Hepatocellular carcinoma (HCC), one of the most common cancers worldwide, usually develops in an already damaged, often cirrhotic liver. Although the etiology of background liver diseases differs geographically, chronic viral hepatitis due to either hepatitis B virus (HBV) or hepatitis C virus (HCV) is the main cause of HCC in most areas. Comparison of treatment outcomes is difficult because there is no universally accepted staging system for HCC. The comparison is further complicated by the fact that not only HCC itself but also the background liver disease should be the target of complete treatment for HCC.

Underlying liver disease

Etiology

The incidence rate of HCC differs according to the geographical area, which is mostly due to varying prevalence of several carcinogenic factors in different populations. The mortality from HCC has more than tripled in Japan since the mid-1970s. This increase in HCC incidence has been almost entirely due to HCV-related HCC. HCV infection is currently responsible for 75%–80% cases of HCC in Japan whereas HBV is responsible for 10%–15% cases. About 40% of HCV-related HCC patients in Japan have a history of blood transfusion and typical patients received blood transfusion in the 1950s or 1960s. During that period, supply for blood transfusion was dependent on paid blood donors. Few of them were also injecting-drug users, mainly methamphetamine, among whom HCV is thought to have spread first. Infection through reused syringes and needles is also suspected. Commercial blood banks were entirely abolished by 1969, and the reuse of syringes and needles was strongly discouraged in the 1970s. The viral spread in Japan started to decline and was almost eliminated after the advent of sensitive HCV detection system in the early 1990s. Thus, there was an interval of 30 years between the peak of HCV spread and that of HCV-related HCC incidence in Japan, which can be considered as the incubation period for carcinogenesis. Countries where spread of HCV occurred more recently are now facing increasing incidence of HCC.

Prevention of HCC

Since chronic viral hepatitis B and C are the predominant causes of HCC, infection control will lead to primary prevention of HCC. In fact, neonatal vaccination for HBV has decreased not only the prevalence of HBV carriers, but also the incidence of HBV-related HCC. HCV spread is currently declining in most countries due to increasing awareness of blood-borne infection control. The effect of interferon therapy on the prevention of development of HCC may be controversial. Studies in USA have failed to show the reduction in HCC incidence after interferon therapy. However, numerous clinical studies done in Japan have clearly demonstrated that HCC incidence was reduced among interferon-treated patients showing sustained virologic response. Resolution of cirrhosis was also noted following sustained virologic response. These effects can be anticipated to be augmented by the advent of combination therapy with peg-interferon...
and ribavirin. The discrepancy in the preventive effect of interferon therapy for HCC in studies from Japan and USA may be partly attributable to different characteristics of patients, such as the ages of HCV-infected patients, but certainly requires further elucidation.

Recent reports of a large-scale, long-term cohort study in Taiwan have shown that that the serum level of HBV DNA is the strongest risk factor for cirrhosis and HCC among HBV-positive patients, independently of serum HBe antigen/HBe antibody status or alanine aminotransferase (ALT) levels. Since HBV-related hepatocarcinogenesis is related, at least in part, to viral duplication and integration of viral DNA into host genome, it is possible that anti-HBV nucleos(t)ide analogs, by suppressing viral duplication, can decrease the risk of HBV-related HCC among chronic hepatitis B patients.

**Table 1: Strategies for prevention of HCC in patients with hepatitis B and C**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>New infection</td>
<td>Neonate vaccination</td>
<td>General infection control</td>
</tr>
<tr>
<td>Existing infection</td>
<td>Antiviral therapy (Suppression) Nucleos(t)ide analogs</td>
<td>Antiviral therapy (eradication) Interferon plus ribavirin</td>
</tr>
<tr>
<td>Treatment*</td>
<td>Early diagnosis and curative treatment</td>
<td></td>
</tr>
<tr>
<td>Prevent recurrence*</td>
<td>Transplantation Antiviral therapy (?) Molecular targeting drugs</td>
<td></td>
</tr>
</tbody>
</table>

Strategies for treatment and prevention of recurrence are similar for both hepatitis B and C.

