead of major hepatectomy should be considered in patients with mild portal hypertension because resection volume is closely associated with the risk of postoperative hepatic insufficiency.

HCC is accompanied by chronic liver disease in most cases. Assessment of future liver volume or remnant liver volume after resection is as important as the hepatic reservoir function test in order to predict postoperative hepatic insufficiency. Although

Table 5. Child-Pugh Classification

	1	2	3
Albumin, g/dL	>3.5	2.8–3.5	<2.8
Bilirubin, mg/dL	<2.0	2.0–3.0	>3.0
Prothrombin time prolonged, sec	0–4	4–6	>6
Ascites	None	Slight	Moderate
Encephalopathy, grade	None	1–2	3–4

Class A ≤6 points, Class B=7–9 points, Class C ≥10 points.

Table 6. Eastern Cooperative Oncology Group Performance Status*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

ECOG, Eastern Cooperative Oncology Group.
*Adapted from Oken MM, *et al.* Am J Clin Oncol 1982;5:649-655, with permission from Wolters Kluwer Health, Inc.[164]

70% to 80% of the volume can be resected in normal liver, a much lower resection volume is allowed for diseased liver. There are few studies about the safe remnant liver volume in patients with cirrhosis. Nevertheless, a remnant liver volume ≥40% is generally recommended in cirrhosis patients for safety.[176] Recently, several noninvasive tests to measure the severity of hepatic fibrosis have been developed. Among them, transient elastography was recently reported to be effective for predicting postoperative hepatic failure and recurrence.[177-180] Dynamic contrast-enhanced CT is the basic test utilized as a preoperative radiologic study to assess the possibility of resection. MRI using a hepatic cell-specific contrast medium is superior to CT for HCC detection, especially for small HCCs <1 cm,[181,182] and may be a useful method to assess resectability and to formulate resection plans. Further examinations may be necessary to find extrahepatic metastases before liver resection in patients with HCC. ^{18}F-FDG PET-CT may be effective for investigating extrahepatic metastasis,[77,183] although its sensitivity is very low for the diagnosis of intrahepatic HCC.[140] In addition, chest CT and bone scan may be helpful.[184]

2. Basic principles of hepatic resection

One reason why hepatic resection has recently become safer is the reduction in the amount of intraoperative hemorrhage, thus minimizing the amount of transfused blood required. Blood transfusion compromises anticancer immunologic mechanisms and increases postoperative recurrence. A recent meta-analysis reports that intraoperative transfusion increases complication rates and reduces overall and disease-free survival rates after resection in HCC patients.[185] Recent transfusion rates in hepatic resection are ≤10% owing to selective hepatic blood flow occlusion, maintenance of low central venous pressure, and precise transection of the hepatic parenchyma.[186] Several retrospective studies[187-192] and a meta-analysis[193] suggest that anatomical resection may be superior to nonanatomical resection in terms of securing the resection margin and removing micro-metastases. However, a recent prospective randomized trial showed that anatomical resection decreased the early recurrence rate within 2 years after hepatic resection, but did not affect 5-year disease-free survival or OS.[194] Securing a tumor-free resection margin is absolutely critical for improving long-term prognosis. One prospective randomized trial showed that a resection margin >2 cm led to better outcomes after HCC resection.[195] However, although a sufficient margin from the tumor and anatomical resection are recommended, patient safety is more important because excessive hepatic resection can be fatal in patients with cirrhosis.[196-198] Transarterial chemoembolization (TACE), performed before hepatic resection for the purpose of improving postoperative prognosis, is not recommended.[199,200] Patients with liver cirrhosis need more sufficient remnant liver volume than patients with normal liver because the remnant liver volume after hepatic resection is an important prognostic factor for hepatic insufficiency.[201,202] When insufficient remnant liver volume is expected, portal vein embolization before hepatic resection or portal vein ligation during hepatic resection may enable extensive hepatic resection by inducing compensatory hypertrophy of

the residual liver.[203-205] The hanging maneuver is frequently used during hepatic resection, although there is no report about the effect of the hanging maneuver on survival or recurrence after HCC resection. Nevertheless, the hanging maneuver can shorten surgical time and reduce the amount of bleeding.[206] The anterior approach, which is often used for the resection of large tumors, is associated with less bleeding, a lower transfusion rate, and better survival according to one prospective study.[207] However, its pathologic advantages require further evaluation.

3. Minimally invasive hepatic resection

Laparoscopic hepatic resection has advanced rapidly, and its indications have been expanded. Many studies reported superior results of laparoscopic hepatic resection in terms of pain, complication rate, and hospital stay,[208,209] along with similar recurrence and survival rates[210,211] compared with open hepatic resection for HCCs located in the left lateral section or on the anteroinferior surface of the right liver. Although laparoscopic major hepatic resection is increasingly being performed as well, it is currently limited to experienced surgeons. Accordingly, its efficacy and safety should be evaluated further.[212] Robotic hepatic resection has recently been tried in very selected cases, and comparative studies between robotic hepatic resection and open or laparoscopic hepatic resection are needed.[213,214]

4. Indications for hepatic resection

The best prognosis after hepatic resection is generally expected in patients with 1 or 2 small tumors. Larger tumors frequently accompany vascular invasion, and result in a poor prognosis even after resection. However, a recent study showed that approximately one-third of large HCCs ≥10 cm had no vascular invasion and achieved favorable results after resection in those cases.[215,216] Therefore, the resectability for HCC should not solely be decided based on tumor size. Recent advances in surgical techniques and improvements in patient management have enabled hepatic resection in elderly patients with comparable short- and long-term outcomes. Nevertheless, major hepatic resection should be considered with caution because the hepatic regenerative capability gradually decreases with age.[217-219]

Although some studies reported that one-stage hepatic resection was an effective method for ruptured HCC in patients with good liver function,[220,221] hemostasis using TACE and subsequent elective surgery after accurate assessment of the hepatic functional reserve would be safer and more effective in hemodynamically unstable patients.[222] However, patients with ruptured HCC have poorer long-term results than those with unruptured HCC.[223,224] Hepatic resection is generally contraindicated in patients with evident tumor invasion to major hepatic or portal veins. However, except for patients with major portal vein invasion, the 5-year survival rate after resection of HCC is reported to be ≥30% in patients with less hepatic fibrosis or those with a well-differentiated HCC of low Edmondson-Steiner grade, with a postoperative mortality rate of 3.7% and median OS of 19.9 months.[225-227] According to a Korean multicenter study, the 5-year survival rate of 32% after resection of HCC with bile duct invasion was satisfactory.[227,228] Hence, surgical resection can be selectively considered even for HCC with major vascular invasion or bile duct invasion.

Recommendations

1. Hepatic resection is the first-line treatment for patients with intrahepatic single-nodular HCC and well-preserved liver function of Child-Pugh class A without portal hypertension or hyperbilirubinemia (**A1**).
2. Limited resection can be selectively applied to HCC patients with liver function of Child-Pugh class A or B7 and with mild portal hypertension or mild hyperbilirubinemia (**C1**).
3. Hepatic resection can be considered in patients with three or fewer intrahepatic tumors with invasion to the hepatic vein, portal vein or bile duct invasion if hepatic function is well preserved and the main portal trunk is not invaded (**C2**).
4. Laparoscopy-assisted resection can be considered for HCC located in the lateral section of the left lobe or the anteroinferior segment of the right lobe (**B2**).

LIVER TRANSPLANTATION

Liver transplantation is the first treatment choice for patients with a single tumor ≤5 cm or those with small multinodular tumors (≤3 nodules ≤3 cm) and advanced liver dysfunction. Liver transplantation involves complete removal of a diseased liver, including HCC, and replacement with a new liver. Theoretically, it is the ideal treatment method. Application of broad selection criteria in the early history of liver transplantation resulted in very poor outcomes with a 5-year survival rate of less than 40%, making liver transplantation a relative contraindication at that time.[229,230] However, it allowed the identification of the best candidates and subsequent studies with a highly selected group of patients reported a 5-year disease-free survival rate of 74%.[231,232] The Milan Group in Italy reported an excellent result, i.e., a 4-year survival rate of 75% and a disease-free survival rate of 83% after liver transplantation in HCC patients with following conditions: (1) no extrahepatic metastasis and no vascular infiltration in the radiologic study before transplantation; (2) a single nodule of 5 cm or less; (3) three or fewer nodules in cases with multiple nodules and each nodule being 3 cm or less. Accordingly, they suggested the criteria of liver transplantation for patients with HCC.[233] Since then, the Milan criteria have widely been used for liver transplantation in patients with HCC in various countries. A recent systematic review of 90 studies, comprising a total of 17,780 patients over 15 years, identified the Milan criteria as independent prognostic factors for outcome after liver transplantation. Overall 5-year survival of patients

meeting the Milan criteria (65% to 78%) was similar compared with that of non-HCC patients according to European and American transplant registries.[234-236]

Recent advances in imaging technologies have enabled non-invasive diagnosis of HCC with higher accuracy. However, small lesions, which could not be detected with imaging studies at the time of the establishment of the Milan criteria, can be seen on imaging studies with current technologies and can cause confusion regarding whether a patient meets the Milan criteria or not. A recent meta-analysis including 22,392 patients concluded that the size of the largest tumor and the total diameter of nodules were the best predictors of outcome, without sufficient evidence supporting the effect of the number of nodules on the outcome of liver transplantation.[237] Sugimachi *et al*.[238] also reported poor diagnostic accuracy of imaging for small (<1 cm) HCCs and their limited effect on prognosis after liver transplantation. Therefore, lesions ≤10 mm or with atypical findings should not be used to make a decision for or against transplantation.

Before transplantation, HCC patients undergo tests for staging in addition to general whole-body examination for liver transplantation. In addition to dynamic contrast enhancement CT or MRI, extrahepatic staging should include CT of the chest, and CT or MRI of the abdomen and pelvis. Imaging of the brain, bone scintigraphy, and ^{18}F-FDG PET-CT can be performed.[239] ^{18}F-FDG PET-CT can help characterizing the biology of HCC because PET-positive tumors more frequently display unfavorable histological features (e.g., high cellular dedifferentiation and microvascular invasion), resulting in poorer recurrence-free survival (RFS) after liver transplantation. There has been no specific study nor consensus on the optimal timing or modality of evaluation of patients on the waiting list to ensure whether they remain within the acceptability criteria for liver transplantation, although dynamic CT or MRI and AFP measurement at a 3-month interval is commonly used.[240]

1. Deceased donor liver transplantation

Many patients are waiting for liver transplantation at any given time because of a shortage of deceased liver donors. A long waiting period is problematic for HCC patients. The American United Network for Organ Sharing introduced the Model for End-Stage Liver Disease (MELD) scoring system in order to decide the priority for liver transplantation. Patients with HCC involving a single nodule between 2 and 5 cm or multinodular tumors (≤3 nodules ≤3 cm) are given the priority MELD score of 28 points, as well as 10% additional points for every 3 months waiting for liver transplantation; thus, they have similar risks.[241,242] Meanwhile, the Korean National Organ Transplantation Management Center operates the Korean Network for Organ Sharing (KONOS) grading system, which gives no additional points to HCC patients. To solve this problem, Korea introduced the MELD score in June 2016. When fulfilling the Milan criteria, patients with a MELD score of 0 to 13 receive an additional 4 points; patients with a MELD score of 14 to 20 also receive additional 5 points, but those with a MELD score of 21 or higher do not.[243] Nevertheless, deceased donor liver transplantation (DDLT) in Korea is mostly performed when the MELD score is above 30. Further studies are needed determining the effect of the MELD score on HCC patients in Korea.

2. Bridging therapy

Because it is difficult to predict the timing of liver transplantation in HCC patients, locoregional treatments, such as TACE, are commonly applied to those patients. The actuarial probability of dropout due to tumor progres¬sion while waiting for liver transplantation is reportedly between 15% and 30% in 1 year.[244,245] Locoregional therapies have reduced the dropout rate to 0%–25%.[246-248] TACE or radiofrequency abla¬tion (RFA) can be performed to prevent tumor progression.[246,247,249-251] Markov-based cost-effectiveness analysis indicates benefits for neoadjuvant treatments when waiting times exceed 6 months.[246] An AFP level increase >15 ng/mL/mo while waiting for liver transplantation is a relevant preoperative prognostic factor for poor OS and disease-free survival.[252]

The effects of neoadjuvant treatments on survival after liver transplantation are difficult to assess. Many studies reported similar survival rates between treated and untreated individuals prior to transplantation.[253-259] Patients who received locoregional treatments before liver transplantation in Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients were more likely to achieve longer survival than those who did not, particularly those with longer waiting periods before transplantation.[260] When the waiting period before liver transplantation is between 6 months and 18 months, the HCC recurrence rate is low after transplantation.[261] However, if the waiting period is prolonged, the possibility of HCC progression becomes higher, necessitating bridging therapy in such patients.[246,261,262] In a recent multicenter study conducted in the United States, locoregional treatments did not affect the recurrence of HCC after transplantation in patients within the Milan criteria. Accordingly, bridging therapy in HCC patients within Milan criteria did not seem to positively affect HCC recurrence or patient survival.[253] In this study, HCC recurrence after transplantation in patients with more than three sessions of locoregional treatment prior to transplantation developed twice as frequently than in patients with less than two sessions, regardless of the type of locoregional treatments.[253] When complete tumor necrosis was confirmed by locoregional treatments in the explanted liver, the possibility of HCC recurrence after transplantation was very low.[253]

3. Downstaging

Regarding downstaging, there are no RCTs, large case-control studies, or large well-designed cohort studies in which patients were treated consistently and properly followed up.

Some prospective studies suggested that patients who achieved downstaging fulfilling the Milan or UCSF criteria following locoregional therapies achieved 5-year survival outcomes similar to those within the Milan or UCSF criteria.[251,259,263-267] Downstaging with TACE seems achievable in 24% to 63% of cases.[268-270] Although downstaging is more effective if the tumor size is <7 cm or tumor numbers are ≤3,[271] there is no clear upper limit for eligibility.[272] Transarterial embolization (TARE) using ^{90}Y for downstaging appears to have similar outcomes after transplantation compared with downstaging with conventional TACE (cTACE).[273,274] However, more studies are required to demonstrate the efficacy of TARE for downstaging.

