Original Article

Excellent Outcomes With Angiographic Subsegmentectomy in the Treatment of Typical Hepatocellular Carcinoma

A Retrospective Study of Local Recurrence and Long-Term Survival Rates in 120 Patients With Hepatocellular Carcinoma

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BACKGROUND: The authors successfully adopted an interesting and effective treatment for hepatocellular carcinoma (HCC) referred to as *angiographic subsegmentectomy* (AS). This treatment involved simultaneous embolization of the peripheral feeding artery and the portal vein. The result was that almost all of the HCC and peripheral liver parenchyma developed complete anatomic necrosis. **METHODS:** To determine the effectiveness of this method, the authors retrospectively studied the local recurrence rates of 49 solitary HCCs and the long-term survival rates of 120 patients with HCC between 2000 and 2008. **RESULTS:** The results indicated that, in 31 small, solitary HCCs (<2.0 cm), the local recurrence rate was only 9.6%; and, in 10 slightly larger HCCs (<3.0 cm), the local recurrence rate was only 10%. The 5-year, 8-year, and 10-year survival rates for patients with stage I and stage I/Child-Pugh grade A HCC were 74.27% and 77.65%, 53.05% and 51.76%, and 53% and 51.76%, respectively; and the 5-year, 8-year, and 10-year survival rates for patients with stage II and stage II/Child-Pugh grade A HCC were 66.21% and 71.41%, 39.9% and 39.60%, and 29.92% and 25%), respectively. There were no severe complications. **CONCLUSIONS:** AS should be investigated further as potential first-line therapy for the treatment of patients with stage I and II HCC. ***Cancer*** **2010;116:393–9.**

KEYWORDS: treatment of hepatocellular carcinoma, chemoembolization, arterial vascularization, portal vein embolization, computed tomographic angiography.

Hepatocellular carcinoma (HCC) is a common malignancy worldwide and has a high mortality rate.[1-4] The treatment of typical HCC is still difficult. There are many treatment methods for HCC, such as liver transplantation, surgical resection, locoregional treatment, and transcatheter arterial chemoembolization (TACE).[5-22] However, each treatment method has some shortcomings. Liver transplantation requires a donor and is a high-cost procedure, and death while awaiting a suitable donor remains problematic [5-9]. Surgical resection is the standard treatment for HCC; however, the 5-year survival rates range from 50% to 70% for patients with stage I and II, Child-Pugh grade A HCC.[5-7,10] Locoregional treatments for typical HCC have high recurrence rates[12] and a risk of dissemination or seeding.[13] Therefore, an improvement in treatment methods clearly is needed. TACE was developed initially in Japan[14-21] and currently is the most common treatment method for HCC worldwide. However, its efficacy is no greater than the efficacy of treatment for unresectable HCC.[23] One investigator in our group (S.I.) has performed TACE for 30 years and previously reported a new procedure, referred to as *angiographic subsegmentectomy* (AS).[21] The recent development of angiographic computed tomography (angio-CT) and microcatheters has enabled us to detect the peripheral feeding artery of HCC by using subsubsegmental CT hepatic arteriography (CTHA) and an iodized oil (lipiodol) infused from the artery that flows into the

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portal vein through drainage vessels of HCC and natural arterioportal shunts or sinusoids.[19-21] On the basis of these developments, the rationale for AS is to simultaneously embolize the peripheral feeding arteries of HCC and the peripheral portal veins of the same portion of the liver. Therefore, AS results in complete necrosis of HCC and of the anatomic peripheral liver parenchyma. The current retrospective study revealed patients who underwent AS had excellent outcomes.

