

Surgical treatment of hepatocellular carcinoma

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Abstract. The effect of surgical treatment for hepatocellular carcinoma (HCC) was evaluated in 149 resected cases, 83.2% of which were associated with liver cirrhosis. The 3- and 5-year survival rates were 60.1% and 39.4%, respectively. The mortality rate was 4.1%. In patients aged over 70 years, liver cirrhosis was found in 53.3% of cases and the mortality rate was 6.7%. The 3- and 5-year survival rates were 50.8% and 33.9%, respectively. Factors that significantly affected survival for more than 5 years were a tumor size of less than 3 cm, Stage I disease, vp(–), IMo, and diploid type. The 5-year survival rate for patients with a single tumor of 3 cm or less was 54.2%, regardless of the surgical procedure. All 15 patients with a solitary tumor of 2 cm or less (Stage I, small liver tumor) were alive with a 5-year survival rate of 100%. The problem is the treatment of patients with a tumor measuring 3–5 cm in diameter and associated liver cirrhosis, because their prognosis after surgery is the worst. HrS (subsegmentectomy) is the minimal procedure of limited hepatectomy for these cases with postoperative multidisciplinary therapy.

rate has increased to over 50% due to advances in imaging modalities and the surgical procedures for HCC. However, the recurrence rate remains high, and the long-term survival of resected patients is not satisfactory. Therefore, we evaluated the results obtained in 149 surgically resected HCC cases.

Subjects and methods

We retrospectively analyzed 149 cases of HCC resected at Mie University during the last 16 years, including 124 cases (83.2%) associated with liver cirrhosis (Table 1). There were 115 men and 34 women. The mean age was 56.3 years and the range was 25–78 years. Partial resections (HrO) were performed in 30 patients; subsegmentectomies (HrS), in 43; segmentectomies (Hr1), in 38; and lobar resections (Hr2 and over Hr2), in 38 (4 extended right lobectomies, 1 extended left lobectomy, 27 right lobectomies, and 6 left lobectomies).

In all 25 tumors were less than 2 cm in diameter (16.8%), 40 measured 2–3 cm in diameter (26.8%), 41 were 3–5 cm in diameter (27.5%), 25 measured 5–10 cm in diameter (16.8%), and 18 were over 10 cm in diameter (12.1%).

The effects of these methods of hepatectomy were evaluated in relation to the following parameters: survival rate for curative resection, disease, Stage, capsule formation (fc), tumor embolus in the

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of death in men and the fourth most common cause of death in women in Japan. The treatments available for HCC can be divided into medical therapy, such as TAE or ethanol injection, and surgical treatment. The resectability

Table 1. Hepatocellular carcinoma

Operation	No. of patients	Liver cirrhosis		Mortality
		(+)	(–)	
Resection	149	124 (83.2%)	25 (16.8%)	8 ^a (5.4%)
Ligation of vessels	16	12	4	1 (6.3%)
Infusion	8	5	3	3 (37.5%)
Others	2	1	1	0 (0)
Totals	175	142 (81.1%)	33 (18.9%)	12 (6.9%)

^a Liver failure 4 cases, MOF 3 cases, pulmonary embolus 1 case

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Table 2. General rules for the clinical and pathological study of primary liver cancer – macroscopic staging [5]

T factor:	
T1:	A single tumor measuring 2 cm or less in its greatest dimension, no vascular invasion
T2:	A single tumor measuring 2 cm or less in its greatest dimension, no vascular invasion Multiple tumors with a maximal diameter of 2 cm or less, confined to one lobe A single tumor with a diameter exceeding 2 cm, no vascular invasion
T3:	A single tumor with a diameter exceeding 2 cm, vascular invasion Multiple tumors with diameter exceeding 2 cm, confined to one lobe
T4:	Multiple tumors in more than one lobe Associated vascular invasion in the first branch of the portal or hepatic vein
N factors:	
N0:	No metastasis in Group 1 lymph nodes ^a
N1:	Metastasis in at least Group 1 lymph nodes
M factor:	
M0:	No distant metastasis
M1:	Distant metastasis

Stage	Factor		
	T	N	M
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1–T3	N1	M0
IV A	T4	N1–N0	M0
IV B	T1–T4	N1–N0	M1

