J Hepatobiliary Pancreat Surg (2008) 15:589–595
DOI 10.1007/s00534-007-1288-4

Journal of HBP Surgery

Original articles

Intrahepatic dissemination of hepatocellular carcinoma after local ablation therapy

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Abstract
Background/Purpose. We aimed to clarify the histological features of and risk factors for intrahepatic dissemination after local ablation therapy (LAT) for hepatocellular carcinoma (HCC).
Methods. Between April 1992 and December 2005, 192 HCC patients underwent hepatic resection at our department, among whom were 17 patients who had local recurrences after LAT. Eight of these 17 patients had intrahepatic dissemination. The clinical and histological characteristics of these 8 surgically treated patients with intrahepatic dissemination were investigated.
Results. Histologically, numerous intrahepatic metastases were observed, mainly in the same section as the treated tumor, together with main or sectional portal vein tumor thrombi. Before the ablation therapy, the average tumor diameter was 2.1 cm, and 62.5% of the tumors were adjacent to the main or sectional portal vein. In terms of therapeutic factors, 25% of the patients had a prior needle biopsy and 62.5% had insufficient safety margins.
Conclusions. LAT for HCCs (even those less than 3 cm in diameter) adjacent less than 5 mm to the main or sectional portal vein possibly promotes intrahepatic dissemination.

Key words Hepatocellular carcinoma · Ablation · Recurrence

Introduction

A number of therapies for hepatocellular carcinoma (HCC) have been introduced, such as hepatic resection, local ablation therapy (LAT), transcatheter arterial chemoembolization (TACE), systemic chemotherapy, radiotherapy, and liver transplantation.[1–3] In particular, LAT has developed as a curative and minimally invasive treatment for small HCCs, and has been widely used around the world.[4–6] LAT includes percutaneous ethanol injection therapy (PEIT), microwave coagulation therapy (MCT), radiofrequency ablation (RFA), and cryoablation.[4–6] To date, complications of LAT, including intraabdominal bleeding, intrahepatic and subcapsular hematoma, hepatic abscess, biliary tract damage, hepatic infarction, hepatic failure, and needle-track seeding have been reported.[7,8] Especially neoplastic seeding is one of the most serious problems resulting in a poor prognosis.

HCC recurrences after LAT can be divided into intrahepatic and extrahepatic patterns. The former includes three modes of recurrence: intrahepatic metastasis of prior HCC, multicentric occurrence with no relationship to the initial HCC, and local recurrence after insufficient LAT. The local recurrence pattern includes relapse only at the therapeutic site and, more unusually, multinodular or diffuse recurrence beyond the ablated region. In the present study, we defined such unusual multinodular or diffuse recurrence after LAT as intrahepatic dissemination (IHD). In patients with local recurrence, several risk factors have been reported; these include tumor size more than 2 cm, subcapsular tumor location, poorly differentiated carcinoma, advanced tumor stage, high α-fetoprotein (AFP) levels, contact with vessels, and an insufficient safety margin.[9–12] In most patients with localized recurrence at the therapeutic site, additional hepatic resection or repeated LAT can be performed successfully. In contrast, there have been few reports of IHD, and its risk factors have never been fully clarified. The aim of the present study was to elucidate the specific histological features of and the risk factors for IHD.

Offprint requests to: H. Baba
Received: September 13, 2007 / Accepted: November 2, 2007

Patients and methods

Between April 1998 and December 2005, 192 HCC patients underwent hepatic resections, and between April 1992 and December 2006, 540 patients underwent LAT at the Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University. Seventeen HCC patients underwent liver resections because of local recurrences after LAT. Eight of these 17 patients were diagnosed with IHD (defined in the present study as a recurrence after LAT), with numerous intrahepatic metastases (IM), mainly in the treated section, together with main or sectional portal vein tumor thrombi (PVTT). The remaining 9 patients had localized solitary recurrences on the ablated area, with no or limited PVTT, and these features were determined as localized recurrences at the therapeutic site. All resected specimens were stained with hematoxylin-eosin and elastica van Gieson. Recurrences and outcomes were closely observed for 1 to 3 months after hepatic resection.