MATERIALS AND METHODS

Patients

Table 1 provides the patients profiles. Of 120 patients, 46 were women, and 74 were men, and the patients ranged in age from 38 years to 88 years. The TNM classification system was used to determine disease stage and indicated that 31 patients had stage I disease, 52 patients had stage II disease, 27 patients had stage III disease, and 10 patients had stage IV disease. The Child-Pugh classification was used to determine tumor grade and indicated that 85 patients had grade A tumors, 32 patients had grade B tumors, and 3 patients had grade C tumors. α-Fetoprotein (AFP) levels were from normal to 153,556 ng/mL and >10 ng/mL in 78 of 120 patients. Des-γ-carboxyprothrombin (DCP) levels were from normal to 81,100 mAU/mL and >40 mAU/mL in 46 of 118 patients. Eighty-nine of 120 patients were positive for AFP or DCP. Ten patients were treated as follows before 2000: AS, 1 patient; subsegmental TACE, 8 patients; and surgical resection, 1 patient. If HCC recurred, then patients underwent AS.

Table 1. Summary of Clinical Characteristics for All Patients

Characteristic	No. of Patients
Total no. of patients	120
Sex	
Men	73
Women	47
Age, y	
Mean	67.2
Range	38.8-88.1
Etiology	
HBs-Ag positive	20
HCV-Ab positive	96
Clinical stage	
I	31
II	51
III	28
IV	10
Liver function: Child-Pugh grade	
A	84
B	33
C	3

HBs-Ag indicates hepatitis B surface antigen; HCV-Ab, hepatitis C virus antigen.

Methods

By using an angio-CT system (Shimazu, SCT 6800 TX; Shimazu Corp., Kyoto, Japan; and BV Pulsera 12; Philps Medical Systems, Best, the Netherlands), arterial portgraphy CT (CTAP), CTHA, and hepatic digital subtraction angiography (DSA) were performed for diagnostic purposes, because the disease sites, characteristics, and disease stage were known with precision in our patients. After a precise diagnosis was made, a small microcatheter (1.8 French Pixie; Tokai Medical Corp., Kasuga, Japan) was introduced into the peripheral feeding artery of the HCC (at the sub-subsegmental level) under DSA guidance using sub-subsegmental CTHA. From 3 mL to 5 mL of emulsion from 10 mL of iodized oil and 50 mg of epirubicin were injected through a microcatheter slowly and carefully without backflow until the portal veins were observed clearly; next, the peripheral feeding artery was embolized completely by the injection of small particles of a gelatin sponge with 5 mg of mitomycin C mixed in iohexol. After AS, the HCC and surrounding liver parenchyma became necrotic, and they disappeared after anatomic surgical resection (Fig. 1). When patients had multiple HCCs, these procedures were repeated at the same time while monitoring the patient's liver function. The authors recommend using a maximum of 10 mL iodized oil.

For CTAP, 90 mL of iohexol (100 mg iodine/mL) was infused through a catheter into the superior mesenteric artery at 3 mL per second using a power injector. The duration of the scan was 25 seconds for a total scan length of 18.0 cm during a single breath hold with a 5-mm slice collimation and a 5-mm reconstruction helical CT started 25 seconds after the start of the infusion. For CTHA, 40 mL of iohexol were infused through a catheter into the hepatic artery at 2 mL per second. The duration of the scan was approximately 20 seconds for a total scan of the liver with the same slice collimation, bed speed, and reconstruction helical CT started at 8 seconds.

If the lesion was enhanced during CTHA, then it was termed arterially supplied. If the nodule revealed low attenuation on CTAP, then it was assumed that the portal vein blood flow was decreased, and a very low attenuation revealed on CTAP was assumed to be a lack of portal flow.

