—Review—

Medical Treatment for Hepatocellular Carcinoma in Japan

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Liver cancer, including hepatocellular carcinoma (HCC), is the fifth most common cause of cancer deaths in Japan. The main treatment options for HCC are surgical resection, liver transplantation, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), and systemic chemotherapy. Here, recent medical treatments for HCC, including surgery, percutaneous ablation, transcatheter arterial chemoembolization/transcatheter arterial embolization, and drug therapy, are reviewed with a focus on Japan. (J Nippon Med Sch 2022; 89: 154–160)

Introduction

Liver cancer, which includes hepatocellular carcinoma (HCC), is the fifth most common cause of cancer deaths in Japan[1]. Liver cancer commonly arises against a background of chronic liver disease, such as hepatitis B and C infection, alcoholic hepatitis, and non-alcoholic steatohepatitis (NASH)[2]. Regarding HBV, the development of HBV-derived HCCs as a distribution of HCCs has not decreased despite the administration of nucleoside analogues in Japan[3]. Regarding HCV, direct-acting antivirals have been approved in most countries including Japan, the sustained virologic response (SVR) rates improved dramatically[4,5]. As a result, the development of HCV-derived HCCs has decreased dramatically. However, the problem of liver carcinogenesis after elimination of HCV remains, that is, post-SVR HCCs[6]. NASH-related HCC has been increasing in frequency, and thus, has become a problem all over the world[7]. Treatment options vary widely because two factors—tumor status (e.g., diameter, number, progression) and liver function—affect the treatment choice. The main treatment options are surgical resection, liver transplantation (LT), radiofrequency ablation (RFA), transarterial chemoembolization, systemic chemotherapy, and radiation[8,9]. However, the general prognosis is still poor, with overall survival (OS) rates of 3%-5%[10]. On the other hand, treatment algorithms differ from region to region depending on the medical background[11]. Therefore, it is important to know the standard treatment for HCC in each region. Here, recent medical treatments for HCC, including surgery, percutaneous ablation, transcatheter arterial chemoembolization (TACE)/transcatheter arterial embolization (TAE), and drug therapy, are reviewed with a focus on Japan.

Treatment Algorithm

To date, many HCC guidelines from around the world have been published and updated. Such guidelines are recommended by practitioners for proper medical decision-making and improving the quality of health care and outcomes for patients[12]. Yu et al.[11] compared eight current HCC guidelines from around the world from 2010 to 2016, including three from Asia, two from Europe, and three from the United States, according to their multi-faceted selection criteria and credibility. They reported that the Barcelona Clinic Liver Cancer (BCLC) staging system has long been dominant for the treatment-guided staging of HCC; however, the BCLC concepts for surgical resection or other locoregional therapy are considered too conservative. The Asian guidelines have reached a consensus about surgical resection

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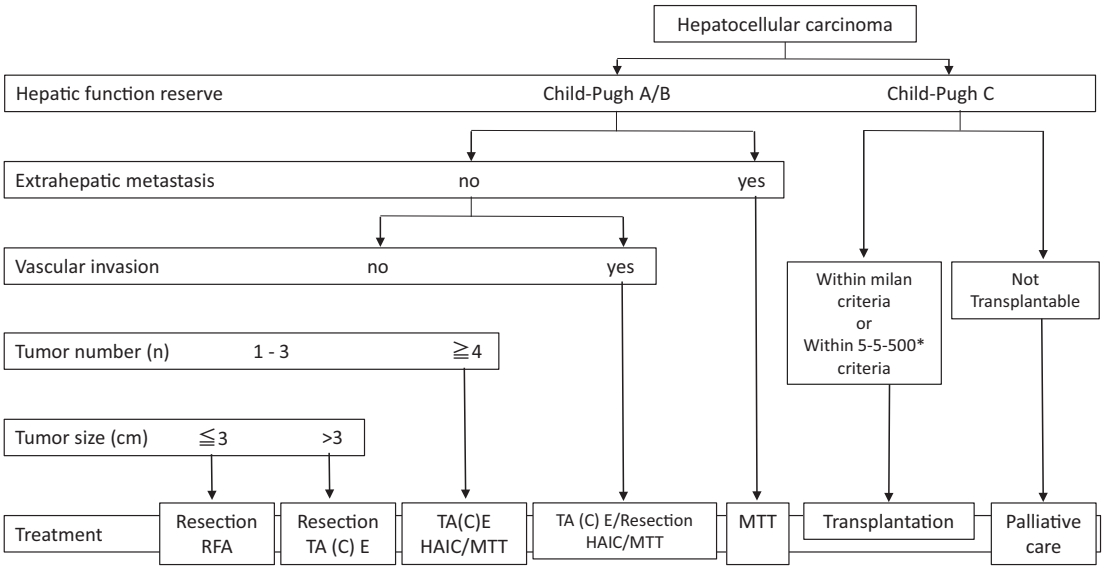