4. Living donor liver transplantation

The number of DDLTs has been increasing in Korea recently due to changes in society's perception of organ donation and the revision of laws to promote organ donation.[275,276] However, living donor liver transplantation (LDLT) is the main type of liver transplantation in Korea because of deceased donor organ shortage. According to the KONOS regulation for registration and allocation in Korea, liver transplantation recipient candidates with HCC can gain higher priority on the waiting list. However, patients with HCC in Korea have a very low probability of receiving DDLT before tumor progression because most deceased donor livers are allocated to patients with a high MELD score (>30). These findings suggest that DDLT is not a feasible treatment modality for HCC patients in Korea. Therefore, LDLT from a healthy donor has emerged as an alternative to DDLT as a treatment modality for HCC. In fact, a significant proportion of the liver transplantation recipients with HCC received transplantations from live donors in Korea. The comparative outcome of LDLT versus DDLT for patients with HCC is controversial. A meta-analysis of 633 LDLTs and 1,232 DDLTs indicates that LDLT is an acceptable option without compromising survival rates.[277] However, the disease-free survival rate is worse with LDLT than with DDLT.[277] Another meta-analysis of 1,310 patients who underwent LDLT and DDLT for HCC showed no difference in survival rate and disease-free survival.[278] Patients undergoing LDLT have a short waiting time and are unlikely to drop out, whereas a dropout rate of 5% to 30% is reported in DDLT. Given that an intention-to-treat analysis can consider patients who dropped out of the waiting list, there was no difference in OS and disease-free survival between the two groups in liver transplantation according to the donation pattern on the intention-to-treat analysis.[279,280] The higher recurrence observed after LDLT in some reports is likely due to differences in tumor characteristics, pretransplant HCC management, and waiting time.[281-283] In order to compare the outcomes of liver transplantation for HCC according to the type of graft, well-designed studies are needed to reflect bias and the effects of tumor biology.

In the DDLT program, the selection criteria have been set to maximize the efficacy-efficiency of donor organs. In contrast to DDLT, the indications for LDLT for HCC are decided based on the balance between donor risks and recipient benefits. Several eligibility criteria besides the Milan criteria for LDLTs have been adopted by many high-volume LDLT centers. At Samsung Medical Center, patient selection according to tumor size <5 cm and AFP <400 ng/mL without limitation of the tumor number expanded patient selection; 1-, 3-, and 5-year survival rates are reported to be 92.2%, 82.6%, and 79.9%, respectively.[284] At Seoul National University Hospital, the 3-year survival rate is reported to be 86.2% if vascular invasion was absent in preoperative radiological studies and preoperative AFP was <400 ng/mL.[285] At Seoul Catholic Medical Center, LDLT is considered the preferred therapeutic option in patients with an AFP level <100 ng/mL and a tumor diameter <5 cm. The 5-year disease-free survival and OS rates after LDLT in all patients with HCC were 80.9% and 76.4%, respectively.[286] At Asan Medical Center, patients with ≤6 HCCs ≤5 cm and without gross vascular invasion are considered eligible for liver transplantation; such patients had a 5-year survival rate of 81.6%.[287] In the selection of HCC patients for liver transplantation, the University of Tokyo has adopted the 5-5 rule, that is, HCC ≤5 cm and ≤5 in number, and a RFS rate of 94% after liver transplantation was achieved.[288] Kyoto University further extended the number of tumors to 10 with serum PIVKA-II levels ≤400 mAU/mL; the resultant 5-year survival rate was 86.7%.[289] At Kyushu University, a 5-year survival rate of 82.7% was achieved in patients with HCCs ≤5 cm and serum PIVKA-II levels <300 mAU/mL.[290] In a study involving 49 centers and 653 patients in Japan, patients with HCCs beyond the Milan criteria but with serum AFP levels ≤200 ng/mL and serum PIVKA-II levels ≤100 mAU/mL had a 5-year disease-free survival rate of 84.3%.[291] Most of these expanded criteria were modified tumor size and number in the Milan criteria. However, the selection criteria have recently been amended to include biological markers such as AFP and PIVKA-II.[292] European multicenter studies have shown that AFP-containing criteria better predict tumor recurrence after liver transplantation than criteria based on the number and size of tumors. There are reports that even if patients with HCC exceed the Milan criteria, they can achieve good results when fulfilling criteria including AFP.[293,294] LDLT has been proposed as an ideal setting for exploring expanded indications for HCC, considering a lack of graft allocation and priority policies. Moreover, the graft of a live donor is a personal gift. If the posttransplant outcomes of several eligible criteria beyond the Milan criteria for LDLTs are comparable with those within the Milan criteria, expanded indications can be accepted as long as the safety of the live donor is ensured.

The safety of the liver donor is of paramount importance in the LDLT. The outcomes of live donors from Korea are excellent.[295-300] According to the Korean Organ Transplantation Registry study including 832 living liver donors, major com-

plication (including bile leakage, biliary stricture, portal vein stricture, wound dehiscence, and pulmonary edema) rates were 1.9% and there was no mortality.[301] The associated probabilities of death and life-threatening complications in LDLT for healthy donors are reported to be 0.2% to 0.3% and about 2%, respectively.[302-305] Because of the complexity of the procedure, LDLT must be restricted to centers of excellence in hepatic surgery and liver transplantation to minimize donor risk and maximize recipient outcome. Careful attention should be given to the psychosocial wellbeing of live donors.

5. Immunosuppression after liver transplantation

Immunosuppressants like calcineurin inhibitors (cyclosporine and tacrolimus) and the mammalian target of rapamycin inhibitors (mTORi) (sirolimus and everolimus) are used for patients with HCC after liver transplantation.[306] Recent studies have shown that the use of mTORi may be helpful for reducing recurrence and prolonging survival in HCC patients after liver transplantation, but further studies are needed.[307]

Recommendations

1. Liver transplantation is the first-line treatment for patients with single nodular HCC <5 cm in diameter or 3 or fewer nodules ≤3 cm in diameter (Milan criteria) who are not indicated for resection (**A1**).
2. In liver transplantation candidates with HCC, locoregional therapies or TACE are recommended if the timing of transplantation is not predictable (**B1**).
3. In patients beyond the Milan criteria, liver transplantation can be considered if successful downstaging to within Milan criteria can be achieved (**C1**).
4. Expanded indications for liver transplantation can be considered in limited HCC cases beyond the Milan criteria without definitive vascular invasion or extrahepatic spread if other effective treatment options are not applicable (**C2**).
5. Salvage transplantation can be indicated for recurrent HCC after resection according to the same criteria as for first-line transplantation (**B1**).

LOCOREGIONAL THERAPIES

Locoregional therapies are widely performed as nonsurgical treatments for HCC because they are easy to perform and induce necrosis of tumor with minimal damage to the normal hepatic parenchyme. In a broader sense, TACE can be categorized as a locoregional therapy; only local ablation therapies will be discussed here, and TACE will be discussed in the following chapter. Among various kinds of locoregional therapies, RFA and percutaneous ethanol injection therapy (PEIT) are accepted as standard local therapies. In recent years, microwave ablation and cryoablation have been considered as effective locoregional treatments, while clinical trials are under way for other modalities, such as laser ablation therapy, intratumoral injection of radioactive holmium-166 microspheres, and high-intensity focused US.

The indications for locoregional therapies include patients with a single HCC nodule ≤5 cm or up to 3 nodules ≤3 cm, although minor discrepancies exist across different investigators and studies. Efforts to apply locoregional treatments to larger HCCs have been made; however, the treatment outcomes are closely associated with tumor size. Contraindications for local therapies include corrected platelet count $<50\times10^3/mm^3$ or prothrombin time prolongation (PT INR >1.5).

1. Radiofrequency ablation

RFA is the most widely used ablation technique for HCC treatment. Very fast alternating currents (460 to 500 kHz) flow in the vicinity of radiofrequency electrodes, inducing internal friction among molecules. The internal heat generated by the internal friction can evoke tissue necrosis. Exposure to temperatures higher than 60°C causes almost immediate protein denaturation and destruction of cell membranes followed by coagulative necrosis. Similar necrotic effects can also be obtained by maintaining the temperature from 45°C to 50°C for ≤3 minutes. The main advantage of RFA compared with PEIT is that fewer treatment sessions are required to achieve complete tumor necrosis. For HCC nodules ≤2 cm, RFA results in a higher complete tumor necrosis rate than PEIT.[308-311] Most procedures are performed via a percutaneous approach; however, a laparoscopic or open surgical approach may be required in some instances.

The initial complete tumor necrosis rates, which were evaluated by CT or MRI within 1 day to 1 week after RFA, were reported to exceed 95%, and if RFA procedures are repeated for residual viable tumors, a complete tumor necrosis rate of almost 100% can be achieved.[257,310,312] However, the 3-year local tumor progression rate after RFA ranges widely from 0.9% to 21.4%.[257,312,313] The local tumor recurrence rate at 10 years after RFA was 3.2% according to Shiina *et al*.[257] However, Kim *et al*.[312] reported a local recurrence rate of 38.2% at 10 years after RFA and there is a big difference across institutions. The independent factors associated with OS after RFA include initial complete tumor necrosis, Child-Pugh score, number and size of tumors, and preoperative serum AFP level. RFA is the most effective treatment for patients with a single HCC smaller than 2 cm in diameter and Child-Pugh class A function. If the tumor is ideally located to perform RFA, the efficacy of RFA is comparable to that of hepatectomy. Hence, there are some reports which suggest that RFA should be considered as a primary treatment.[136,313]

The long-term survival outcomes of HCC patients after RFA is dependent on tumor size. For Child-Pugh class A patients with tumors <2 cm, the 3- and 5-year OS rates after RFA are reported to be approximately 90% and 65% to 70%, respectively.[257,312,313] Meanwhile, those for tumors 2 to 5 cm are 65% to 75% and

50%, respectively.[257,312] The 10-year OS rate of Child-Pugh class A patients with a single HCC ≤3 cm is 41.3%.[257]

Most of the studies comparing RFA with hepatic resection for HCC are not RCTs and even with RCTs, their sample size was too small to make a definite conclusion.[314] Three RCTs, including the recently published study, showed no significant difference in survival rate between the two treatments.[315-317] In RCTs that reported a difference in survival rates, the number of patients included in the single nodule <3 cm group was small, and the one-year survival rate of RFA was 91%, which is substantially lower than the 100% survival rate for hepatic resection.[318] A meta-analysis of RCTs showed that the 5-year survival and recurrence-free rates were significantly higher in the hepatic resection group of HCC patients within the Milan criteria;[319] however, there was no significant difference in the survival rates between the two treatment groups for HCC of 3 cm or less.[320] In another meta-analysis of patients with Child-Pugh class A HCC, there was no difference in 5-year survival rates between the two treatment groups with tumor size <3 cm.[321] In a simulation study of patients with a single HCC less than 2 cm in diameter, long-term survival rates were similar in the group treated with RFA as the primary treatment compared with the group who underwent hepatectomy.[322] In a prospective controlled study recently published in Korea, there was no difference in the survival rates between hepatectomy and RFA. Although the disease-free survival rate was longer in the hepatectomy group,[323] other non-RCTs have reported no significant difference in survival rates between hepatectomy and RFA in the treatment of HCC of 3 cm or less in diameter.[324-326] Hepatectomy had a higher incidence of complications and a longer hospital stay of 8 to 9 days on average.[320]

For HCCs larger than 3 cm, the local recurrence rates after RFA are reported to range from 30% to 50%[312] and combined treatment with TACE and RFA can be considered for these tumors. When three or fewer HCCs of ≤3 cm in diameter were compared, the survival rate and recurrence rate were not significantly different between the combined treatment and RFA alone.[327] In contrast, when the size of HCC ranges from 3 to 5 cm, the local recurrence rate and survival rate are better in the combined treatment group.[328,329] A meta-analysis of seven RCTs showed better survival in the combination treatment group than in the RFA monotherapy group; however, the subgroup comparison of tumors less than 3 cm in size showed no significant difference in survival rate between the combined treatments and RFA alone.[330] In a meta-analysis of eight RCTs comparing RFA alone and combined treatment with RFA and TACE, combined treatment showed better survival and recurrence rates; however, there was no significant difference in the major complication rate between the two groups.[331,332] Considering the results above, the combination of RFA and TACE in the treatment of HCC of 3 to 5 cm showed a higher survival rate and lower recurrence rate than RFA alone and there was no significant difference in the incidence of complications between the two treatments.

Despite these favorable outcomes, RFA has some disadvantages. First, the risk of major adverse events is usually higher than that of PEIT, particularly when the tumors are located near the liver hilum or major abdominal organs, such as the colon. In addition, the heat sink effect may hinder effective transmission of heat energy to a tumor that is adjacent to relatively large intrahepatic vessels.[311,333,334] Sometimes, the risk of thermal injury to the adjacent abdominal organs can be overcome by inducing artificial ascites.[335] Another major limitation of RFA is that HCC nodules <2 cm may not be visible on conventional US. However, recent applications of US contrast agents and fusion imaging techniques have broadened the indications for RFA to such cases.[336,337]

The mortality rate due to procedure-related complications after RFA is reported to be 0.1%–0.5%, and the major complication rate after RFA is less than 5%.[313,333,334] Major complications include needle tract tumor seeding, hemoperitoneum, hemothorax, liver abscess, massive infarction of liver parenchyma, intestinal perforation, and pneumoperitoneum.[257]

In conclusion, for HCCs that are within the Milan criteria, hepatic resection showed a lower recurrence rate than RFA and the rate of postoperative complications was significantly higher; however, further study is warranted to verify the difference in the survival rate. For single nodule HCCs of 3 cm or less in diameter, RFA has an equivalent survival rate, higher local recurrence rate, and lower complication rate than surgical resection. Therefore, it can be used instead of surgery for HCCs in an ideal location to perform RFA.

