J Hepatobiliary Pancreat Sci (2010) 17:422–424
DOI 10.1007/s00534-009-0239-7

Single HCC smaller than 2 cm: surgery or ablation?

Surgeon's perspective

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Received: 1 August 2009 / Accepted: 1 September 2009 / Published online: 21 November 2009

Abstract
Purpose For hepatocellular carcinoma (HCC), surgical resection and radiofrequency ablation (RFA) are accepted as effective treatments. To clarify the long-term outcome in patients with small HCC, we analyzed data from a nationwide survey of Japan.
Methods Between 2000 and 2003, a total of 2,550 patients who had undergone resection ($n = 1,235$) or RFA ($n = 1,315$) for single small HCC (≤ 2 cm) were registered to the database of the Liver Cancer Study Group of Japan (LCSGJ).
Results After a median follow-up period of 37 months, disease-free survival after resection was significantly better than after RFA (1-year, 91 vs. 87%; 2-year, 46 vs. 25%; $P = 0.001$), but overall survival after resection and RFA were similar (98 vs. 99%; 94 vs. 95%, $P = 0.28$). In the patients of Child–Pugh class A, disease-free survival was significantly better after resection ($n = 1,056$) than after RFA ($n = 965$) ($P = 0.001$), while overall survival was not significantly different ($P = 0.16$). In the patients of Child–Pugh class B, both disease-free and overall survival were almost similar ($P = 0.63$ and $P = 0.66$) after resection ($n = 136$) and RFA ($n = 303$).
Conclusions For single small HCC (≤ 2 cm), surgical resection provides better disease-free survival than does RFA. Longer follow-up is needed to regard this indication as conclusive.

For the Liver Cancer Study Group of Japan.

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Introduction

Recent progress in imaging modalities has facilitated recognition of small hepatocellular carcinoma (HCC), which seems to be curable by surgery or ablation, in high-risk patients who undergo regular medical check-ups for chronic viral hepatitis or cirrhosis [1]. Based on the accumulating information on small HCC, Japanese researchers proposed to define the pathological concept of early HCC (carcinoma in situ) [2], which was proved to be the earliest clinical entity, with a high cure rate (stage 0 HCC) [1]. To clarify survival in patients with single HCC smaller than 2 cm, we compared long-term outcomes after surgical resection and radiofrequency ablation (RFA) based on data obtained in the latest Japanese survey [3].

Methods

The patients with primary liver cancer in about 800 institutions have been registered every 2 years and followed prospectively in a nationwide survey conducted by the Liver Cancer Study Group of Japan (LCSGJ). Between 2000 and 2003, a total of 2,550 patients who had undergone resection ($n = 1,235$) or RFA ($n = 1,315$) for single HCC smaller than 2 cm were registered to the database of the LCSGJ [3].

Relevant clinical data were collected and analyzed. Regarding liver function, the resection group had significantly higher proportions of Child–Pugh class A (88 vs. 75%, $P = 0.001$) and better indocyanine clearance rate [15% (10–22%) vs. 23% (15–34%), $P = 0.001$] than did the RFA group. Regarding tumor-related factors, maximum tumor diameter was larger in the resection group than in the RFA group [18 (15–20) mm vs. 16 (14–20) mm, $P = 0.001$]. The level of alpha-fetoprotein was not significantly different between the two groups [16 (15–83) ng/ml vs. 18 (15–59) ng/ml, $P = 0.44$]. Overall and recurrence-free survival curves were made by the Kaplan–Meier method and compared by the log-rank test. The therapeutic impact of surgical resection and RFA was estimated using a Cox proportional-hazards model, including the variables associated with HCC.

Results

After a median follow-up period of 37 months, disease-free survival after resection was significantly better than that after RFA (1-year, 91 vs. 84%; 2-year, 70 vs. 58%; $P = 0.001$) (Fig. 1), but overall survival after resection and RFA were similar (98 vs. 99%; 94% vs. 95%, $P = 0.28$). Using multivariate analyses, we found three independent prognostic factors for recurrence of HCC: alpha-fetoprotein, therapy, and Child–Pugh class. The relative risk for recurrence in resection was 0.71 [95% confidence interval (CI) 0.56–0.90; $P = 0.004$], as compared with ablation. In the patients of Child–Pugh class A, disease-free survival was significantly better after resection ($n = 1{,}045$) than after RFA ($n = 946$) ($P = 0.001$), while overall survival was not significantly different ($P = 0.16$). In the patients of Child–Pugh class B, both disease-free and overall survivals were almost similar ($P = 0.28$ and $P = 0.66$) after resection ($n = 132$) and after RFA ($n = 301$).

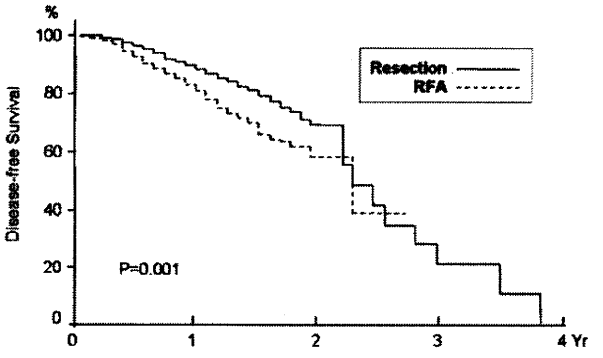

Fig. 1 Disease-free survival in single HCC smaller than 2 cm. The resection group ($n = 1{,}235$) had significantly better disease-free survival than the RFA group ($n = 1{,}315$) ($P = 0.001$)

Discussion

For single HCC smaller than 2 cm, hepatic resection provides better disease-free survival than RFA, although overall survival at 1 and 2 years were similar for both treatments [3]. A larger Japanese study demonstrated a similar outcome in patients with no more than 3 tumors ($\leq$3 cm) [4]. Whether the improvement in recurrence-free survival seen with resection will translate into better overall survival more that 2 years out following therapy remains unanswered at present.

Current imaging modalities have high sensitivity and positive predictive value for diagnosing overt HCC, but they are less sensitive for detecting early HCC, missing tumors smaller than 2 cm or that are well differentiated [5]. Computed tomography (CT) and magnetic resonance (MR) imaging perform poorly for detection and characterization of precursor lesions, but the use of intravenous contrast material with multiphasic imaging can enhance their ability to characterize such early focal lesions accurately [6, 7]. The chance of diagnosing and treating small HCC will increase in due time.

From the treatment perspective, data from the East and West indicates that single small HCC has a high chance for cure by resection [3], ablation [8] or transplantation [9]. However, interpretation of these outstanding outcomes should be cautious, as the results are probably affected by potential sources of lead-time bias and length bias. Whether resection or RFA is the better treatment for small HCC has been debated. A recent randomized trial concluded that the therapeutic impact in both options would be similar [10]. However, the trial had some drawbacks in terms of study design, small sample size, and high conversion rates from RFA to resection. Whether increased recognition of early HCC in clinical practice will contribute to improved patient survival will require further study.

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Current Approaches to the Treatment of Early Hepatocellular Carcinoma

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Key Words. Hepatocellular carcinoma • Liver transplantation • Ablation techniques • Operative surgical procedure

Disclosures: Sheng-Long Ye: None; **Tadatoshi Takayama:** None; **Jeff Geschwind:** *Consultant/advisory role:* Biosphere Medical, Biocompatibles, Bayer HealthCare, Guerbet; *Research funding/contracted research:* Biosphere Medical, Biocompatibles, Genentech, Bayer HealthCare, Philips Medical, Context Vision, Gideon, RSNA; **Jorge A. Marrero:** *Honoraria:* Bayer, Onyx; *Research funding/contracted research:* Bayer; **Jean-Pierre Bronowicki:** *Honoraria:* Bayer Pharma, Bristol-Myers Squibb.