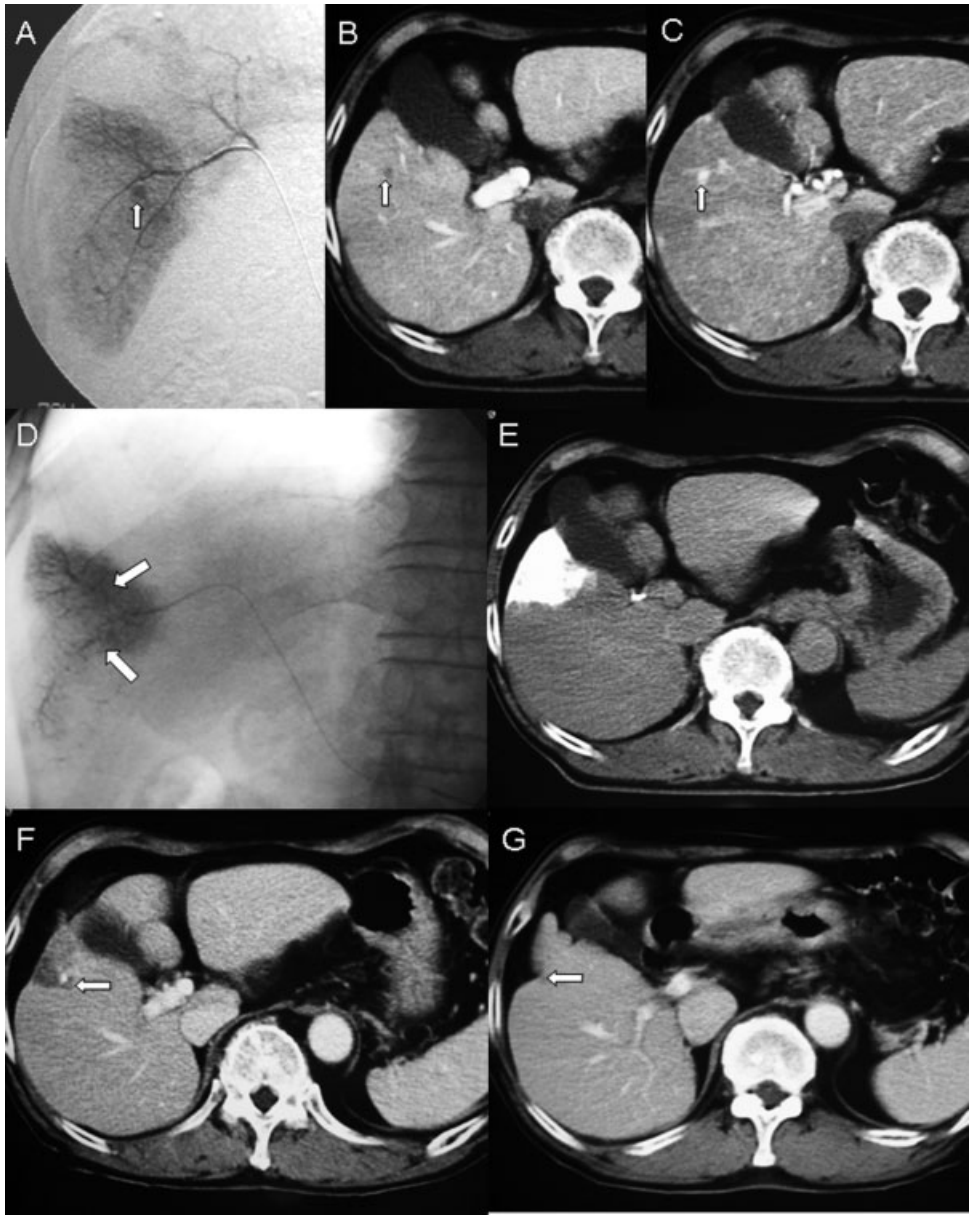

Figure 1. Imaging studies, including (A) hepatic digital subtraction angiography, (B) computed tomographic arterial portgraphy, and (C) and computed tomographic hepatic arteriography, revealed a small, typical hepatocellular carcinoma (HCC) in liver segment 5. An emulsion of iodized oil and epirubicin was injected from a branch of A-5, and portal branches also were observed (D). (E) This computed tomography scan was obtained immediately after the patient underwent angiographic subsegmentectomy (AS). After AS, (E) HCC and liver parenchyma became necrotic and disappeared, and (F) the area had the appearance of a systemic surgical resection.

For sub-subsegmental CTHA, from 5 mL to 10 mL of iohexol (100 mg iodine/mL) was infused through a microcatheter at 0.5 mL to 1.0 mL per second. A helical CT was started at the same time of infusion with care taken to avoid backflow. In addition to our original angio-CT system, the cost performance with this method is good, because the system is used both as a conventional helical CT and as an angio-CT system.

