The effectiveness of subsegmental transcatheter arterial embolization (TAE) therapy for small hepatocellular carcinomas (HCCs) was retrospectively analyzed. TAE was performed in 100 patients with liver cirrhosis. There was a total of 124 nodular-type HCCs less than 4 cm in diameter. TAE was performed by injecting a mixture of iodized oil and anticancer drugs followed by gelatin sponge particles or a mixture of iodized oil and absolute ethanol into the more distal branches of the subsegmental artery. Complete necrosis was seen at histologic examination in seven of 11 resected lesions. Among the remaining 113 lesions in 90 patients followed up without surgery, the 1- and 4-year local recurrence rates after TAE were 18% and 33%, respectively. The 1- and 4-year survival rates for 82 patients with Child class A or B disease were 100% and 67%, respectively. No substantial deterioration of liver function was observed. Subsegmental TAE improved the prognosis of the patients with liver cirrhosis associated with small HCCs.

Index terms: Alcohol • Arteries, therapeutic blockade, 952.1264 • Liver, cirrhosis, 761.794 • Liver neoplasms, 761.321 • Liver neoplasms, angiography, 761.1242 • Liver neoplasms, therapy, 761.321

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With advances in imaging modalities and the establishment of the high-risk group for hepatocellular carcinoma (HCC), it has become possible to diagnose HCCs less than 2–3 cm in diameter (1). About 70% of the HCCs detected at our institution are less than 3 cm in diameter (Matsui O, unpublished data, 1992). However, because of the associated liver cirrhosis and occasional multicentricity, about 70%–80% of cases are inoperable (2). Therefore, transcatheter arterial embolization (TAE) plays an important role in the treatment of small HCCs. However, according to our experience and that of other institutions, it is almost impossible to achieve complete tumor necrosis with conventional TAE, and repeat TAE has an adverse effect on liver function (3–5).

To achieve more complete tumor necrosis and to reduce the damage to the liver parenchyma with TAE, we recently introduced subsegmental TAE for small HCCs with use of microcatheters (6). In subsegmental TAE, a microcatheter is inserted into the more distal branches of the subsegmental artery of the liver, and the small HCC and surrounding subsegment are embolized.

We performed a retrospective study to analyze the local recurrence rate of the small HCC nodules treated with subsegmental TAE, the survival rate of the patients in whom all HCCs were treated with subsegmental TAE, and the effect of subsegmental TAE on liver function.

MATERIALS AND METHODS

From January 1988 to October 1991, 100 patients with cirrhosis and 124 nodular-type HCCs less than 4 cm in diameter (average, 2.3 cm) underwent subsegmental TAE at Kanazawa University Hospital and Toyama Prefectural Central Hospital, Kanazawa, Japan. The patients ranged in age from 47 to 76 years (mean, 61 years). There were 75 men and 25 women. During the same period, selective catheterization distal to the subsegmental artery failed or was anatomically impossible in 29 small HCC nodules (29 patients) that were indicated for subsegmental TAE. Therefore, the success rate of subsegmental catheterization was 81% (124 of 153 HCCs).

Lesion diameters were determined with ultrasound, computed tomography (CT), or digital subtraction angiography (DSA). At DSA, the size of the HCC was calculated by comparing it with the size of the angiographic catheter used for hepatic angiography. All lesions were demonstrated as nodular stains at DSA. As we have reported previously (8), almost all HCC nodules that stain at hepatic arteriography are classic HCCs with Edmondson and Steiner grades 2–4 anaplasia (moderately or poorly differentiated HCCs). Two lesions were seen in 28 patients at the start of the TAE therapy, and subsegmental TAE for one of the two lesions was impossible in four patients. Patients with three or more HCC nodules were excluded from the study because subsegmental TAE is not indicated in such patients.

Of the 100 patients, 20 had hepatitis B–related cirrhosis, 71 had hepatitis C–related cirrhosis, five had both hepatitis B– and C–related cirrhosis, and four had alcoholic-related or cryptogenic cirrhosis. With respect to the stages of liver cirrhosis, 63 patients had Child class A, 34 had Child class B, and three had Child class C cirrhosis.

Subsegmental TAE was performed as follows. After selective celiac and superior mesenteric arteriography was performed, a 5-F catheter was inserted into the common or proper hepatic artery and hepatic arteriography was performed with DSA. After evaluation of the feeding arteries and surrounding vascular anatomy, a microcatheter (Tracker 18 Vascular Access System; Target, San Jose, Calif) was inserted into the 5-F catheter, which remained in the proximal hepatic artery. For the superselective insertion of microcatheters, repeat angiography and road-mapping guidance with DSA were used.