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ABSTRACT

For patients with early-stage hepatocellular carcinoma (HCC), potentially curative treatment options exist, including liver transplantation, surgical resection, and ablation therapy. These treatments are associated with survival benefits, and outcomes are optimized by identification of appropriate patients. However, further studies are needed to definitively confirm optimal treatment approaches for all patients.

Treatment patterns vary in different parts of the world as a result of geographic differences in the incidence and presentation of the disease. In particular, because of successful screening programs, a high proportion of tumors that are identified in Japan are amenable to curative treatments, which are appropriate in a smaller proportion of patients in the west, although screening is now widely carried out in industrialized countries. Differences in the applicability of transplantation are also evident between the west and Asia.

Although existing treatments for early-stage HCC are supported by considerable evidence, there remain significant data gaps. For example, further data, ideally from randomized controlled trials, are needed regarding: the use of neoadjuvant and adjuvant therapy to decrease the rate of recurrence after resection or ablation, further investigation of the role of chemoprevention following resection, and prospective analysis of outcomes of living donor compared with deceased donor liver transplantation. *The Oncologist* 2010;15(suppl 4):34–41

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INTRODUCTION

Hepatocellular carcinoma (HCC) is an increasingly prevalent clinical problem worldwide and is the third most common cause of cancer-related death [1, 2]. The presence of cirrhosis is a key risk factor [3]. HCC is a complex disease involving many factors, and HCC staging systems can be very complicated [4]. The widely used, comprehensive Barcelona Clinic Liver Cancer staging system takes into account variables related to tumor stage, liver function, physical status, and cancer-related symptoms to generate a treatment algorithm [5].

Treatment is most effective in the early stages of disease, but diagnosing early-stage HCC is difficult because the diagnosis of cirrhosis is often not made before the emergence of HCC. Patients at high risk for developing HCC (e.g., those with cirrhosis, hepatitis B virus, or hepatitis C virus) should be entered into surveillance programs using ultrasound and serum α-fetoprotein (AFP) [3, 6, 7]. Based mainly on observational data on tumor-volume doubling time, a screening interval of 6 months is commonly used by physicians in the West, in contrast to the Far East, where a 3-month screening interval is generally implemented [8]. In a recent meta-analysis, a significantly higher sensitivity for early HCC was observed with a 6-month interval than with annual surveillance [9]. Because of the high rates of false-positive and false-negative results in patients with chronic liver disease, the American Association for the Study of Liver Diseases (AASLD) does not recommend the use of AFP alone as a screening method, unless ultrasound is not available. Information from a recent meta-analysis demonstrated that AFP provided no additional benefit to ultrasound, further supporting this guidance [9]. In contrast, abdominal ultrasonography combined with measurements of tumor markers is recommended for HCC screening, and assessments of AFP, protein induced by vitamin K absence or antagonist-II, or AFP lectin fraction are routinely performed in Japan [10].

Individuals with abnormal screening results require further investigation (e.g., with computed tomography scanning, magnetic resonance imaging, or liver biopsy) to confirm a diagnosis of HCC. Although surveillance programs can lead to detection of HCC at early stages when the tumors are amenable to curative treatment, guidelines are not always followed and are not always reproducible from large hospitals to nontertiary hospitals. Further studies are warranted to determine the optimal surveillance methods, which may also involve evaluation of novel biomarkers in the future.

Treatments for early-stage HCC include hepatectomy, liver transplantation, and local ablation therapy (Fig. 1) [6, 10–13]. However, there are no large randomized controlled trials (RCTs) comparing these treatments directly, nor are there any studies comparing these treatments with best supportive care [6]. In an intent-to-treat analysis in cirrhotic patients with HCC, early findings suggested similar survival rates in a comparison of resection with transplantation [14]. However, patient dropouts from waiting lists significantly impacted the longer-term findings in the transplantation group, and the authors concluded that resection may provide a better outcome for properly selected candidates. Further research is needed to confirm the optimal strategy based on the currently available treatments, and careful selection of patients is important in all approaches. Applicability of these treatments varies according to geographic distribution, with 50%–70% of cases in Japan (where there is widespread surveillance and a broad application of treatments) being suitable for curative treatment, compared with 25%–40% of cases in Europe and the U.S., and <10% in Africa [15]. Data from a nationwide survey in Japan indicate that a single early HCC patient has a high chance of prolonged survival with resection, ablation, or transplantation [16]. The aim of this article is to review the therapeutic options and associated outcomes for the management of patients with early HCC.

OUTCOMES AND TOLERABILITY OF EARLY-STAGE HCC TREATMENTS

Resection

Patients with early-stage HCC are those most likely to benefit from curative interventions. In a study of patients diagnosed with HCC in 1988–1998 in the Surveillance, Epidemiology, and End Results database, 417 of the 4,008 patients were candidates for surgical resection. The study showed that surgery was associated with longer survival in patients with unifocal, nonmetastatic HCC tumors <5 cm. In patients receiving surgery, the 5-year overall survival (OS) rate was 33%, compared with 7% without surgery [17].

Surgical resection is recommended as treatment for early HCC in noncirrhotic patients, or in patients with cirrhosis who have a single lesion and well-preserved liver function, normal bilirubin, and no portal hypertension [6, 13]. However, there are data that suggest that portal hypertension may not necessarily be a contraindication for resection. Patients with the same model for end-stage liver disease score and extent of hepatectomy had similar outcomes, whether or not they had portal hypertension [18], whereas several other studies found that resection can be performed safely in selected patients even in the presence of portal hypertension [19, 20]. Patients with multiple tumors may also be suitable for resection, although tumor multiplicity is an independent risk factor for postoperative recur-

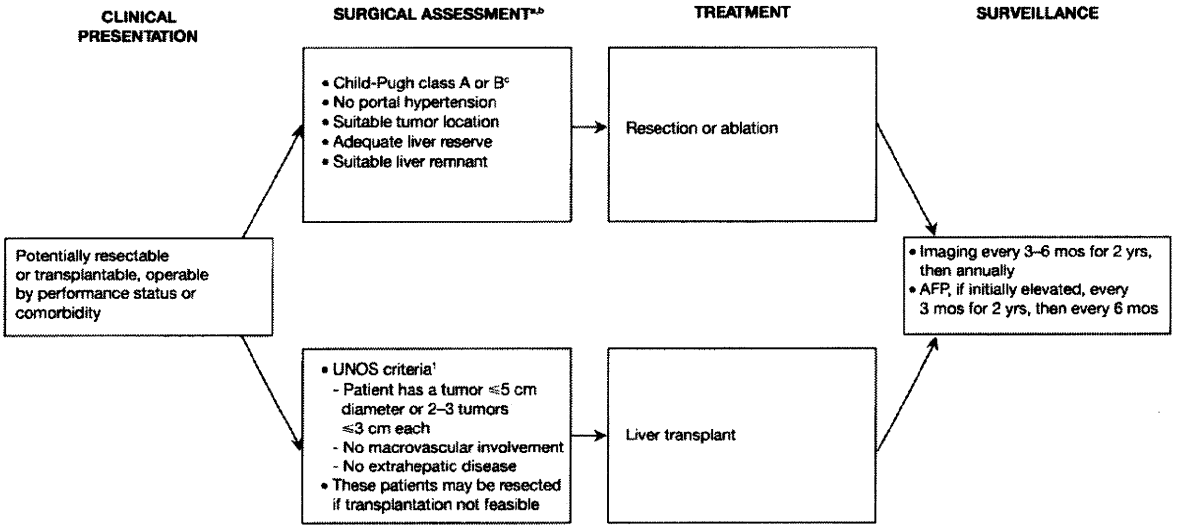

Figure 1. National Comprehensive Cancer Network guidelines for the treatment of potentially resectable disease.