2. Percutaneous ethanol injection therapy

PEIT was widely used in the treatment of HCC because it is relatively simple to perform and adverse reactions are infrequent. However, PEIT has been largely replaced by RFA, mainly because it has to be performed repetitively in contrast to RFA and it is difficult to obtain complete necrosis for tumors larger than 3 cm. The tumor necrosis rate of PEIT was reported to be 66%–100% depending on the study.[309-311,338] Tumor size is important, and tumors less than 2 cm in diameter have more than a 90% tumor necrosis rate. However, as the tumor size increases, the necrosis rate decreases and the tumor necrosis rate is only 50% for tumors 3 to 5 cm in size. Local tumor progression rates after PEIT range between 24% and 34%, although there is no consensus on the definition of local tumor progression.[339-341] For patients with Child-Pugh class A function and a solitary HCC smaller than 2 cm, the 3- and 5-year OS rates are 70% to 80% and ≥50%, respectively. For HCCs 2 to 3 cm in diameter, the 3-year OS rate ranges from 47% to 64%.[309,338]

Among the RCTs comparing RFA and PEIT in patients with HCC,[309-311,338,342,343] except those published in Italy,[342,343] RFA showed a significantly lower local recurrence rate and a higher survival rate. In particular, in a meta-analysis of four RCTs, the

3-year survival rate of RFA was significantly higher than that of PEIT.[344-347] However, there was no significant difference in the survival rate among the subgroups of HCCs less than 2 cm in diameter.[346] These results suggest that the RFA group has a lower local recurrence rate and a higher survival rate than the PEIT group; however, further study is needed. In HCCs less than 2 cm in diameter, studies report a similar OS rate and PEIT can be considered if RFA is not feasible.[348] PEIT can be performed to treat perivascular tumors to reduce the heat sink effect of RFA. However, the risk of biliary stricture is not avoided with PEIT if the tumors are located in the liver hilum.[349,350]

3. Microwave ablation and cryoablation

Recently, locoregional therapy for HCCs including microwave ablation and cryoablation is being more commonly used. The advantage of microwave ablation over RFA is that treatment efficacy is less affected by vessels located near the tumor and the ablation size is larger. In addition, effective ablation can be expected even for tissues with low electrical conductivity and an ablation temperature over 100°C can be achieved rapidly.[351] Cryoablation has the advantage of monitoring the ablation extent because the ice ball shows a clear margin in an US scan, non-enhanced CT scan, or MRI. Moreover, cryoablation has less procedure-related pain.[351,352] However, cryoablation with a single probe generates a small ablation zone and thus, multiple probes are required to treat larger tumors.

In Child-Pugh class A and B HCC patients with a tumor size ≤5 cm or up to 3 nodules ≤3 cm, an RCT showed no significant differences in the 1-, 3-, and 5-year OS rate or in the disease-free survival rate between RFA and microwave ablation.[353] In chronic hepatitis patients with HCC size ≤4 cm and up to 3 nodules, a multicenter randomized control study between RFA and cryoablation did not show a significantly different local tumor progression rate and OS rate over 20 months; however, its short follow-up period is a limitation.[354] A meta-analysis study that aimed to compare RFA and other ablation techniques revealed that there is no significant difference in the OS rate and major complication rate between RFA and cryoablation.[347] In Child-Pugh class A and B liver cirrhosis patients with one or two HCCs, a multicenter RCT showed no significant difference in the 1-, 3-, and 5-year OS rate, disease free survival rate, and major complication rate between RFA and cryoablation.[355]

In the limited RCTs and meta-analysis studies mentioned above, microwave ablation and cryoablation showed similar results in terms of the OS rate, recurrence rate, and major complication rate compared with RFA. Additional large-scale prospective RCTs are needed to confirm the difference in definitive treatment effects.

4. Other locoregional therapies

Clinical trials on other local therapies, such as high-intensity focused ultrasound, laser ablation, and holmium injection therapy are under way. However, as there are few comparative studies with standard treatment, further technological developments and outcomes from the ongoing clinical trials are required to verify their efficacy in the management of HCC.

Recommendations

1. RFA has the equivalent survival rate, a higher local tumor recurrence rate, and a lower complication rate than hepatic resection in patients with a single nodular HCC ≤3 cm in diameter (**A1**).
2. RFA is superior to PEIT in terms of tumor necrosis effect and survival rate (**A1**). For HCCs ≤2 cm in diameter, PEIT can be considered if RFA is not feasible because the outcomes of both modalities are similar (**A2**).
3. Combined therapy with RFA and TACE increases the survival rate for HCCs ranging from 3 to 5 cm in size that are not amenable to surgical resection compared with RFA alone (**A2**).
4. In the treatment of HCC, microwave ablation and cryoablation are expected to produce comparable rates of survival, recurrence, and complications to those of RFA (**B2**).

TACE AND OTHER TRANSARTERIAL THERAPIES

The majority of HCCs are unresectable at the time of diagnosis because of portal hypertension, poor liver function, multiplicity of tumors, portal vein tumor invasion, inability to secure sufficient resection margin, old age, and severe comorbidities.[356] TACE is the most commonly used nonsurgical treatment modality for these patients; meanwhile, tumor necrosis can be achieved by the combined effects of antitumor chemotherapy and selective ischemia of tumor tissue.[275,356,357] In clinical practice, TACE is most widely utilized as a primary treatment modality for HCC.[358] TACE can be classified as cTACE using lipiodol and drug-eluting bead TACE (DEB-TACE).[359,360] It is important to note that TACE should be distinguished from transarterial embolization, which uses only embolic materials, and hepatic arterial infusion chemotherapy (HAIC), which uses only antitumor chemotherapeutic agents.[361,362]

1. Conventional TACE

The cTACE procedure involves an injection of a mixture of chemotherapeutic agents, such as doxorubicin, cisplatin, and mitomycin, with iodized oil into the feeding artery as an emulsion. This is followed by embolization of the same feeding artery using gelatin sponge particles, polyvinyl alcohol particles, or microspheres, which induce selective tumor ischemia. The most important technique for maximizing the antitumor effect and minimizing liver toxicity when performing TACE is to superselect the feeding arteries of tumors as distally as possible.[363] Superselective chemoembolization of feeding arteries can significantly increase tumor necrosis and the local control

rate.[364,365] In addition, cone-beam CT during chemoembolization can help detect tumors and tumor-feeding arteries more precisely, thus resulting in a better therapeutic effect.[366-368] Regarding the repetition strategy of TACE, on-demand repetitions to treat the residual or recurrent tumors can minimize the incidence of procedure-related liver toxicity, which is therefore preferable to on-schedule regular repetitions every 1 to 2 months.

Compared with best supportive case, several RCTs and meta-analyses confirm that TACE results in a more favorable tumor response, time to progression, and survival outcomes in patients with unresectable HCC.[132,369-371] A prospective cohort study by the Japanese Liver Cancer Study Group reports that the 1-, 3-, 5-, and 7-year survival rates of 8,510 patients who underwent TACE were 82%, 47%, 26%, and 16%, respectively; for tumors larger than 5 cm, the 1-, 3-, and 5-year survival rates were 63%, 30%, and 16%, respectively.[372] In a prospective multicenter study performed in 27 Japanese and South Korean centers, the complete or partial remission rate according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria was 73% and the 2-year OS rate was 75%; these figures are higher than those previously reported in the literature.[373] These results are supported by a recent systematic review of 101 articles on cTACE published over the last 30 years, which showed that OS was 70.3% at 1 year, 51.8% at 2 years, 40.4% at 3 years, and 32.4% at 5 years.[371] This outcome is similar to those of published RCTs.

Portal vein tumor invasion is found in approximately 30% of HCC patients at initial diagnosis in Korea.[357] According to the AASLD practice guidelines, systemic chemotherapy with sorafenib is the standard primary treatment for HCC with portal vein invasion.[77] However, in practice, more aggressive treatment and various kinds of combined therapy are attempted[358] because the expected survival benefits are modest and there have been no study comparing sorafenib and locoregional treatment such as TACE.[374] When TACE is performed for HCC patients with good hepatic function but portal vein tumor invasion, the risk of hepatic functional deterioration after TACE is reported to be acceptably low.[375-378] The 1- and 3-year OS rates of such patients after repeated TACE range from 25% to 35% and 9% to 10%, respectively.[372,379,380] In patients with unresectable HCC with portal vein invasion, survival outcomes are more favorable in the TACE-treated group than in the supportive treatment group.[380-382] Among HCC patients with portal vein invasion, patients with Child-Pugh class A function,[375] tumors localized within the liver, tumors showing nodular growth,[377,379] or portal vein invasion not involving the main portal vein[378] showed a better prognosis. A recent retrospective study comparing standard sorafenib treatment, TACE, and TACE combined with radiation therapy in HCC patients with portal vein invasion showed that patients who underwent TACE combined with radiation therapy had longer median OS.[383] Furthermore, there are retrospective studies showing that TACE is associated with survival gain, when intrahepatic HCC is treated with TACE in patients with extrahepatic metastasis.[384-386] Recently, a Korean single center RCT reported that cTACE combined with radiation therapy significantly increased OS, the objective response rate (OSS), and time-to-progression (TTP) compared with sorafenib monotherapy in patients with HCC localized in the liver and portal vein invasion.[387]

Local tumor response after cTACE can vary substantially according to the size and number of tumors, as well as patterns of tumor growth, such as tumor encapsulation and vascular invasion. The complete remission rate is quite low for large or multiple tumors despite multiple TACE sessions. However, in small tumors, complete tumor necrosis can be obtained in more than 50% of cases after superselective TACE.[388] A prospective cohort study from Korea comparing surgical resection after primary TACE with TACE monotherapy published reports that the survival rates were similar between the two treatment groups with stage T3 disease. In addition, the survival rate of the TACE group with stage T1 and T2 disease was similar to that of the surgical resection group if iodized oil was compactly retained within the tumor.[389] In a prospective cohort study of BCLC stage A disease patients in whom resection or ablation could not be performed, the 1-month complete remission rate according to the mRECIST criteria was 67% and the 3-year OS rate was 80%.[390] In another retrospective study comparing resection, RFA, and TACE as initial treatments for a single small HCC <3 cm in diameter, the unadjusted 5-year OS rate of the TACE group was the lowest at 74.2%. However, after adjusting for liver functional status, thrombocytopenia, varix, etc., the differences in the survival outcomes among the groups did not reach statistical significance.[324] Given the potential selection bias of the above-mentioned studies, TACE can be considered as an alternative treatment with curative intent when a patient refuses surgical treatment, or is at high risk for undergoing surgery, or HCC is not suitable for RFA.

The most common complication after TACE is post-embolization syndrome (PES), which is a complex of symptoms, including fever, abdominal pain, nausea, and vomiting. Serious liver-related complications, including irreversible hepatic failure, hepatic infarction, abscess, and biliary injury can occur. Sepsis, pulmonary oil embolism, cholecystitis, gallbladder infarction, and gastrointestinal complications also occur.[391] The frequency and severity of complications are related to tumor size, hepatic functional reserve, portal vein invasion, extent of chemoembolization, and dose of chemoembolic agents. According to a systematic review, the most common complication after TACE was fever (57.8%), followed by liver enzyme abnormalities (52.0%), PES (47.7%), abdominal pain (42.5%), fatigue/malaise (39.9%), anorexia (38.0%), vomiting (34.2%), nausea (32.4%), and hepatological/bone marrow toxicity (28.6%). Hepatic failure occurred in only 1% of patients and no new or unexpected safety concerns were identified.[371] Recently, the use of anti-

inflammatory drugs, such as dexamethasone or parecoxib, to reduce post-symptomatic syndrome before and after TACE has been reported in RCTs,[392-394] and clinical application can be considered. However, caution needs to be taken because of the risk of adverse effects, such as worsening of viral hepatitis or diabetes.

In conclusion, cTACE is expected to have the best efficacy and safety in patients with nodular HCCs with preserved liver function and performance and no vascular invasion. A future RCT should evaluate the survival benefits of TACE for patients with unfavorable prognostic factors, such as a poor performance status, major portal vein tumor invasion, Child-Pugh class C function, and extrahepatic metastasis.

2. Drug-eluting bead TACE

Drug-eluting beads refer to microspheres loaded with high-dose doxorubicin, which can embolize tumor feeders. Embolization of the tumor feeders with microspheres has several benefits, such as tumor ischemia, higher intratumor drug concentration, and lower serum drug concentration due to the slow release of doxorubicin from the microspheres.[395]

Prospective RCTs did not show a significant difference in the response rate, time-to-recurrence, and OS between the DEB-TACE group and cTACE group.[396-398] A meta-analysis of four RCTs and eight observational studies also showed no significant difference in the 1-, 2-, and 3-year survival rates, response rate, and complication rate between two groups.[399] However, pain after the procedure was less severe and frequent, and the length of hospital stay was also shorter by one day in the DEB-TACE group.[400,401]

A prospective multicenter registry including 152 Korean patients showed a complete remission and OSS of 40.1% and 91.4% at 1 month, and 43.0% and 55.4% at 6 months, respectively. There was no mortality related to liver abscess or other complications. In subgroup analysis, the OSS in the group with a tumor less than 2 cm tends to be lower than that in the group with a 2 to 5 cm tumor. This result suggests that the therapeutic effect of DEB-TACE may be lower than that of cTACE if the tumor is too small.[402]

In conclusion, DEB-TACE has similar long-term survival, less PES, and shorter hospital stay than cTACE. Thus, further studies are needed to establish optimal indications for DEB-TACE, considering cost-effectiveness and the trend that small tumors have lower response rates.