^a Group 1 lymph nodes:

a, subdiaphragmatic lymph nodes of the upper region of the liver;

b, lymph nodes in the hepatic porta

Table 3. General rules for the clinical and pathological study of primary liver cancer [5]

Extent of resection (Hr):	
Hr0:	Resection of less than one subsegment
HrS:	Resection of one subsegment
Hr1:	Resection of one segment
Hr2:	Resection of two segments
Hr3:	Resection of three segments
Hr4:	Resection of four segments
Extent of lymph node dissection (R):	
R0:	Liver resection with no dissection or incomplete dissection of group 1 lymph nodes
R1:	Liver resection with dissection of group 1 lymph nodes
R2:	Liver resection with dissection of group 1 and confirmed group 2 lymph nodes
Macroscopic classification (TW):	
TW (–):	No macroscopic cancerous infiltration within 10 mm of the cut liver surface in freshly excised specimens
TW (+):	Macroscopic cancerous infiltration within 10 mm of the cut liver surface in freshly excised specimens

portal vein (Vp), intrahepatic metastasis (IM), liver cirrhosis, tumor size, survival rate in aged patients, and factors affecting survival for more than 5 years. The clinical and pathological findings were classified according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer in Japan (Tables 2, 3).

Absolute curative resection was defined as liver resection without macroscopic cancerous infiltration within 10 mm from the cut liver surface in freshly excised specimens [TW(–)] in Stage I disease (Table 3). Relative curative resection was defined as liver resection with TW(–), but with tumor tissue removed in Stage I disease, or liver resection [extent of resection > present area of tumor (number of Hr > number of H), extent of lymph node dissection > position of metastatic lymph nodes (number of R > number of N) and TW(–)] in Stage II or III disease. In either case, there should be no tumor embolus remaining in the portal vein or bile duct on images of the remnant liver (Tables 2, 3).

Results

1. Survival rate in resected cases

The 3- and 5-year survival rates were 60.1% and 39.4%, respectively, for all of the resected cases. The 5-year survival rate was 61.9% for curative resection, 44.8% for curative resection without recurrence, and 5.7% for non-curative resection. Moreover, no patient undergoing non-curative resection remained without recurrence for more than 4 years (Fig. 1). Operative death occurred in 5 (4.1%) of the 149 resected cases.

1. *Stage.* The 5-year survival rate of patients with Stage I disease was 100%, whereas in Stage IV disease the 3-year survival rate was 29.2% (Fig. 2a).

2. *Capsule formation (fc).* The 5-year survival rate of patients with fc-inf(–) was 59.9% and that of those with fc(–) or fc-inf(+) was 41.5% and 40.3%, respectively (Fig. 2b).

3. *Tumor embolus in the portal vein (Vp)*[vp: microscopically]. The 5-year survival rates of patients with vp(–) and vp(+) were 58.8% and 40.0%, respectively, but in Vp₁ cases it was 20.2% (Fig. 2c).

4. *Intrahepatic metastasis (IM).* The 5-year survival rate for patients with IM₀ was 67.5%, but for IM₁ and IM₂ cases the rates were 26.1% and 22.4%, respectively (Fig. 2d).

5. *Liver cirrhosis.* Among the 149 resected cases, cirrhosis was found in 124 cases (83.2%). Even in the cirrhotic cases, the 5-year survival rate with curative resection was 62.7% (Fig. 3).

6. *Tumor size.* The 5-year survival rate of patients with tumors measuring less than 2 cm in diameter or between 2 and 3 cm in diameter were 56.7% and 54.2%, respectively. However, the 5-year survival rate of patients with tumors measuring over 5 cm in diameter was only 13.3% (Fig. 4). Even for large hepatomas, the 5-year survival rates without recurrence for patients with tumors sized 5–10 cm in diameter or over 10 cm in diameter were 83% and 80%, respectively, in the curative resection group (Fig. 5). However, the 5-year survival rate of patients with tumors measuring 3–5 cm in diameter was only 39%.

Prognosis after hepatectomy of solitary tumors measuring 3–5 cm in diameter: Surgically, it is important to determine the most appropriate method for hepatectomy to be performed for solitary tumors sized 3–5 cm in diameter.