RESULTS

Thirty-one of 26 small, typical HCCs (<2.0 cm) did not recur by the first AS, and another 2 HCCs located at the porta hepatis did not recur by the second AS. The other 3 HCCs had indistinct borders and did recur. Nine of 10 slightly larger HCCs (<3.0 cm) did not recur. Four of 8 larger HCCs (maximum size, 6.0 cm) also did not recur, and those tumors

had clear borders. Follow-up ranged from 0.5 years to 8 years (Table 2).

The 5-year, 8-year, and 10-year survival rates after treatment with AS for patients with stage I, II, and III HCC were as follows: 5 years: 74.27%, 66.21%, and 47.47%, respectively; 8 years: 53.05%, 39.90%, and 16.96%, respectively; and 10 years, 53% and 29.92% for patients with stage I and stage II disease, respectively. There was no significant difference between stage I and stage II (Fig. 2). In patients who had stage I/Child-Pugh grade A disease and stage I/Child-Pugh grade B disease, the 5-year survival rates were 77.65% and 66.67%, respectively; the 8-year survival rates were 51.76% and 66.67%, respectively; and the 10-year survival rates were 51.76% and 66.67%, respectively. In patients who had stage II/Child-Pugh grade A disease and stage II/Child-Pugh grade B disease, the 5-year survival rates were 71.41% and 50.79%, respectively; the 8-year survival rates were 39.60% and 50.79%, respectively; and the 10-year survival rate for patients who had stage II/Child-Pugh grade A disease was 26.46%. There were no significant differences between patients who had stage I/Child-Pugh grade A and stage I/Child-Pugh grade B or between patients who had stage II/Child-Pugh grade A and stage II/Child-Pugh grade B (Figs. 3, 4). Even in for patients

Table 2. Local Recurrence Rate in 49 Solitary Hepatocellular Carcinomas

Tumor Size, cm	No. of Tumors	No. of Local Recurrences	Local Recurrence Rate, %
<2	31	28	9.67
<3	10	9	10
>3	8	4	50
Total	49	41	16.64

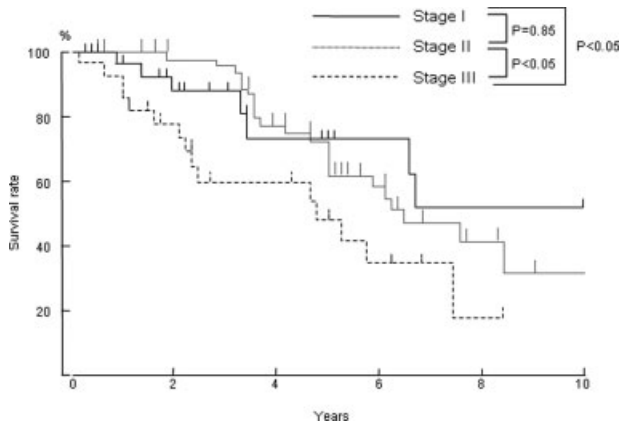

Figure 2. Long-term survival curves for patients with stage I, II, and III hepatocellular carcinoma (HCC) were calculated by using the Kaplan-Meier method. For patients who had stage I, II, and III HCC, the 5-year survival rates were 74.27%, 66.21%, and 47.47%, respectively; and the 8-year survival rates were 53.05%, 39.90%, and 16.96%, respectively. For patients who had stage I and II HCC, the 10-year survival rates were 53% and 29.92%, respectively. There was no significant difference between stage I and stage II.