3. Transarterial radioembolization using yttrium-90 (^{90}Y) microspheres

TARE involves the injection of implantable radioactive microspheres into tumor-feeding arteries in order to expose the tumor to highly concentrated radiation while protecting the normal parenchyma. Yttrium-90 (^{90}Y) is the most commonly used radioisotope and emits high-energy and pure β-rays with a half-life of 64.2 hours, and mean and maximum tissue penetration of 2.5 and 11 mm, respectively. The microspheres available for ^{90}Y infusion are 20 to 60 μm in diameter and are made of resin or glass. The small size of the injected microspheres and their concentration in hypervascular HCC minimize the embolic effect on surrounding tissue. Preprocedural angiography and ^{99m}Tc-labeled macroaggregated albumin scans are required to determine the treatment site and radiation dose, and assess the degree of shunting to the lungs and any other extrahepatic organs. In particular, the lung dose achieved via hepatopulmonary shunt is important; thus, the radiation dose to be delivered should be adjusted so that the lung dose does not exceed 30 Gy per treatment and 50 Gy cumulatively.[403]

In a prospective single-arm phase II study of 52 patients with intermediate or advanced HCC treated with TARE, the objective tumor response rate (i.e., the complete or partial remission rate) was 40.4%, and the median survival period was 15 months.[404] In a recent prospective multicenter study performed in Korea on 40 HCC patients with BCLC stage B or C disease, the 3-month tumor response rate was 57.5% and the 3-year OS rate was 75%.[405] However, two recent phase III RCTs on advanced HCC failed to show survival gain compared with sorafenib, although TARE showed a higher response rate and lower toxicity.[406,407] The results of small RCTs and meta-analyses comparing TARE with cTACE or DEB-TACE differ between studies; however, the survival rate, OS, and safety were not significantly different between the two treatments, and TTP of TARE tends to be longer.[408-413]

The most frequent adverse effect after TARE is transient fatigue. However, TARE less frequently causes postembolization syndrome because the embolic effect is minimal, and it can be safely performed even in patients with portal vein tumor invasion. Elevated serum bilirubin levels occur in 20% of patients, and the mortality rate within 1-month ranges from 0% to 3%.[404,414,415] Severe complications, such as radiation pneumonitis and gastroduodenal ulcer, can occur in the event of inadvertent embolization into the extrahepatic organs. Therefore, ^{90}Y TARE requires meticulous treatment planning and operator experience.

In summary, TARE has not shown survival gain compared with standard treatment, including sorafenib and TACE in RCTs, until now. However, TARE can minimize PES and is expected to enhance the response rate and prolong TTP compared with TACE; thus, TARE can be an alternative treatment to TACE in select patients, considering cost-effectiveness. An ongoing RCT on combined treatment of TARE and sorafenib (NCT01556490) is under way.

Recommendations

1. cTACE is recommended for HCC patients with a good performance status without major vascular invasion or extrahepatic spread who are ineligible for surgical resection,

liver transplantation, RFA, or PEIT (**A1**).
2. cTACE should be performed through tumor-feeding vessels using selective/superselective techniques to maximize antitumor activity and minimize hepatic damage (**B1**).
3. In cases of HCC with portal vein invasion, cTACE alone (**B2**) or combined therapy of cTACE and external beam radiation therapy (EBRT) (**B1**) can be considered for patients with localized tumors and well-preserved liver function.
4. DEB-TACE has similar therapeutic efficacy and results in less PES compared with cTACE (**B2**).
5. TARE can be considered as an alternative treatment to TACE when patients have preserved liver function and reduction of PES is required (**B2**).

EXTERNAL-BEAM RADIATION THERAPY

EBRT for the treatment of HCC is commonly used for lesions that are surgically unresectable and not amendable with other local modalities.[416] Child-Pugh class A or B7 are liver functional criteria for EBRT. The reported overall response rates and median survival after EBRT are 40% to 90% and 10 to 25 months, respectively.[417] EBRT requires computerized radiation therapy planning by CT, and the liver volume receiving ≤30 Gy must be ≥40% of the total liver volume for patients with Child-Pugh class of A or B7 function in three-dimensional radiotherapy planning-based dose-volume analysis.[418] For hypofractionated EBRT consisting of ≤10 fractions, the normal liver volume receiving <15 Gy must be ≥700 mL and the dose to the normal liver volume excluding the tumor should be limited to ≤28 Gy (corrected to 2 Gy per fraction-equivalent dose).[419,420] For patients with a Child-Pugh score of B8 or higher, it is necessary to apply more stringent dose-volume constraints than for patients with Child-Pugh class of A or B7.[421-423]

Hypofractionated radiation therapy, stereotactic body radiotherapy, or particle therapy for HCC resulted in 3-year local control and OS rates of 70% to 100% and 45% to 80%, and 5-year local control and OS rates of 69% to 96% and 40% to 70%, respectively.[424-449] A meta-analysis reported that the use of TACE in combination with EBRT significantly improved the tumor response, 1-, and 3-year survival rates compared with TACE monotherapy.[450] One study reported that when EBRT was used for patients unsuitable for TACE owing to severe tumor-induced arteriovenous shunts, 20% of these patients were able to undergo TACE successfully after radiation therapy-induced vascular occlusion.[451] Moreover, the addition of EBRT for HCC after incomplete TACE resulted in a complete response rate of 20% to 25%.[452,453] The sequential combination of EBRT 2 weeks after TACE may be complicated by liver dysfunction; however, Common Terminology Criteria of Adverse Events grade ≥3 liver dysfunction was reported in only 2.5% of all patients.[454]

EBRT can be performed safely for HCC patients with macrovascular invasion by the tumor. The reported overall response rates and median survival after EBRT for HCC patients with major vascular invasion are 30% to 83% and 7 to 34.4 months, respectively.[429,432,438,451,455-472] Furthermore, combined treatment of TACE and EBRT for HCC patients with inferior vena cava invasion resulted in a superior median survival of 11.7 months compared with the historical cohort treated with TACE alone.[460] In a Korean multicenter retrospective cohort analysis, 67% of patients who received EBRT for HCC with portal vein invasion received combined treatment with TACE or HAIC.[473] A recent meta-analysis reported that combination therapy of TACE or HAIC and EBRT for HCC patients with portal vein invasion significantly improved the objective response and OS rates compared with TACE or HAIC monotherapy.[474] In retrospective series[383,475,476] and a recent prospective RCT,[387] combination therapy of TACE and EBRT for HCC patients with portal vein invasion significantly improved survival compared with sorafenib monotherapy.

TACE or HAIC combined with EBRT for locally advanced HCC resulted in a median survival of 13 to 20 months.[431,457,477] Surgical resection can be considered for patients with locally advanced HCC who achieved downstaging with EBRT, which was reported to be safe and effective.[478-480] In addition, EBRT can be considered as a bridging treatment for patients awaiting liver transplantation,[481-483] or as a second-line treatment for recurrent HCC after surgical resection, RFA, PEIT, or TACE.[416,425,484-487]

EBRT is also effective for relieving symptoms, such as cancer pain.[417,488,489] In HCC patients with jaundice due to malignant biliary obstructions, EBRT successfully reduced tumor size with alleviation of symptoms; accordingly, EBRT is also expected to improve survival in these patients.[490,491] In patients with abdominal lymph node metastases, EBRT results in response rates of approximately 75% to 95% with improved survival.[492-498] In patients with adrenal metastases, EBRT achieved disease control in more than 90%.[499] In addition, EBRT for lung metastases resulted in response rates from 65% to 75% while symptom relief was achieved in 90% of symptomatic patients.[496,500] EBRT is reported to relieve pain in 75% to 99% of patients with symptomatic bone metastases.[501-507] Moreover, in a previous study, EBRT for spinal cord compression from vertebral metastases is reported to prevent neurologic dysfunction in 63% to 83% of patients.[508-510] In case of brain metastases from HCC, patients can receive EBRT to relieve symptoms.[511-513]

Recommendations

1. EBRT can be considered for HCC patients ineligible for surgical resection, liver transplantation, other local modalities, or TACE (**C1**).
2. EBRT is feasible in HCC patients if their liver function is Child-Pugh class A or B7 and the irradiated total liver volume receiving ≤30 Gy is ≥40% (**B1**).
3. EBRT can be performed for HCC patients who exhibit an incomplete response to TACE (**B2**).

4. EBRT can be performed for HCC patients with portal vein invasion when the dose-volume criteria in Recommendation 2 are met (**B2**).
5. EBRT can be performed to alleviate symptoms caused by metastases (**B1**).
6. EBRT can be considered for HCC patients who have recurrent or refractory disease after local therapy (**C1**).

SYSTEMIC THERAPIES

Systemic therapy refers to any type of drug treatment that travels the bloodstream to reach cancer cells throughout the body. Systemic therapies include conventional cytotoxic chemotherapeutic agents, as well as molecularly targeted therapy (MTT) which targets the intracellular signals involved in the growth and metastasis of cancer cells, and immunotherapy which stimulates the host immune system to fight the cancer cells. Currently, conventional chemotherapy, MTT agents, and immune checkpoint inhibitors (a type of cancer immunotherapy) are utilized as systemic therapies for HCC.

1. Sorafenib

Sorafenib is a multi-kinase inhibitor that targets vascular endothelial growth factor receptor-2 (VEGFR-2), platelet-derived growth factor receptor (PDGFR), Raf-1, and c-kit. Sorafenib was the first MTT agent approved for the treatment of advanced HCC. In the SHARP study, a global phase III trial, the median survival of HCC patients with portal vein tumor invasion or extrahepatic metastasis treated with sorafenib was 10.7 months, which was significantly longer than the 7.9-month survival of patients who received a placebo (HR, 0.69; 95% CI, 0.55 to 0.87; p=0.0006).[514] The TTP in the sorafenib group was 5.5 months, which was also significantly longer than the 2.8 months in the control group. In the Asia-Pacific phase III trial that included Korean patients with unresectable HCC, patients who received sorafenib had a significantly longer median survival (6.5 months) than patients in the control group (4.2 months: HR, 0.68; 95% CI, 0.50 to 0.93; p=0.01).[515] Five randomized controlled phase III trials and one phase II trial tested novel MTT agents in which all patients in the control group were treated with sorafenib; the median survival of patients treated with sorafenib was consistently reported to be approximately 10 months (range, 8.4 to 12.3 months).[516-520]

The two previously mentioned phase III trials for sorafenib (the SHARP and Asia-Pacific trials) recruited HCC patients with Child-Pugh class A liver function and an ECOG performance status of 0-2. In real-world practice, the safety and efficacy of sorafenib are reported to be comparable between Child-Pugh class A and B function patients;[521-523] however, the presence of ascites and a higher Child-Pugh score are significantly associated with the poor prognosis of sorafenib-treated patients.[524] The GIDEON study, which was a large-scale observational study involving 3,171 patients from 39 nations who were treated with sorafenib, reported that overall adverse events and treatment-related adverse events were not significantly different according to Child-Pugh class. However, serious adverse events (SAEs) were significantly more frequent in Child-Pugh B patients than in Child-Pugh A patients. Moreover, within Child-Pugh B patients, Child-Pugh B8-9 patients experienced SAEs more frequently than Child-Pugh B7 patients. Median OS was different according to Child-Pugh class: 13.6 months for class A, 6.2 months for B7, 4.8 months for B8, and 3.7 months for B9.[17] Although sorafenib can be considered for patients with poor liver function (i.e., Child-Pugh B7 patients), further interventional study is warranted to determine the optimal use of sorafenib in these patients.

Since sorafenib's introduction to clinical practice, all of the clinical trials that evaluated treatment outcomes of combination treatment with TACE plus sorafenib or other MTT agents to improve OS have failed to show gains in OS compared with sorafenib monotherapy.[525] Recently, a Korean randomized controlled multicenter phase III trial reported that sorafenib with concurrent cTACE failed to significantly prolong OS of advanced HCC patients compared with sorafenib alone (median OS, 12.8 months vs 10.8 months; HR, 0.91; 95% CI, 0.69 to 1.21; p=0.290). However, combination treatment with sorafenib and concurrent cTACE significantly improved the secondary outcomes of progression-free survival (PFS), TTP, and tumor response rate compared with sorafenib alone. *Post-hoc* analysis showed that OS was significantly longer in the combination treatment group than in the sorafenib alone group if the patients received more than two sessions of cTACE (median OS, 18.6 months vs 10.8 months; HR, 0.58; 95% CI, 0.40 to 0.82; p=0.006).[526]

The most common adverse event related to sorafenib treatment is hand-foot skin reaction (HFSR); other common adverse events include fatigue, skin rash, hypertension, hoarseness, anorexia, weight loss, constipation, and alopecia. HFSR tends to resolve spontaneously after 3 months of treatment; therefore, it is important to continue therapy with patient education and proper management. For example, creams containing urea may be helpful for preventing dryness of the hands and feet. It is recommended that patients remove thick calluses, wear comfortable shoes with cushioning, avoid bathing with hot water, and take analgesics, if necessary, to mitigate and alleviate the symptoms associated with HFSR.[527] Since HFSR and hypertension have been reported as potential surrogate predictors of a good response to sorafenib, the management of adverse events needs to be emphasized to clinicians and patients.[528]

Second-line treatments for patients who experience tumor progression with sorafenib include regorafenib, nivolumab, cabozantinib, and ramucirumab. These agents have proven efficacy in clinical trials, which will be described in the "Second-line Therapy after Sorafenib Failure" section.

2. Lenvatinib

Lenvatinib is an oral multi-kinase inhibitor targeting VEGFR-1/2/3, fibroblast growth factor receptor (FGFR)-1/2/3/4, PDGFR-α, ret proto-oncogene (RET), and c-kit. In a recently published randomized controlled non-inferiority phase III trial, lenvatinib demonstrated non-inferior OS compared with sorafenib for advanced HCC patients with a tumor occupying less than 50% of the liver and no bile duct or main portal vein invasion (HR, 0.92; 95% CI, 0.79 to 1.06).[519] This was the first OS success reported in HCC in the 10 years since sorafenib's initial success. Median OS was 13.6 months (95% CI, 12.1 to 14.9 months) for the lenvatinib group and 12.3 months (95% CI, 10.4 to 13.9 months) for the sorafenib group. PFS and TTP, both secondary outcomes, were significantly longer in the lenvatinib group than in the sorafenib group (PFS: 7.4 months vs 3.7 months; HR, 0.66; 95% CI, 0.57 to 0.77, p<0.00001; TTP: 8.9 months vs 3.7 months; HR, 0.63, 95% CI, 0.53 to 0.73; p<0.0001). In the masked independent imaging review according to RECIST 1.1, the ORR was significantly higher in the lenvatinib group (18.8%: complete response <1%, partial response 18%) than in the sorafenib group (6.5%: complete response <1%, partial response 6%) (OR, 3.34; 95% CI, 2.17 to 5.14; p<0.0001).