In the eight IHD patients, LAT prior to hepatic resection was performed for only two patients in our department, and in the remaining six, LAT was performed at other hospitals. To analyze the risk factors for IHD in the initial LAT, the following items were examined. In terms of the tumor characteristics before LAT, tumor size, vascularity of the tumor on enhanced computed tomography (CT) or magnetic resonance images (MRI), macroscopic tumor type, adjacency to the vasculature on ultrasonography (US) and CT images, and pretreatment levels of serum AFP and protein induced by vitamin K absence-II (PIVKA-II) were examined. In terms of therapeutic factors, biopsy prior to LAT, disappearance of tumor enhancement, presence of a safe surgical margin, number of LAT sessions, and arterioportal shunt (A-P shunt) after LAT on images were investigated. The distance between the treated tumor and the main or sectional portal vein was analyzed with the use of US and 5-mm-width multidetector CT scanning. Widths less than 5 mm were defined as being adjacent to the portal branch. With regard to the LAT procedure, safety margins greater than 5 mm in all directions around the tumor were defined as sufficient.

The institutional review board approved this study and informed consent was obtained from all patients before hepatic resection.

Results

The clinical characteristics of the IHD patients are summarized in Table 1. The LAT procedures were as follows: two patients had PEIT alone, three had MCT, two had RFA alone, and one had PEIT in combination with RFA. Resection of one section was performed in four patients, and resection of two or more sections was performed in four. The mean interval from the initial LAT to the diagnosis of IHD was 17.5 months (range, 3 to 29 months). In patients with PVTT, sectional attenuation was often observed on enhanced CT or MRI; therefore, the diagnosis of the recurrences was quite difficult and the interval from the initial LAT to the hepatic resection tended to be longer. Histologically, the tumors in four patients contained poorly or moderately to poorly differentiated components and the tumors in the remaining four were diagnosed as moderately differentiated HCC. All patients had countless IM and main or sectional PVTT in the same section as

Table 1. Clinical characteristics in patients with intrahepatic dissemination after LAT treated with hepatic resection

Patient no.	Sex	Age (years)	HBs antigen	HCV antibody	Initial LAT	Interval from initial LAT to HR (months)	Hepatic resection (HR)	Histological differentiation at HR
1	Male	74	Negative	Negative	PEIT and RFA	18	Right hepatectomy	Moderate
2	Male	65	Positive	Negative	PEIT, five times	29	Posterior sectionectomy	Mod-poor
3	Male	57	Positive	Negative	MCT	22	Extended posterior sectionectomy	Moderate
4	Male	61	Positive	Negative	PEIT	22	Extended posterior sectionectomy	Moderate
5	Male	80	Negative	Positive	MCT, twice	10	Anterior and median sectionectomy	Poor
6	Male	52	Positive	Negative	RFA	27	Right trisectionectomy	Poor
7	Male	70	Negative	Positive	MCT	3	Anterior-Inferior subsectionectomy	Mod-poor
8	Male	63	Negative	Positive	RFA	9	Right hepatectomy	Moderate

LAT, local ablation therapy; HR, hepatic resection; PEIT, percutaneous ethanol injection therapy; RFA, radiofrequency ablation; MCT, microwave coagulation therapy; ND, not determined

Table 2. Tumor factors in patients with intrahepatic dissemination at the time of initial LAT

Patient no.	Tumor size (cm)	Number of Tumors	Tumor vascularity	Gross tumor type	Adjacency to portal vein (less than 5 mm)	Serum AFP (ng/ml)		Serum PIVKA-II (mAU/ml)	
						Before LAT	Before HR	Before LAT	Before HR
1	3	1	Yes	SN	Yes (secondary PV)	33.4	2598	ND	20
2	2	1	Yes	SN	No	15.1	22.9	ND	15
3	1.5	1	Yes	SN	Yes (secondary PV)	4.1	11	271	751
4	2.5	1	Yes	SN	No	4.7	70.2	21	213
5	2	1	Yes	SN	Yes (secondary PV)	68	9252	20	300
6	1.5	1	Yes	SN	Yes (sectional PV)	31.5	20.3	26	229
7	1.5	2	Yes	SN	No	81.1	575	ND	592
8	3	2	Yes	SNEG	Yes (primary PV)	2818	5280	1759	1432

LAT, local ablation therapy; HR, hepatic resection; SN, single nodular type; SNEG, single nodular with extranodular growth type; PV, portal vein; ND, not determined

Table 3. Therapeutic factors in patients with intrahepatic dissemination

Patient no.	Biopsy prior to LAT	Disappearance of enhancement	Surgical margin (greater than 5 mm)	Number of LAT sessions	A-P shunt after LAT
1	No	Incomplete	Insufficient	2	No
2	No	Complete	Sufficient	5	No
3	Yes	Complete	Sufficient	1	No
4	No	Complete	Insufficient	1	No
5	No	Complete	Sufficient	2	No
6	No	Complete	Insufficient	1	No
7	No	Incomplete	Insufficient	1	No
8	Yes	Incomplete	Insufficient	2	No

LAT, local ablation therapy; A-P shunt, arterioportal shunt; ND, not determined

the treated HCC. Especially, IM were spread like a stream from the ablated lesion.