Abbreviations: DSA = digital subtraction angiography, HCC = hepatocellular carcinoma, PEI = percutaneous ethanol injection, TAE = transcatheter arterial embolization.
After the microcatheter was inserted into the subsegmental feeding arteries, 0.5–1.0 mL of 2% lidocaine was intraarterially injected to prevent pain and vasoconstriction. TAE was then performed by injecting either a mixture of iodized poppyseed oil (Lipiodol; Andre Guerbet, Aulnaysous-Bois, France) and anticancer drugs followed by gelatin sponge particles (Gelfoam; Upjohn, Kalamazoo, Mich) or a mixture of iodized oil and absolute ethanol. For the former technique ("iodized oil TAE"), a solution of 1–5 mL of iodized oil, doxorubicin (10–30 mg), mitomycin C (2–6 mg), and 0.5–1 mL of contrast medium (eg, iohexol) mixed by repeated pumping was performed. A mixture of iodized oil and ethanol was injected through a three-way stopcock was injected, followed by 1-mm-square gelatin sponge particles. For the latter technique ("ethanol TAE"), the absolute ethanol and iodized oil were combined by mixing equal volumes with a puncture needle on the basis of the method of experimental renal artery embolization reported by Park et al (7): 1–4 mL of this mixture was injected.

Under microscopic observation, various sizes of iodized oil particles, usually less than 50 μm in diameter were not dissolved by iodized oil. Embolic materials were injected until feeding arteries were completely obliterated. Ethanol TAE was performed only when the microcatheter was inserted deep into the distal portion of the subsegmental artery (6). When the blood supply was from two different subsegmental arteries, both were embolized.

In 10 patients (11 lesions), subsegmental TAE was performed to prevent the dissemination of the tumor cells during subsequent surgery, although its effect has not been proved yet. Among those 11 lesions, iodized oil TAE was performed in four and ethanol TAE in seven. The remaining 113 lesions in 90 patients were followed up for at least 6 months after TAE (range, 6–52 months; average, 23 months). Iodized oil TAE was performed in 88 of those 113 lesions, and ethanol TAE was performed in 25.

Among the 90 patients who underwent follow-up, the local recurrence of each lesion was evaluated with histologic or imaging examination. The local recurrence rates and survival rates were calculated according to the Kaplan-Meier method. Changes in laboratory data after subsegmental TAE were analyzed in 30 patients for whom the periodic check of the laboratory data was performed during the early period of this study.

Local recurrence was judged to be present when disappearance of iodized oil from the lesion was seen at CT or a solid viable tumor was revealed within the lesion or the embolized subsegment at dynamic CT, dynamic magnetic resonance imaging, or DSA. One of these imaging methods was performed within every 3–4 months after subsegmental TAE.

**RESULTS**

Of the 11 resected lesions, complete necrosis was revealed in seven (three of the four lesions treated with ethanol TAE and four of the seven lesions treated with iodized oil TAE) (Fig 1); 50%–80% necrosis was seen in the remaining four lesions. In two of the four lesions with incomplete necrosis, retrospective analysis indicated that one of the small feeding arteries was not embolized because the microcatheter was advanced too far.

The local recurrence rates for the 113 unreported lesions are shown in Figure 2. The 1-year local recurrence rate after one subsegmental TAE was 18%, the 2-year rate was 30%, the 3-year rate was 33%, and the 4-year rate was 33% (Figs 3, 4). No substantial difference in the local recurrence rates was found between iodized oil and ethanol TAE groups. Of the 16 lesions that showed local recurrence after initial TAE therapy, 11 were locally controlled with massive necrosis of the tumors by repeat TAE.

Survival rates were calculated for the patients with Child class A or B cirrhosis in whom all lesions were treated with subsegmental TAE. The three patients with Child class C cirrhosis, the two patients each who died of choledochal cancer or cardiac infarction, and the three patients in whom subsegmental TAE was impossible in one of the two lesions were excluded from this analysis. Thus, a total of 82 patients were included in this analysis. As shown in Figure 5, the 1-year survival rate was 100%, the 2-year rate was 92%, the 3-year rate was 78%, and the 4-year rate was 67%.

Eight patients died during the follow-up period. Three patients died of intrahepatic or extrahepatic extension of the tumors, and five died of hepatic failure without remarkable tumor extension. Hepatic failure occurred 16–41 months after subsegmental TAE and was considered unrelated to the procedure. All but one of the deaths due to hepatic failure were seen in patients with Child class B disease. When the survival rates were calculated in the patients with Child class A disease, the 1-year survival rate was...
100%, the 2-year rate was 97%, the 3-year rate was 97%, and the 4-year rate was 83% (Fig 5). During the follow-up period, recurrent lesions outside of the embolized subsegment were seen in 22 of the 82 patients (27%), most of which were treated with TAE.

