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Subsegmental transcatheter arterial embolization for small hepatocellular carcinomas: local therapeutic effect and 5-year survival rate

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Abstract. The local therapeutic effects and 5-year survival rates obtained following subsegmental transcatheter arterial embolization (TAE) therapy for small hepatocellular carcinomas (HCCs) were retrospectively analyzed. A total of 124 nodular-type HCC lesions measuring less than 4 cm in diameter in 100 patients with liver cirrhosis were subjected to the analysis. All lesions became opaque on digital subtraction angiography. Complete necrosis was seen in 64% of 11 resected lesions. Among the remaining 113 lesions, the 1- and 5-year local recurrence rates following one performance of TAE were 18% and 33%, respectively. The 1- and 5-year survival rates were 100% and 53%, respectively. No significant side effect was observed after TAE therapy. Subsegmental TAE therapy significantly improved the long-term survival rates of patients with small HCCs associated with liver cirrhosis as compared with those treated by conventional TAE therapy.

Introduction

Recently, about 70%–80% of the hepatocellular carcinomas (HCCs) detected at major Japanese institutions measured less than 3 cm in diameter. However, because of associated liver cirrhosis and occasional multicentricity, about 70%–80% of such small HCCs are inoperable. Therefore, transcatheter arterial embolization (TAE) plays an important role in the treatment of even small HCCs. However, the long-term survival rates of cirrhotic patients with small HCCs treated by TAE had not been satisfactory as compared with the rates reported for surgery [2] or percutaneous ethanol injection (PEI) therapy [10].

According to our analysis [1] and reports from other institutions [8, 13], the major reasons for the relatively poor survival rates obtained with conventional TAE therapy are its relatively poor tumor necrosis effect and damage to the liver parenchyma due to repeated performance of TAE. To improve these shortcomings of conventional TAE, we introduced intentional subsegmental TAE for small HCCs using microcatheters and reported its short-term usefulness [4, 6]. We present herein our 5-year experience with subsegmental TAE therapy for small HCCs.

Materials and methods

Technique of subsegmental TAE

After precise evaluation of the feeding arteries and surrounding vascular anatomy, a microcatheter (Tracker 18 vascular access system) is inserted into the feeding subsegmental artery through a 5-F catheter indwelling in the proximal hepatic artery. Before the TAE, 0.5–1.0 ml of 2% xylocain is intra-arterially injected to prevent pain and vasospasm.

As embolic materials, a mixture of iodized poppyseed oil (Lipiodol) and anticancer drugs followed by Gelfoam particles or a mixture of Lipiodol and absolute ethanol is used. For the former "Lipiodol TAE," 1–5 ml of a mixture of Lipiodol, doxorubicin (10–30 mg), mitomycin C (2–6 mg), and 0.5–1 ml of a contrast medium such as Iohexol mixed by repeated pumping (about 10–20 times) through a 3-way stopcock is injected, followed by 1-mm-square Gelfoam particles. For the latter "ethanol TAE," absolute ethanol and Lipiodol are combined by simple mixing of equal volumes based on the method of experimental renal artery embolization reported by Park et al. [9], and 1–4 ml of this mixture is injected. Embolic materials are injected until complete obliteration of the feeding arteries is observed. Ethanol TAE is performed only when the microcatheter is inserted deeply into the distal portion of the subsegmental artery.

Patients

From January 1988 to October 1991, 100 cirrhotic patients with 124 nodular-type HCC lesions measuring less than 4 cm in the largest diameter received subsegmental TAE at Kanazawa University Hospital