SAEs were significantly more frequent in the lenvatinib group than in the sorafenib group (43% vs 30%: OR, 2.34; 95% CI, 1.80 to 3.04; p<0.0001).[519] HFSR was less frequent in the lenvatinib group (27%) than in the sorafenib group (54%), and hypertension was more frequent in the lenvatinib group (42%) than in the sorafenib group (30%). Other adverse events frequently observed in the lenvatinib group were diarrhea (39%), anorexia (34%), weight loss (31%), fatigue (30%), proteinuria (25%), and hypothyroidism (16%).

The efficacy and safety of lenvatinib for Child-Pugh B patients has not been evaluated. Additionally, no second-line treatment has been established for patients who experience tumor progression with lenvatinib treatment.

3. Nivolumab

Nivolumab is an immune checkpoint inhibitor that disrupts programmed cell death receptor-1 (PD-1). It is a recombinant human IgG4 monoclonal antibody that can be administered intravenously. The CheckMate-040 trial (ClinicalTrials.gov ID: NCT01658878), a non-comparative phase I/II trial that evaluated the efficacy of nivolumab for patients with advanced HCC, demonstrated an overall ORR of 20% (complete response 1%, partial response 18%) and a duration of response of 9.9 months.[529] In a subgroup analysis involving sorafenib-naïve patients, the ORR was 20% (complete response 1.3%, partial response 18.8%) according to RECIST 1.1, which was similar to the ORR of the sorafenib-experienced group. Since the median OS was as long as 28.6 months,[530] nivolumab may have a promising role as a first-line treatment. Currently, a randomized controlled multicenter phase III trial comparing nivolumab and sorafenib as first-line treatment for advanced HCC (CheckMate-459, ClinicalTrial.gov ID: NCT025276509) is ongoing, and the results will be noteworthy.

Recommendations

1. Sorafenib is recommended for HCC patients who have regional lymph node involvement, distant extrahepatic metastasis, or intrahepatic vascular invasion, or patients who experienced tumor progression with other treatments if they have very well-preserved liver function (Child-Pugh class A) and a good performance status (ECOG 0-1) (**A1**). For patients who are indicated for sorafenib treatment, combination treatment with sorafenib and cTACE is generally not recommended (**A1**).
2. Lenvatinib is recommended for HCC patients who have regional lymph node involvement, distant extrahepatic metastasis, or portal vein tumor invasion (not extending to the main portal vein) or patients who experienced tumor progression with other treatments, if they have a tumor occupying less than 50% of the liver, very well-preserved liver function (Child-Pugh class A), and a good performance status (ECOG 0-1) (**A2**).
3. Sorafenib is considered for HCC patients with liver function classified as Child-Pugh score B7 and a good performance status if the conditions listed in Recommendation 1 are satisfied (**C1**).

ADJUVANT THERAPY

Adjuvant therapy usually refers to an additional treatment after definitive or curative therapy to prevent recurrence. As the 5-year recurrence rate even after curative resection for HCC is very high at 50% to 70%,[154,531,532] an effective adjuvant therapy is urgently required. Although many studies for adjuvant therapy after curative therapy in HCC through TACE,[533] ^{131}I infusion via the hepatic artery,[534] vitamin K_2,[535] and vitamin A analogue[536] have been performed, there is still no proven clinical significance.[77] Cytotoxic systemic chemotherapy[537] and sorafenib[538] also have no clinical evidence for adjuvant therapy.

After a Japanese study reported that adjuvant therapy of cytokine induced killer (CIK) cells reduced the 3-year HCC recurrence rate by up to 15% in CIK cell-treated patients compared with control patients.[539] several prospective RCTs have been conducted.[540-544] In a recent Korean phase III RCT,[541] adjuvant therapy with CIK cells significantly improved RFS (HR, 0.63; 95% CI, 0.43 to 0.94) and OS (HR, 0.21; 95% CI, 0.06 to 0.75) in AJCC stage I or II HCC patients after curative resection or local ablative therapy (RFA or PEI). An extended follow-up study (median, 68.5 months) also showed a sustained improvement in both RFS (HR, 0.67; 95% CI, 0.48 to 0.94; p=0.009) and OS

(HR, 0.67; 95% CI, 0.48 to 0.94; p=0.009) and the 5-year RFS rate was 44.8% in the CIK cell group and 33.1% in the control group.[545] In a phase III RCT in China, CIK cell treatment showed significantly prolonged time-to-recurrence (13.6 months in the CIK group and 7.8 months in the control group, p=0.01). However, in that study, there was no statistically significant difference in either RFS or OS.[540] In a meta-analysis involving RCTs of adjuvant therapy with CIK cells in HCC patients after curative treatment, adjuvant CIK cell therapy significantly improved RFS and OS up to 3 years.[546]

Even for resectable HCC, TACE can be applied prior to resection as a neoadjuvant therapy. However, there is no evidence that TACE followed by resection increases disease-free survival compared with resection only in resectable HCC.[547]

Recommendations

1. Patients with AJCC I, II stage HCC could be considered for adjuvant immunotherapy with CIK after curative resection or local ablation therapy (RFA or PEI) (**B2**).
2. Adjuvant therapy with TACE, sorafenib, or cytotoxic chemotherapy is not recommended for HCC patients treated with curative therapy (**B1**).

SECOND-LINE TREATMENT AFTER FAILURE OF FIRST TREATMENT

The second-line treatment to improve survival in HCC that has recurred after liver resection, liver transplantation, and RFA is very important; however, a prospective comparative study comparing the guidelines and each treatment has not been conducted except for second-line systemic treatment. Nevertheless, in actual clinical practice, the second-line treatment after the first treatment failure of HCC is very common due to the nature of the HCC. Therefore, the current evidence for second-line treatment after first treatment failure is described in this guideline.

1. Treatment of intrahepatic metastasis after hepatic resection

The rate of postoperative recurrence with intrahepatic metastasis owing to local dissemination or de novo carcinogenesis is about 50% to 70% at 5 years after surgical resection. Recurrence of the tumor with intrahepatic metastasis usually presents as intrahepatic multiple recurrence. In such cases, it is often impossible to repeat curative treatment and the risk of recurrence after treatment is high. In contrast, de novo recurrence can be the target of curative re-operation or local treatment.[154,169,531,548-550] Typically, recurrence within 2 years after surgery is classified as early recurrence and recurrence after 2 years is classified as late recurrence.[154,551] The risk factors for recurrence can be divided into tumor-related factors and underlying liver disease-related factors. Tumor-related risk factors include tumor size, number, degree of differentiation, vascular involvement, serum AFP level (elevated before surgery), lack of adequate resection margin, and non-anatomical resection, which are mainly associated with early recurrence.[154,158,548,549,552,553] The risk factors for underlying liver disease are high serum HBV DNA levels before and after surgery for chronic hepatitis B[159,554-556] and persistent active inflammation and degree of hepatic fibrosis for chronic hepatitis C;[556,557] these are associated with late recurrence. According to many retrospective studies, recurrent hepatectomy for intrahepatic recurrence has been recognized as an effective treatment with a 5-year OS rate of 52% (range, 22% to 83%).[152,552,558] Salvage liver transplantation is one of the most effective treatments to increase disease-free survival and OS rates compared with repeated hepatectomy, but the occurrence of complications related to surgery[549] is significantly higher.[559] However, the patients who undergo repeated resection are limited in clinical practice because they have a small residual liver parenchyma after resection and are at risk of recurrence.[560] Liver transplantation is more limited because of the shortage of donors. For recurrent HCC which is not indicated for repeated hepatic resection, nonsurgical local treatments such as RFA and TACE can be applied. RFA has been extensively performed as a minimally invasive treatment for small relapsing HCC.[561,562] TACE is the most widely used treatment for multiple HCC recurrences.[562-564] The meta-analysis[565-569] comparing the effects of each of the above-mentioned treatments revealed that there was no difference in survival benefit among the treatment modalities for recurred tumors after surgery. Therefore, considering the remaining liver function and the location and number of recurrences, appropriate treatment options should be selected.

2. Treatment of intrahepatic metastasis after radiofrequency ablation

Local recurrence was reported to be higher in patients who underwent local treatment, such as RFA or PEI.[318,570] Local recurrence is defined as recurrence of the tumor at the treatment site or margins after curative treatment. Local recurrence rates up to 2 years after treatment are reportedly 2% to 18% for RFA and 11% to 45% for PEI.[309-311,338,342] For PEI, the diffusion of injected ethanol may be blocked by the fibrous septum or tumor capsule, resulting in a decreased therapeutic effect. Specifically, since the local recurrence rate was reported to be as high as 43% after percutaneous injection for lesions larger than 3 cm in diameter, special caution is needed.[571]

A large-scale retrospective study at a single institution in South Korea reported that the 5- and 10-year cumulative recurrence rates were 73.1% and 88.5%, respectively, after RFA for a single, ≤5 cm-sized tumor or three ≤3 cm-sized nodules.[312] RFA showed the best therapeutic efficacy for patients with small single nodular HCC (especially HCC of ≤2 cm) and well-preserved liver function with a 5-year survival rate of 70%.[313] Since repeated RFA for recurred HCC after RFA can improve survival

if it achieves a complete response, the early detection of local recurrence is important.[572] Surgical treatment, such as surgical resection and salvage liver transplantation, for recurrent cancer after RFA showed a similar therapeutic effect compared with repeated RFA.[573,574] If surgical treatment or RFA is not feasible, TACE can be applied.[575]

3. Treatment of recurrent HCC after liver transplantation

The recurrence rate has been reported to range from 8% to 20% even after liver transplantation for HCC within the Milan criteria.[576] Due to the influence of immunosuppression after liver transplantation, the prognosis of recurrent HCC after LT is poor. The median OS after diagnosis of recurrence is less than 12 months, and 5-year survival rates are only 22%.[576,577] Among 119 patients who underwent liver transplantation for HCC, HCC recurrence occurred in 15 patients (13.4%) during a median 17.2 months of follow-up, and intrahepatic recurrence was the most common.[578] In another study of 857 patients who underwent liver transplantation for HCC, 106 patients (12.4%) experienced HCC recurrence during a median 15.8 months of follow-up after liver transplantation, and the median OS after recurrence was 10.6 months. The sites of recurrence were the lung (55.7%), liver (37.8%), abdominal cavity (37.7%), and bone (25.5%).[579] Since the prognosis of patients with recurrent HCC after liver transplantation is associated with treatment modality after recurrence, as well as to time-to-recurrence, multiple organ involvement, pre-liver transplantation HCC stage, and pathological stage of the explanted liver, an individualized approach might be required to improve the outcomes.[580]

Survival rates can be increased if curative therapy is applicable even in patients with recurred HCC after liver transplantation. Among 121 patients who had recurrent HCC after liver transplantation for HCC, 38 (31.4%) underwent resection or loco-regional therapies, 51 patients (42.1%) received palliative therapies, and the other 32 (26.4%) received supportive therapy.[581] The median OS in patients who underwent curative therapies was significantly longer than that in patients who underwent other therapies. A Japanese study analyzed 17 patients who experienced HCC recurrence among 101 patients who had undergone LDLT) between 1996 and 2007. Among the included patients, nine underwent surgical treatments, including six with hepatic resection, 10 with lung metastatectomy, and three with lymph node dissection, and the remaining eight patients received nonsurgical treatment. The 1-, 3-, and 5-year survival rates of the surgical treatment group were 100%, 87.5%, and 87.5%, respectively, while those in non-surgical treatment group were 50%, 12.5%, and 0%, respectively, which reached statistical respectively.[582]

For recurrent HCC confined to the liver after liver transplantation which is not feasible for surgical resection, RFA can result in a good outcome. Among 78 patients who experienced HCC recurrence after liver transplantation, surgical resection, RFA, and supportive care were performed for 15, 11, and 52 patients, respectively. The 1-, 3-, and 5-year survival rates were in 92%, 51%, and 35% in the resection group, respectively, and 87%, 51%, and 28% in the RFA group, respectively. There was no significant difference in survival between the two groups (p=0.879). There was also no difference of RFS between the two groups: the 1-, 3-, 5-year RFS rates were 83%, 16%, 16% in the resection group, respectively, and 76%, 22%, and 0% in the RFA group, respectively (p=0.745).[583]

Because a significant proportion of recurrent HCC patients have multiple intrahepatic lesions or extrahepatic metastasis after liver transplantation, it is infrequently possible to apply curative treatment, such as resection or RFA. There have been few reports on the efficacy and safety of TACE for post-liver transplantation recurrent HCC. In a study of 14 patients with intrahepatic and extrahepatic recurrence after liver transplantation, the rates of partial response, stable disease, and progressive disease were 57%, 28%, and 14%, respectively. The 6-, 12-, and 24-month survival rates in patients who underwent TACE were 64.3%, 50%, and 22.2%, respectively, while the rates were 35.7%, 21.4%, and 10.7% in patients who received systemic chemotherapy, respectively (p=0.034).[584] The Child-Pugh score was not elevated after TACE for recurrent HCC after liver transplantation, and there was no SAE. The severity of PES was also comparable with that in patients who did not undergo liver transplantation. In a study from Taiwan, the median OS was 6.6 months (range, 0.3 to 12.7 months) and the 1-year survival rate was 12.5% in 11 patients who underwent TACE for recurrent intrahepatic HCC after liver transplantation.[585]

Sorafenib is indicated in patients with widespread recurrence after liver transplantation for whom resection, RFA, or TACE is not feasible, or in patients with progressive disease after loco-regional therapy. However, there has been no well-designed RCT to validate the efficacy and safety of sorafenib in those patients. In a case-control study of 39 patients with recurrent HCC after liver transplantation, 24 patients received best supportive care and 15 received sorafenib. The median OS after tumor recurrence was significantly longer in the sorafenib group (21.3 months) than in the best supportive care group (11.8 months) (HR, 5.2; p=0.0009).[586] There was no SAE associated with sorafenib administration. However, another study reported a higher risk of sorafenib-related toxicity in patients with liver transplantation.[587] A case report demonstrated increased mortality due to gastrointestinal bleeding in patients who received combination therapy with sorafenib and everolimus, an mTOR inhibitor, to enhance anti-tumor activity.[588] In another study including 34 patients with post-liver transplantation recurrent HCC, 17 received sorafenib treatment and the remaining 17 received supportive care. The 3- and 12-month survival rates were 100% and 62% in the sorafenib group, respectively, which were significantly higher than the 73% and 23%, respectively, in patients receiving supportive care. The common adverse events

were diarrhea (18%), elevation of transaminase (11%), fatigue (11%), HFSR (6%), and nausea (6%).[589]

Recommendation

1. Recurrent HCC after resection, RFA, or liver transplantation can be retreated with appropriate treatment modalities considering the timing of recurrence, residual liver function, performance status, and the size, location, and number of recurrent tumors (**C1**).