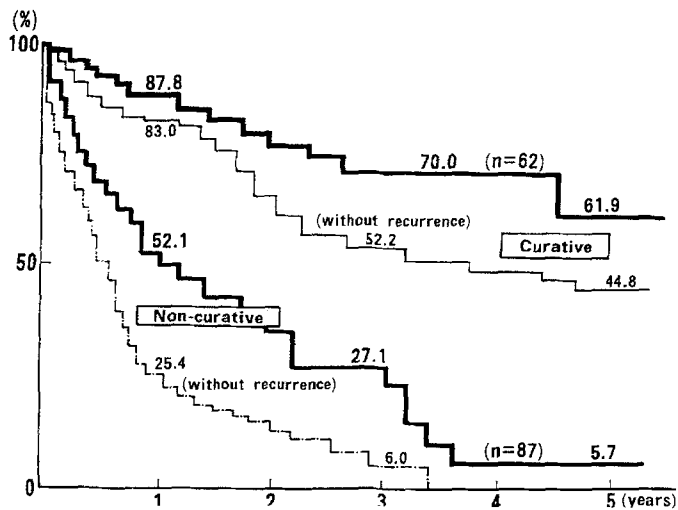


Fig. 1. Cumulative survival rate of HCC (Kaplan-Meier); curative versus noncurative treatment $P < 0.01$