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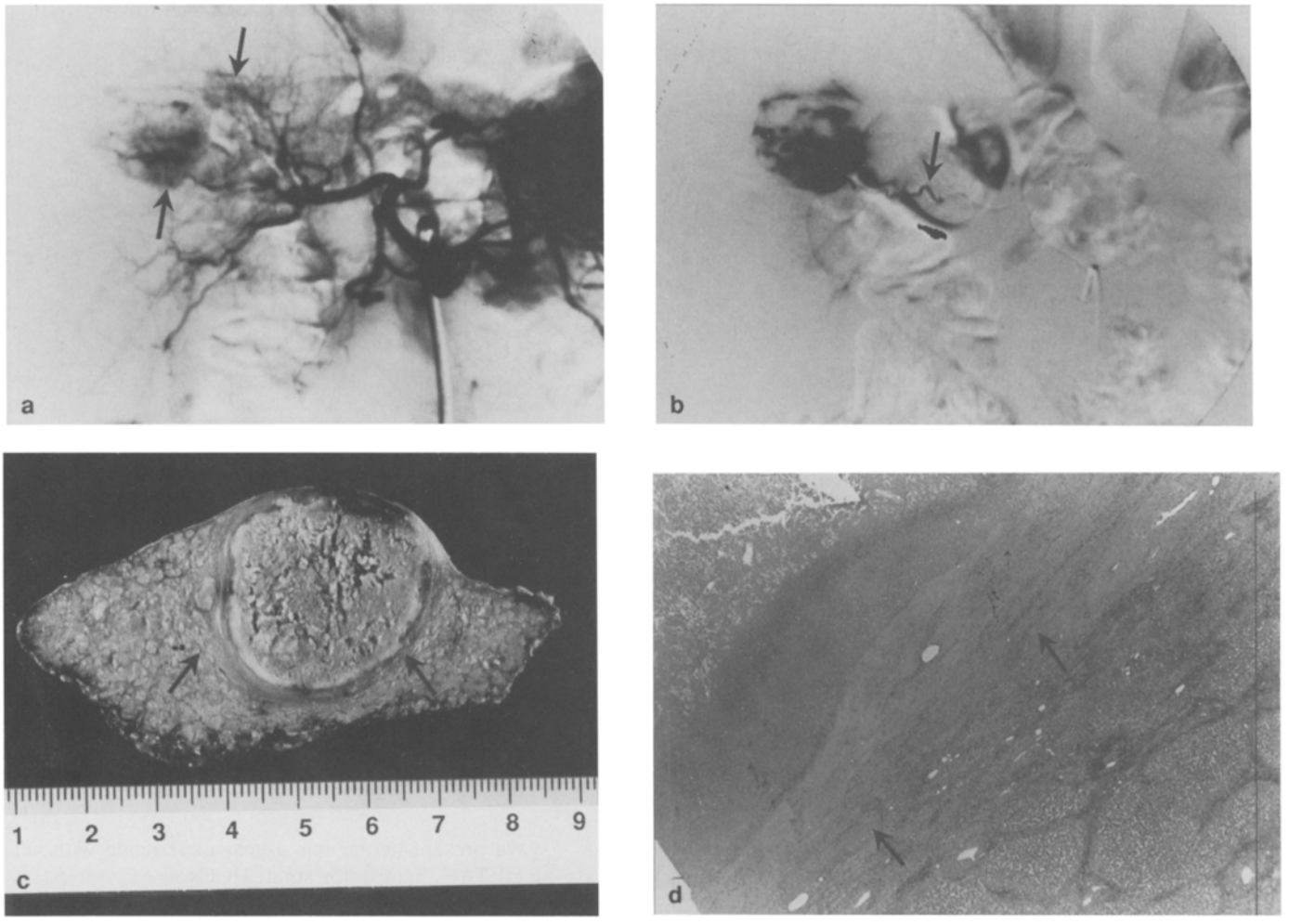

Fig. 1. (**a**) Two small HCCs are seen as nodular stains on digital subtraction angiography (DSA, *arrows*) (**b**) A microcatheter was inserted into the distal portion of the anterior inferior subsegmental artery (*arrow*), and subsegmental transcatheter arterial embolization (TAE) with a mixture of ethanol and Lipiodol was carried out for one of the two lesions. (**c, d**) At 1 week following TAE, the lesion was resected and complete necrosis was revealed histologically (*arrows*)

and Toyama Prefectural Central Hospital. The patients ranged in age from 47–76 years (mean age, 61 years) and included 75 men and 25 women. All lesions were demonstrated as nodular stains on digital subtraction angiography (DSA) and measured less than 4 cm (average, 2.3 cm) in the largest diameter. As we reported earlier [5], almost all HCC nodules stained on hepatic arteriography are classic-type HCCs with Edmondson and Steiner grade 2 or greater cancer-cell anaplasia (moderately or poorly differentiated HCCs).