Fig. 1
Recent treatment algorithm for hepatocellular carcinoma in Japan
(modified the algorithm of 4th JSH-HCC guidelines)
Abbreviations; RFA: radiofrequency ablation, TA (C) E: transchatheter arterial (chemo) embolization, HAIC: hepatic arterial infusion chemotherapy, MTT: molecular-targeted therapy

and TACE indications for advanced tumors. For example, the treatment algorithm published by the Japan Society of Hepatology[13] recommends treatment based on a combination of five core factors: hepatic functional reserve as evaluated based on the Child-Pugh classification, extrahepatic metastasis, vascular invasion, tumor number, and tumor size (**Fig. 1**). The treatment algorithm is recommended for selecting the treatment modality best suited to the disease condition of HCC.

Type of Medical Treatment

A. Surgery

Surgical resection should be the first option for non-cirrhotic patients with local lesions. Most HCCs develop from the liver with potential portal hypertension. For patients with decompensated cirrhosis in Europe and the USA, hepatic resection is formally contra-indicated, and LT should be considered based on BCLC staging and treatment strategies[14].

In the Japanese guidelines, hepatectomy is considered based on the five factors mentioned above, including liver damage grade, which includes consideration of the indocyanine green retention rate at 15 min (ICGR15). The ICGR15 is especially appropriate for deciding the indications for surgery in Japan[15]. Makuuchi et al.[16] established criteria that clearly define the indications and contraindications for hepatectomy (determined based on ascites, total serum bilirubin values, and the ICGR15) and acceptable resection volume, and these have been commonly used in Japan. These criteria might have led to the low mortality rate in Japan (≤ 3%) after liver resection. If a discrepancy in liver function is seen between the ICGR15 and other parameters, hepatobiliary scintigraphy with ^{99m}Tc-GSA is also useful to assess liver damage[17].

Hepatectomy is generally recommended for patients with Child-Pugh A/B liver function without extrahepatic metastasis or vascular invasion and up to three HCCs (≤ 3 cm), the same as the indication for RFA. Furthermore, hepatectomy is recommended as the first-line therapy for solitary HCC regardless of size. However, although only interim results, an interesting randomized controlled study report conducted as a multicenter randomized controlled trial (SURF trial) was announced at the 2019 Annual Meeting of the American Society of Clinical Oncology to evaluate the efficacy of surgery vs. RFA for small HCCs. Briefly, in that study, patients with good liver function (Child-Pugh score ≤ 7) were receiving initial treatment for up to three HCCs (≤ 3 cm) without extrahepatic metastases. Surgeons and specialists assigned equal numbers of patients who seemed to be ade-

quately adapted to the study to a surgery and an RFA group. In total, 301 patients (150 in the surgery group vs. 151 in the RFA group) were enrolled. Although OS was not reported, median recurrence-free survival (RFS) was 2.98 years in the surgery group and 2.76 years in the RFA group (hazard ratio [HR]: 0.96, 95% confidence interval: 0.72-1.28, p = 0.793), and no perioperative deaths occurred in either group. Therefore, the guidelines for up to three HCCs (≤ 3 cm) might need to be modified.

