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Treatment of choice for unresectable small liver cancer: percutaneous ethanol injection therapy or transarterial chemoembolization therapy

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Abstract. Early detection of hepatocellular carcinoma (HCC) has become easier with recent advances in imaging diagnosis, but the tumor is frequently unresectable due to underlying advanced liver cirrhosis. In this study, we evaluated the therapeutic effect of percutaneous ethanol injection therapy (PEIT) and transarterial chemoembolization therapy (TACE) for small liver cancers measuring 3 cm or less in diameter and discussed the treatment of choice for unresectable cases. The tumors were divided into two groups on the basis of size: 1.5 cm or less (group A) and 1.6–3 cm in diameter (group B). In group A, the estimated 1- and 3-year survival rates were both 82% for a total of 19 cases. The survival value determined for 10 patients treated with PEIT was slightly higher than that found for 9 patients treated with TACE. In group B, the overall 1-, 2-, and 3-year survival values for a total of 56 patients were estimated at 83%, 60%, and 35%, respectively. The survial rates for 41 patients treated with TACE were 82%, 53%, and 28% at 1, 2, and 3 years, respectively. PEIT was performed on only 6 patients, whose survival rate was equivalent to that of a surgical resection group. The 1-, 2-, and 3-year survival rates for 9 patients who underwent surgical resection were estimated to be 100%, 85%, and 68%, respectively. Based on these results, PEIT seems to be the treatment of first choice for patients with small liver cancers measuring less than 1.5 cm in diameter if the tumor is thought to be unresectable because of associated severe liver cirrhosis. On the other hand, tumors measuring 1.6–3 cm in diameter must first be treated with TACE using a long-acting Lipiodol-carcinostatic suspension, even if resectable. In addition to the tumor size, dynamic CT is also useful for prospective decision of the therapeutic strategy. If the mass is demonstrated to be a hypervascular lesion by dynamic CT, TACE must be selected as the treatment of first choice, even for small lesions measuring 1.5 cm or less in diameter.

Introduction

With recent advances in noninvasive imaging modalities such as ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI), small liver cancers measuring less than 3 cm in diameter have become easily detectable during follw-up of chronic liver diseases. However, a good many patients with small liver cancers cannot be treated by surgical resection due to underlying advanced liver cirrhosis, although the surgical technique has been improving. There is therefore growing interest in the choice of treatments for unresectable cases of small hepatocellular carcinomas (HCCs).

As reported previously [4, 8], either transcatheter arterial embolization therapy (TAE) or transarterial chemoembolization therapy (TACE) is effective against relatively large tumors, but the effectiveness against small liver cancers remains controversial. Recently, percutaneous ethanol injection therapy (PEIT) has been adopted for the treatment of small HCCs measuring less than 3 cm in diameter and has achieved survival equivalent to that of patients treated by surgery [3, 7].

In this report, we present the results we obtained on the efficacy of TACE using a Lipiodol-Adriamycin suspension [4] and PEIT against small HCCs measuring 3 cm or less in diameter, which is followed by a discussion of the treatment of choice for unresectable cases.

Patients and methods

The subjects of this study comprised 75 consecutive patients with solitary or multiple HCCs measuring 3 cm or less in diameter. The

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Table 1: Patients' background characteristics in each group

Tumor Size	~1.5 cm	1.6~3 cm
Mean Age (years, M±S. D.)	61.8±8.5	60.1±8.6
Sex (M:F)	3.8:1	3.0:1
Viral Markers		
HBV	31.6%	23.4%
HCV	52.6%	50.0%
Mixed	15.8%	16.6%
Child's Classification		
A	52.6%	31.7%
B	21.0%	50.0%
C	26.4%	18.3%

tumors were classified into two groups on the basis of the maximal diameter measured on images: 1.5 cm or less (group A, n = 19) and 1.6–3 cm (group B, n = 56).

The mean age of the patients was 61.8 ± 8.5 years for group A and 60.1 ± 8.6 years for group B. Hepatitis B virus markers, including HBcAb, were positive in 31.6% of the patients in group A and 23.4% of those in group B (Table 1). On the other hand, the positive rates for anti-hepatitis C virus (HCV-Ab) were 52.6% and 50% in groups A and B, respectively. Additionally, 15.5% of group A and 16.6% of group B were positive for both HBV and HCV markers and, thus, the prevalence of HCV infection was about 70%.