REFRACTORINESS TO TRANSARTERIAL CHEMOEMBOLIZATION

cTACE is a standard treatment for patients with intermediate-stage HCC based on its survival benefit in patients with unresectable HCC reported in previous studies.[77,79,132,370,590,591] Given that TACE is usually performed repeatedly in individual HCC patients due to its palliative nature,[592] development of untreatable progression of HCC, in which TACE cannot be considered any further, is regarded as TACE refractoriness or failure.[370,593-595] Recently, several studies have attempted to define TACE refractoriness. In a single-institutional study from Korea, researchers defined stage progression despite repeated TACEs as a surrogate endpoint of TACE refractoriness. They suggested predictors of TACE refractoriness as either development of disease progression or the need for three sessions of TACE, during the first 6 months following the initial TACE, which enables prompt switching to other treatments.[596] However, these criteria did not include deterioration of hepatic function, and have not been fully validated. The Assessment for Retreatment with TACE (ART) score was developed by researchers from Austria, which integrated the radiologic tumor response, impairment of hepatic function, and liver damage (increase in aspartate aminotransferase).[597] The ART score identified patients with a poor prognosis (score ≥2.5 after the first TACE) who would not benefit from repeated TACE sessions. Likewise, a French group developed the ABCR (AFP, BCLC, Child-Pugh, and response) score which combined AFP, tumor stage, change in liver function, and radiologic tumor response, suggesting patients with a score ≥4 may not benefit from further sessions of TACEs.[598]

Recent practice guidelines on HCC have defined TACE refractoriness in different ways. The guidelines from the EASL recommended switching to sorafenib in case of untreatable progression on TACE in patients with intermediate-stage HCC.[77] Previous Korean guidelines regarded upward stage migration following repeated TACE as refractoriness, suggesting a switch to sorafenib therapy.[79] Japanese guidelines provided criteria for TACE refractoriness as follows: (1) consecutive insufficient tumor response (≥2 sessions); (2) two or more consecutive progressions in tumor number; (3) continuous elevation of tumor markers; (4) development of vascular invasion; and (5) development of extrahepatic spread.[591]

To date, various definitions of TACE refractoriness exist, and a treatment strategy to overcome such a condition has not been well established. Sorafenib has been recommended as a treatment option for TACE refractoriness based on its survival benefit in advanced HCC. A sub-analysis of the SHARP trial showed survival benefit of sorafenib in patients with prior TACE compared with placebo.[599] A retrospective study from Japan demonstrated prolonged TTP and OS with a switch to sorafenib compared with continued TACE in patients with TACE refractoriness.[600] In a retrospective study including patients with TACE refractoriness from Japan, HAIC showed promising results in terms of tumor response and survival.[601] Collectively, direct evidence on the efficacy of various treatment modalities in TACE refractoriness is insufficient. The therapeutic role of recently developed systemic agents needs to be investigated in the setting of TACE refractoriness in the near future.

Given the potential ischemic injury due to tissue ischemia following TACE, combination treatment strategies are under investigation, such as TACE plus systemic agents with antiangiogenic property (e.g., sorafenib).[602] Enrolled patients in those clinical trials appear heterogeneous in terms of tumor stage.[603] In other words, a clinical trial designed solely for TACE refractoriness has not yet been conducted. Several recent studies on combination treatments have reported mixed results. A systematic review with a meta-analysis reported that prolonged TTP without significant improvement in OS was achieved with combined TACE and sorafenib compared with TACE alone.[604] A global clinical trial of combined sorafenib plus TACE with doxorubicin-eluting beads did not reach clinical significance in terms of TTP.[605] Another large-scale European study comparing TACE using drug-eluting beads plus sorafenib versus TACE with placebo did not improved PFS in unresectable, liver-confined HCC.[606] Likewise, an Asian multi-institutional study comparing orantinib versus placebo combined with TACE did not improve OS in patients with unresectable HCC.[607] In conclusion, evidence supporting combination treatment of TACE and systemic agents is insufficient at present.

Recommendation

1. After on-demand two or more session of TACE within 6 months from the first TACE, development of one or more of the following condition in patients with unresectable HCC is defined as TACE refractoriness, and a switch to other treatments needs to be considered: (1) absence of objective response (complete or partial response); (2) new appearance of vascular invasion; and (3) new appearance of extrahepatic spread (**C1**).

SECOND-LINE THERAPY AFTER SORAFENIB FAILURE

Sorafenib failure is usually defined as pre-existing disease progression or appearance of a new intrahepatic or extrahepatic

lesion during sorafenib treatment, and various patterns of disease progression after sorafenib failure are associated with prognosis.[608] In clinical practice, the median duration of sorafenib administration is 12 weeks.[523,609] Long-term administration of sorafenib is often prohibited by disease progression, adverse events, and deterioration of liver function.

To develop second-line systemic therapy for HCC patients who stopped sorafenib due to disease progression or adverse events, several phase III clinical trials have been conducted using targeted agents such as brivanib, which inhibits FGF and VEGF,[610] everolimus, which is an mTOR inhibitor,[611] ramucirumab, which blocks VEGF-2,[612] and tivantinib, which is a non-selective c-Met inhibitor.[613] However, all these new agents failed to show improved survival compared with placebo.

1. Regorafenib

Regorafenib is an oral multikinase inhibitor that blocks the activity of protein kinases involved in angiogenesis, oncogenesis, metastasis, and tumor immunity. Although regorafenib has a similar molecular structure to sorafenib, it has a distinct molecular target profile and had more potent pharmacological activity than sorafenib in preclinical studies.[614-616] A international phase III RCT was conducted to validate the efficacy and safety of regorafenib as a second-line therapy for HCC patients with Child-Pugh A function and an ECOG score 0-1 who progressed after sorafenib treatment. Participants tolerated sorafenib (≥400 mg/day for ≥20 days of last 28 days of treatment), progressed on sorafenib, and had Child-Pugh A liver function. They were randomly assigned to receive regorafenib or placebo in a 2:1 ratio fashion. Regorafenib improved OS with an HR of 0.63 (95% CI, 0.50 to 0.79; p<0.0001); median survival was 10.6 months (95% CI, 9.1 to 12.1 months) for regorafenib versus 7.8 months (95% CI, 6.3 to 8.8 months) for placebo. Based on this result, regorafenib was the first drug to show an improvement in survival as second-line systemic therapy.[617] Median PFS by mRECIST was 3.1 months (95% CI, 2.8 to 4.2) with regorafenib and 1.5 months (95% CI, 1.4 to 1.6 months) with placebo (p<0.001). Median TTP by mRECIST was 3.2 months (95% CI, 2.9 to 4.2 months) with regorafenib and 1.5 months (95% CI, 1.4 to 1.6 months) with placebo (p<0.001). The mean duration of regorafenib administration was 5.9 months and that with sorafenib was 3.3 months. Grade 3 or 4 adverse events associated with regorafenib were hypertension (15%), HFSR (13%), fatigue (9%), and diarrhea (3%).[617]

2. Nivolumab

Nivolumab, a checkpoint inhibitor, is a fully human IgG4-type, monoclonal inhibitory antibody against PD-1. As an anti-PD-1 inhibitor, it binds to the PD-1 receptor on the T-cell to restore the suppressed tumor-killing effect. In a phase I/II, open-label, non-comparative, dose escalation and expansion trial of nivolumab, patients with histologically confirmed HCC with or without hepatitis C or B infection were recruited. The patients had compensated liver function (Child-Pugh score ≤6 in the dose expansion group, ≤7 in the dose escalation group), ECOG score 0-1, and HBV DNA <100 IU/mL if the etiology was HBV.[529] Patients received intravenous nivolumab 0.1 to 10 mg/kg every 2 weeks in the dose-escalation phase and nivolumab 3 mg/kg was administered every 2 weeks in the dose-expansion phase in four cohorts: sorafenib untreated or intolerant patients without viral hepatitis, sorafenib progression patients without viral hepatitis, HCV infected patients, and HBV infected patients. The primary endpoints were safety and tolerability for the escalation phase and OSS for the expansion phase. In a total of 262 treated patients (48 in the dose-escalation phase and 214 in the dose-expansion phase), the response rate was 20% (95% CI, 15% to 26%) in the dose-expansion phase and 15% (95% CI, 6% to 28%) in the dose-escalation phase. Three patients (6%) had treatment-related SAEs (pemphigoid, adrenal insufficiency, and liver disorder).[529,530] The U.S. Food and Drug Administration conditionally approved nivolumab as a second-line therapy after sorafenib failure based on the results of a randomized phase I/II trial, and it is also prescribed in Korea. However, the final approval of nivolumab as first-line therapy for HCC needs data from CheckMate-459 (ClinicalTrials.gov ID: NCT025276509), which is a phase III, multi-institutional, RCT to compare the efficacy and safety of nivolumab.

3. Cabozantinib

Cabozantinib is an oral, molecular targeted agent which blocks MET, VEGFR-2, and RET. An international phase III RCT was conducted to validate the efficacy and safety of cabozantinib as second- or third-line therapy in patients with advanced HCC who failed sorafenib treatment and had Child-Pugh A liver function and ECOG score 0-1. Enrolled patients had showed progressive diseases in spite of one or two systemic therapies, including sorafenib, prior to participating in the study. The primary endpoint was OS, and the secondary endpoint was PFS and ORR according to RECIST 1.1. Among all the participants, 27% received two systemic therapies, including sorafenib. The median OS in the cabozantinib group was 10.2 months, which was significantly longer than 8.0 months in control group (HR, 0.76; 95% CI, 0.63 to 0.92; p=0.0049). Thus, the clinical trial met the primary endpoint. In subgroup analysis, among patients who experienced sorafenib alone, the median OS in the cabozantinib group was 11.3 months, which was also significantly longer than 7.2 months in the control group (stratified HR, 0.70; 95% CI, 0.55 to 0.88). The median PFS was longer in the cabozantinib group (5.2 months) than in the control group (1.9 months) (HR, 0.44; 95% CI, 0.36 to 0.52; p<0.001), and ORR was also higher in the cabozantinib group than in the control group (4% vs 0.4%, p=0.0086). The median duration of cabozantinib therapy was 3.8 months. The grade 3 or 4 adverse events were reported in 68% of the patients in the cabozantinib group and

in 36% in the placebo group. The most common grade 3 or 4 AEs were HFSR (17%), hypertension (16%), elevation of transaminase levels (12%), fatigue (10%), and diarrhea (10%).[618]

4. Ramucirumab

Ramucirumab is an intravenous monoclonal antibody targeting VEGFR-2. A phase III RCT (REACH, ClinicalTrials.gov ID: NCT01140347) of ramucirumab as a second-line therapy for patients with advanced HCC who failed sorafenib was conducted. The trial failed to meet the primary endpoint of improvement of OS compared with control.[612] However, in a *post-hoc* subgroup analysis, the OS in patients with a serum AFP level ≥400 ng/mL was 7.8 months, which was significantly higher than 4.2 months in the placebo group (HR, 0.67; 95% CI, 0.51 to 0.90). Based on this result, a subsequent phase III RCT of 2:1 assignment to ramucirumab or placebo for patients with high AFP levels (REACH-2, ClinicalTrials.gov ID: NCT02435433) was conducted. Enrolled patients had progressive HCC even after sorafenib or stopped sorafenib due to adverse events. The Child-Pugh class in the patients was A, the ECOG score was 0 to 1, and the serum AFP level was ≥400 ng/mL. The primary endpoint of the study was OS. The OS in patients who received 8 mg/kg of ramucirumab every 2 weeks was 8.5 months, which was significantly longer than 7.3 months in the placebo group (HR, 0.71; 95% CI, 0.531 to 0.949; p=0.0199). Thus, the trial met the primary endpoint. The median PFS in the ramucirumab group was 2.8 months, which was also significantly longer than 1.6 months in the control group (HR, 0.452; 95% CI, 0.339 to 0.603; p<0.0001). The DCR in the ramucirumab and control group was 59.9% and 38.9%, respectively (p=0.0006); however, there was no difference in ORR between the two groups. The median duration of ramucirumab administration was 12 weeks. SAE of any grade and cause were recorded in 35% of participants in the ramucirumab group and 29% in the placebo group. The most common grade 3 or 4 adverse event that were noted in 5% or more of patients was hypertension and hyponatremia.[619]