Imaging modalities

The detection of HCC primarily depends on imaging studies, where ultrasonography (US) has been playing an essential role. The resolution of US in detecting small intrahepatic nodules has been greatly improved with technological developments. Ultrasound examination detects HCC nodules because their echogeneity is different from the surrounding liver. Small tumor nodules are typically hypoechoic and become hyperechoic as they enlarge. The presence of a capsule may also be noted. Although confirmatory diagnosis of HCC usually depends on contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), color Doppler US and US using contrast agents may provide additional qualitative information. Several new contrast agents are being evaluated as an aid to diagnose HCC or evaluate the effectiveness of ablation or assistance for US-guided ablation therapy. In particular, Sonazoid, a new contrast agent commercially available in Japan since 2007, is very useful in detecting malignant liver tumors, including metastatic tumors, due to the long duration of Kupffer imaging (Figure 1).

Recent improvements in CT imaging of HCC include the use of spiral scanners that allow very rapid imaging of the liver following infusion of intravenous contrast agents. CT plays a pivotal role in detecting small HCC nodules. MRI may be the diagnostic procedure of choice for HCC depending on its availability. Recent advances in MRI technology include scanner hardware, software, and new contrast agents.

Tumor markers

Several tumor markers are used in clinical setting for the diagnosis of HCC, evaluation of treatment efficacy and surveillance for recurrence. Alpha-fetoprotein (AFP) may be the best known among them. Serum AFP level is elevated above 20 ng/mL in >70% of patients with HCC. However, AFP levels may be also elevated in benign liver diseases, such as chronic hepatitis or cirrhosis, indicating a low specificity. Moreover, a small HCC is less likely to
be AFP-producing compared to large HCC detected decades before. Thus, the usefulness of AFP in the diagnosis of HCC is rather controversial.

AFP is heterogeneous in relation to the degree of sugar chain fucosylation, which can be distinguished by the binding affinity to lectin (Lens culinaris agglutinin). Lectin fraction-3 of AFP (AFP-L3) is highly specific to HCC. AFP-L3 is considered not only a very specific marker of HCC, but also an indicator of poorly-differentiated histology and unfavorable prognosis.

Des-gamma-carboxy-prothrombin (DCP) is an abnormal prothrombin induced by vitamin K deficiency. Although its sensitivity for the detection of HCC is lower than that of AFP, the combination of DCP and AFP has the sensitivity of >80% among HCC 3 cm – 4 cm in diameter and 70% among HCC 2 cm – 3 cm diameter. The positivity for DCP is reportedly associated with the risk of portal vein invasion, one of the main end-stage sequelae of HCC.

**Evaluation of liver function reservoir**

Liver function is one of the decisive factors in considering the indication of treatment for HCC. Few treatments are applicable to HCC in patients with decompensated cirrhosis regardless of tumor stage. Several hepatic function tests have been developed and applied to patients in the 1980s and 1990s. Currently, the most frequently used assessment is the Child–Pugh classification. In Europe and USA, the absence of clinically relevant portal hypertension, as reflected by a hepatic venous pressure gradient <10 mmHg, is often emphasized. Blood coagulation factors, especially prothrombin activity, are used as a rapid turnover index of liver function. Galactose elimination capacity, indocyanine green elimination test and aloscintigraphy may provide additional information. Patients under consideration for liver transplantation are evaluated based on the Model for End-stage Liver Disease (MELD) scoring system, which consist of serum creatinine, total bilirubin, and prothrombin INR.

**Treatment of HCC**

Although anti-viral therapies may reduce the risk of HCC, secondary prevention, i.e. early diagnosis and treatment, is still essential. There have been great advances in diagnostic imagings such as CT and US. Simultaneously, much progress has been made in the treatments of HCC, some of which will be illustrated here. The choice of optimal treatment for individual patients may be sometimes controversial. Generally speaking, treatment options are broader when the cancer is detected at earlier stages. However, some treatments may be contraindicated due to accompanying liver diseases. Indeed, the prognosis of patients with HCC is dependent not only on the stage of tumor but also on the background liver function reservoir (Figure 2). Survival of HCC patients grouped based on treatment modality, as reported by the Liver Study Cancer Group of Japan, is shown in Table 2. The survival of patients who underwent RFA is not inferior to that of patients who received surgical resection, although the former group...
Surgical resection

Ever since acceptable safety was achieved in hepatectomy, surgical resection has been considered as the sole potentially curative treatment for HCC, although currently it competes with transplantation and percutaneous ablation. Resection is usually indicated in patients with solitary HCC and preserved liver function. The liver function reservoir limits the extent of hepatic resection. This poses no difficulty when HCC arises in a normal liver. However, since HCC usually develops in cirrhotic liver, the preoperative evaluation of liver function is essential. Perioperative mortality can be less than 1%. The use of intraoperative ultrasonography (IOUS) allows precise localization and staging of the tumor. Anatomical resection is