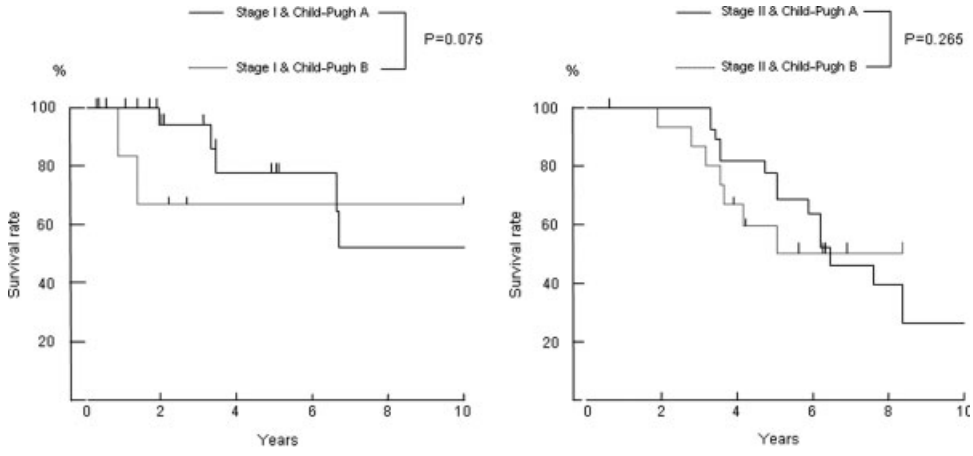

Figure 3. Long-term survival curves were calculated by using the Kaplan-Meier method for patients with stage I/Child-Pugh grade A hepatocellular carcinoma (HCC), patients with stage I/Child-Pugh grade B HCC, patients with stage II/Child-Pugh grade A HCC, and patients with stage II/Child-Pugh grade B HCC. For patients who had stage I/Child-Pugh grade A HCC, the 5-year, 8-year, and 10-year survival rates were 77.65%, 51.76%, and 51.76%, respectively; for patients who had stage I/Child-Pugh grade B HCC; the 5-year, 8-year, and 10-year survival rates were 66.67%, 66.67%, and 66.67%, respectively; and there was no significant difference between patients who had stage I HCC with grade A or grade B disease. For patients who had stage II/Child-Pugh grade A HCC, the 5-year, 8-year, and 10-year survival rates were 71.41%, 50.79%, and 25%, respectively; for patients who had stage II/Child-Pugh grade B HCC; the 5-year and 8-year survival rates were 50.79% and 50.79%, respectively; and there was no significant difference between patients who had stage II HCC with grade A or grade B disease.

