INTRODUCTION

The prognosis of hepatocellular carcinoma (HCC) is extremely poor in patients with advanced HCC, and the majority of those patients live no longer than 6 months from the day of initial diagnosis. Screening tests for HCC in the high-risk population can detect tumors at an early stage and thus offer a higher chance of receiving curative treatment. Therefore, the climate of thinking concerning HCC is changing, and it is now being thought of as a curable disease. But the question as to whether any apparent improvement in survival by screening is caused by early detection or lead-time bias, remains unresolved. However, the prolongation of median survival in patients with subclinical HCC diagnosed by screening is unlikely to be the result of lead-time bias alone. Because the early detection of HCC is important for effective treatment and because it makes HCC a curable disease, the timing of the diagnosis substantially governs the type of treatment. When diagnosis is made early, the treatment has curative intent. But when diagnosis is made at a late stage, treatment may be palliative.

Patients having early stage HCC may benefit from radical options, such as surgical resection or local ablation therapy (LAT), which result in a high rate of complete responses. Hepatic surgical resection LAT, such as percutaneous ethanol injection (PEI), and transcatheter arterial embolization (TACE) have been used for the treatment of patients with small-sized HCC. However, the indications for these therapeutic modalities remain unclear. Surgical resection is generally accepted as being the most effective treatment for HCC and improvements in surgical procedures and perioperative management have decreased the morbidity and mortality associated with hepatic resection in patients with liver cirrhosis. However, the characteristic nature of HCC, for example its multicentric origin, tendency towards intrahepatic metastasis and its association with cirrhosis, limits the surgical options. In addition, complete tumor removal or necrosis by effective therapy is not synonymous with a permanent cure. Therefore, surgical resection has a limited role in the treatment of HCC, and seems to have been gradually replaced by liver transplantation or non-surgical therapies such as LAT or TACE, despite the greater efficacy of surgical removal. At present, surgical resection is usually restricted to single asymptomatic HCC in patients with a preserved liver function. Various non-surgical attempts have been made to treat HCC. The potential impact of treatment is more important in early stage HCC patients than in advanced-stage patients. Hepatocellular carcinoma prognosis is affected by many factors, such as tumor stage, degree of liver reserve function, the patient’s general condition, and treatment efficacy. To estimate the prognoses of patients with HCC and to assess prognostic value using randomized stratifications in therapeutic and clinical trials, host factors such as performance status and liver function, and tumor-related factors should be considered. Thus, a proper worldwide staging system is needed to assess prognostic value in HCC. The CLIP score consists of four variables: the Child–Pugh class, tumor morphology, α-fetoprotein (AFP), and portal vein invasion. However, although this score is easy to calculate and is based on variables routinely assessed, it is not generally used.

NON-SURGICAL TREATMENT OF HCC

The range of treatment options is wide and the choice is not always easy. Because the long-term outcome of treatment is not permanently curative, the therapist should consider the therapeutic costs and risks to the remaining liver as well as therapeutic efficacy. Furthermore, the antitumoral effect and survival benefit of radical treatments for small HCC, including hepatic resection, liver transplantation, and LAT remain a controversial issue because of the relatively small number of controlled trials performed. Despite the availability of...
comparable results for LAT from previous studies, it is still not clear whether it can replace hepatic resection.\textsuperscript{3,10}

\section*{LOCAL ABLATION THERAPY}

Local ablation therapy induces a local tumor necrosis by the selective injection of tumor necrosis agent or thermoablation with radiofrequency, microwave or laser. This therapy can be performed percutaneously under imaging guidance. Because LAT is a minimal invasive therapy with minimal systemic side-effects, it can be performed despite moderate liver function impairment. Local ablation therapy is the best alternative non-surgical curative therapy for early HCC patients. The therapeutic effect is usually affected by tumor size, number, location and operator skill. Local ablation therapy is more effective when a HCC nodule is \textless 3 cm in size and there are three or fewer present. Overall, LAT may achieve a comparable long-term survival rate for patients with small HCC by the proper selection of indication and treatment.\textsuperscript{11}

\section*{PERCUTANEOUS ETHANOL INJECTION}

This is one of the most widely performed procedures and, in the case of small tumors, has become the standard because of its effectiveness, minor complications, and cost-effectiveness.\textsuperscript{3-6} But PEI is associated with incomplete tumor ablation, leading to local recurrence and intrahepatic spread. The main limitation of PEI stems from its decreased efficacy in tumors >3 cm, which results from inhomogeneous distribution, presence of intratumoral septa and extracapsular cancer spread before treatment. To solve these problems, other agents such as acetic acid and hot saline have been tried and found to have marginal benefits in terms of induced tumor necrosis.\textsuperscript{11-13}

\section*{Holmium-166}

This is a radioisotope derived from Holmium-165. It emits beta-rays (94\%) of high energy, which are useful for killing tumor, and gamma-rays (6\%), which are useful for imaging. Because its penetration depth in soft tissue is up to 8.4 mm from the injection area, a HCC including its pericapsular lesion can be destroyed by internal radiation with minimal damage to the surrounding non-tumor tissue. We investigated the therapeutic effect and safety of a percutaneous intratumoral injection of Holmium-166 (Hol-166) for a small HCC. No serious complication was encountered, and its efficacy was found to be comparable to PEI with one or two sessions. The results obtained indicated that the percutaneous intratumoral injection of the Hol-166 macroaggregate for the treatment of small HCC is very promising.\textsuperscript{14}

\section*{Radiofrequency ablation}

Radiofrequency ablation (RFA) is an emerging technology that has been proposed as an alternative to PEI for non-surgical HCC. It is the most commonly applied locoregional therapeutic technique; alternatives such as microwave, laser therapy, or cryosurgery have limited use or are still under investigation.\textsuperscript{11,15-17} Recent RFA studies have suggested that RFA achieves objective response rates that are similar to those obtained with PEI, but using fewer sessions. However, RFA is more invasive and expensive than PEI. Therefore a randomized study is needed to prove its advantages.