Hepatectomy is also recommended for patients in a good condition, as mentioned above, regardless of tumor size. Furthermore, hepatectomy for multiple HCCs might not be contraindicated if the remnant liver function allows[18]. For portal vein tumor thrombosis, which is the most influential prognostic factor for HCC, surgery might be indicated because the outcomes of resection are reportedly similar between mild Vp4 and ordinary Vp3 tumor thrombus[19]. Furthermore, HCC occasionally invades the hepatic vein and bile duct as a tumor thrombus, which contributes to the poor prognosis. Although further study is needed, a few studies have reported that hepatectomy for HCC with hepatic vein or bile duct thrombus improves prognosis[20,21].

The indications for surgery in older patients are difficult because they might have background factors compared with younger patients. Kinoshita et al.[22] reported that OS and RFS rates did not differ significantly between older patients aged < 80 years and those aged ≥ 80 years. Furthermore, the indications for surgery should be investigated from the perspective of PS. Therefore, the indications for hepatectomy should be determined on a case-by-case basis.

On the other hand, laparoscopic liver resection (LLR) is now widely and rapidly performed not only in Japan, but also all over the world. The national health insurance system in Japan has covered partial hepatectomy and lateral segmentectomy since 2010. Furthermore, almost all other hepatectomy procedures have been covered since 2016, except for hepatectomies with revascularization or biliary tract reconstruction.

Generally speaking, LLR has advantages compared with open hepatectomy, such as being minimally invasive and having a magnifying effect. For example, LLR was found to be significantly associated with lower blood loss, less of a need for a blood transfusion, and the successful achievement of R0 resection, as well as a wider resection margin, a shorter hospital stay, and lower morbidity and 30-day mortality rates. Meanwhile, no differences in operative time, tumor recurrence, 1-, 3-, and 5-year OS, and 1-, 3-, and 5-year disease-free survival have been reported between LLR and open hepatectomy[23]. However, LLR, especially in advanced procedures, should be conducted in high-volume centers that have a sufficiently experienced medical team for open and laparoscopic hepatectomy. In Japan, this procedure has spread steadily[24,25]. This is likely because the Japanese system consists of training programs and a prospective resister system for all LLRs that was maintained by the Japanese Endoscopic Liver Surgery Study Group from 2011 and 2015, as well as an endoscopic surgical skill qualification system implemented by the Japan Society for Endoscopic Surgery since 2015. As a result, The Japanese Endoscopic Liver Surgery Study Group reported excellent results in terms of mortality rates, such as 0.12% for 30-day and 0.22% for 90-day mortality in all LLRs, and 0.22% for 30-day and 0.67% for 90-day mortality in all advanced LLRs (subsegmentectomy, segmentectomy, and lobectomy) conducted from 2011 to 2017. The safety is also reported for repeated hepatectomy[26] and is being secured by technological developments such as the indocyanine green fluorescence navigation method[27].

On the other hand, LT is an excellent treatment modality for HCC and cirrhosis, even in patients with grade C liver damage (Child-Pugh C liver function). Although HCCs might recur frequently after LT, in 1996, Mazzaferro et al.[28] demonstrated improved outcomes within the Milan criteria based on the relationship between tumor size and number seen on preoperative imaging (a solitary tumor [≤ 5 cm] or up to three tumors [≤ 3 cm] without vascular invasion or extrahepatic metastasis). The national health insurance system in Japan covers LT only for patients with HCC within the Milan criteria and decompensated cirrhosis. These criteria have been very important to exclude recipients with a high risk of recurrence in the indications for LT under the background of an organ shortage. However, the criteria established about 25 years ago and many factors related to outcomes have been analyzed during this period. Recently, new criteria, the so-called 5-5-500 rule (nodule size ≤ 5 cm in diameter, nodule number ≤ 5, and an α-fetoprotein [AFP] value ≤ 500 ng/mL) have been added the national insurance system[29].