Tumor characteristics at the initial LAT in the patients with IHD are shown in Table 2. The mean tumor size was 2.1 cm in diameter (range, 1.5 to 3.0 cm). High tumor vascularity was observed in all patients; simple nodular tumors were observed in seven, and tumors adjacent to the main or sectional portal vein in five. The serum AFP level was above 200 ng/ml in one patient, and serum PIVKA-II levels were above 200 mAU/ml in two.

Therapeutic factors in patients with IHD are shown in Table 3. Needle biopsies prior to LAT were performed in two patients, and the disease in the remaining six patients was diagnosed as HCC with US and enhanced CT imaging. Five patients underwent LAT with an insufficient surgical margin. No apparent A-P shunts after LAT were observed on diagnostic imagings.

All eight patients underwent hepatic arterial chemotherapy with an implanted reservoir immediately after hepatic resection for IHD;[13] however four of the eight had recurrence within 3 months after the hepatic resection and died within 1 year.

Patients' presentations

Preoperative images and findings of the resected specimen in patient 4 with IHD (patient number according to numbering in Tables 1–3) are shown in Fig. 1. After TACE and PEIT, progressive elevation of the PIVKA-II level was observed. A recurrence with massive PVTT was diagnosed by CT, 22 months after the initial LAT. He underwent three courses of adjuvant hepatic arterial chemotherapy with cisplatin in combination with 5-fluorouracil (FU) after hepatic resection, and, fortunately, has been doing well without recurrence for 21 months after the hepatectomy.

Preoperative images and findings of the resected specimen in patient 6 with IHD are shown in Fig. 2. Three courses of adjuvant hepatic arterial chemotherapy with cisplatin in combination with 5-FU were performed immediately after hepatic resection. However, rapid tumor progression occurred a month after the hepatectomy. Unfortunately, he died 5 months later.