Table 2: Survival of HCC patients according to treatment modality (1992–2003)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number</th>
<th>1</th>
<th>3</th>
<th>5</th>
<th>Liver damage* (N)</th>
<th>1</th>
<th>3</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection</td>
<td>27062</td>
<td>87.8</td>
<td>69.2</td>
<td>52.1</td>
<td>A (17433)</td>
<td>89.9</td>
<td>73.4</td>
<td>58.4</td>
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<td></td>
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<td></td>
<td></td>
<td>B (7260)</td>
<td>85.2</td>
<td>59.4</td>
<td>45.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C (631)</td>
<td>74.1</td>
<td>69.6</td>
<td>35.5</td>
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<tr>
<td>Radiofrequency ablation (1998–2003)</td>
<td>5478</td>
<td>94.9</td>
<td>76.7</td>
<td>57.3</td>
<td>A (2927)</td>
<td>97.1</td>
<td>82.7</td>
<td>73.6</td>
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<td></td>
<td></td>
<td></td>
<td>B (2123)</td>
<td>94.4</td>
<td>72.2</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C (277)</td>
<td>80.7</td>
<td>52.4</td>
<td>–</td>
</tr>
<tr>
<td>Percutaneous ethanol injection</td>
<td>14726</td>
<td>91.3</td>
<td>63.0</td>
<td>39.4</td>
<td>A (7257)</td>
<td>94.7</td>
<td>72.2</td>
<td>48.4</td>
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<td>B (5243)</td>
<td>91.8</td>
<td>57.7</td>
<td>32.9</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C (1237)</td>
<td>76.8</td>
<td>36.7</td>
<td>19.2</td>
</tr>
<tr>
<td>Transcatheter arterial chemoembolization 30490</td>
<td>74.5</td>
<td>40.2</td>
<td>21.3</td>
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<td></td>
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<tr>
<td></td>
<td>83.7</td>
<td>51.4</td>
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<td>75.4</td>
<td>37.5</td>
<td>18.2</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>56.8</td>
<td>19.8</td>
<td>7.0</td>
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</table>

* The liver function classification reported by the Liver Cancer Study Group of Japan using the category indocyanine green retention rate at 15 min [ICG(R15)] instead of encephalopathy in the Child–Pugh classification.
preferred by some surgeons, who perform segment-wise hepatectomy whenever possible. This is based on the idea that intrahepatic microscopic metastasis is likely to occur in the same segment as the original tumor via portal veins. Survival of properly selected patients receiving surgical hepatectomy exceeds 70% at 5 years, although the overall survival is substantially reduced without strict selection of patients.\(^3\)\(^3\) Thus, hepatectomy plays a limited role in the treatment of overall HCC.\(^3\)\(^4\) Only 20%–30% of patients can be candidates for hepatectomy, with the other patients not being considered either because of severely impaired liver function or advanced tumor stage. Most importantly, even after apparently curative surgical resection, 80% of patients develop recurrent HCC within 5 years\(^3\)\(^5\) because of latent intrahepatic metastasis or metachronous multicentric carcinogenesis.

**Liver transplantation**

The restriction on hepatic resection posed by poor liver function reservoir can be lifted in case of liver transplantation. Although extrahepatic comorbidity and old age can limit the indication for transplantation, the status of background liver will not be a contraindication, whatever the degree or severity of liver dysfunction, whatever the degree or severity of the underlying cirrhosis.\(^3\)\(^6\),\(^3\)\(^7\) Indeed, the recovery of liver function is the chief object of liver transplantation for liver failure without HCC, and this is also applicable to patients with HCC. The restriction on resection posed by multiplicity of HCC lesions can be also conquered by liver transplantation when the restriction is due to the fact that the expected remnant liver volume is too small. Of course there is a certain limitation concerning the stage of tumor, beyond which post-transplant HCC recurrence is likely to occur. Post-transplant HCC recurrence is usually of aggressive nature and associated with poor prognosis, probably because of immunosuppressant use. Pre-transplant tumor invasion into large vessels is a definite contraindication for transplantation. Currently, the Milan criteria are widely accepted as indication criteria for liver transplantation with HCC: solitary tumor of 5 cm or less in diameter or three or fewer lesions each 3 cm or less in diameter.\(^3\)\(^7\),\(^3\)\(^8\) However, the Milan criteria were not established on exhaustive evidence and there have been ceaseless efforts to extend the criteria. What is really needed is not a static anatomic description of the extent of HCC, but more sophisticated prognosticators of the behavior of an individual tumor, possibly obtainable through genomics or proteomics.