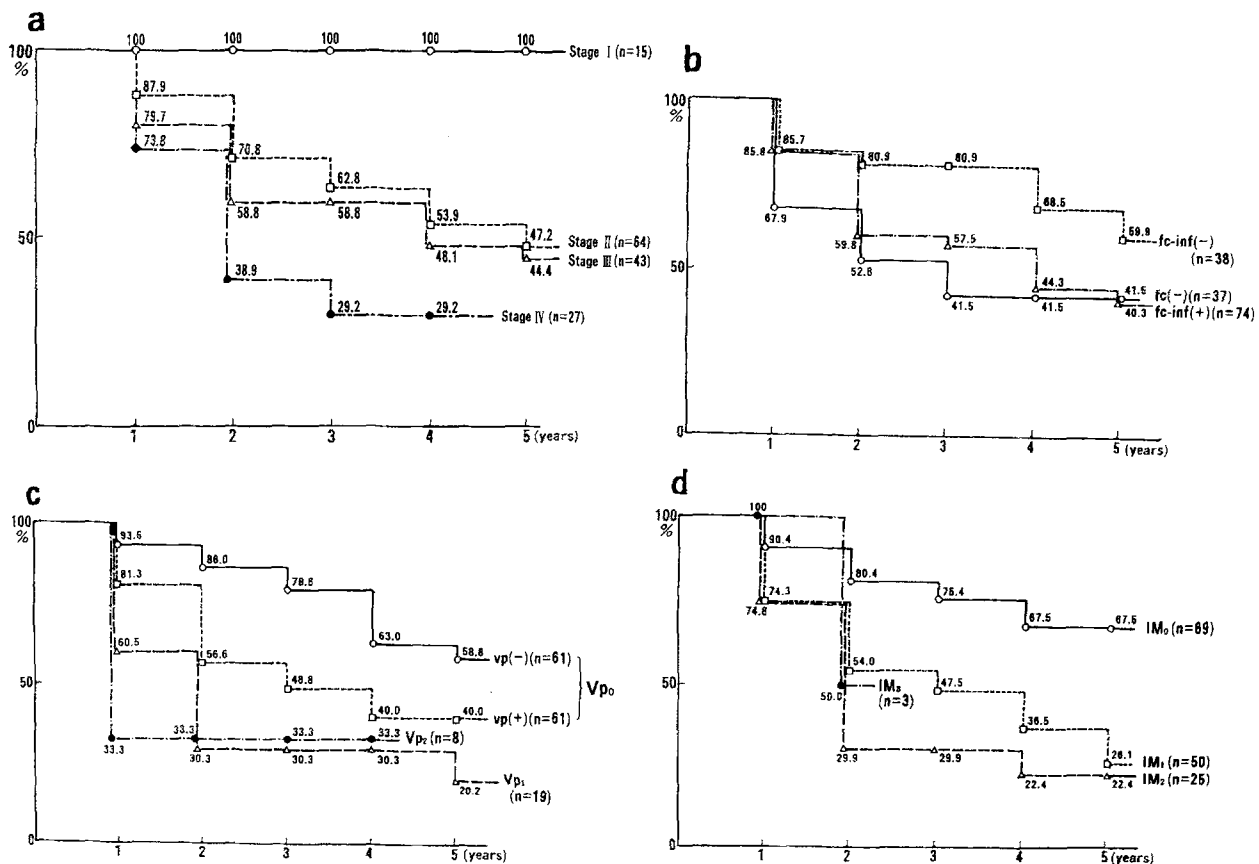


Fig. 2. a Stage and survival rate (Kaplan-Meier). b Capsule formation (fc) and survival rate (Kaplan-Meier); fc-inf(-) versus fc-inf(+), $P < 0.05$. c Tumor embolus in portal vein (Vp) and survival rate (Kaplan-Meier); Vp, macroscopically; vp, microscopically. d Intrahepatic metastasis (IM) and survival rate (Kaplan-Meier); IMo versus IM1 or IM2, $P < 0.01$

Without liver cirrhosis, Hr1 or over Hr2 hepatic resections were performed without any difficulty or severe complication. Both the 3- and 5-year survival rates were 100%. However, in cirrhotic patients, large hepatectomy was limited, and Hr0 resection was performed in 12 cases. The 3- and 5-year survival rates were 66.7% and 66.7%, respectively, in HrS resection.

2. Survival rate in aged cases

Among the 149 resected cases, there were 15 patients aged over 70 years, and 8 of these cases (53.3%) were associated with liver cirrhosis. Partial hepatic resection (Hr0) was performed in 5 cases (33.3%); HrS, in 4 (26.7%); Hr2, in 4 (26.7%); and over Hr2 (extended right lobectomy), in 2 cases (13.3%). Among the 15 cases, there was only 1 postoperative death, and the mortality rate was only 6.7%.

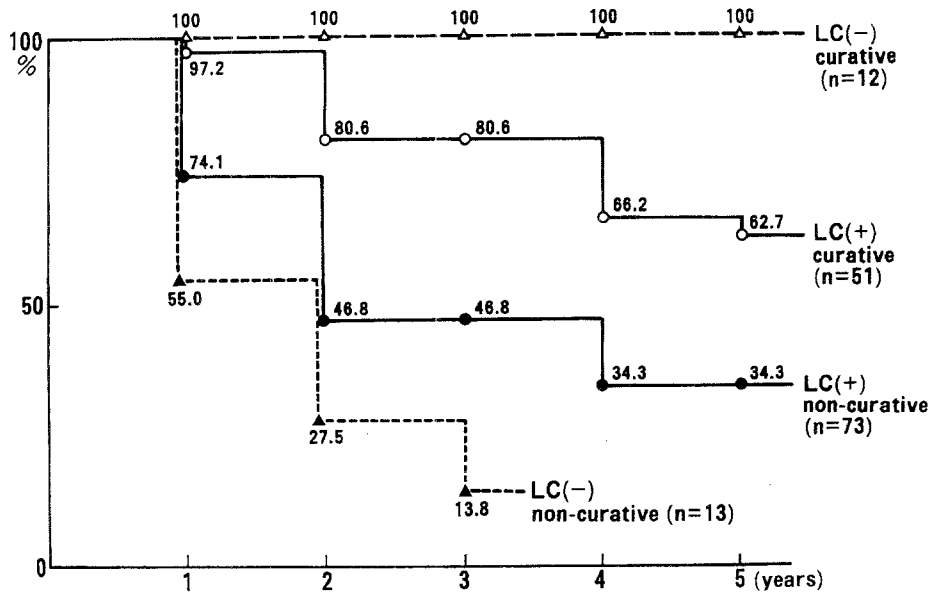


Fig. 3. Survival rate and curability with and without liver cirrhosis (Kaplan-Meier)