B. Percutaneous Ablation

Percutaneous ablation therapy, a percutaneous transhepatic approach to tumors using ultrasound (US), has three main types: percutaneous ethanol injection (PEI), which involves the injection of pure ethanol into tumors; microwave coagulation therapy (MCT), which involves

needle puncture into tumors that produces electromagnetic microwaves by agitating the water molecules in the surrounding tissue, resulting in friction and heat that cause cellular death via coagulative necrosis; and RFA, which is a similar type of thermal technique as MCT using radiofrequency energy. PEI was developed in 1983 by Ebara et al.[30]. For many years, PEI played a central role in percutaneous ablation and was frequently indicated for patients with up to three HCCs (≤ 3 cm). MCT was developed in 1994 by Seki et al.[31] and RFA in 1995 by Rossi et al.[32]. RFA has been covered by the national health insurance system since 2004 and is currently the standard percutaneous ablation treatment for HCC in Japan. Based on the Japanese guidelines, RFA is recommended for up to three HCCs (≤ 3 cm) with Child-Pugh A/B liver function without extrahepatic metastasis or vascular invasion. As mentioned above, the Surf trial revealed the equivalent median RFS and perioperative death rates after RFA compared with those of hepatectomy for HCCs. Therefore, the guidelines might revise RFA and hepatectomy as having the same priority as a first-line treatment for such HCCs. In percutaneous ablation, it becomes increasingly difficult to ensure sufficient ablative margins as the tumor diameter increases. Therefore, the indications for RFA should be decided only after careful consideration of the tumor condition, patient background, and operator skills. In other words, the success rate must be based largely on the ability of the practitioner. Technological advances such as the bipolar RFA device, electrodes with adjustable tip lengths, cryoablation systems, and irreversible electroporation devices also provide support for such HCCs. Combination RFA and TACE can provide synergistic efficacy that improves survival in patients with relatively large tumors and fewer complications[33–35]. Furthermore, percutaneous ablation therapy has evolved with numerous technological advances in medical devices and imaging. New knowledge is expected with additional developments in ablation therapy in the future.

C. Transcatheter Arterial Chemoembolization (TACE) and Transcatheter Arterial Embolization (TAE)

Recent technological advances in catheterization, guidewire systems, and imaging devices have improved the identification of the arterial feeder of liver cancer. TACE/TAE is essential for advanced inoperable HCCs that are not indications for percutaneous ablation. Generally, HCCs that are indications for TACE/TAE are classic HCCs (moderately and poorly differentiated HCCs) or a focus of early-stage HCCs, and they appear as hyperintense signals on hepatic arteriographic images. It is strongly recommended that TACE/TAE be considered for patients with BCLC stage B (intermediate stage: PS 0, Child-Pugh A/B, and four or more lesions) hypervascular HCCs regardless of size that are inoperable and not indications for percutaneous ablation.

On the other hand, TACE/TAE can preserve the function of liver tissues not affected by cancer, thereby substantially improving prognosis[36,37]. In 2006, the Liver Cancer Study Group of Japan published a prospective cohort study of prognosis factors in 8,510 patients with unresectable HCC after Lipiodol® emulsion and gelatin sponge (Lip-TACE) between 1994 and 2001. They reported that the 5-year survival rate was 25%, and that liver damage grade, tumor stage, and serum AFP levels (≥ or < 401 ng/mL) were independent prognostic factors[38]. In 2012, the Liver Cancer Study Group of Japan published a study reporting that among 4,966 patients between 2000 and 2005, the 5-year survival rate was 34%, and added protein induced by vitamin K absence/antagonist-II to the list of independent prognostic factors[39]. Future challenges in applying TACE/TAE for advanced HCC include indications in a subgroup of patients with BCLC stage B and the utility of TACE/TAE and combination therapy with molecular-targeted drugs centering around sorafenib in patients with stage C HCC (advanced stage) accompanied by intravascular tumor thrombus (especially portal vein tumor thrombus). Although conventional TACE with Lipiodol® and porous gelatin particles of TACE with drug-eluting beads (DEBs) is strongly recommended, at present, no anticancer drug is recommended specifically for use in TACE/TAE. The iodized oil Lipiodol® is characteristically trapped and immobilized in tumor vessels and sinusoids in vivo, and has been used in ≥ 90% of TACE cases in Japan[40]. On the other hand, in drug delivery systems, Lipiodol® emulsion mixed with an anticancer drug plays the role of a carrier. Furthermore, among the spherical embolic substances, DEBs also serve as a carrier. It has also been pharmacokinetically proven that with DEBs, the loaded anticancer drug remains in high concentrations in the tumor and has reduced flow into the peripheral blood. Therefore, it is regarded as an ideal treatment method with few systemic side effects and favorable short-term clinical results[41,42]. Miriplatin hydrate, a platinating agent that is lipophilic and easily suspended in Lipiodol®, can also be used[43]. Local recurrence and the appearance of new multiple hypervascular HCCs are considered indications for re-embolization therapy, and on-demand embolization