[a]Discussion of surgical treatment with patient and determination of whether patient is amenable to surgery.

[b]Patients with Child-Pugh class A liver function who fit UNOS criteria and are resectable could be considered for resection or transplant. There is controversy over which initial strategy is preferable to treat such patients. These patients should be evaluated by a multidisciplinary team.

[c]In highly selected Child-Pugh class B patients with limited resection.

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Abbreviations: AFP, α-fetoprotein; UNOS, United Network for Organ Sharing.

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rence, and the OS time is shorter in these patients [20]. However, among patients with both multiple tumors and better liver function (Child-Pugh class A), an absolute 5-year survival rate of 58% was achieved. Although there is no limitation on tumor size for resection, the risk for vascular invasion and dissemination increases with size. The amount of liver that can be resected depends on the degree of cirrhosis, the functional liver reserve, and the regenerative capacity of the liver [7]. Strict selection criteria are required in order to avoid treatment-related complications such as liver failure. Survival rates of ~70% at 5 years have been achieved in patients with a normal bilirubin concentration and no clinically significant portal hypertension [6]. In Japan, the indocyanine green retention rate, a marker of hepatic clearance, is commonly used to predict the safe limit of liver resection and posthepatectomy liver failure [21]. Preoperative portal vein embolization (PVE) has been used to evaluate the regenerative abilities of the liver, with lack of hypertrophy following PVE indicating an inability of the liver to regenerate, therefore contraindicating major liver resection [22]. Furthermore, preoperative PVE has been shown to improve outcomes following major hepatectomy [23]. In patients with very early HCC (carcinoma in situ) undergoing surgery, the best 5-year survival rate so far, 93%, was demonstrated [24]. Only 10%–30% of HCC cases are suitable for "curative" surgical resection at the time of diagnosis, and recurrent HCC has been reported in 50%–80% of patients 5 years after resection [7]. Key predictors of recurrence are the presence of microvascular invasion and/or further tumor sites in addition to the primary lesion. Preoperative transcatheter arterial chemoembolization (TACE) has been evaluated but has shown no benefit in this setting [7]. AASLD and Japanese guidelines conclude that there is currently no preoperative or postoperative adjuvant therapy that can be recommended for improving prognosis after hepatic resection [6, 10]. Further investigation is required for neoadjuvant and adjuvant therapies that may decrease the incidence of recurrence following resection.

Transplantation

Liver transplantation as a treatment for early-stage HCC is well established in the U.S. and Europe and is associated

with 5-year survival rates of ~70% [6], comparable with those of noncancer liver recipients. In most centers, candidates for transplantation are deemed not resectable. In some parts of the world, transplantation is not available or has very limited applicability [6]. The benefits of liver transplantation over resection include removal of the tumor and the underlying diseased liver and also improvement in portal hypertension. Because of the limited supply of donor organs, identification of the patients most likely to receive maximum benefit from a transplant is of utmost importance. For over a decade, the Milan criteria for HCC (one lesion ≤5 cm or two to three lesions ≤3 cm) have been widely used for the selection of candidates for liver transplantation. However, there is an ongoing debate on whether expanded criteria may be adopted, to enable patients with slightly more advanced HCC to also benefit from liver transplantation [25]. A 5-year survival rate of ~50% was described in patients selected with such expanded criteria, but there are currently no clear data to define the new limits [6]. In addition, expanding the criteria may cause harm to other patients without cancer who need a transplant, as a result of fewer donors being available [26]. Because the waiting time for an organ to become available may exceed 12 months in some western countries [27], the dropout rate is high (up to 50%). Most centers administer adjuvant treatments to prevent tumor progression while patients are on the waiting list, but these are often chosen based on observational studies, because robust data from RCTs are not available. Such bridging therapy before transplantation may include locoregional therapy such as chemoembolization, which has been investigated as a means of downstaging tumors to facilitate liver transplantation [25]. Information from a liver transplant waiting list in the U.S. showed that HCC patients who received pretransplant ablation treatments had a higher adjusted 3-year post-transplant survival rate than HCC transplant patients who did not (79% versus 75%; $p = .03$) [28]. However, in another retrospective cohort study in the U.S., using data from a liver transplant waiting list, the authors concluded that the effects of downstaging with neoadjuvant treatment were difficult to evaluate [29]. It has also been suggested that resection can be used as a bridging therapy for patients who have already been enlisted for liver transplant [30]. There is no definitive evidence confirming that the use of bridging therapies confers an advantage post-transplantation in terms of survival and recurrence rates, and no specific recommendations in relation to bridging strategies (for either TACE or local ablation therapy) are currently made in the guidelines [7, 13].

An alternative strategy to increase the pool of available donor livers is the use of live donor transplantation, which originated in Asia as a result of the legal and societal constraints on cadaveric liver transplantation [27, 31]. The results appear to be comparable with those from cadaveric donation [7, 32]; however, this is a complex intervention and may not have wide applicability.

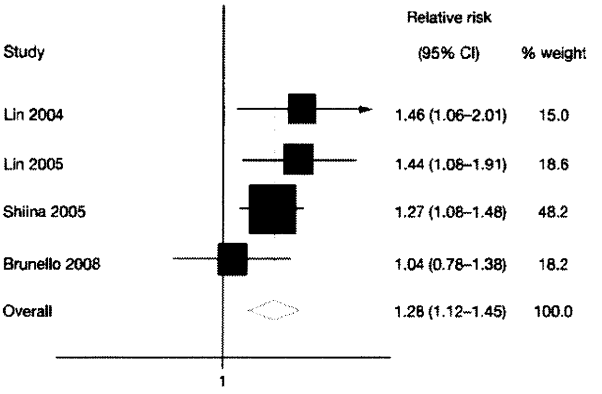

Figure 2. Radiofrequency ablation versus percutaneous ethanol injection: results of the meta-analysis on overall survival at 3 years. All based on random-effects meta-analysis.

Abbreviation: CI, confidence interval.

From Bouza C, López-Cuadrado T, Alcázar R et al. Meta-analysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. BMC Gastroenterol 2009;9:31, with permission. Originally published by BioMed Central.

Ablation

Local ablation therapy, with either radiofrequency ablation (RFA) or percutaneous ethanol injection (PEI), is commonly used to treat small HCCs confined to the liver that may be unresectable because of the poor general condition or compromised liver function of the patient. In an RCT comparing RFA with PEI for early HCC, the 1-year complete response rate was better with RFA than with PEI, although no clear survival advantage was observed in cirrhotic patients [33]. However, other RCTs [34–36] and a recent meta-analysis [37] have shown evidence of the superiority of RFA over PEI, in terms of longer survival and better local control of disease, in patients with relatively preserved liver function and early-stage nonsurgical HCC (Fig. 2). At 3 years, the pooled analysis showed an OS rate of 73% in the RFA group, compared with 58% in the PEI group ($p < .001$) [37]. However, RFA was associated with a statistically significant higher rate of adverse events ($p < .001$), with 19% of patients (95% confidence interval [CI], 15%–23%) experiencing complications, compared with 10.5% of those treated with PEI (95% CI, 7%–13.5%) [37]. The most frequent complication observed in that study was severe pain, which was more common with RFA than with PEI [37]. For studies that reported major complications, the

incidence in RFA-treated patients was 4.1% (95% CI, 1.8%–6.4%), including hemothorax requiring thoracostomy drainage, gastric bleeding, hemoperitoneum, transitory icterus, liver infarction, cutaneous burn, and tumoral cell seeding, and in PEI-treated patients it was 2.7% (95% CI, 0.4%–5.1%), including liver abscess, hemoperitoneum, tumoral cell seeding, and one procedure-related death; however, this difference was not statistically significant. This safety profile should be taken into consideration as part of the overall risk–benefit profile in each individual case. Further support for the benefit of RFA was provided by a different meta-analysis, which was more selective in the studies that it included and showed a higher 3-year OS rate with RFA than with PEI (odds ratio, 0.47; 95% CI, 0.340–0.670; $p < .001$) in patients with small HCCs [38].