5. Cytotoxic chemotherapy and hepatic arterial infusion chemotherapy

Cytotoxic chemotherapy can be considered for patients with HCC for whom primary or secondary systemic treatments—such as sorafenib, lenvatinib, regorafenib, nivolumab, cabozantinib, and ramucirumab— have failed, or for patients with progressive HCC for whom systemic treatments cannot be used, but who have good remnant liver function.[620-622]

Doxorubicin is the most commonly used systemic drug for HCC treatment; however, in most cases, the response rate of patients taking doxorubicin is less than 20%.[623-625] Other systemic treatments, including 5-fluorouracil,[626] gemcitabine,[627,628] oxaliplatin,[629] capecitabine,[630] irinotecan,[631] octreotide,[632,633] interferon,[634] and tamoxifen,[635] also failed in demonstrating effectiveness and improving survival rates. Combination chemotherapy has been tested, since single-drug therapy had minimal effects on HCC. FOLFOX (oxaliplatin/fluorouracil/leucovorin) combination therapy has been studied the most. A multicenter RCT (EACH study) including 317 Asian patients (China [70%], Korea [14%], Thailand [11%], and Taiwan [5%]) compared FOLFOX combination chemotherapy with doxorubicin single-drug therapy. The combination chemotherapy did not significantly extend median survival time, which was the primary outcome measure (6.4 months vs 2.9 months; p=0.07) or the PFS time (2.9 months vs 1.77 months; p<0.01). Moreover, the stable disease rate (52.2% vs 31.6%; p<0.001) was higher compared with doxorubicin single-drug therapy.[636] Interestingly, sub-analysis of the results of Chinese patients alone in the EACH study suggested that FOLFOX combination chemotherapy significantly extended survival time compared with doxorubicin single-drug therapy.[637]

A multicenter retrospective study of 204 patients with progressive HCC evaluated the effectiveness of GEMOX (oxaliplatin/gemcitabine) combination therapy. The PFS time and OS time were 4.5 months and 11.0 months, respectively.[638] Another retrospective study of 40 patients with progressive HCC not responding to sorafenib therapy also evaluated the effectiveness of GEMOX combination chemotherapy as a secondary anticancer therapy. The partial response and stable disease rates in this study were 20% and 46%, respectively. The PFS time was 3.1 months and the median survival time was 8.3 months.[639]

A meta-analysis of 17 oxaliplatin clinical studies comprising 800 patients revealed that the partial reaction rate was 16%, while the median PFS and median OS were 4.2 months and 9.3 months, respectively.[640] Another meta-analysis, which included studies written in Chinese,[641] suggested that the partial reaction rate of combination chemotherapy, including oxaliplatin, was 14%, while the median PFS time and median OS time were 4.7 months and 9.5 months, respectively.

In most cases, HCC is accompanied by cirrhosis, which affects the absorption and metabolism of anticancer drugs. Therefore, drug-induced toxicity may increase, and often administration of the therapeutic dose becomes impossible.[642] Therefore, cytotoxic chemotherapy needs to be used in a limited manner in HCC patients with good systemic condition and liver function. To prevent a decline in the quality of life, less toxic drugs need to be used as per the requirements for each case or dose reduction needs to be considered if the drug has strong toxicity.

HAIC is a type of cytotoxic chemotherapy that involves direct injection of the cytotoxic anticancer drugs into the hepatic artery, thus causing fewer adverse systemic reactions, while exposing HCC to high concentrations of anticancer drugs. The most commonly used HAIC drug is 5-fluorouracil, which is used alone or in combination with cisplatin. Studies have shown that the overall response rate in patients with progressive HCC was 3.8% to 38.5% with a partial response rate of 7% to 81% and a median survival time of 5 to 19.5 months.[643-647] A long-

term (median follow-up period: 28 years) retrospective study conducted in Japan evaluated the outcomes of HAIC treatment in 14,246 cases. The 5-year survival rate was 32% and the median survival time was 31 months. Moreover, the results were similar to that of cTACE.[647] Factors affecting the poor outcomes of HAIC treatment were the remaining liver function and an increased Child-Pugh score assessed 4 weeks after HAIC treatment.[648] There are no reports of a prospective study that directly compared the efficacy of sorafenib with that of HAIC. However, a retrospective study suggested that HAIC resulted in a longer survival time and higher tumor response than sorafenib,[648-651] but there was no difference in survival time between the two groups. A sub-analysis of progressive HCC patients with hepatic portal vein invasion also suggested that HAIC produced better results than sorafenib.[652] A domestic multicenter retrospective study of progressive HCC patients with main hepatic portal vein invasion compared HAIC and TACE. This study showed that HAIC resulted in higher tumor response and survival rates than TACE.[118] A phase II RCT conducted in Japan in a small group of patients with progressive HCC revealed that the sorafenib-HAIC combination chemotherapy group had higher survival rates than the sorafenib single-drug therapy group.[653] In contrast, a phase III RCT in 210 patients showed no difference in survival rates between the sorafenib-HAIC combination chemotherapy group and the sorafenib monotherapy group.[654]

Recommendations

1. Regorafenib is recommended for patients with progressive HCC after at least 3 weeks of sorafenib (≥400 mg/day) treatment and with Child-Pugh class A and good performance status (ECOG score 0-1) (**A1**).
2. Nivolumab could be used for patients with progressive HCC after sorafenib or for those intolerant of sorafenib and with Child-Pugh class A and good performance status (ECOG score 0-1) (**B2**).
3. Cabozantinib is recommended for patients with progressive HCC after one or two systemic therapies including sorafenib and with Child-Pugh class A and good performance status (ECOG score 0-1) (**A1**).
4. Ramucirumab has shown survival benefit in patients with progressive HCC and serum AFP level ≥400 ng/mL after sorafenib treatment or sorafenib-intolerance and with Child-Pugh class A, ECOG score 0–1 (**A2**).
5. Cytotoxic chemotherapy can be considered for patients with HCC for whom primary or secondary systemic treatments, such as sorafenib, lenvatinib, regorafenib, nivolumab, cabozantinib, or ramucirumab have failed, or cannot be used, and who still have both good liver function and good performance status (**C1**).
6. HAIC might be considered for patients with progressive HCC and portal vein invasion for whom systemic therapies, such as sorafenib, lenvatinib, regorafenib, nivolumab, cabozantinib, or ramucirumab, have failed or cannot be used, and who still have both good liver function and good performance status (**C2**).

PREEMPTIVE ANTIVIRAL TREATMENT

1. HBV-related HCC

The rate of HBV reactivation in HCC patients after cytotoxic chemotherapy varies widely from 30% to 60%,[655,656] and the subsequent mortality rate is reported to be approximately 30% of all deaths resulting from HBV reactivation. HBV reactivation with concomitant elevation of the serum HBV DNA level or abnormality of biochemical liver function is observed in 20% to 50% of all HBV carriers who receive immunosuppressants or cytotoxic chemotherapy for the treatment of malignancies other than HCC (e.g., breast cancer, hematologic malignancies, and other solid cancers).[655,657-660] Therefore, the test for HBsAg must be performed in patients at high risk of HBV infection prior to immunosuppressive therapy or cytotoxic chemotherapy.[661] Antiviral drugs should be preemptively administered in HBV carriers at the onset of the cytotoxic chemotherapy or immunosuppressant administration and must be continued for at least 6 months. Although further research is required to clarify the adequate serum HBV DNA level, recurrence is more likely after the discontinuation of antiviral drugs in patients with high HBV DNA levels prior to cytotoxic chemotherapy. Therefore, in patients with HBV DNA levels >2,000 IU/mL prior to cytotoxic chemotherapy, continuation of antiviral treatment should be considered until the treatment goal of chronic hepatitis B is reached.[661] Most studies on preemptive antiviral treatment are limited to lamivudine; however, other recently developed antiviral drugs can be used. In cases of lamivudine resistance, antiviral drugs should be replaced according to the treatment guidelines for resistance.[662,663] In particular, in cases in which antiviral therapy is expected to continue for more than 12 months, the antiviral drug with the minimum resistance profile should be selected.[664] Interferon is not recommended as a preemptive treatment because of the risk of bone marrow suppression and transient aggravation of hepatitis. In HBsAg-negative, anti-HBc-positive, and anti-HBs-positive patients, HBV reactivation can develop very rarely, and there is little evidence to recommend uniform preemptive treatment owing to a lack of research.[661]

Many studies have evaluated HBV reactivation during TACE for the treatment of HCC; HBV reactivation is reported to occur in 4% to 40% of patients.[655,656,665-668] According to a study comparing preemptive lamivudine treatment to an untreated control group during TACE,[666] significant differences were observed with respect to HBV reactivation (2.8% and 40.5%), as well as the consequent occurrence of hepatitis (2.8% and 19.7%) and liver failure (0% and 8.1%). Another study[669] compared preemptive entecavir treatment and an untreated control group following TACE treatment and reported a significant difference in vi-

rus-related events (6.8% and 54.4%) and acute decompensation (0% and 11.6%).[670] Hence, preemptive antiviral treatment can be considered for HBV-positive HCC patients undergoing TACE. However, differences in chemotherapeutic agents, and treatment interval and frequency may have resulted in discordant HBV reactivation rates.[666-668] Therefore, additional research is required to determine the serum HBV DNA levels and biochemical liver function test levels that require preemptive antiviral treatment.

HBV reactivation rates after HAIC for HCC (24% to 67%) are reported to be higher than those after TACE, which is possibly because of the higher dose of chemotherapeutic agents, as HAIC is carried out in shorter intervals.[656,671,672] However, more research is needed to support the claim that HAIC has a higher reactivation rate than TACE, as only a few studies with a limited number of participants have been reported and no comparative study with TACE has been performed.

Following surgical resection of HCC, HBV reactivation with concomitant elevation in the HBV DNA level or an abnormal biochemical liver function test is observed in 14% to 32% of patients.[673] In a prospective study comparing preemptive telbivudine administration to an untreated control group from the day of resection, the HBV reactivation rates were 2.5% and 31.8%, respectively. While 57.1% of the control group showed HBV reactivation within 1 week following surgical resection, only 2.5% of the telbivudine-administered group showed reactivation within 4 weeks. The authors of that study recommend preemptive antiviral treatment before the surgical resection of HCC.[664]

In an RCT comparing preemptive adefovir therapy to a control group after R0 resection, the 1-, 3-, and 5-year RFS rates were superior in the adefovir group compared with the control group (85.0%, 50.3%, and 46.1% vs 84.0%, 37.9%, and 27.1%, respectively).[674] The corresponding OS rates were also superior in the adefovir group (96.0%, 77.6%, and 63.1% vs 94.0%, 67.4%, and 41.5%, respectively). The relative risks of recurrence and death for antiviral treatment were 0.651 and 0.420, respectively. Antiviral therapy was an independent protective factor for late tumor recurrence.[673]

A study comparing preemptive lamivudine administration and an untreated control group following radiotherapy for HCC reports the HBV reactivation rates to be 0% and 21.8%, respectively; meanwhile, alanine transaminase elevation occurred in 2.3% and 12.5% of patients, respectively.[675] Another recent report suggests concurrent TACE and external radiotherapy may double the HBV reactivation rate compared with TACE alone.[670] However, it is difficult to recommend preemptive antiviral treatment before external radiotherapy for HCC because of the lack of controlled prospective studies.

There are limited studies regarding HBV reactivation from PEI or RFA; nonetheless, the HBV reactivation rates for these therapies are reported to be 0% and 5.6% to 9.1%, respectively.[676, 677]

HBV reactivation during sorafenib treatment is currently controversial. A Korean retrospective study reported no HBV reactivation during sorafenib treatment.[523] while another study reported a higher risk of HBV reactivation during sorafenib treatment.[678]

In hepatitis B patients with a high viral load, antigen-specific T cells are functionally exhausted, which is caused by immune checkpoints such as PD-1.[679] In HBV e antigen (HBeAg)-positive chronic hepatitis B patients with a high viral load, the number of PD-1 and cytotoxic T-lymphocyte antigen 4 (CTLA-4)-positive T cells increased. Therefore, blockade of PD-1 using immune checkpoint inhibitors could lead to activation of $CD8^+$ T-effector cells, leading to increased HBV core antigen (HBcAg)-specific interferon gamma expression. Therefore, in patients with a high HBV viral load, HCC treatment with immune checkpoint inhibitors could cause liver injury through T cell activation. In conclusion, in HBV-related HCC patients receiving immune checkpoint inhibitor treatment, such as nivolumab, effective antiviral treatment should be considered to lower HBV DNA levels.

2. HCV-related HCC

Regarding HCV-related HCC, there are almost no reported cases of HCV reactivation or aggravation of hepatitis after HCC treatment. In a recent retrospective study on hepatitis virus reactivation comparing HCV- and HBV-related HCC after TACE, the rates of viral reactivation, hepatitis, and liver failure were 26.5%, 10.2%, and 0%, respectively, in HCV-related HCC patients and 32.5%, 34.8%, and 10.9%, respectively, in HBV-related HCC patients.[680] No significant difference was observed between the HCV and HBV groups with respect to the reactivation rate, but the risk of hepatitis and liver failure were significantly lower in the HCV-related HCC group. Hepatitis C treatments can be considered in patients with active chronic hepatitis C and completely eradicated HCC. As interferon and ribavirin administration may cause bone marrow suppression and transient aggravation of hepatitis, they are not recommended as preemptive treatments before cytotoxic chemotherapy in HCC patients.

Recommendations

1. Patients should be tested for hepatitis B surface antigen before starting cytotoxic chemotherapy or immunosuppressive therapy (**A1**).
2. Preemptive antiviral therapy is recommended for HBV carriers undergoing cytotoxic chemotherapy to prevent reactivation (**A1**). Preemptive antiviral therapy is considered for HBV-infected patients receiving TACE (**B1**), HAIC (**C1**), surgical resection (**C1**), EBRT (**C1**), or immune checkpoint inhibitor therapy (**C1**) to prevent reactivation.

   Preemptive antiviral therapy with DAAs cannot be recommended for HCV carriers undergoing HCC treatments.