Various measurements of liver function, including alanine aminotransferase, aspartate aminotransferase, serum albumin, total bilirubin, and cholinesterase levels and the hepaplastin test, were analyzed in 30 patients (12 underwent ethanol TAE and 18 underwent ioxidized oil TAE) during the early stage of the introduction of subsegmental TAE therapies. As shown in Figure 6, no substantial changes were seen after subsegmental TAE; therefore, laboratory studies were not routinely performed in the remaining patients. Except for mild fever of about 37.5°–38°C, no definite deterioration of physical condition attributable to subsegmental TAE was detected in any patient.

**DISCUSSION**

TAE has been widely performed for the treatment of inoperable HCC since its introduction in patients with cirrhosis by Yamada et al in 1977 (9). Its usefulness has subsequently been confirmed by many authors (10,11). However, long-term management of even small HCCs with TAE is not yet satisfactory. The problems associated with conventional TAE include incomplete tumor necrosis and the adverse effect on liver function induced by repeat TAE. To overcome these shortcomings, Uchida et al (11) introduced segmental TAE. However, because we thought that segmental TAE was still too invasive for small HCCs and because recent advances in microwater systems have facilitated catheterization into more distal branches of the subsegmental artery of the liver, we began to routinely perform subsegmental TAE for small HCCs at the beginning of 1988. It is well known that HCCs are supplied exclusively by the hepatic artery (12,13). However, as previously reported by us (8) and others (13), well-differentiated small HCCs are occasionally partially supplied by the portal vein, especially when there is a lack of capsule formation around the tumors (13). Therefore, to achieve complete necrosis of HCCs, complete blockage of arteries including the peribiliary plexus (14,15), simultaneous embolization of feeding arteries and peripheral portal venules surrounding the tumors, and infarction of the surrounding liver parenchyma are necessary. Nakao et al (16) reported the usefulness of simultaneous embolization of both the hepatic artery and portal vein. However, this method is very invasive and time-consuming, thereby precluding its routine use.

Conversely, Nakamura et al (17) found that iodized oil injected into the hepatic artery occasionally appeared in portal veins. This phenomenon was confirmed by Kan et al (18).
with use of vital microscopy. Therefore, iodized oil can be used to temporarily embolize both hepatic arteries and portal vessels. Nakamura et al. (19) also reported that TAE with a large volume of iodized oil in the limited area of the liver induced 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. Injection of 1-5 mL of iodized oil into the subsegment is considered to correspond to injection of 8-40 mL into the entire liver.

We used absolute ethanol as an embolic material to obtain a more powerful medical segmentectomy effect because our previous experience with TAE using an optimal dose of absolute ethanol for chemically induced HCCs in rat livers revealed a strong tumor necrosis effect without severe damage to liver parenchyma (20). However, when the amount of ethanol was excessive, it caused necrosis of the liver parenchyma (20). Therefore, we used absolute ethanol only when the catheter was inserted deep into the more distal portion of a subsegmental artery. To monitor the injection of ethanol, a 50% mixture of absolute ethanol and iodized oil was employed (7). However, as a result, there was no definite difference in the local recurrence of tumor between the iodized oil TAE and ethanol TAE groups, and now we usually perform iodized oil TAE.

Complete necrosis occurred in about 70% of the HCCs in our study after one subsegmental TAE session. Complete or partial necrosis was achieved in most of the remaining tumors after repeat subsegmental TAE. To our knowledge, there have been no reports on the local recurrence rates after TAE therapy. A recent retrospective analysis revealed that about 70% of small HCCs showed local recurrence during 19-month follow-up after embolization of the right or left hepatic arteries with conventional iodized oil TAE (Miyayama S, unpublished data, 1992). Therefore, our local recurrence rates with subsegmental TAE are extremely low compared with those of conventional TAE.

Clinically, the damage to liver function induced by subsegmental TAE was almost negligible, and mild fever was the only notable physical finding attributable to subsegmental TAE. These adverse effects are definitely less than those of conventional TAE (3,5), and no hepatic decompensation directly caused by subsegmental TAE was seen.

In their large series of more than 1,000 cases of HCC including large inoperable HCCs treated with conventional TAE with gelatin sponge particles and anticancer drugs, Yamada et al (4) reported a 1-year survival rate of 51%, a 2-year rate of 28%, a 3-year rate of 13%, a 4-year rate of 8%, and a 5-year rate of 6%. Ohishi et al (21) performed conventional iodized oil TAE in more than 500 inoperable HCCs and reported a 4-year survival rate of 20.4%. As shown in the Table, when the survival rates were analyzed in small HCCs treated with conventional TAE, Nakao et al (10) reported that the 4-year survival rate was 22% in their series of 108 HCCs less than 3 cm in diameter. In comparison with these reported results of conventional TAE, we think that the prognosis of patients with cirrhosis and small HCCs treated with TAE was substantially improved with the introduction of subsegmental TAE.