Local ablation therapy has been compared with resection in a number of retrospective studies and clinical trials. Long-term outcomes in 87 patients with single-nodule HCCs treated with either surgical resection or RFA were similar [39]. Similarly, 5-year survival rates were comparable in a study of 224 patients with Child-Pugh class A cirrhosis treated with either resection (70.4%) or RFA (76.8%) ($p = .561$) [40]. A study of 186 patients with small (<5 cm) HCCs found that the choice of treatment should be based on local factors, such as the availability of resources and expertise [41]. In contrast to these findings, a study of 149 patients with HCCs ≤4 cm comparing resection with percutaneous ablation found that resection provided better local control and better long-term survival (median survival time, 122 months after hepatectomy compared with 66 months after ablation; $p = .0123$) [42]. A nationwide survey in Japan generated data on survival following resection or RFA [16]. In 2000–2003, 1,235 patients with a single early HCC (<2 cm) underwent resection and 1,315 patients received RFA. Although, with a median follow-up of 37 months, the disease-free survival rate was significantly better after resection than after RFA (1 year, 91% versus 84%; 2 years, 70% versus 58%; $p = .001$), there was no significant difference in the OS rate between the two groups (98% versus 99%; 94% versus 95%; $p = .28$). However, it is currently unknown whether the better disease-free survival seen with resection will translate into longer survival over a longer time period following therapy. Local ablation therapy was compared with resection in two RCTs in patients with small HCCs, with comparable survival results [43, 44]. Based on a trial of 180 patients, Chen et al. [43] concluded that RFA was as effective as surgical resection in the treatment of solitary and small HCCs, with the advantage of being less invasive. In a smaller study of 76 patients, Huang et al. [44] reported that PEI appeared to be as safe and effective as resection. Recent studies have shown that, in some centers, RFA is regarded as the first-line treatment for small, operable HCCs (≤2 cm), with 68.5% of patients surviving at 5 years [45]. Furthermore, in a simulated randomized trial comparing hepatic resection with RFA for very early HCCs (<2 cm), the OS times were similar for resection and RFA followed by resection for cases of initial local failure, suggesting that RFA could be considered as a primary treatment for very early HCC [46]. Given these equivocal results, larger RCTs are needed before there is any change in the recommended treatment of patients with good surgical risk and before ablation therapy is confirmed as an alternative to surgery for potentially resectable HCC.

TACE

Embolization procedures are used in patients with inoperable or unresectable disease. However, the place of TACE for the treatment of early HCC is not clear, and official guidelines do not currently recommend it. Caution should be exercised regarding the use of TACE for early HCC, and it should be considered only when curative treatment (e.g., transplantation, resection, or RFA) is contraindicated.

Differences in the Treatment of Early HCC and Outcomes Between Populations

As described above, well-defined treatment options for early HCC exist; however, there are inevitable differences in the treatment received, and hence the outcome achieved, in different populations worldwide. There are geographic variations in the incidence and etiology of HCC, and a difference in tumor size at presentation. Japanese patients have been shown to present with smaller tumors than patients in the U.S. and Europe, likely as a result of the more widespread screening carried out in Japan [47]. This, together with differences in hepatitis B or C virus status, has resulted in more limited surgical resections being necessary in Japan, compared with more extended resections in the U.S.

In a more recent comparison, analysis of the medical records of 353 patients subject to surgical resection for HCC at two referral centers in China and Japan highlighted differences between populations [48]. As well as demographic differences in age of incidence, serum examination, and history of viral infection, differences in outcome were observed. Patients in Japan were diagnosed earlier, were subject to more standard treatment, and had better prognoses than those in China. However, these results were based only on HCC at each center and not on HCC detected in a surveillance program. In addition, the demographic disparities in survival in patients with localized HCC in the U.S. were investigated in a retrospective cohort study using data from the Surveillance, Epidemiology, and End Results

population-based cancer registry [49]. That study found substantial and significant disparities by race/ethnicity in the 3-year survival rate, therapy administered, and stage-specific survival rate for individual therapies. These differences were not explained by age, date of diagnosis, or geography, but may have resulted from differences in treatments received by different demographic groups or variations in treatment response, which may be influenced by compliance or differences in disease biology. However, these patients were not identified through a surveillance program, but were patients diagnosed with HCC, which may be associated with lead-time bias. In a prospective cohort study in Europe, hepatic resection performed under strict intraoperative ultrasonographic guidance had low mortality and acceptable morbidity, even in patients with intermediate and advanced HCC [50].

Improving Treatment Options

There remains a considerable number of unanswered questions in the recommendations for treatment of early-stage HCC, many of which require a definitive answer to be provided through robust data from RCTs. Key areas for consideration include: the use of neoadjuvant or adjuvant therapy to decrease or delay recurrence after resection or ablation, chemoprevention after resection or ablation, and the use of molecular profiling of HCC to provide additional tools to define those patients most at risk for recurrence following resection. Indeed, a number of clinical trials are ongoing in these areas. Three ongoing phase IV trials are investigating radiotherapy (ClinicalTrials.gov identifier, NCT00557024), TACE (ClinicalTrials.gov identifier, NCT00556803), and lamivudine or entecavir (ClinicalTrials.gov identifier, NCT00555334) as adjuvant therapies after RFA, and are due to complete in 2010. Furthermore, sorafenib (Nexavar®; Onyx Pharmaceuticals, Inc., Emeryville, CA; Bayer HealthCare Pharmaceuticals, Inc., Wayne, NJ; Bayer Schering Pharma AG, Berlin, Germany) is being investigated as adjuvant treatment in the prevention of recurrence of HCC following either surgical resection or local ablation, in the large phase III randomized, double-blind, placebo-controlled Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma (STORM) trial (ClinicalTrials.gov identifier, NCT00692770), due to complete in 2011. With regard to liver transplantation, bridging therapy before transplantation, including the questions of which treatment to give and when [7], and prospective analysis of outcomes of living donor compared with deceased donor transplantation are areas that warrant further study.

Important considerations in future trials include analysis of the cost-effectiveness of the treatments under investigation and also the use of genomics- and proteomics-based technologies [51], in order to add to the body of information on the biologic behavior and natural history of HCC, which should help guide the diagnosis and management of HCC.

Conclusions

Early diagnosis remains a key goal in order to improve the prognosis of HCC patients. Surgical resection and liver transplantation are usually considered as first-line options because they offer the possibility of prolonged survival in patients with early disease and have excellent outcomes in well-selected patients. Local ablation therapy, using RFA or PEI, also has a role to play. Further improvements in the outcome of patients with early HCC may be achieved once outstanding questions have been answered by prospective RCTs.