DRUG TREATMENT FOR CANCER PAIN IN HCC

The prevalence of pain in cancer patients ranges from 45% to 53%.[681-683] Early, aggressive palliative care including pain management could improve quality of life in cancer patients[684-686] and could improve survival in lung cancer patients.[687] A few studies have investigated the prevalence of pain in HCC patients, which is reported to range from 22% to 66.8%.[682,688,689] Therefore, pain management should be considered an important aspect of palliative care for HCC patients. As most HCC patients have chronic liver disease and/or liver cirrhosis, their drug metabolism may be altered according to the degree of liver dysfunction.[690] Furthermore, HCC patients receiving analgesics may suffer from more frequent and severe side effects. However, there is a paucity of studies on pain management for patients with HCC and liver disease.[691] Therefore, drug treatment for cancer pain in HCC patients should generally follow the principles of pain management for general solid tumors.[692-694] However, drug selection, dosage, and administration interval might need to be adjusted according to the degree of liver function impairment.

The universal strategy for cancer pain treatment is based on a sequential three-step analgesics ladder approach from non-opioids to weak opioids and finally to strong opioids according to pain intensity and the efficacy of pain control.[692-694] The main non-opioid analgesics, such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), are indicated for the treatment of mild pain (numerical rating scale, 1 to 3). Meanwhile, weak opioids, such as codeine, hydrocodone, and tramadol, are indicated for mild to moderate pain (numerical rating scale, 4 to 6). Finally, strong opioids, such as morphine, oxycodone, hydromorphone, fentanyl, and their analogues are the mainstay of analgesics for treating moderate to severe cancer-related pain (numerical rating scale, 7 to 10).

Acetaminophen is the most common cause of fulminant hepatic failure,[44,58,695,696] however, clinically significant hepatic injury is very rare when the dosage is limited to 4 g/day.[697] Nonetheless, it has been recommended that the dosage of acetaminophen per unit (tablet or capsule) in all prescription analgesics combined with acetaminophen should be limited to less than 325 mg of acetaminophen to avoid liver injury.[698] Although one case report demonstrates that even therapeutic doses of acetaminophen less than 4 g/day in alcoholic patients without liver cirrhosis can result in acute liver failure,[699] other studies show that 4 g/day in alcoholic patients is not associated with a significant increase in liver toxicity.[700,701] Moreover, one study shows a significant increase in the liver enzyme levels of alcoholic patients taking acetaminophen 4 g/day.[702] In patients with cirrhosis, acetaminophen 2–3 g/day is not associated with acute hepatic decompensation.[703] Even though the half-life of oral acetaminophen is twice as long in patients with cirrhosis compared with that in healthy controls,[704] significant hepatic injury is rare in patients with liver disease and/or cirrhosis at a dosage of less than 4 g/ day.[704,705] Nonetheless, most experts recommend lowering the dosage of acetaminophen to 2–3 g/day in patients with liver cirrhosis because of the possibility of altered drug metabolism and increased half-life.[706,707]

The unbound drug concentrations of NSAIDs are generally elevated in liver disease patients, which can lead to more severe side effects and toxicity.[708] Indeed, roughly 10% of total drug-induced hepatotoxicity cases are related to NSAIDs,[709] and NSAID-induced liver injury is well documented.[695,710] Moreover, NSAIDs can cause adverse effects, including nephrotoxicity,[711] gastric ulcer, hemorrhage,[59,60,712,713] and decompensation of liver function.[703]

As the liver is the major site of metabolism for most opioids, impaired metabolism and excretion of opioids due to underlying liver disease in HCC patients can lead to increased side effects. Moreover, opioids are well-known major precipitants of hepatic encephalopathy.[705] Therefore, careful selection of the correct opioid, and dosage and interval adjustment of drugs are required according to the liver metabolism of each opioid.[707,714] Morphine is an active analgesic compound by itself, and more than 90% of metabolites are renally excreted after glucuronidation in the liver. The half-life of morphine is approximately twice as long in cirrhosis patients as that in healthy controls.[715,716] Furthermore, its bioavailability is 4-fold greater in patients with HCC (68%) than in healthy controls (17%).[717] As the analgesic effect of codeine is presumed to be secondary following its conversion to morphine, it is not expected to be present in serum. The ceiling effect of codeine may cause side effects before achieving a sufficient analgesic effect. Similarly, hydrocodone is metabolized to hydromorphone before producing an analgesic effect, which results in variable serum levels. Meanwhile, tramadol has a 10-fold lower affinity for opioid receptors than codeine and exerts its analgesic effect via the peripheral pain pathway, which may result in fewer side effects in patients with liver disease. However, its elimination half-life is up to 3-fold greater in patients with primary liver carcinoma than that in controls.[718] Oxycodone is converted to various metabolites including oxymorphone (an active metabolite), which may result in variable serum levels of metabolites and an unpredictable analgesic effect. The elimination half-life of oxycodone is prolonged, while its clearance is diminished with significant ventilation depression in pre-liver transplantation liver cirrhosis patients compared with post-liver transplantation patients.[719] Hydromorphone is an active analgesic compound by itself and is metabolized and excreted after glucuronidation. Liver dysfunction does not have a particularly substantial effect on hydromorphone; the half-life of hydromorphone does not differ significantly in patients with moderate hepatic impairment compared with controls.[720] Although fentanyl is metabolized by cytochrome, its metabolism does not yield toxic metabolites or significantly alter serum levels in cirrhosis patients. Further-

more, it is not influenced by renal dysfunction.[707,714,721]

Recommendations

1. Careful consideration is required for pain management with medication in patients with HCC and underlying liver disease. The dosage and dosing intervals of analgesics should be determined on the basis of liver function (**C1**).
2. In patients with HCC and chronic liver disease, the dosage of acetaminophen should be lowered (**C1**) and NSAIDs should be used with caution (**B1**).
3. In patients with HCC and chronic liver disease, opioid analgesics and their dosage should be selected carefully on the basis of drug metabolism and liver function (**C1**).

ASSESSMENT OF TUMOR RESPONSE AND POST-TREATMENT FOLLOW-UP

1. Tumor response

The major primary aim of cancer treatment research is the improvement of OS. Nonetheless, tumor response and TTP are also considered pivotal for the surrogate assessment of efficacy. In oncology, tumor response was initially measured according to the 1979 WHO criteria (Table 7).[722] However, several problems arose when applying these definitions to clinical practice. For example, there were discrepancies in the criteria for measuring tumor size among researchers. Furthermore, some researchers define progressive disease on the basis of the change in the size of one tumor, while others define it on the basis of the sum of the changes in the sizes of all tumors. Another limitation of the WHO criteria is properly reflecting the changes in tumor volume determined by recent advanced CT and MRI technologies. In order to overcome these problems, the RECIST criteria and RECIST version 1.1 were developed and released in 2000 and 2009, respectively.[723,724] However, these criteria were primarily designed to evaluate cytotoxic agents. Therefore, they do not address measures of antitumor activity besides tumor shrinkage; thus, the best response in these criteria might be stable disease. As acknowledged in the original RECIST publication, assessments based solely on changes in tumor size can be misleading when applied to other anticancer drugs, such as molecular targeted therapies or other therapeutic interventions.[725] Therefore, these determinations may be inaccurate. Several clinical studies on HCC demonstrate that the RECIST criteria do not mirror the extent of tumor necrosis induced by interventional therapies or new molecular targeted drug.[514,726] In theory, viable tumor formation should be assessed by CT or MRI studies, and tumor viability should be defined according to the uptake of contrast agent in the arterial phase of dynamic imaging studies. In fact, extensive tumor necrosis, which develops after local treatment, may not be paralleled by a decrease in lesion diameter. To overcome these limitations, the EASL developed new criteria for HCC treatment response that take into account the degree of necrosis.[727] Furthermore, mRECIST criteria were first proposed by a panel of experts.[551,728] This proposal is based on the fact that the diameter of the target lesions with viable tumors should guide all assessments. Specific modifications to the original criteria regarding the assessment of vascular invasion, lymph nodes, ascites, pleural effusion, and new lesions are summarized in Table 7. However, a limitation that should be noted is that the assessment of the response to treatment based on the mRECIST criteria can be influenced by the image quality of CT/MRI, as well as the subjective decisions of radiologists.

Pseudo-progression can be observed in the early phase of treatment in patients who are receiving immune therapy. An incorrect diagnosis of progressive disease could be made if the RECIST criteria were considered for assessment of tumor response to these agents. Thus, the modified RECIST 1.1 for immune-based therapeutics (termed iRECIST) was suggested for the assessment of tumor response after immune therapy. The iRECIST is characterized by unconfirmed progressive disease (iUPD) and confirmed progressive disease (iCPD). Unconfirmed progressive disease was judged by initial observation of progressive disease, which becomes confirmed progressive disease when the tumor size gradually increases or new lesions are observed in subsequent imaging studies. Further validation and improvement should be undertaken for the assessment of future developing immune therapies.[729]

Although these criteria were validated for the prediction of treatment outcome and prediction prognosis in several retrospective studies, future studies should be followed for efficacy in a large prospective cohort. Because there is no solid evidence indicating which set of criteria is superior, the panel of experts recommends determining whether a set of criteria outperforms the conventional RECIST criteria, as well as identifying correlations with pathologic studies and outcome prediction. Tumor markers are useful when recurrence is suspected without obvious radiologic evidence or when measurement of tumor size is difficult. However, the assessment of treatment response should not be made only using tumor marker.[730]

Recommendation

1. Assessment of response should follow both the RECIST and mRECIST criteria using dynamic contrast enhanced CT or MRI (**B1**).

2. Follow-up after complete response

Follow-up data after a complete response in HCC are very limited. In cases of a complete response after hepatic resection, transplantation, or percutaneous local ablation, follow-up studies should be made by dynamic contrast-enhanced CT or MRI along with assessment of liver function, and follow-up intervals are determined on the basis of pretreatment risk factors and the treatment-specific risk of recurrence.

Recurrence usually develops within 2 years after potentially

Table 7. Assessment of Tumor Response*

	RECIST	mRECIST
Target lesions response		
CR	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
PR	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	At least a 30% decrease in the sum of the diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD	Any cases that do not qualify for either PR or PD	Any cases that do not qualify for either PR or PD
PD	An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started
Non-target lesions response		
CR	Disappearance of all nontarget lesions	Disappearance of any intratumoral arterial enhancement in all nontarget lesions
IR/SD	Persistence of one or more nontarget lesions	Persistence of intratumoral arterial enhancement in one or more nontarget lesions
PD	Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions	Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions
mRECIST recommendations		
Pleural effusion and ascites	Cytopathologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required to declare PD.	
Porta hepatis lymph node	Lymph nodes detected at the porta hepatis can be considered malignant if the lymph node short axis is at least 2 cm.	
Portal vein invasion	Malignant portal vein invasion should be considered as a non-measurable lesion and thus included in the nontarget lesion group.	
New Lesion	A new lesion can be classified as HCC if its longest diameter is at least 1 cm and the enhancement pattern is typical for HCC. A lesion with atypical radiological pattern can be diagnosed as HCC by evidence of at least 1 cm interval growth.	

Overall response assessment in mRECIST

Target lesions	Nontarget lesions	New lesions	Overall response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, modified RECIST; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; IR, incomplete response; HCC, hepatocellular carcinoma.
*Adapted from European Association for the Study of the Liver, *et al*. J Hepatol 2012;56:908-943[77] and Lencioni *et al*. Semin Liver Dis 2010;30:52-60, with permission from Georg Thieme Verlag KG.[728]

curative treatments. Because early detection of recurrence allows the possibility of the reapplication of curative treatment modalities, posttreatment monitoring should be performed frequently enough to detect recurrence as early as possible.[731] However, the ideal monitoring intervals and methods require further research. Therefore, we recommend follow-up with dynamic enhanced imaging (i.e., CT or MRI) or MRI with liver-specific contrast agent every 2 to 6 months for the first 2 years after curative treatment. After 2 years without recurrence, follow-up can be performed at 6-month intervals.[71,77,732] In addition, the monitor-

ing interval should be individualized on the basis of patient-specific risk factors according to tumor biology and underlying liver diseases.[733-735]

Recommendation

1. Patients with a complete response after treatment should be followed up with imaging studies (i.e., dynamic contrast-enhanced CT/MRI or MRI with liver-specific contrast agents) and serum tumor markers every 2 to 6 months in the first 2 years; thereafter, patients should be followed by regular checkups at individualized intervals (**B1**).

CONFLICTS OF INTEREST

Conflicts of interests among the members are summarized in Appendix 1.

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Contributors: 2018 KLCA-NCC Korea HCC Practice Guidelines Revision Committee (Appendix 2). **Chairman**: Joong-Won Park. **Head of Department**: June Sung Lee (Hepatology), Kyung-Suk Suh (Surgery), Jin Wook Chung (Radiology), Jinsil Seong (Radiation Oncology). Members; **Internal Medicine**: Do Young Kim, Ji Hoon Kim, Hyeong Jun Kim, Hwi Young Kim, Soo Young Park, Joo Hyeon Shim, Jeong Hoon Lee, Young-Suk Lim, Ho Yeong Lim, Jeong Won Jang, Jae Young Jang, Dae Won Jeon. **Surgery**: Yang Seok Ko, Kyung Sik Kim, Dong-Sik Kim, Seong Hoon Kim, Seong Hoon Kim 2, Jong Man Kim, Yeong Cheol Yun, Dong Hwan Jeong, Jai Young Cho. **Radiology**: Young Hwan Koh, Kyeong Min Kim, So Yeon Kim, Young Hwan Kim, In Joon Lee, Jeong Min Lee, Hyeon Cheol Lim, Sung Ki Cho, Ho Jong Cheon, Jun Il Choi. **Radiation Oncology**: Chul Seung Kay, Mi-Sook Kim, Tae Hyun Kim, Hee Chul Park, Sun Hyeon Bae, Sang Min Yoon, Won Sup Yoon, Won Il Jang.

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