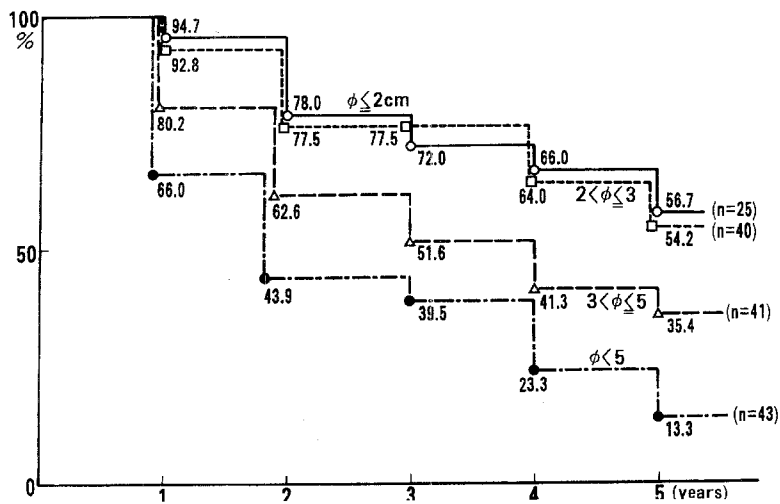


Fig. 4. Tumor size and survival rate (Kaplan-Meier)

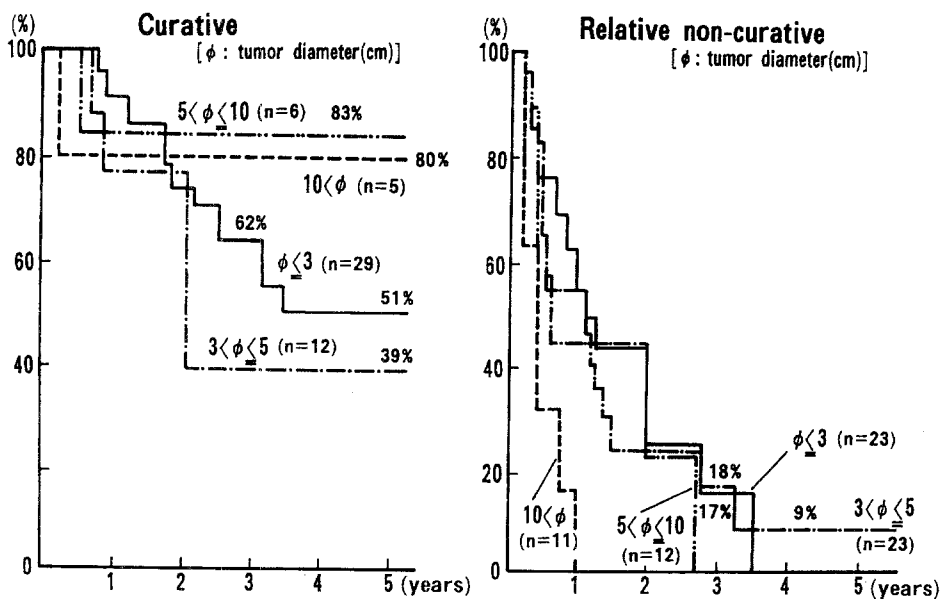


Fig. 5. Cumulative survival rate without recurrence of HCC after resection (Kaplan-Meier)

Survival for more than 5 years (n=23)				Factor	Death due to recurrence within 5 years (n=33)		
				Tumor size (cm)			
$\phi > 5$ 17.4	$5 \leq \phi < 3$ 17.4	$3 \leq \phi < 2$ 30.4	$\phi \leq 2$ 34.8		$2 < \phi \leq 3$ 15.2	$5 \leq \phi < 3$ 42.4	$5 < \phi$ 42.4
				Stage			
III 21.7	II 43.5		I 34.8		II 45.5	III 45.5	IV 9.0
				Vp			
Vp ₁ 34.8		Vp ₀ 65.2			Vp ₀ 12.2	Vp ₁ 63.6	Vp ₂ 24.2
				IM			
IM ₂ 8.7	IM ₁ 21.7	IM ₀ 69.6			IM ₀ 36.4	IM ₁ 27.2	IM ₂ 36.4
				DNA ploidy			
Aneuploid 21.0		Diploid 79.0			D 36.0	A 64.0	

Fig. 6. Factors affecting survival for more than 5 years

The 3- and 5-year survival rates were 50.8% and 33.9%, respectively.

3. Factors affecting survival for more than 5 years

Among the 149 resected HCC cases, 23 patients survived for more than 5 years. The differences between the two groups were analyzed: group 1 survived for more than 5 years, whereas group 2 died of recurrence within 5 years. Significant differences were observed in the incidence of a tumor size of less than 3 cm (65.2% in group 1), of Stage I disease (34.8% in group 1), of Vp₁ (63.6% in group 2), of IM₀ (69.6% in group 1), and of diploid type (79.0% in group 1) and aneuploid type (64.0% in group 2) between groups 1 and 2 (Fig. 6).