In group A, 10 patients were treated with PEIT and 9 were treated with TACE using the Lipiodol-Adriamycin suspension [4]. In group B, on the other hand, 9 patients underwent surgical resection, 6 patients were treated with several sessions of PEIT, and 41 patients were treated with repeated TACE.

The methods used for PEIT and TACE were the same as those reported previously [3, 8]. Survival rates were calculated by the Kaplan-Meier method, and the significance of differences was evaluated by the generalized Wilcoxon test.

Results

Figure 1 shows the cumulative survival of the patients in both groups. The 1-, 2-, and 3-year survival values determined for the patients in group B were 83%, 60%, and 35%, respectively, whereas the 3-year survival value found for the patients in group A was 82%. Significant differences in the 2- and 3-year survival rates were found between the two groups, whereas the severity of underlying liver cirrhosis differed slightly between the groups. Next, we assessed the cumulative survival rates of the patients treated with different modalities in both groups. In group A, the survival rate of 90% estimated for the 10 patients treated with PEIT was slightly higher than the 80% survival rate estimated for the 9 patients treated with TACE (Fig. 2).

In group B, on the other hand, the survival rates estimated for the 9 patients who underwent surgical resection were 100%, 85%, and 68% at 1, 2, and 3 years, respectively (Fig. 3). The survival rates of the 6 patients treated with PEIT alone were similar to those of the resection group, but the survival rate of the 41 patients treated with TACE was significantly lower. The 1-, 2-, and 3-year survival rates obtained with the TACE regimen were estimated to be 82%, 53%, and 28%, respectively (Fig. 3).

In the analysis of the causes of death, hepatic failure showed a high incidence in both patient groups. In all, 1 patients treated with TACE and 2 patients treated with PEIT died of hepatic failure, which seemed to be chiefly a result of worsening of underlying liver cirrhosis. Furthermore, lethal gastrointestinal bleeding and intraperitoneal bleeding were encountered in 4 patients and 1 patient treated with TACE, respectively.

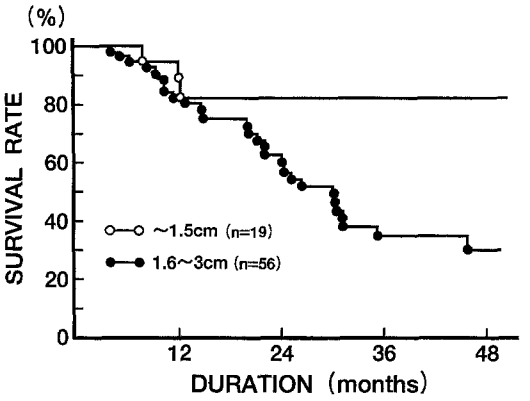

Fig. 1. Cumulative survival of patients in group A (○) and group B (●)

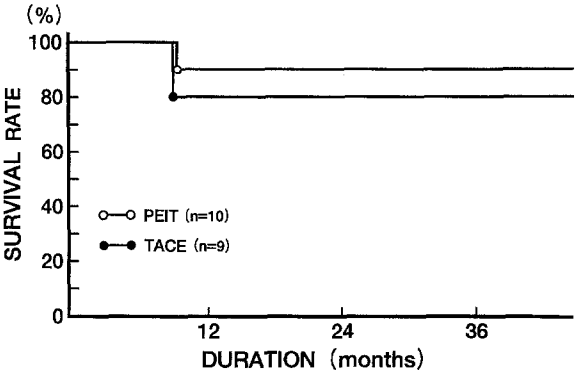

Fig. 2. Cumulative survival in group A as a function of different therapeutic modalities

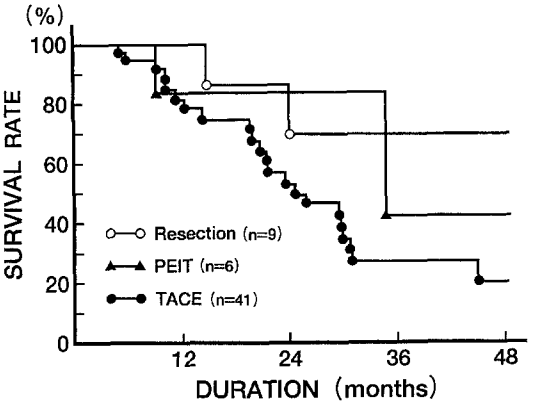

Fig. 3. Cumulative survival in group B as a function of different therapeutic modalities