The waiting list of potential recipients continues to be long as the demand for donor liver keeps going up. The scarcity of donor organ is a universal issue. With a waiting list of 12 months, up to 25% of patients are estimated to be excluded from liver transplantation due to tumor advance, an unfortunate event that translates to 60% survival on intention-to-treat basis.\(^3\)\(^9\) The lack of cadaveric donors is very intense in Japan, where cadaveric liver transplantation has been performed only in 52 cases in 9 years. Living donor liver transplantation has been adopted as the practical alternative for cadaveric transplantation.\(^4\)\(^0\) After the first successful attempt,\(^4\)\(^1\) more than 3000 living donor operations have been performed worldwide. Results from Asia\(^4\)\(^1\),\(^4\)\(^3\) and a recent survey in Japan\(^4\)\(^4\),\(^4\)\(^5\),\(^4\)\(^6\) suggest that living donor liver transplantation is accompanied by favorable outcomes comparable to cadaveric transplantation. A decision analysis indicated that, based on the risk for the donor as 0.3%–0.5% mortality, living donor transplant is a cost-effective approach if the waiting time exceeds 7 months.\(^4\)\(^7\) However, this is a complex intervention that should be undertaken only by expert surgeons to ensure the lowest morbidity and best outcome to both the recipient and the donor.

Recrudescence of viral hepatitis is a substantial problem for liver transplantation in HCC patients because the majority of them have HBV or HCV infection pre-transplant. Measures have been taken to prevent post-transplant viral infection, such as nucleos(t)ide analogues and hepatitis B immunoglobulin (HBIG) for HBV and peginterferon-ribavirin combination for HCV.\(^4\)\(^8\),\(^4\)\(9\),\(^5\)\(0\)

**Local ablation therapies**

Not only cadaveric liver transplantation, but also living donor liver transplantation is frequently infeasible because of the absence of an appropriate donor or the conditions of the recipient. Consequently, the clinical need for non-surgical therapies of HCC remains unmitigated. Among them, image-guided local ablation therapies, such as percutaneous ethanol injection\(^5\)\(^1\),\(^5\)\(^2\) and radiofrequency ablation,\(^5\)\(^3\)–\(^5\)\(^6\) have been playing important roles, because they are potentially curative, less-invasive, and easily repeatable. At the authors’ institution, about 90% of naïve HCC patients are treated with local ablation therapies. We treated a total of 2000 cases with ethanol injection starting in 1985, with satisfactory long-term results. The major treatment modality has been shifted to radiofrequency ablation (RFA) since 1999, which has been shown to be superior to ethanol injection in randomized controlled trials including ours.\(^5\)\(^7\),\(^5\)\(8\)

In an RFA procedure, an ablation electrode at the tip of a needle is placed percutaneously into the targeted tumor under ultrasound guidance. Radiofrequency electromagnetic waves are transmitted from a generator and converted to heat in tissues surrounding the electrode. There are several types of RFA electrode with distinct size and shape and the details of ablation procedure differ
according to the type of electrode.

We have adopted the following indication criteria for RFA: (i) HCC lesions are unresectable or patient refuses surgery; (ii) three or fewer lesions, each 3 cm or less in diameter; (iii) no extrahepatic metastasis or vascular invasion; (iv) no excessive bleeding tendency, platelet count must be greater than 50 X 10^9/L and prothrombin activity must be better than 50%; (v) no refractory ascites; and (vi) total bilirubin level of <3.0 mg/dL.\(^{58,59}\)

Reportedly complete tumor necrosis can be achieved by RFA in 80%–100% of cases. The difference in complete necrosis rates seems to represent not only the difference in patients’ characteristics but also the difference in expertise among institutions. According to the authors’ experience in RFA for HCC, viable lesions remained only in 14 (0.6%) out of 2350 sessions (1219 patients), although we put no restriction on the location of tumor.\(^{60}\) To accomplish these outcomes, we have used artificial pleural effusion technique, artificial ascites technique\(^{61}\) and guidewire method. The therapy has not been compromised if the target lesions were at so-called difficult locations, i.e. on the surface of liver, beneath the diaphragm, near the large vessels, or adjacent to other organs. We have treated 652 patients with naïve HCC by RFA. The overall survival rates among these patients at 1, 2, 3, 4, 5, and 6 years were 96%, 88%, 80%, 69%, 58%, and 53%, respectively.