Discussion

In recent years, HCC cases have been treated either conservatively, or surgically by hepatectomy. The conservative therapies include TAE, ethanol injection (PEI or PEIT), and local anticancer therapy using a one-shot injection or a reservoir via a catheter placed in the intrahepatic artery. At present, multidisciplinary therapies are being applied even after surgical treatment [4].

About 75%–80% of HCC cases are associated with liver cirrhosis. Many patients have postoperative complications, and mortality is high. Therefore, we determined the surgical indication for high-risk patients based on the results of liver-function tests and various other tests. In 1978, we established criteria for evaluating the risk [7], and since then we have selected surgical cases using these criteria.

Child's criteria were designed for evaluating the risk in cases associated with liver cirrhosis [2], and they are widely used in various countries. In Japan, the clinical stage of HCC patients is determined according to the General Rules of the Liver Cancer Study Group of Japan [5], which comprise two liver-function tests, including the indocyanine green retention rate at 15 min (ICG R15), the

prothrombin activity, and items from Child's criteria. However, in Japan, each institution has its own criteria for this evaluation [6, 9, 10]. If the mortality rate is reduced to 5%–10% and the quality of the patient's life is taken into consideration, surgical treatment will be meaningful, regardless of the criteria used.

HCC patients in whom a large proportion of the liver has been surgically resected show a low frequency of recurrence and a good prognosis [8]. Many cases of HCC are associated with liver cirrhosis, and some of these patients are poor risks. Determining the appropriate extent of resection becomes a major issue. The term "limited hepatectomy" [3] is used for patients with HCC associated with liver cirrhosis. What is limited? What surgical procedure is limited? Prior to a discussion of limited hepatectomy, the purpose of surgical treatment of HCC should be clarified. If the HCC tumor mass is large and is treated by reduction surgery, there will be no problem. Even if the HCC tumor masses are 10 cm or larger in size, the prognosis is favorable in some patients, i.e., those undergoing curative surgery. In the 15 elderly patients (aged over 70 years) who underwent hepatic resection at our institution, the mortality rate was 6.7% and the 3- and 5-year survival rates were 50.8% and 33.9%, respectively. The results of hepatectomy were thus satisfactory, and hepatic resection can be surmised to be appropriate even in aged patients.

There were 23 patients who survived for at least 5 years. The various factors found to affect survival included the Stage, tumor size, vp(–), IM₀, and diploid type. The tumor size was especially important: the 5-year survival rate for patients with a single tumor sized 2 cm or less was 56.7%, regardless of the surgical procedure (i.e., HrO, HrS or Hr1). In 15 patients with a solitary tumor measuring 2 cm or less in diameter, referred to as small liver cancer, and Stage I disease in Japan who underwent absolute curative resection, the 5-year survival rate was 100%. Moreover, a single tumor measuring approximately 1 cm or less in diameter is defined as "early HCC" [11].

For patients with a tumor of less than 3 cm, the internist or radiologist may recommend PEI or PEIT. However, if the patient is at low risk and has a solitary mass in a su-

perforial layer of the liver, hepatic resection should be recommended. Chen et al. [1] reported that the survival rate of patients with tumors of less than 3 cm in diameter was no better than that of patients with tumors sized between 3 and 5 cm. The problem is how to treat patients with solitary tumors measuring 3–5 cm in diameter and liver cirrhosis. Hr0 was undertaken in 12 (40%) of 30 patients, and the 3- and 5-year survival rates were 40.9% and 13.6%, respectively. The 5-year survival rate for seven patients who underwent HrS was 66.7%, showing that HrS is the upper range of limited hepatectomy for a single tumor of 3–5 cm. Therefore, intensive treatment should be performed immediately after HrS in these patients. We performed percutaneous selective arterial catheterization for prophylactic purposes at 1 month after the surgery. The catheter was connected to a reservoir for one-shot or continuous infusion therapy. Ethanol injection and TAE are used by some institutions, but if there is no problem of risk, the tumor should first be confirmed as solitary by preoperative and/or intraoperative ultrasonography. This is really one of the indications for limited hepatectomy, and this point is what we want to emphasize.

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