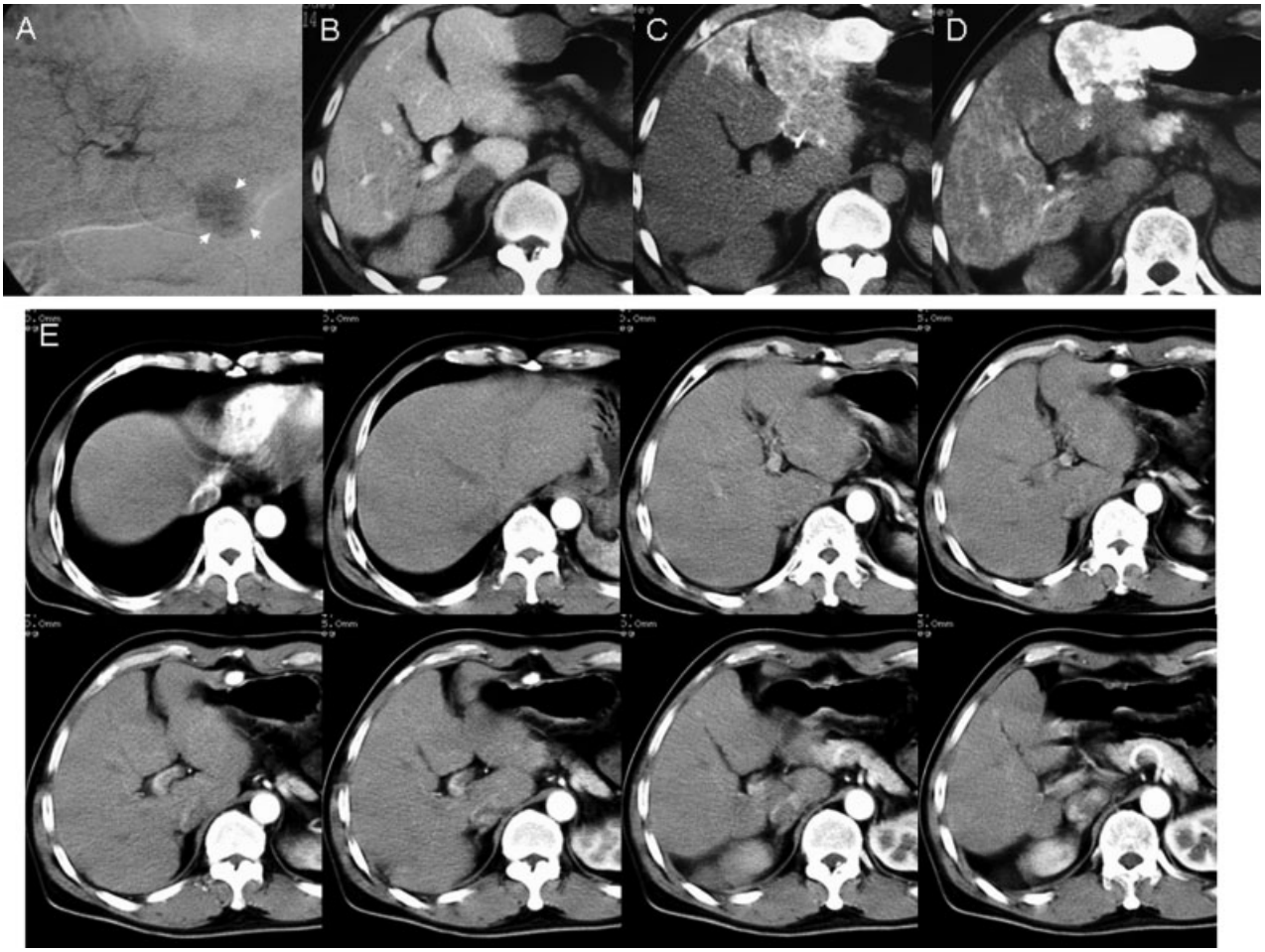

Figure 4. Imaging studies, including (A) hepatic digital subtraction angiography, (B) computed tomographic arterial portgraphy, (C) and computed tomographic hepatic arteriography, revealed typical hepatocellular carcinoma that measured 3.0 cm. (D) After undergoing angiographic subsegmentectomy, the patient has remained alive for 8 years without recurrence.

with stage III HCC, the 5-year survival rate was 47.47%; and, for patients with stage III/Child-Pugh grade A, the 5-year survival rate was 59.24% (Fig. 5). Ten patients in who had stage IV disease lived longer than expected after they underwent treatment with AS and received several remedies.

There were no severe complications. No treatment deaths or bilomas were recorded. Fever and abdominal pain were inevitable, however, but hydrocortisone or analgesics controlled those symptoms easily. A few patients had ascites or pleural effusions. Diuretics and albumin were administered as indicated. Alanine aminotransferase levels rose higher than with conventional TACE after AS (sometimes >1000 IU/L). The average hospitalization period was 2 weeks (Fig. 6). Massive ascites or icterus (bilirubin >2.0 mg/dL) or renal failure (creatinine >2.0 mg/dL) were contraindications for AS.

DISCUSSION

Although several methods for treating HCC have been developed, the prognosis for patients with HCC remains poor.[22] TACE was used first in Japan as a treatment method for typical HCCs with rich arterial vascularization[14-21] and currently is the most common treatment method in the world.[23] The original method of TACE has been modified to subsegmental TACE[16,18] and now to AS [21] or ultraselective TACE[20] by the development of an angio-CT system and microcatheters. In typical HCCs fed by arterial flow, however, embolization of the artery alone was not satisfactory, so Nakamura et al[17,19] tried simultaneous embolization of the artery and portal vein. Now, their trials have led to the development of AS or ultraselective TACE as a safe and effective treatment method for HCC. To perform AS successfully requires skill and the careful monitoring of patients to prevent