Discussion

Recent advances in various imaging modalities, especially ultrasonography, have increased the chance of early detection of small HCCs. However, surgical resection is sometimes limited because of underlying severe liver cirrhosis or multifocality. In Japan and other Far East countries, HCV-related HCCs have been increasing in incidence, and our unpublished data show that a majority of HCV-

Table 2. Tumor detectability of US, CT, MRI, angiography, and Lipiodol-CT for 102 lesions of small HCC

size	US	CT	MRI	AG	Lip-CT
~1.5 cm (n = 24)	23/24 (95.8%)	17/24 (72.0%)	21/24 (87.5%)	5/16 (31.3%)	9/16 (56.3%)
1.6~3 cm (n = 78)	75/78 (96.2%)	67/73 (91.8%)	61/63 (96.8%)	48/65 (73.8%)	58/64 (90.0%)
Total	98/102 (96.1%)	84/97 (86.6%)	82/87 (94.3%)	53/81 (65.4%)	67/80 (83.8%)

AG: Angiography Lip-CT: Lipiodol-CT

related HCCs are associated with more advanced liver cirrhosis as compared with HBV-related HCCs. Therefore, the resectability rate of HCCs, even small HCCs, seemed to be decreasing year by year [6, 9]. Recurrence after resection is also a significant problem for surgical indication [5]. For these reasons, nonsurgical treatments such as TAE, TACE, and PEIT have recently been developed, and the strategy for the treatment of small HCCs is a current topic.

The definition of "small HCC" varies in the literature. According to the agreement of the Liver Cancer Study Group of Japan, small liver cancer is defined as being 2 cm or less in diameter. In the present study, small liver cancer included a slightly larger size, i.e., 2.1–3 cm in diameter, and the tumors were divided into two groups on the basis of size: group A (≦1.5 cm) and group B (1.6–3 cm). This classification was based mainly on the findings of angiography and Lipiodol-CT (CT images taken 2–3 weeks after transarterial injection of Lipiodol or the suspension). As shown in Table 2, the tumors measuring 1.5 cm or less in diameter (group A) showed relatively poor vascularity and Lipiodol accumulation as compared with the lesions measuring 1.6–3 cm in diameter (group B).

Recently, the treatments of choice for small liver cancer have been confined to surgical resection, transplantation, PEIT, TAE, and TACE [2], whereas TAE using gelatin sponge does not seem to be very effective for small liver cancers [1, 4]. Surgical resection is a curative treatment if there is sufficient liver function to permit surgery. Yamasaki et al. [9] reported that the postoperative cancer-free survival of patients with small HCC (less than 3 cm in diameter) was more than 90% at 1 year and 35% at 3 years, but the survival of patients with multiple lesions was worse than that of patients with a solitary lesion. They also reported that the survival of patients with a tumor measuring less than 2 cm was superior to that of patients with a tumor measuring less than 3 cm in diameter. Our data indicated a 3-year survival rate of 68% in the patients with an HCC measuring 3 cm or less, but surgery was indicated in only 12% of a total of 75 patients with small HCCs. Therefore, nonsurgical modalities have become a standard for the treatment of small liver cancer in our department.

PEIT seems to be an alternative therapy to surgery for small HCCs, although it is not as effective by itself against HCCs measuring more than 3 cm in diameter [7]. Ebara et al. [3] reported that the 3- and 5-year survival rates of patients treated with PEIT were 65% and 28%, respectively. In our series, the 3-year survival rate was more excellent,