To our knowledge, there have been no reports concerning the long-term

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**Summary of Survival Rates in Patients with Small HCC**

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Size of Tumors (cm)</th>
<th>Treatment</th>
<th>Survival Rates (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakao et al (10)</td>
<td>108</td>
<td>&lt;3</td>
<td>Conventional TAE</td>
<td>73, 64, 34, 22</td>
</tr>
<tr>
<td>Uchida et al (11)</td>
<td>99</td>
<td>&lt;5</td>
<td>Segmental TAE</td>
<td>NA, NA, 55, NA</td>
</tr>
<tr>
<td>Liver Cancer Study</td>
<td>347</td>
<td>&lt;2</td>
<td>Surgery</td>
<td>87, 82, 75, NA</td>
</tr>
<tr>
<td>Group of Japan (22)</td>
<td>87</td>
<td>&lt;5</td>
<td>Surgery</td>
<td>86, 78, 49, 45</td>
</tr>
<tr>
<td>Kawasaki et al (22)</td>
<td>112</td>
<td>&lt;3</td>
<td>PEI</td>
<td>93, 84, 63, 49</td>
</tr>
<tr>
<td>Ebara et al (25)</td>
<td>217*</td>
<td>&lt;3</td>
<td>PEI</td>
<td>NA, 87, 73, 61</td>
</tr>
<tr>
<td>Tanikawa et al (2)</td>
<td>82</td>
<td>&lt;4</td>
<td>Subsegmental TAE</td>
<td>100, 92, 78, 67</td>
</tr>
</tbody>
</table>

Note—NA = not applicable.
* Almost half of the lesions were well-differentiated HCCs.

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results of subsegmental TAE for HCCs. However, Uchida et al. (11) reported that the 3-year survival rate was 55% in their series of 99 HCCs smaller than 5 cm treated with segmental iodized oil TAE (Table). Their results also support the usefulness of segmental or subsegmental TAE.

Surgical resection and percutaneous ethanol injection (PEI) are also effective treatments for small HCCs. However, because of associated liver cirrhosis and occasional multicentricity (1,2), there has been some controversy regarding the selection of treatment methods. Therefore, the treatment method is selected according to the individual case, taking into consideration the patient’s age, the stage of liver cirrhosis, the location and number of lesions, and the general condition of the patient, making it now possible to compare the survival rates in similar patient groups undergoing surgery, PEI, and subsegmental TAE.

According to the report from the Liver Cancer Study Group of Japan (22), the 5-year survival rate in patients with HCCs smaller than 2 cm in diameter treated by resection was 61% (Table). Kawasaki et al. (23) reported that the 4-year survival rate of patients with HCCs less than 5 cm in diameter treated with subsegmentectomy was 49% (Table). Yamasaki et al. (24) found that the recurrence rates within about 8 years after surgical resection were as high as 36%-66% (24), probably because of multicentric carcinogenesis. As for the treatment results of PEI, Ebara et al. (25) reported a 4-year survival rate of 49% in their series of 112 HCCs less than 3 cm in diameter, and Tanikawa (2) reported a 4-year survival rate of 61% in his series of 217 HCCs less than 3 cm in diameter (Table). However, a relatively larger percentage of well-differentiated HCCs were treated with PEI because TAE is usually performed in hypervascular classical types of HCC. Tanikawa also analyzed the survival rates of 47 patients with classical type small HCCs treated with PEI and reported a 4-year survival rate of 44.3% and a 5-year rate of 26.6% (2).

One of the problems of PEI is the high frequency of disease recurrence. Recurrence rates of 70%-90% have been reported within 5 years after PEI (2,25), although the reasons for these high rates are unknown. Considering the stages of liver cirrhosis in the patients who underwent surgical resection (almost all of whom had Child class A disease) and the grade of cancer cell differentiation, we think that, as far as the treatment of classical type HCCs is concerned, our results of subsegmental TAE are similar to or superior to those of PEI or surgery. However, continuing efforts should be made for further comparative evaluation with these three modalities.

In conclusion, subsegmental TAE was technically successful in about 80% of patients with small HCCs, and complete necrosis could be achieved in about 70% of hypervascular HCCs less than 4 cm in diameter with one subsegmental TAE session. Subsegmental TAE with both iodized oil and ethanol caused little adverse effect on hepatic function. Consequently, the survival rates of the patients with cirrhosis and small HCCs treated with TAE were substantially improved by the introduction of subsegmental TAE.

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References