Acknowledgments

The authors take full responsibility for the scope, direction, and content of the manuscript and have approved the submitted manuscript. They would like to thank Karen Brayshaw, PhD, at Complete HealthVizion for her assistance in the preparation and revision of the draft manuscript, based on detailed discussion and feedback from all the authors. Editorial assistance was supported by a grant from Bayer HealthCare Pharmaceuticals.

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Annals of Surgical Oncology **15**(4):972–978
DOI: 10.1245/s10434-007-9685-0

Early Hepatocellular Carcinoma: Pathology, Imaging, and Therapy

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Background: In 1987, Japanese researchers proposed to define the pathological concept of early hepatocellular carcinoma (HCC). However, there are some conceptual differences between the East and the West in the diagnosis and treatment of early HCC.

Methods: To provide up-to-date data for making a worldwide consensus, this article has collected six papers focused on the management of early HCC, which were presented in the Fifth International Meeting of "Hepatocellular Carcinoma: Eastern and Western Experiences" in Houston in January 2007.

Results: In the pathological perspective, the common criteria to discriminate early HCC from dysplastic nodule included hepatocytic invasion of portal triads and septa (stromal invasion). The current imaging modalities such as contrast-enhanced ultrasound (CEUS), computed tomography (CT), and magnetic resonance imaging (MRI) with the use of intravenous contrast material with multiphasic imaging could enhance their ability to accurately characterize early HCC. From the treatment perspective, a single early HCC had a high chance for cure by resection, ablation, or transplantation, which proved to be the earliest clinical entity (Stage 0 HCC).

Conclusions: Early HCC is characterized by its incipient malignant nature and by an extremely favorable clinical outcome, thereby justifying its definition.

Key Words: Hepatocellular carcinoma—Early HCC—Pathology—Imaging—Therapy.

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death in the world, and the rising incidence in the West is a crucial problem.[1] Recent progress in imaging modalities has facilitated recognition of small HCC, which seems to be curable by surgery or ablation, in high-risk patients who undergo regular medical checkups for chronic viral hepatitis or cirrhosis.[2] Based on the accumulating information on small HCC, Japanese researchers proposed to define the pathological concept of early HCC (carcinoma in situ),[3,4] which proved to be the earliest clinical entity with a high

Received June 1, 2007; accepted September 25, 2007; published online January 31, 2008.
Proceedings of the Fifth International Meeting Hepatocellular Carcinoma: Eastern and Western Experiences held in Houston, TX, January 11–13, 2007.
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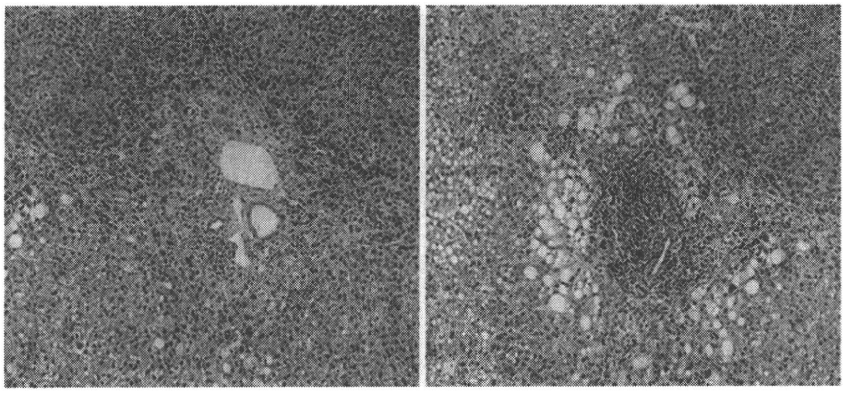

FIG. 1. Stromal invasion. In early HCC, tumor cells invade into intratumoral portal tracts.

cure rate (Stage 0 HCC).[2] However it should be noted that there are some conceptual differences between the East and the West in the diagnosis and treatment of early HCC.

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PATHOLOGY

The Eastern Perspective

An increasing number of small equivocal nodular lesions such as large (macro) regenerative nodule (RN), dysplastic nodule (DN), and small HCCs have been detected in the cirrhotic liver among the high-risk population of HCC.

Among 128 consecutively resected HCCs associated with hepatitis C virus (HCV)-related cirrhosis, 18 RNs, 14 low-grade DNs (10.9%), 10 high-grade DNs (7.8%), and 12 well-differentiated HCCs (9.3%) were detected.[4,5] Low-grade DNs are distinct or indistinct nodules around 1.0 cm in diameter, not encapsulated, and slightly more yellowish than the surroundings. The hepatocytes are minimally abnormal and portal tracts are present in the nodules. The cytoplasm is more eosinophilic, and nuclear-cytoplasmic (N/C) ratio is slightly increased. Cell density is approximately two times higher than that of the surrounding liver tissue, and a trabecular arrangement is more distinct compared with the surrounding liver tissue. High-grade DNs are vaguely nodular, not encapsulated, and are macroscopically impossible to differentiate from small HCC of the vaguely nodular type. Histologically, they show more cytological and architectural atypia than low-grade DNs, but these changes are not sufficient for the diagnosis of HCC. Cytologically, cytoplasmic eosinophila or basophilia, and a high N/C ratio are observed.

Most of high-grade DNs are hypovascular on angiography and/or contrast-enhanced computed tomography (CT). Similarly, low-grade DNs have comparable hypovascular characteristics. However, unpaired arteries are occasionally present. These vascular profiles are also similar to those of highly differentiated HCC of the early stage. Early HCC is defined as a vaguely nodular and hypovascular well-differentiated HCC less than 2 cm in size. The presence of tumor cell invasion into the intratumoral portal tracts (stromal invasion) differentiates these early HCC from high-grade DNs (Fig. 1). Fatty change is not seen in RNs and low-grade DNs, while it is found in about 40% of high-grade DNs and well-differentiated HCCs. Iron deposits are found in 11% of RNs, 30% of DNs, but not in the well-differentiated HCCs. Interestingly, when HCC develop within a DN with iron deposits, the cancerous nodule usually shows no iron deposits.

Multistep or gradual evolution from a DN to HCC has been confirmed in both a morphologic and a clinical follow-up study.[6] The high frequency in which DNs and/or early HCC coexist in the vicinity of resected HCCs suggests that the true prevalence may be much higher in the whole liver. This finding likely explains the frequent postoperative recurrence of HCC, which results from the multicentric presence of DNs and early HCCs throughout the liver of a patient with cirrhosis. High-grade DN and early HCC show similar morphology and the only morphologic clue for the differentiation between the two

entities is the presence or absence of "stromal invasion."

The Western Perspective

HCC that develops in the background of chronic liver disease is accompanied by smaller nodules representing the various steps of the carcinogenic sequence. Those lesions that show various degree of cytological and architectural atypia have been termed RNs, DNs, and early HCCs.