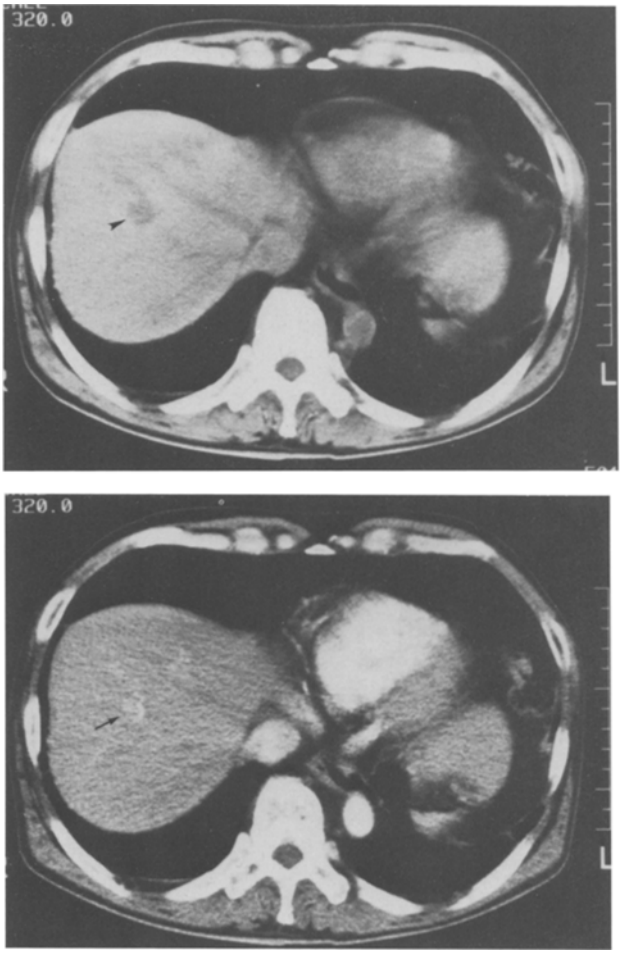

Fig. 4. Dynamic CT images of small HCC. (**a**) Plain CT image showing a hypodense lesion (*arrowhead*). (**b**) Arterial phase of the dynamic study. The tumor is demonstrated as a hypervascular lesion (*arrow*), and TACE was thus selected as the treatment of first choice

reaching even 90%, in patients with HCCs measuring less than 1.5 cm in diameter. On the other hand, TACE seems to be of limited value in the treatment of tumors measuring 1.5 cm or less in diameter, because tumors of this size occasionally show hypovascularity on angiograms and poor retention of Lipiodol on CT (Table 2). The best therapeutic modality for group A is therefore considered to be PEIT, whereas a 3-year survival rate of 80% was achieved with TACE in this study.

TACE is particularly efficacious for a hypervascular mass of medium size. In group B, angiography demonstrated hypervascularity in 74% of the lesions and CT after injection of Lipiodol depicted Lipiodol accumulation in 90% of the tumors as shown in Table 2. These findings suggest that TACE is the treatment of first choice for unresectable tumors measuring 1.6–3 cm in diameter. However, only a few papers have described the survival rates of patients with small HCCs measuring 3 cm or less treated by embolization. Arai et al. [1] reported that the survival rates for HCCs measuring less than 3 cm were 89% and 28% at 1 and 3 years, respectively. Kumada et al. [6] also reported that the survival rates for HCCs measuring 2 cm or less

treated with TACE were 90% at 1 year and 18% at 3 years. In the present study, comparable results were obtained: 82% at 1 year and 28% at 3 years. This 3-year survival rate was worse than that obtained with resection or PEIT. One reason for this result would be exacerbation of underlying liver cirrhosis caused by TACE. In fact, some patients treated with TACE succumbed to hepatic failure, mainly due to tumor progression and to gradual worsening of the liver cirrhosis.

On the basis of these clinical results, we conclude that PEIT is the treatment of choice for unresectable HCCs measuring 1.5 cm and less in diameter, whereas TACE is the treatment of first choice for tumors measuring 1.6–3 cm. In addition to the tumor size, dynamic CT can be useful in deciding the most appropriate therapeutic modality. With the use of high-speed scanning during contrast infusion, hemodynamic characterization of HCCs can be achieved even for tumors measuring 1.5 cm or less in diameter (Fig. 4). If an increase in tumor vascularity is observed in the arterial phase of dynamic CT, TACE should be selected as the treatment of first choice rather than PEIT when the tumor is judged to be unresectable because of severe liver cirrhosis.

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