In all, 2 lesions were seen in 28 patients at the start of the TAE therapy, and subsegmental TAE for 1 of the 2 lesions was impossible in 4 patients. Patients with three or more HCC nodules were excluded from the study because subsegmental TAE is not indicated in such patients. Among the 100 cirrhotic patients, 20 had hepatitis B-related cirrhosis, 71 had hepatitis C-related cirrhosis, 5 had hepatitis B- and C-related cirrhosis, and the remaining 4 had alcoholic-related or cryptogenic cirrhosis. With respect to the stage of liver cirrhosis, 63 patients were classified as Child's class A; 34, as Child's class B; and 3, as Child's class C. For 11 lesions in 10 cases, preoperative subsegmental TAE was performed. The remaining 113 lesions in 90 patients were followed for more than 12 months. The follow-up period ranged from 12 to 62 months (average, 31 months). Lipiodol TAE was performed for 95 lesions and ethanol TAE, for 29 lesions.

Among these patients, the local recurrence of each lesion was evaluated by histological examination or imaging diagnosis. The local recurrence rates and survival rates were calculated according to the Kaplan-Meier method. The changes in laboratory data were analyzed following subsegmental TAE in 30 patients for whom periodic laboratory tests were performed.

Local recurrence was judged to be present when disappearance of Lipiodol from the lesion was seen on CT or a solid viable tumor was revealed on dynamic CT, dynamic MRI, or DSA within the lesion or the embolized subsegment.

Results

Complete necrosis was revealed in 7 of 11 resected lesions (3 of 4 lesions treated with ethanol TAE and 4 of 7 lesions treated with Lipiodol TAE; Fig. 1), and 50%–80% necrosis was seen in the remaining 4 lesions. In 2 of the 4 lesions without complete necrosis, retrospective analysis indicated that 1 of the small feeding arteries had not been embolized because the microcatheter had been inserted too distal to it.

The local recurrence rates were calculated according to the Kaplan-Meier method in the 113 unoperated lesions. The local recurrence rates following one performance of subsegmental TAE were 18% at 1 year, 30% at 2 years,

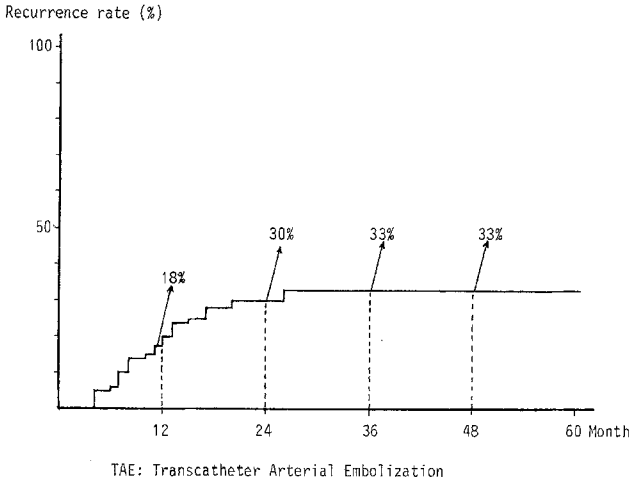

Fig. 2. Local recurrence rates of small HCCs treated by subsegmental TAE (n = 113, <4 cm; Kaplan-Meier method)

33% at 3 years, and 33% at 5 years (Figs. 2, 3). No significant difference in the local recurrence rates was found between the "Lipiodol TAE" and "ethanol TAE" groups. Of 16 lesions that showed local recurrence following the initial TAE, 11 were locally controlled, with massive necrosis of the tumors being induced by repeated TAE.