**Transcatheter arterial chemoembolization**

Transcatheter arterial chemoembolization (TACE) has been widely performed for unresectable HCC. TACE is based on the fact that HCC derives its blood supply predominantly from the hepatic artery, whereas surrounding liver receives portal-dominant blood supply. TACE is effective for multiple or large lesions and can be performed in cases of impaired liver function. The catheter tip was advanced at the nearest site of the feeding artery as possible. The emulsion of anticancer agent and lipiodol followed by gelatin sponge particles was carefully injected under fluoroscopic monitoring. The dose of emulsion of anticancer agent and lipiodol and the pieces of embolic materials used for TACE were determined based on the tumor size and extension of the lesions. The patients were followed by dynamic CT or MRI every 3–4 months, and repeated TACE was determined when the local recurrence, intrahepatic metastases, and/or second primary HCC was found. The effects of TACE are limited in cases with capsular invasion, extracapsular growth, or vascular invasion. Complete necrosis of whole lesions is rarely achieved and the indication should be limited to advanced HCC that cannot be treated by resection nor ablations. At present, options such as radio-labeled yttrium glass beads and radio-labeled lipiodol remain experimental. Despite huge efforts in this area, beneficial effects on survival are not clear.\(^{34,62}\) However, two recently published trials have shown a survival benefit of TACE using either doxorubicin or cisplatin compared with best supportive care only, and deserve attention.\(^{63,64}\) From Japan, Takayasu et al reported that TACE demonstrated a 5-year survival rate of 26%, a mortality rate of 0.5% in 8510 patients with unresectable HCC and the hepatic function, tumor characteristics (size, number, and presence of portal vein tumor thrombus), and AFP value were independent predictors of survivals of patients.\(^{65}\)

**Conventional chemotherapy**

Although a huge number of randomized and non-randomized clinical trials have been published to evaluate the usefulness of a single agent or a combination of agents as chemotherapy to highly advanced HCC, current outcomes are dismal.\(^{66–69}\) Recently, a combination therapy with subcutaneous interferon and intra-arterial infusion of 5-FU was reported with promising results in 116 HCC patients with portal vein invasion.\(^{70}\) One cycle of treatment consisted of 4 weeks, where 5,000,000 U (5 MU) IFN (OIF; Otsuka Pharmaceutical, Tokyo, Japan) was administered intramuscularly on days 1, 3, and 5 of each week, resulting in a total dose of 60 MU in a cycle. 5-FU (500 mg/day, Kyowa Hakko, Tokyo, Japan) was administered into the hepatic artery over 5 hours using a portable infusion pump on days 1–5 of the first and second weeks through the intra-arterial catheter (5 g in a cycle). Nineteen (16%) patients showed complete response and other 42 (36%) showed partial response. Adverse events were limited to nausea and appetite loss. The overall survival rates at 12 and 24 months among patients were 34% and 18%, respectively, and those among complete responders were 81% and 59%, respectively.

**Molecular-targeted chemotherapy**

Antiangiogenic molecular-targeted chemotherapy usually uses antibodies to an extracellular growth factor receptor, or inhibitors to a receptor tyrosine kinase. Epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VFGFR) are usual targets of new drugs intended to suppress tumor-related angiogenesis. The EGFR-inhibiting agents gefitinib and erlotinib are approved for lung cancer and cetuximab is for irinotecan–refractory metastatic colorectal cancer. Gefitinib inhibited cell proliferation and metastatic properties of HCC both in vitro and in an animal model.\(^{71}\) Recent data from two clinical trials suggested some prolongation of progression-free survival in HCC patients by erlotinib.\(^{72,73}\)