therapy after the confirmation of such tumors has shown favorable results compared with periodic embolization therapy[44]. In addition, cases are considered to be TACE refractory if any of the following are observed: I. the therapeutic effect of the target lesion is insufficient even after two courses of TACE or the appearance of a new intrahepatic lesion; II. the appearance of vascular invasion and/or intrahepatic metastasis; or III. a continuous increase in tumor markers[13,42]. Regarding TACE refractory disease status, it is often impossible to introduce molecular-targeted drugs because of deteriorated liver function. Therefore, as described in the next chapter, it is necessary to switch to molecular-targeted drugs as soon as possible before the development of TACE refractory.

D. Drug Therapy

As with other carcinomas, molecular-targeted drugs have come to be used for HCCs, and recently, even immune checkpoint inhibitors (ICIs) have been used. ICIs are indicated for not only advanced HCCs but also intermediate to advanced HCCs, that are, unresectable HCCs and not indicated for LT. These treatment modalities began in the randomized clinical trial conducted by the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol Investigators Study Group, in the so-called SHARP trial, in 2008. The SHARP trial reported that sorafenib improved the prognosis for advanced HCC compared with placebo. For about the next 10 years, no new or more effective drugs have been made available. However, the REFLECT trial reported that lenvatinib was non-inferior to sorafenib. In addition, a subgroup analysis demonstrated the superiority of lenvatinib in OS HRs adjusted for AFP values[45]. The efficacy of lenvatinib-TACE sequential therapy has also been reported[46]. Immune checkpoint inhibitors are also causing a paradigm shift in HCC treatment as same as other cancers[47]. In 2019, in the IMbrave150 trial, atezolizumab combined with bevacizumab showed superior OS, progression-free survival, and quality of life compared with sorafenib[48]. This treatment is a combined immunotherapy of an ICI and an anti-vascular endothelial growth factor drug, and its combined use has shown additive and synergistic effects. In the 4th edition of the Hepatocellular Carcinoma Treatment Manual[49], atezolizumab and bevacizumab combination therapy is recommended as the first-line treatment for unresectable HCCs, sorafenib and lenvatinib as the second-line treatment, and regorafenib, ramucirumab, and cabozantinib as the third-line treatment. In addition, in HCCs in the intermediate stage, TACE and molecular-targeted therapy play complementary roles, and it is important to use or combine them properly according to disease status. TACE is considered unsuitable in the following cases: 1) a TACE refractory condition (Up-to-7 OUT), 2) when TACE enforcement tends to cause Child-Pugh B (Up-to-7 OUT, ALBI grade 2), and 3) when no TACE effect can be expected (e.g., poor differentiation, non-simple nodular type, changes in sarcoma). This therapy might be indicated for combination drugs[42,49]. At present, some important issues remain, such as how drugs should be adapted, in what order, and at what time. It is therefore extremely important to establish an effective therapeutic sequence for advanced HCCs in clinical practice in the future.

Conclusion

The treatment of HCCs is wide-ranging and includes other types of radiation therapy not mentioned in this article. Further improvements in treatment outcomes are expected as a result of technological innovation and the emergence of newly developed drugs.

Conflict of Interest: None.

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