Survival rates were calculated according to the Kaplan-Meier method for patients in whom the stage of liver cirrhosis was Child's class A or B, and all lesions were first treated by subsegmental TAE. A total of 82 cases were subjected to the analysis. The 1-year survival rate was 100%, the 2-year rate was 93%, the 3-year rate was 73%, and the 5-year rate was 53% (Fig. 4). In all, 12 deaths occurred during the follow-up period; 6 of them were caused by intrahepatic or extrahepatic extension of the tumors, and the remaining 6 deaths were due to hepatic failure without remarkable tumor extension. The hepatic failure in these cases occurred more than 16 months after the first subsegmental TAE and was considered to be unrelated to the procedure. When the survival rates were

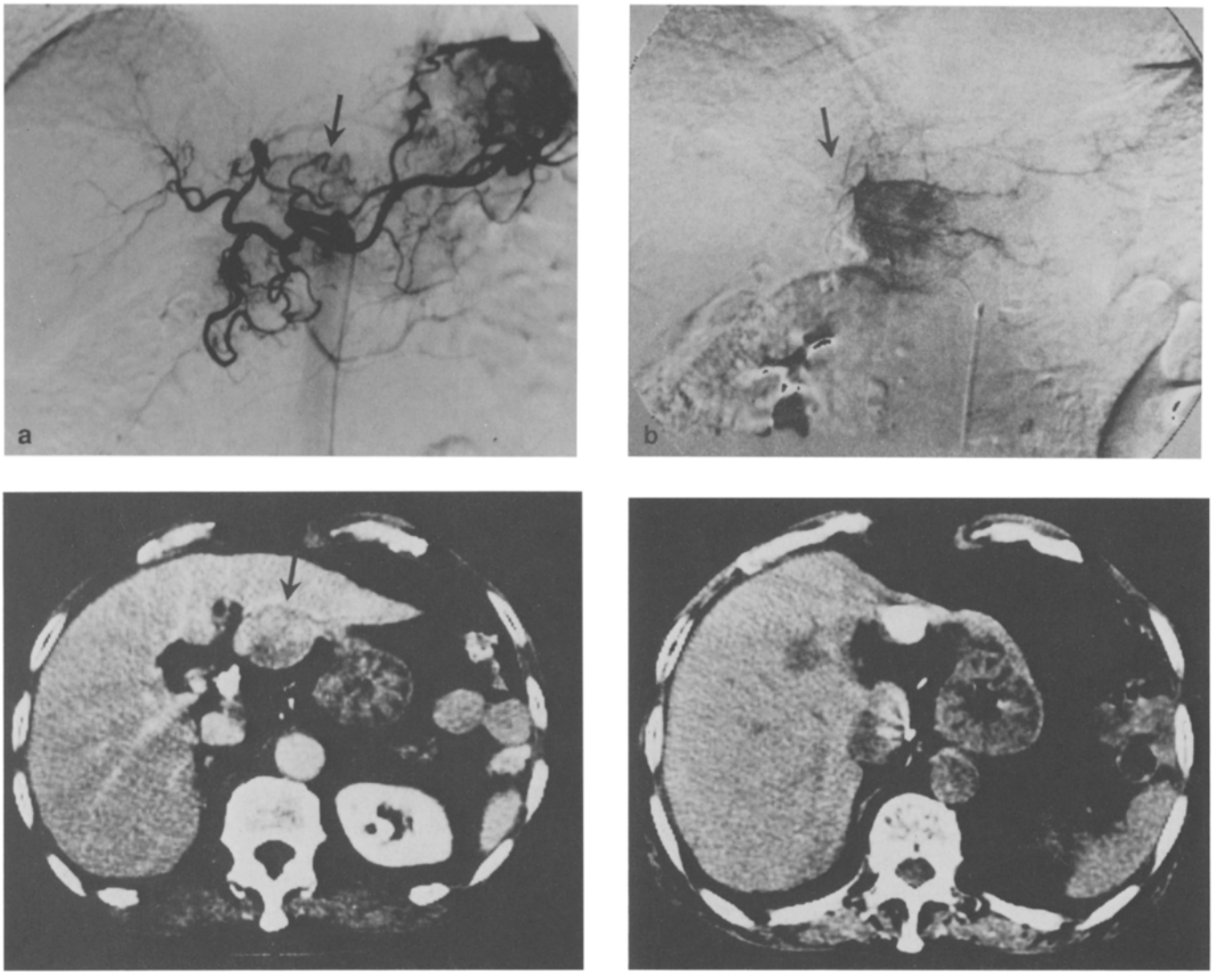