A variety of agents that interfere with VEGFR signaling are being investigated. The monoclonal antibody bevacizumab is approved for metastatic colorectal cancer in
combination with fluorouracil-based chemotherapy. Recent data for bevacizumab indicate that bevacizumab can be administered safely in carefully selected HCC patients. Caution must be exercised in using antiangiogenic agents in HCC patients with esophageal varices, vascular thrombi, and coagulation disorders. A novel inhibitor of raf kinase and VEGFR signal transduction sorafenib showed promising clinical activity in HCC, median time to progression of 4.2 months, and median overall survival of 9.2 months in phase II trial. In phase III trial, sorafenib hepatocellular carcinoma assessment randomized protocol (SHARP) trial, the median time to radiologic progression was 5.5 months in the sorafenib group and 2.8 months in the placebo group (p<0.001) and median overall survival was 10.7 months in the former and 7.9 months in the latter. However, 96.7% of patients were Child–Pugh class A and median survival was not satisfactory even in the sorafenib group. Moreover, since molecular-targeted drugs are costly, a cost–benefit analysis might be needed.

Other options

Radionuclide yttrium-90, a pure beta emitter, is a form of hepatic artery-directed therapy. Microspheres of approximately 25 ìm in diameter containing yttrium-90 are lodged via a catheter insertion into the lobar or segmental level of either hepatic artery and emit local radiation with limited exposure to adjacent healthy tissue. Recently, there are no data to suggest its superiority over ablative therapies.

High-intensity focused ultrasound (HIFU) therapy has been developed for the treatment of tumors of solid organs. HIFU focuses an extracorporeal source of US to a target lesion inside the body. The US energy passes harmlessly through overlying tissues en route to a tightly focused target area. The rapid rate of energy deposition generates a rapid rise in temperature, which results in irreversible cell death with defined region of tissue necrosis. The disadvantages of HIFU therapy are: it is a time-consuming procedures (average 3–4 hours) and sometimes needs rib resection when the tumor is located behind the rib bone. There are a few reports about the long-term efficacy of HIFU for advanced HCC.

Prevention of recurrence

Short-term prognosis of HCC patients has been much improved recently due to advances in early diagnosis and treatment as shown above. However, long-term prognosis is as yet far from satisfactory, as indicated by the fact that overall survival at 10 years after apparently curative treatment of HCC is as low as 22%–35%. In a typical cumulative survival curve of HCC patients after treatment, the slope of curve does not level out over time in contrast to the slope of cumulative survival curves after relatively curative treatment of most other malignancies. In other words, HCC is rarely treated curatively, with the exception of successful liver transplantation. The primary reason for poor long-term survival is extremely frequent intrahepatic recurrence of HCC even after apparently curative treatment, either local ablation or surgical resection. These are locoregional therapies and in contrast to liver transplantation, may not remove microscopic metastasis in the remaining liver. However, this does not explain the fact specific to HCC that the risk of recurrence does not decline over time, which continues to occur at a rate of 10%–20% per year. This continual recurrence of HCC is considered to be mostly due to multicentric de novo carcinogenesis. Also in this respect liver transplantation exceeds locoregional therapies.

However, strategies similar to those of primary prevention of HCC may be applicable to HCC recurrence due to multicentric carcinogenesis. Interferon therapies have been performed on HCV-related HCC patients after initial treatment and there was a possible reduction in recurrence incidence. Liver function did not deteriorate in patients who achieved sustained virologic response by interferon therapy, among whom there was no death due to liver failure. Consequently, overall survival was improved in patients treated with interferon. For HBV-related HCC, recently developed oral nucleos(t)ide analogs are also promising, particularly because the relation between serum viral load and the risk of HCC has been recently shown. In contrast to interferon, these anti-HBV drugs can be given to patients with advanced cirrhosis. Although the effects of these drugs on the prevention of HBV-related HCC recurrence are yet to be shown, we can expect at least that the anti-HBV drugs prevent further deterioration of liver function by suppressing hepatitis.

Early diagnosis and complete removal of primary HCC lesions are prerequisites for tertiary prevention. For moderately-advanced HCC where microscopic metastasis can be suspected safe and effective chemotherapeutic agents would be useful as adjuvant or neoadjuvant. However, conventional chemotherapeutic agents are not satisfactorily effective against HCC, nor safe enough for long-term use. Hasegawa et al reported that the administration of uracil-tegafur (UFT) as an adjuvant chemotherapy for hepatic resection offered no evidence to support potential benefits and overall survivals appeared to be worse in the treatment group. They suggested that a reason for the poor survival in the treatment group was the adverse effects of UFT on liver function. Some agents appears promising in terms of safety, but the effects remain yet to be confirmed. Prevention of recurrence of HCC, or tertiary prevention, is one of the most challenging tasks in current hepatology.
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