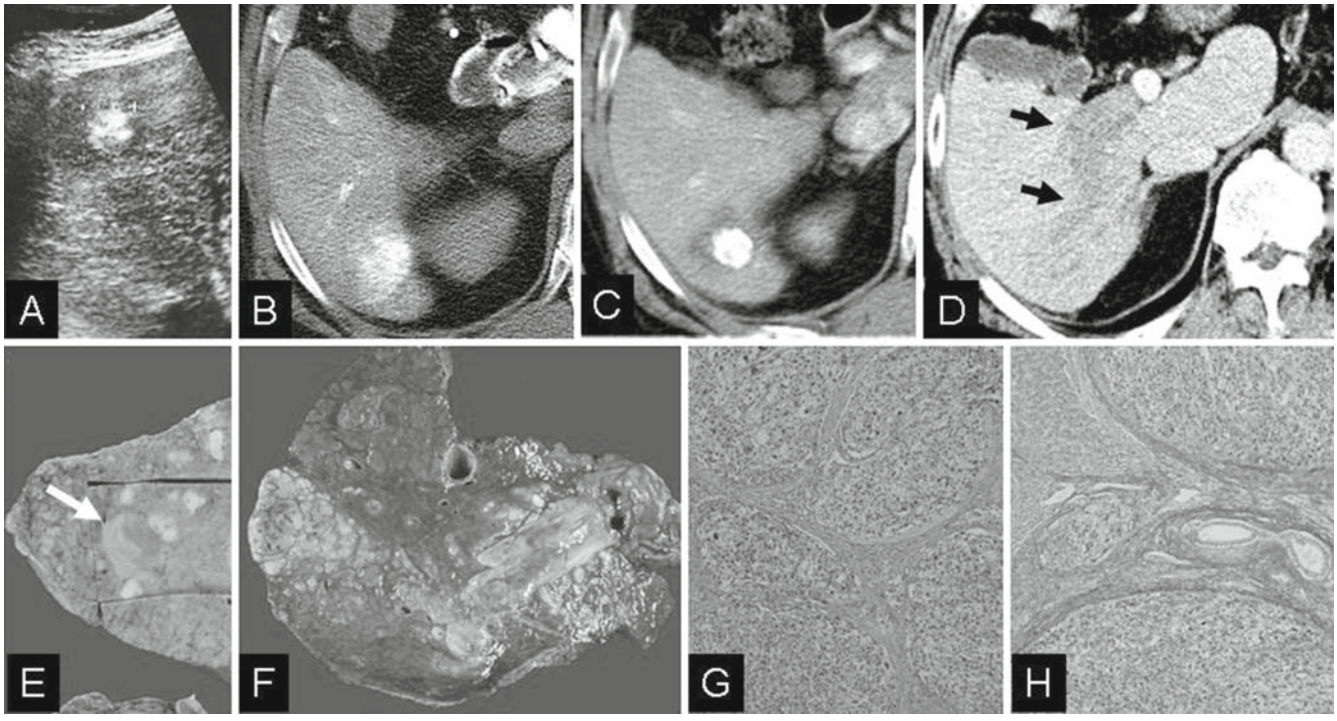

Fig. 1A–H. Preoperative images and findings of the resected specimen in the fourth patient with intrahepatic dissemination (IHD). **A** The tumor was 2.5 cm in diameter on ultrasound (US) imaging. **B** The tumor was well enhanced on computed tomography during hepatic arteriography (CTHA). Transcatheter arterial chemoembolization (TACE) in combination with percutaneous ethanol injection therapy (PEIT) had been performed. However, the surgical margin was determined to be insufficient by enhanced CT a month after local ablation therapy (LAT; **C**). Eleven months after the LAT, the serum level of protein induced by vitamin K absence-II (PIVKA-II) had been progressively increasing. Recurrence was recognized on CT 22 months after the initial LAT. The recurrence was diagnosed as portal vein tumor thrombi (PVTT) in the right posterior portal branch (*arrows*; **D**). The resected specimen showed an ablated tumor (*white arrow*; **E**) and contiguous numerous intrahepatic metastases (IM) and massive PVTT in the entire posterior section (**F**). Countless numbers of IM and PVTT were observed (**G**). The walls of arteries and bile ducts surrounded by the multiple IM were stained with elastica van Gieson (**H**). (**G** H&E, ×40; **H** H&E, ×40)

Discussion

In order to avoid local recurrences, LAT requires an adequate safety margin to ablate microscopic invasion around the periphery of the tumor.[10,14] Mulier et al.[15] noted that the local recurrence rate was higher when the physician did not aim to coagulate a peritumoral margin of 1 cm. In their investigation of the pathological findings of 209 resected primary HCCs less than 3 cm in diameter, Nakashima et al.[16] reported that intrahepatic metastases were found in 22 patients (11%), and 91% of all the metastatic lesions were within 5 mm. Similar to hepatic resection, it is important to ablate the tumor with enough surrounding tissue (5 mm in width at least).[10,14–16] In the present study, the surgical margin was insufficient in five of the eight patients. Similarly, insufficient surgical margins were observed in six of the nine patients with localized recurrence at the therapeutic site after LAT (data not shown).

In the IHD patients, the mean tumor size before LAT was relatively small, 2.1 cm in diameter (range, 1.5 to 3.0 cm) and all patients met the Milan criteria.[17] The therapeutic effects and complication rates were reported to be satisfactory in small tumors compared to tumors larger than 3 cm.[4,5] It is quite important to consider that IHD can occur after LAT even in patients with small HCCs. Single nodular type HCCs with extranodular growth and confluent multinodular type HCCs often show high rates of PVTT and IM.[16,18] Therefore, LAT should not be employed for tumors that are macroscopically diagnosed as non-single-nodular type on preoperative images. If untreated satellite nodules remain around the tumor after LAT, they may have a high risk of rapid development in an infiltrative fashion.[19]

Histologically, half of the tumors in our IHD patients were poorly or moderately to poorly differentiated HCCs, and the remaining tumors were moderately differentiated. All patients showed recurrence with numerous IM and PVTT. PVTT was detected in the main portal vein branches in three patients and in the sectional branches in five. Uncountable numbers of IM were observed in the same section as the ablated tumor