Fig. 3. (**a**) A small HCC nodule fed by a lateral inferior subsegmental artery is demonstrated on DSA (*arrow*). (**b**) A microcatheter was inserted into the feeding subsegmental artery, and TAE was performed with a mixture of ethanol and Lipiodol (*arrow*). (**c**) CT before TAE therapy shows a small HCC measuring about 3 cm in diameter (*arrow*). (**d**) CT at about 2 years after TAE shows dense accumulation of Lipiodol in the entire tumor (complete necrosis of the tumor) and severe atrophy of the surrounding subsegment (*arrows*)

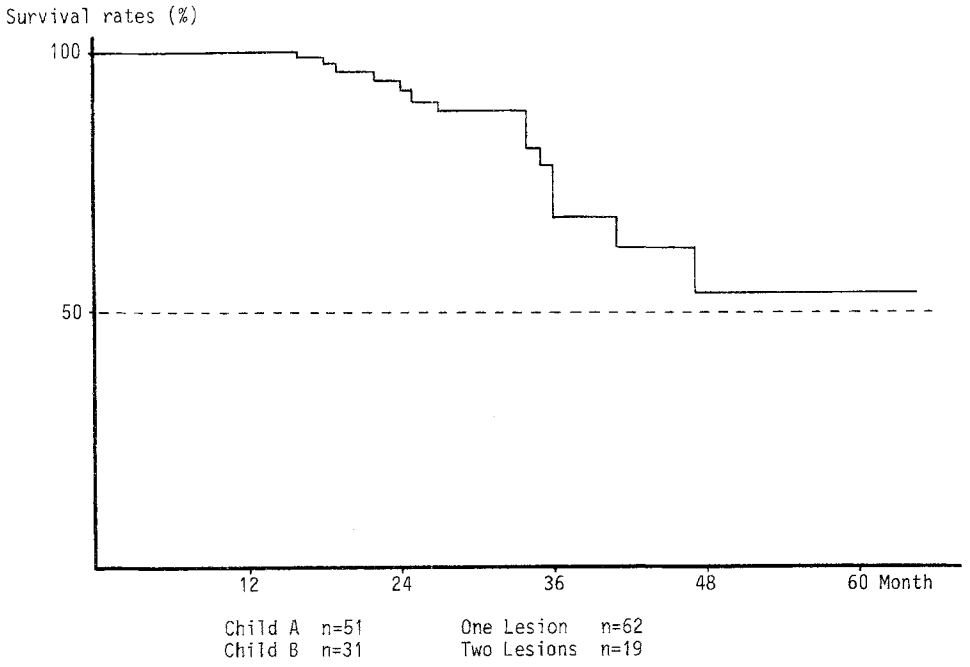

Fig. 4. Survival rate of patients with small HCCs treated by subsegmental TAE (n = 82; Kaplan-Meier method)

calculated for patients with Child's class A, the 1-year survival rate was 100%, the 2-year rate was 95%, the 3-year rate was 87%, and the 5-year rate was 60%. During the follow-up period, recurrent lesions outside of the embolized subsegment were seen in 22 patients (27%), and most were treated by TAE.