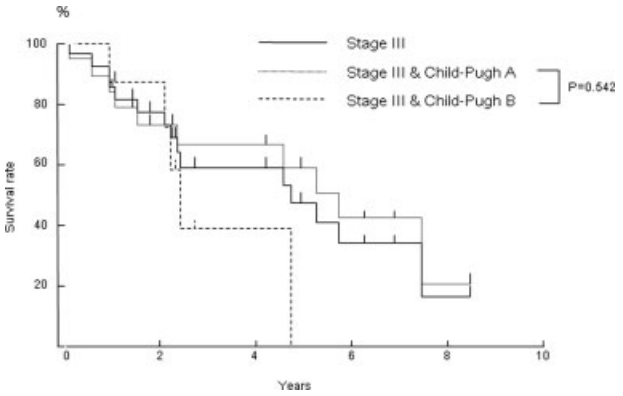

Figure 5. These long-term survival curves for patients with stage III hepatocellular carcinoma (HCC) reveal that, even in patients who had stage III disease, the 5-year survival rate was 47.47%. In patients who had stage III/Child-Pugh grade A disease, the 5-year survival rate was 59.24%.

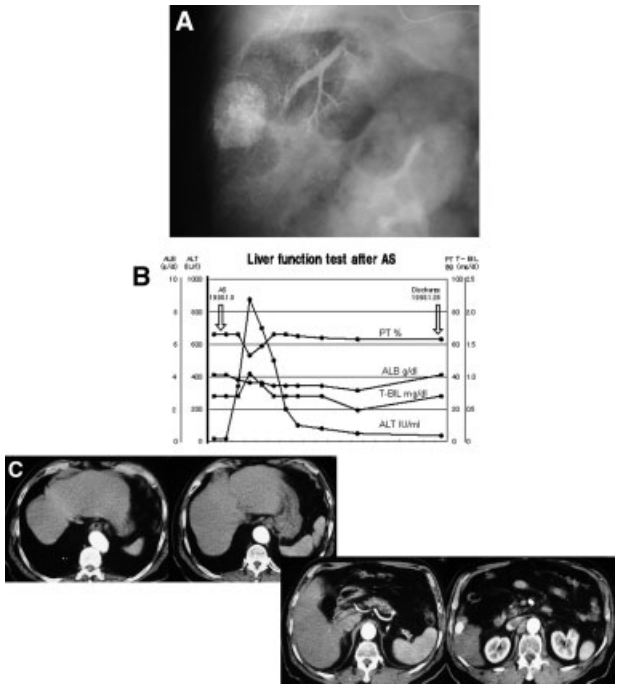

Figure 6. (A) After this patient underwent angiographic subsegmentectomy (AS), digital subtraction angiography revealed a hepatocellular carcinoma that measured 3.0 cm. (B) The alanine aminotransferase (ALT) level increased to 880 IU/mL but normalized after 18 days. ALB indicates albumen; PT, platelets; T-BIL, total bilirubin. (C) The patient has remained alive for 11 years without recurrence.

spasm of the arterioles or backflow of the embolus. To introduce iodized oil into the portal vein from a peripheral feeding artery, sufficient arterial flow is needed. Therefore, the thinnest microcatheter is useful for AS. Of course, iodized oils injected from the artery flew into both the portal vein and the venous channel, so we recommend a maximum amount of 10 mL iodized oil during a single AS treatment. Larger HCCs or HCCs at the liver hilum have several feeding arteries, so the AS procedure must be done carefully with attention to liver function. In our study, AS was recommended as first-line treatment for patients with stage I and II HCC. If a patient's liver function was tolerable, then even patients with stage III disease lived longer after AS. Patients with HCC >5.0 cm should undergo surgical resection. Massive ascites or icterus (bilirubin >2.0 mg/dL) and renal failure (creatinine >2.0 mg/dL) are contraindications for AS, and liver transplantation is recommended for patients who have Child-Pugh grade C disease. Recent improvements in imaging modalities have facilitated the detection of small nodules of cirrhosis. However, we have no consensus regarding whether a nodule is early cancer or how to manage early cancer. Therefore, the treatment of small, typical HCCs is important to improve the prognosis of HCC. In our experience, 7 patients with small, typical HCCs who underwent radiofrequency ablation had local recurrences in all 7 HCCs, and 3 of those patients died secondary to dissemination or seeding to the chest wall. In conclusion, AS should be investigated further as potential first-line therapy for the treatment of patients with stage I and II HCC.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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