\section*{TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION}

This can allow both tumor ischemic necrosis by embolization and the selective prolonged accumulation of anticancer drugs in the tumor with fewer systemic side-effects. The advantages of TACE are in the offering of diagnostic and therapeutic approaches, and of an intense and simultaneous antitumoral effect against multinodular tumors as well as single tumors. Thus, it is the most widely used treatment modality for unresectable HCC, especially in Asia. But the role of TACE appears to be limited because of incomplete tumor necrosis, deteriorated liver function and frequent side-effects. In addition, there are still arguments concerning the uncertainty of its survival benefits by randomized controlled trial.\textsuperscript{18-20} Although survival benefit was not proven in a randomized controlled trial, TACE could play a role in the prevention of HCC progression and is recommended in selected patients.\textsuperscript{21-23}

\section*{RADIATION THERAPY}

Radiation therapy alone has been of only modest benefit in the treatment of HCC due to the lower tolerance of the whole liver to radiation. Radiotherapy has been tried alone or in combination with chemotherapy for the treatment of unresectable HCC. Local radiotherapy alone can achieve some clinical benefit but is far from being an effective treatment for unresectable HCC. Radiotherapy in combination with chemotherapy has been performed in various combination, and radiotherapy has also been tried with concurrent chemotherapy.

These investigations indicate that concurrent intraarterial chemotherapy and radiotherapy may have some effect in the treatment of unresectable HCC.\textsuperscript{24-26} However, further investigation is needed to improve treatment results.

Combined TACE and local radiotherapy are an option for non-surgical treatment for unresectable HCC.\textsuperscript{26-27} In our study the response and survival rates suggest that it constitutes a promising treatment method, and its toxicity is acceptable. The addition of external radiotherapy to TACE could not only overcome the unsatisfactory efficacy of TACE alone but
also synergistically interact with the chemotherapeutic drug. Local radiotherapy, not whole liver radiotherapy, focuses on the tumor site and minimizes radiation-induced liver damage. Further investigation is warranted to improve its efficacy, with an emphasis upon preserving liver function and tumor control.

OTHER TREATMENTS AND NEW INSIGHTS FOR ADVANCED HCC

For unresectable advanced HCC, intra-arterial chemoinfusion and embolization, systemic chemotherapy, radiotherapy, hormonal therapy, immunotherapy and gene therapy, are some of the available therapeutic options. Although some responses have been attributed to these modalities, they have not always provided us with satisfactory responses. To date a number of studies have been undertaken to examine the effects of a relatively small number of prognostic factors upon advanced HCC.

There are problems, however, in evaluating the results of new therapies in patients with HCC. First, as stated by Okuda, there are ethical and methodological problems. Second, it is difficult to select patients with equivalent conditions with respect to their degrees of tumor progression, the health status of patients, and in particular with respect to hepatic function. Therefore it is hard to compare the efficacies of treatment modalities and prognoses under equivalent conditions.

Prospective studies are limited because it is hard to compare patients with equivalent conditions. Therapeutic efficacy and prognosis could vary due to these differences, and the analysis of these factors may be useful in deciding upon the proper treatment methods.

Multimodality therapy

Multimodality therapy may be attempted, such as neoadjuvant therapy, combined therapy or multistep therapy if a single treatment for HCC has proven to be incomplete. Multimodal approaches can increase not only the therapeutic effect, but also the risks and the costs involved. The advantages of a combined therapy should be proven to ensure that its associated risks have been properly considered.

Recently we tried concurrent chemoradiation therapy (CCRT) in patients with advanced HCC with portal vein thrombosis (PVT). A total of 54 patients were enrolled and randomized. Nineteen patients were treated with external beam radiotherapy (45 Gy/5 weeks) and intrahepatic arterial 5-fluorouracil (5-FU) infusion (350 mg/m² on days 1–5 and days 30–35, respectively) via implanted chemoport during the first and the last week of radiotherapy. Before CCRT, the chemoport (Deltac, St Paul, MN, USA) was implanted for continuous intra-arterial chemoinfusion. The other patients were treated with an intrahepatic arterial cisplatin infusion (80 mg/m²). The median survival time was 11.6 months in the CCRT group and 4.8 months in the intrahepatic arterial cisplatin infusion therapy group, and CCRT produced better response rates and longer survival time (P<0.05). Because CCRT achieved favorable results in advanced HCC with PVT, it may be tried as a treatment option for the management of advanced HCC.

CONCLUSION

Given that HCC are now being detected at an earlier stage, more effective loco-regional therapy is needed for small HCC.

Despite the concentrated efforts of many kinds of therapists (surgeons, interventional radiologists, radiotherapists, hepatologists, and oncologists), the results have still achieved only very limited success. However, interdepartment cooperation is mandatory to treat HCC effectively. In addition, the well-advised selection of therapeutic modality in selected subjects and a multidisciplinary approach can improve patients survival and quality of life within a limited situation.

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