RNs that measure at least 5 mm are otherwise indistinguishable from other cirrhotic nodules. DNs, which are distinct from the surrounding parenchyma in terms of color, may sometimes bulge from the cut hepatic surface. Low-grade DNs, which are well defined but not encapsulated, usually present with uniformly distributed portal tracts. They are either devoid of cytological atypia or display the so-called large cell changes. Kinetic studies and statistical evaluation of the association with HCC indicate that they are reactive changes but indicate an increased risk for HCC.[7,8] Small cell changes and architectural atypia characterize high-grade DNs. Cellular atypia correspond to the presence of homogeneous, small, and crowded hepatocytes with basophilic cytoplasm and increased N/C ratio. Similarly to well-differentiated HCC, pseudoacinar structures can be seen in high-grade DNs. The cytological and architectural changes may be either focal or diffuse.[7,8]

Early HCCs, measuring up to 2 cm in diameter, may present as two different types. The distinctly nodular type is not diagnostically challenging. As it is frequently encapsulated, it is commonly moderately differentiated. The vaguely nodular type, the less common variant, is more difficult to diagnose. It is poorly demarcated and characterized by very well differentiated cytological changes that push and compress the residual DN in an apparently seamless fashion; it has been studied mostly in Japan. Where to draw a diagnostic line between "dysplasia" and HCC is difficult since they both belong to a spectrum of stepwise morphologic progression with increased aneuploidy and clonal selection. Features such as fatty and clear cell changes can be observed. The fatty change can reflect either clonal changes in lipid metabolism or ischemia related to altered arterial to portal blood flow ratio during neoplastic progression. Other changes of neoplastic progression include clustering of hepatocytes with Mallory's hyaline and iron resistance in an otherwise siderotic lesion. The former may represent either a marker of clonality or evidence of cholestasis in a nodule with modified biliary drainage.[8,9] Reported discrepancies between Japanese and Western investigations regarding the diagnoses of high-grade DNs and early HCCs have reflected differences in detection, interpretation, and nomenclature. In 2002, an international meeting comparing diagnoses for a range of hepatocellular neoplastic lesions by Japanese and Western pathologists highlighted the lack of agreement between those two groups.

Since then, efforts have been established to develop universally acceptable diagnostic criteria. Furthermore, pathologists have evaluated "objective" features commonly identified in mature HCC with the goal that they may help distinguish between early HCC and the immediately preceding lesions. Those include loss of reticulin, CD34 expression (evidence of sinusoidal "capillarization"), Glypican-3 expression, and hepatocytic invasion of portal triads and septa as evidenced by differential expression of CK7 immunohistochemistry.[8,10,11] Given the efforts under way it is likely that we will very soon see the establishment of universally acceptable diagnostic criteria. This outcome is significant to appropriately evaluate the progression of early HCC and to assess the value of preventive therapy.

ULTRASOUND IMAGING

Contrast-enhanced ultrasound (CEUS) is a dynamic real-time examination performed with intravascular microbubble contrast agents. It shows lesional and liver enhancement analogous to that shown on contrast-enhanced CT or magnetic resonance (MR) scan. The ability of CEUS to characterize liver masses has been confirmed by us and others,[12,13] and the agreement of CEUS with contrast-enhanced CT and MR is shown to be high, particularly in the arterial phase.[14,15]

Unique to CEUS, however, is its ability to show lesional vascularity more akin to that seen on angiography and impossible on current CT or MR performed with an intravenous injection of contrast agent. Further, the real-time performance of CEUS may show vascularity and enhancement changes regardless of the timing, duration, or intensity with which they occur. A new technical advancement in CEUS, maximum intensity projection (MIP) imaging, much like time-lapse photography, integrates information about the microbubble pathway between frames and allows exquisite detail of lesional vessels with the potential to show both their mor-

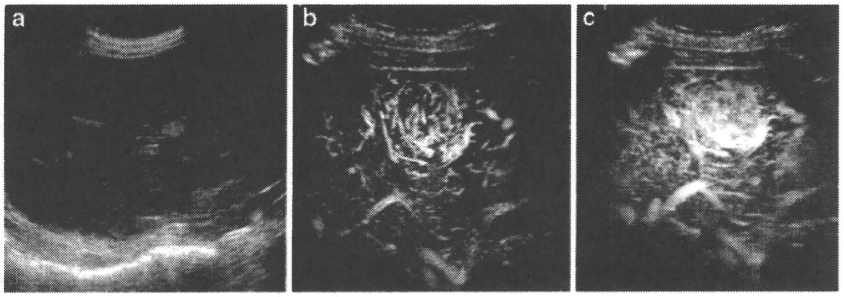

FIG. 2. Contrast-enhanced ultrasound. (a) Baseline sonogram shows a focal hypoechoic HCC. (b) In the early arterial phase, there is hypervascularity with dysmorphology of the visualized tumor vessels. (c) At the peak of arterial phase, the lesion is very bright compared with the surrounding liver.

phology and direction of filling, often differentiating one lesion type from another. The detection and characterization of nodules in a chronic fibrotic liver is both challenging and interesting and comprises a major imaging challenge for all cross-sectional imaging modalities. However, CEUS is easily performed at the time of detection of liver nodules on surveillance ultrasound in patients at risk for HCC and may be repeated with very low risk of adverse events. Specific enhancement patterns have been confirmed for RNs compared with DNs and also HCCs. CEUS is also invaluable for the resolution of indeterminate lesions on contrast-enhanced CT and MR scans. It is now an integral part of our imaging protocols for management of patients at risk for HCC. The classic description of enhancement for HCC is an arterially enhancing mass with washout in the portal venous phase.[12–14] This has been substantiated in studies with CEUS, but we have also noted that there are variations of this classic description. In our own study correlating enhancement features of HCC with their degree of histopathologic differentiation, moderately differentiated HCC comprised the majority of tumors and most often showed classic features of arterial phase hypervascularity and portal venous phase washout (Fig. 2). Well differentiated and poorly differentiated HCC, while less frequently encountered, account for most examples of atypical enhancement including hypovascularity in the arterial phase and delayed or no washout in the portal venous phase. Frequent observation of delayed washout emphasizes the necessity for observation of suspicious lesions on CEUS for 300 seconds following contrast injection on CEUS. In addition, increasing hypoechogenicity in the portal venous phase, mimicking washout, in the absence of prior arterial phase hypervascularity may occur in infrequent cases, and its recognition is essential to avoid missing atypical HCC.

CEUS makes a valuable contribution to the difficult characterization of liver nodules in a cirrhotic liver.

COMPUTED TOMOGRAPHY

In the diagnostic setting of patients with high clinically suspicious HCC, current imaging techniques such as CT or magnetic resonance imaging (MRI) have a very high sensitivity and positive predictive value. However, in the setting of a screening examination in patients with cirrhosis and no known HCC and using explanted liver as the gold standard, the sensitivity of detecting HCC by current imaging studies is only about 50%. It is also noted that a more invasive technique can improve the sensitivity of lesion detection. The diagnosis is often missed in tumors smaller than 2 cm and well-differentiated tumors. Both CT and MR performed poorly in the detection of DNs in the background of cirrhotic liver.

HCC in the cirrhotic liver is characterized by hyperdense enhancing nodules caused by an increase in arterial supply during the early phase of contrast enhancement when compared with the background of liver parenchyma. The density of the lesions becomes lower than the surrounding hepatic parenchyma during the later phase of contrast enhancement because of the lack of portal venous supply. The presence of a capsule improves the positive predictive value for the diagnosis.

HCC in a noncirrhotic liver is characterized by a large dominant, hyperdense enhancing mass with areas of hemorrhage and necrosis. It is usually larger than HCC found in cirrhotic liver, and they are more commonly better differentiated than HCC found in a cirrhotic liver. A solitary or dominant mass was found in 82% of patients. Lesions contain areas of necrosis, hemorrhage, or scar in 50–97%. Fat content

can be seen in about 10% and calcification in 28%.[16] Some of these features can make it difficult to differentiate HCC from a large hepatic adenoma or fibrolamellar HCC based on imaging findings alone.

MAGNETIC RESONANCE IMAGING

The detection of small HCC with imaging is highly critical to patient outcome. MRI is superior to CT and ultrasound in detecting and characterizing HCC in the cirrhotic liver.[17] Recent advances in MRI software and hardware, including the use of parallel imaging and surface phased array coils, provide faster sequences that can be acquired within a breath-hold, decreasing motion and respiratory artifacts. The use of intravenous contrast material with multiphasic imaging is essential to accurately identify and characterize focal hepatic lesions.