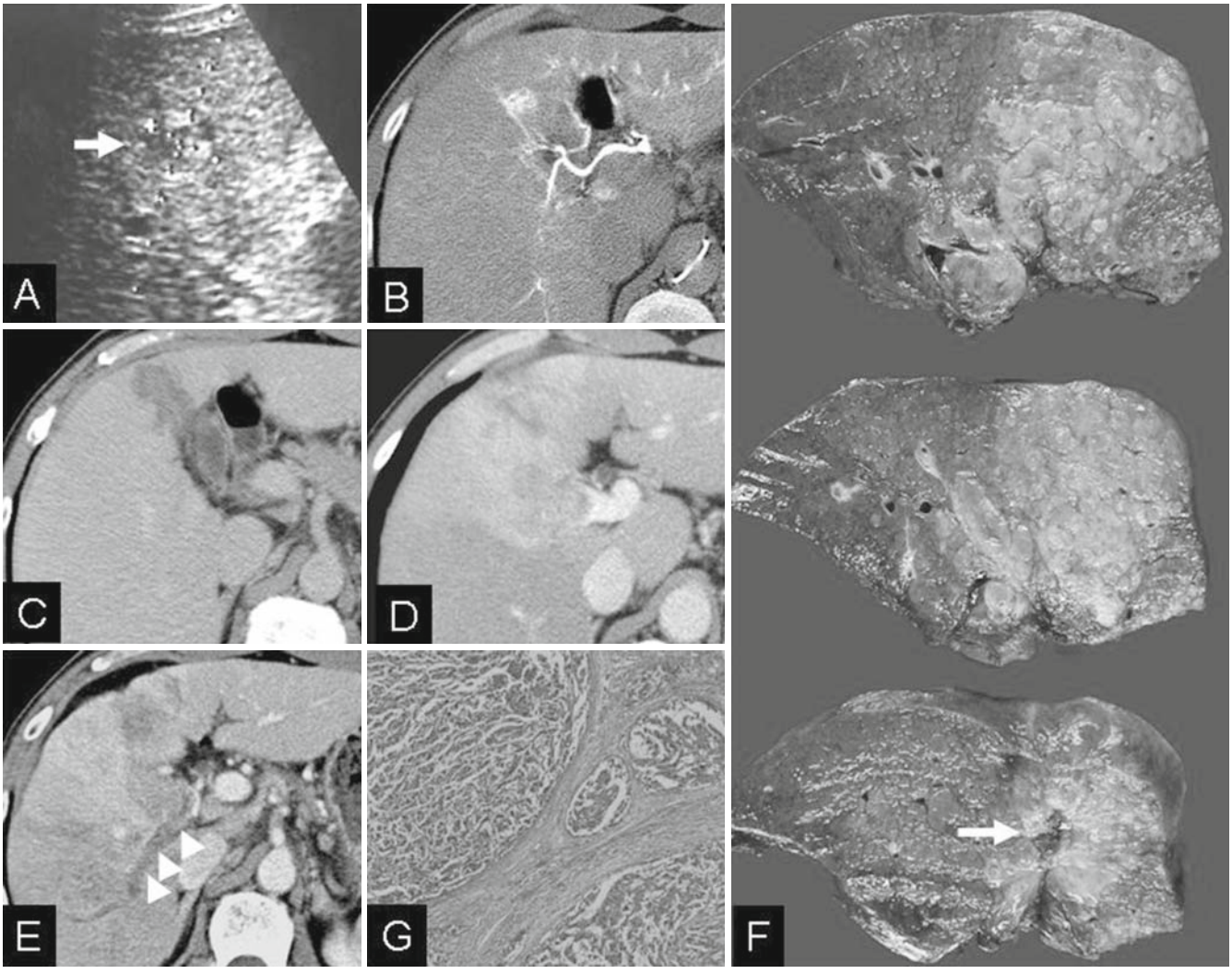

Fig. 2A–G. Preoperative images and findings of the resected specimen of the sixth IHD patient. The tumor was located in the anterior-inferior section. The tumor was 1.5 cm in diameter and had a low echoic capsule shown by US imaging (*arrow*; **A**). The tumor was in contact with the sectional Glisson's capsule on CTHA before radiofrequency ablation (RFA; **B**). RFA was performed; however, the surgical margin was insufficient (**C**). Twenty-three months after the RFA, a recurrence was detected as PVTT of the right portal branch (**D**). In order to achieve a safe hepatic resection, percutaneous transhepatic portal vein embolization of the right portal vein was performed (**E**). The embolized right portal vein was detected as a linear unenhanced area (**E**; *arrowheads*). A right trisectionectomy was successfully achieved. Limitless numbers of sectional IM and massive PVTT continuing from the ablated area (*arrow*) were observed in the resected specimen (**F**). Microscopic examination of countless IM revealed poorly differentiated hepatocellular carcinoma (**G**; H&E, ×40)

and/or in sections adjacent to the ablated tumor, together with advanced PVTT. The PVTT originated from the ablated tumor.