No significant change in the laboratory data was seen after the subsegmental TAE therapies. No definite deterioration of physical findings attributable to the subsegmental TAE, except for a mild fever, was detected in any of the patients.

Discussion

TAE has been widely performed for the treatment of inoperable HCCs since its introduction for cirrhotic patients by Yamada et al. in 1977 [12]. However, its long-term control of even small HCCs remains unsatisfactory. To overcome these shortcomings f conventional TAE for small HCCs, Uchida et al. [11] introduced "segmental TAE." However, because we thought that "segmental TAE" was too invasive for small HCCs and since the recent advances in microcatheter systems have facilitated intentional catheterization into more distal branches of the subsegmental artery of the liver, we started routine performance of subsegmental TAE for small HCCs at the beginning of 1988. Nakamura et al. [7] found that Lipiodol injected into the hepatic artery occasionally appeared in the portal veins. Therefore, Lipiodol can embolize both hepatic arteries and portal venules temporarily, and a large volume of Lipiodol in a limited area of the liver induces not only massive necrosis of the tumor but also atrophy of the surrounding liver parenchyma (medical segmentectomy effect). In subsegmental TAE, we intended to evoke this "medical subsegmentectomy" effect in the tumor-bearing subsegment. The injection of 1–5 ml of Lipiodol into the subsegment is considered to correspond to that of 8–40 ml into the entire liver. We also introduced absolute ethanol as an embolic material to obtain a more powerful "medical segmentectomy" effect. Our earlier experimental TAE using an optimal dose of absolute ethanol for chemically induced HCCs in rat livers had produced a strong tumor necrosis effect without causing severe damage to the liver parenchyma. However, when the volume of ethanol used was excessive, it led to necrosis of the liver parenchyma [3]. Therefore, we used absolute ethanol only when the catheter was inserted deeply into the more distal portion of a subsegmental artery. However, as a result, there was no definite difference in the local recurrence of the tumor between the Lipiodol TAE and ethanol TAE groups, and we therefore now mainly perform Lipiodol TAE.

In the present study, about 70% of small HCCs measuring less than 4 cm in diameter were considered to be completely cured locally by one performance of subsegmental TAE. A majority of the remaining tumors were cured or reduced in size by repeated subsegmental TAE. The damage to liver function induced by subsegmental TAE was almost negligible clinically, and no hepatic decompensation caused directly by the subsegmental TAE was seen. Concerning the survival rates of patients with small HCCs treated by conventional TAE, Nakao et al. [8] reported that the 1-, 2-, 3-, and 5-year survival rates were 72.9%, 64.0%, 34.2%, and 9.2%, respectively, in their series of 108 small HCCs measuring less than 3 cm in diameter. Therefore, we think that the prognosis of cirrhotic patients with small HCCs treated by TAE was significantly improved by the introduction of subsegmental TAE therapy.

Surgical resection and percutaneous ethanol injection (PEI) are also very effective treatments for small HCCs. According to a report of the Liver Cancer Study Group of Japan [2], the 5-year survival rate in patients with HCCs smaller than 2 cm in diameter treated by resection was

61%. Using PEI therapy, Tanikawa [10] obtained a 5-year survival rate of 48.4% in a series of 217 small HCCs measuring less than 3 cm in diameter, including a relatively large percentage of well-differentiated HCCs. Therefore, we think that as far as the treatment of classic-type HCCs is concerned, the results we obtained with subsegmental TAE are almost the same as those obtained with surgery and superior to those reported for PEI. However, continuing efforts should be made for further comparative evaluation among these three modalities.

Conclusions

About 70% of hypervascular small HCCs measuring less than 4 cm in diameter are expected to be completely cured locally by one performance of subsegmental TAE. Subsegmental TAE with both Lipiodol TAE and ethanol TAE resulted in little adverse effect on the hepatic function. As a consequence, the survival rates of cirrhotic patients with small HCCs treated by TAE were significantly improved by the introduction of subsegmental TAE.

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