A small HCC is defined by a size <2 cm. Small HCCs have a variable appearance on T1-weighted images.[18] On T2-weighted images, HCCs are classically hyperintense.[19] However, well-differentiated HCC lesions can be isointense on T2-weighted images.[20] A focus of high signal intensity on T2 within a hypotense or isointense nodule ("nodule within a nodule" sign) is highly suggestive of an HCC focus developing within a DN.[21] A diffuse nodular miliary pattern can be present, being difficult to diagnose at imaging and pathology. Since HCC obtains its blood supply almost exclusively from the hepatic artery, most HCCs are best seen on arterial phase images.[22] This allows differentiation from RNs and DNs, which are not hyperintense during the arterial phase images. In the portal venous phase, HCC appears hypertense, isotense, or hypointense relative to the background liver. A minority of well-differentiated HCCs are hypovascular and best seen during the portal venous phase.[20] Delayed images can show late enhancement of the fibrous capsule, but not of RNs or DNs. RNs are benign lesions, whereas DNs are thought to represent premalignant nodules.[6] Both are typically hypovascular lesions with predominantly portal blood supply, with enhancement similar to that of the adjacent parenchyma, although increased arterial flow has been described in a small minority of DNs.[20] Hemosiderin deposition can be present in both RNs and DNs (siderotic nodules) and produces specific imaging features on MRI.[23] DNs are usually larger than RNs, but the two may be impossible to distinguish pathologically[7] and on MRI.[24] On T1-weighted images, most high-grade DNs have high signal intensity on T1-weighted images.[19] On T2-weighted images, most DNs are hypointense, rarely hyperintense.[19]

The widespread use of arterial phase CT and MRI in cirrhotic patients has revealed the existence of enhancing "pseudolesions" (small hepatic nodules with arterial phase enhancement, becoming invisible on the portal venous phase images), that may be wedge-shaped, geographic, or oval or round in shape. These lesions may represent arterioportal shunts, portal venous obstruction, nonportal splanchnic vein drainage, rib compression, or are unknown in origin. These pseudolesions are usually identified only at the arterial phase with isointensity on T1- and T2-weighted images.[25] Sometimes, differentiation between "pseudolesions" and small HCCs can be difficult with MRI. Thus, follow-up serial imaging is required. Pseudolesions will show no interval growth or disappearance of the shunts, whereas HCC will have a tendency to grow.

THERAPY: RESECTION, RADIOFREQUENCY ABLATION, OR LIVER TRANSPLANTATION

Hepatic resection,[2,26,27] radiofrequency ablation (RFA),[28] and liver transplantation[29] are accepted as effective treatments for HCC. To clarify the long-term outcome in patients with early HCC (<2 cm), we analyzed the data from the nationwide survey of Japan.

Between 2000 and 2003, a total of 2550 patients who had undergone resection ($n = 1235$) or RFA ($n = 1315$) for a single early HCC (<2 cm) were registered to the database of the Liver Cancer Study Group of Japan (LCSGJ). Between 1989 and 2003, living liver transplantation for HCC was performed in 316 patients, 43 of whom had had a single early HCC (<2 cm), independently registered by the Japanese Study Group on Organ Transplantation.[29] These two types of cohorts were the patients of interest for this study. After a median follow-up period of 37 months, the disease-free survival after resection was significantly better than that after RFA (1-year, 91% vs 84%; 2-year, 70% vs 58%; $P = .001$) (Fig. 3), but the overall survival after resection and RFA were identical (98% vs 99%; 94% vs 95%, $P = .28$) (Fig. 4). Using multivariate analyses, we found three independent prognostic factors for recurrence of HCC: alpha-fetoprotein, therapy, and Child-Pugh class. The relative risk for recurrence in resection was 0.71 (95% CI 0.56–0.90; $P = .004$), compared with ablation. In the patients of Child-Pugh A, the disease-free survival was significantly better in resection ($n =$

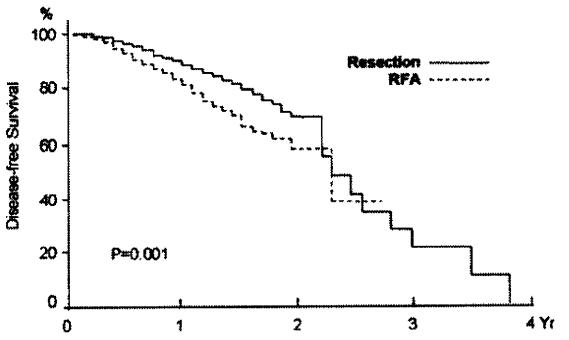

FIG. 3. Disease-free survival in a single early HCC. The resection group (n = 1235) had a significantly better disease-free survival than the RFA group (n = 1315) (P = .001).

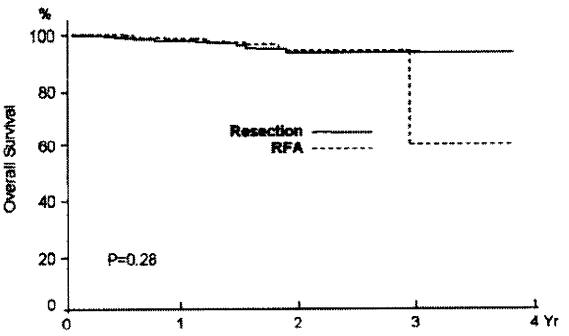

FIG. 4. Overall survival in a single early HCC. There was no significant difference in overall survival between the resection group and the RFA group (P = .28).

1045) than in RFA (n = 946) (P = .001), while the overall survival was not significantly different in the two options (P = .16).

In the patients of Child-Pugh B, both the disease-free survival and overall survival were almost similar (P = .28 and P = .66) in resection (n = 132) and RFA (n = 301). In the 43 patients undergoing living liver transplantation, no patient had HCC recurrence up to a median follow-up of 16 months, and the 1- and 3-year overall survival rates were 83% and 77%, respectively.

For a single early HCC (< 2 cm), hepatic resection provides better disease-free survival than RFA, although overall survival at 1 and 2 years was identical for both treatments. Whether the improvement in disease-free survival seen with resection will translate into better overall survival more than 2 years out following therapy remains unanswered at present. Alternatively, liver transplantation may be the therapeutic choice for cure, as no recurrence of HCC was seen in any of the study patients. Transplantation for cirrhotic patients with early HCC has the same prognosis as it does for those without HCC.[29] However, the relatively short follow up in this study precludes a definitive recommendation for liver transplantation as the treatment of choice in this setting at the present time.

CONCLUSIONS

Early HCC is a distinct pathological and clinical entity. The lesion can be a carcinoma-in situ because of a very well-differentiated tumor invading the intratumoral portal triads. From the pathological perspective, a great concern is to discriminate early HCC from high-grade DN. The common criteria presented include hepatocytic invasion of portal triads and septa (stromal invasion) and immunohistochemical findings such as loss of reticulin, CD34 expression, and Glypican-3 expression. The current imaging modalities such as CEUS, CT, and MRI have a high sensitivity and positive predictive value in diagnosing overt HCC, but they are less sensitive for detecting early HCC and miss tumors that are smaller than 2 cm or that are well differentiated. CT and MR perform poorly for the detection and characterization of precursor lesions, but the use of intravenous contrast material with multiphasic imaging can enhance their ability to accurately characterize such early focal lesions. From the treatment perspective, data from the nationwide survey of Japan indicate that a single early HCC has a high chance for cure by resection, ablation, or transplantation. However, interpretation of these outstanding outcomes should be cautious, as the results probably are affected by potential sources of lead-time bias and length bias. Once information on the natural history of early HCC is available, the absolute therapeutic impact of these treatments will be clarified.

Early HCC is characterized by its incipient malignant nature and by an extremely favorable clinical outcome, thereby justifying its definition. Whether increased recognition of early HCC in clinical practice will contribute to improved patients' survival will require further study.

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Hepatology Research

Hepatology Research 2010; 40: 278–286 doi: 10.1111/j.1872-034X.2009.00591.x

Original Article

Postoperative surveillance with monthly serum tumor markers after living-donor liver transplantation for hepatocellular carcinoma

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Aim: Recurrence of hepatocellular carcinoma (HCC) after liver transplantation decreases patient survival. The usefulness of post-transplant surveillance with tumor markers, however, is not clear. We evaluated our cumulative experience with recurrent HCC detected during post-transplant surveillance.

Methods: We analyzed 100 patients with HCC detected in the explanted liver. Monthly to bimonthly measurement of tumor markers and yearly computed tomography were scheduled postoperatively.

Results: Preoperatively, 82 met the Milan criteria. The histological findings indicated that 61 fulfilled the Milan criteria. In nine patients, HCC recurred 10 months (2–29) after liver transplantation in the graft ($n = 1$), lung ($n = 2$), bone ($n = 3$) and multiple organs ($n = 3$). In all nine recipients, HCC was first suspected based on an increase in tumor marker levels. Recurrent HCC was confirmed by computed tomography ($n = 7$) or magnetic resonance imaging ($n = 2$) within 4 months (0–6) after first identifying an increase in the tumor marker levels. Six cases were treated surgically, two of which achieved prolonged survival of 16 and 38 months.

Conclusion: Frequent measurement of α-fetoprotein and des-γ carboxy prothrombin was useful for detecting recurrent HCC and may be useful long-term follow-up markers for post-transplant surveillance.

Key words: α-fetoprotein, des-γ carboxy prothrombin, hepatocellular carcinoma, liver transplantation, surveillance.

INTRODUCTION

LIVER TRANSPLANTATION IS an established therapeutic option for patients with small hepatocellular carcinoma (HCC) and advanced cirrhosis. Application of the well-established inclusion Milan criteria, namely, a single nodule of 5 cm or less or 2–3 nodules all 3 cm or less, has increased patient survival to 70% at 5 years with a less than 10% recurrence of HCC.[1,2] Reported risk factors for HCC recurrence include tumor size and number, bilobar spread of the tumor, elevated serum α-fetoprotein (AFP) and des-γ carboxy prothrombin (DCP) levels, poorly differentiated HCC, positive lymph nodes and vascular invasion.[3–9] Several centers have attempted to expand the Milan criteria based on the application of preoperatively-measureable risk factors.[7–10] Application of the University of California at San Francisco criteria successfully increased the indication for liver transplantation in patients with HCC, with a similar probability of HCC recurrence post-transplantation.[11,12]

Hepatocellular carcinoma recurs in 10–20% of transplant recipients, however, despite careful patient selection.[1,2,13,14] Once recurrence occurs, survival time is usually less than 1 year.[13,14] Surgical treatment of HCC

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Received 11 April 2009; revision 30 May 2009; accepted 3 July 2009.

recurrence improves the prognosis. For example, Regalia *et al.*[13] compared the prognosis between seven patients with resectable recurrent disease and 14 patients with unresectable disease and found significantly longer survival in the resected group. Roayaie *et al.*[14] reported that the absence of bone metastases, recurrence more than 12 months after transplantation and surgical treatment of the recurrence were independently associated with significantly longer survival from the time of recurrence. One of the aims of postoperative surveillance for HCC recurrence is to detect HCC recurrence at the resectable stage. Postoperative surveillance is now routinely performed in many centers, although the most effective modality for detecting HCC recurrence is not yet established. For postoperative surveillance, monthly to bimonthly testing for serum tumor markers with annual imaging studies are performed at our center. We herein report 100 HCC cases that we followed after transplantation, and report the efficiency of serum tumor marker measurements.

METHODS

Patient population

FROM JANUARY 1996 to March 2008, 330 adult patients underwent primary living donor liver transplantation (LDLT) in our program. Retrospective review of records of all liver transplant recipients at the University of Tokyo was approved by the University of Tokyo Institutional Review Board. Among these 330 recipients, HCC was histologically confirmed in the isolated livers of 100 recipients. HCC was preoperatively diagnosed in 95 recipients and incidentally identified in the explant in the remaining five. The recipients comprised 82 men and 18 women with a median (range) age of 56 years (40–67). Their underlying liver diseases were hepatitis C cirrhosis ($n = 59$), hepatitis B cirrhosis ($n = 30$), hepatitis B virus and hepatitis C virus dual infection ($n = 2$), alcoholic cirrhosis ($n = 2$), primary biliary cirrhosis ($n = 1$) and cryptogenic cirrhosis ($n = 6$). All received partial living donor grafts (right in 71, left in 26, and posterior in three).

Preoperative evaluation of HCC

The preoperative diagnosis of HCC was based on the findings of multi-phase dynamic helical computed tomography (CT) with contrast enhancement taken within 1 month prior to LDLT.[15] Images were reviewed by experienced radiologists, and the typical radiological characteristics of classical HCC, that is, lesions with enhancement in the arterial phase and low density during the portal phase, were diagnosed as HCC. Lesions not fulfilling these criteria, such as lesions that only showed early staining or low density in the portal phase were considered as regenerative or dysplastic nodules and were thus excluded from the staging established prior to transplantation. Chest CT scan and bone scintigraphy were routinely performed preoperatively to rule out metastatic lesions.

Based on the pre-transplantation imaging studies, 82 patients met the Milan criteria and 13 did not. Single nodules were present in 45 cases, two nodules in 27, and three or more nodules were detected in 23 cases. Mean (± standard deviation) maximum tumor size was 2.5 ± 1.3 cm (range, 0.7–8.0 cm). Vascular invasion and extrahepatic metastasis were ruled out.

Surgical procedure and immunosuppression

Our selection criteria for live liver donors, surgical techniques and use of immunosuppressants for LDLT are described elsewhere.[16–19] The post-transplant immunosuppression regimen consisted of steroid induction with tacrolimus or cyclosporin in case of tacrolimus intolerance and steroids for maintenance. The average hospitalization duration was 43 days after transplantation. Adjuvant chemotherapy was not performed in any of the cases.

Follow up after LDLT and recurrence

The postoperative surveillance schedule for patients with HCC was as follows. AFP and DCP were measured monthly for 2 years and every 2 months afterward. Abdominal helical CT with dynamic contrast was performed postoperatively at 1, 6 and 12 months, and yearly thereafter. In case of renal failure, superparamagnetic iron oxide-enhanced magnetic resonance imaging was performed. When an increase in the serum AFP (>10 ng/mL) or DCP (>40 mAU/mL) levels was noted, imaging studies were performed to rule out HCC recurrence; such imaging studies included abdominal ultrasonography, chest and abdominal CT scan with contrast, bone scintigraphy, head CT and positron emission tomography scan. Imaging studies were repeated until the recurrence sites were detected and in most of the cases two to three imaging studies were ordered monthly. Recurrence was defined as emergence of radiological findings compatible with HCC, or the appearance of new suspicious lesions. Recurrence-free survival was defined as the interval between LDLT and the date