Extrahepatic tumor seeding was reported in 13% of 32 patients with HCC after RFA, all of whom had undergone prior needle biopsy.[20] The risk factors for extrahepatic tumor seeding after LAT were as follows: subcapsular location, poor differentiation of HCC, and high AFP levels (more than 100 ng/ml).[20] In contrast, Livraghi et al.[21] reported that RFA resulted in extrahepatic tumor seeding in only 0.9% of 1314 patients, and the seeding was diagnosed between 5 and 20 months (mean, 13.6 months) after RFA. They concluded that only previous tumor biopsy was associated with extrahepatic tumor seeding. Tarantino et al.[22] reported that extrahepatic seeding after PEIT for HCC occurred at a frequency of 0.2% to 1.4%. In the present study, needle biopsies prior to LAT were performed in only two patients (25%). In order to avoid needle-tract seeding, endoscopic or open approaches must be selected for subcapsular HCCs.[23] Needle puncture during LAT may cause an A-P shunt, and as a result, HCC cells can reach the portal branch and develop metastases. The risk of IHD incurred by the insertion of an LAT needle must

Table 4. Reported cases of intrahepatic neoplastic progression after LAT

Author	Year	Age (years)	Sex	Tumor size (cm)	Initial LAT	Interval from initial LAT to recurrence (months)	Treatment for recurrence
Seki et al.[24]	2001	75	Male	2.5	RFA + TACE	1.5	TACE
Takada et al.[19]	2003	68	Female	2.7	RFA	4	HAI
Takada et al.[19]	2003	64	Male	2	RFA	6	None
Nicoli et al.[25]	2004	66	Female	3.5	RFA	2	None
Ruzzenente et al.[26]	2004	66	Male	3.5	RFA	ND	Two of four patients received TACE
Ruzzenente et al.[26]	2004	75	Male	3.8	RFA	ND	
Ruzzenente et al.[26]	2004	59	Male	4.5	RFA	ND	
Ruzzenente et al.[26]	2004	62	Male	4.5	RFA	ND	
Izai et al.[27]	2005	71	Male	2	RFA	1	Hepatic resection

LAT, local ablation therapy; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; ND, not determined

be considered.[15,25,26] Although no apparent A-P shunts after LAT were detected in the diagnostic images after LAT in the present study, it is possible that IHD might occur without biopsy prior to LAT.

Several patients with intrahepatic neoplastic progression after RFA have been reported recently (Table 4),[19,24–27] although reports of patients who underwent hepatic resection for such recurrences are few. Of note, the criteria for these progressions were not clearly defined. In the present study, IHD was defined as a recurrence with numerous IM with massive PVTT after LAT at the treated section, based on the histological findings. Ruzzenente et al.[26] have suggested that the risk factors to be considered are: a high AFP level (>200 kU/l), location of the tumor near the portal vein branches (<1 cm from main or segmental portal branches), and poor differentiation. During thermal ablation, circulating bubbles in the venous system were observed on ultrasonography.[24] With the increased intratumoral pressure during thermal ablation, tumor cells may flow into the adjacent portal vein, and as a result, dissemination may occur throughout the liver.[24,26,28] Izai et al.[27] reported a patient with rapid progression of PVTT after RFA. Microscopically, necrotic HCC cells were detected in the portal vein within the ablated area with elastica van Gieson staining.[27] Preexisting microscopic portal venous invasion may have been responsible for the massive PVTT.[19,27] If we can avoid increasing intratumoral pressure during LAT, the subsequent explosive growth of the ablated tumor and the frequency of eventual IHD can be decreased.[29] When a tumor is located adjacent to a large vessel in the liver, the ablated area will become smaller because of a cooling effect, and this may result in an increased chance of HCC cell dissemination into drainage veins.[12] In patients with viable PVTT, even microscopically, LAT would promote the migration of tumor cells into the adjacent hepatic parenchyma. In the present study, HCCs were located adjacent to the major or sectional portal vessels in 62.5% of the IHD patients. In contrast, in only two of the nine patients with localized recurrence after LAT were the HCCs located close to the portal vein (data not shown). Adjacency (less than 5 mm) to the major portal vein may be a risk factor for IHD after LAT.

Although complete tumor necrosis was achieved with LAT, rapid intrahepatic neoplastic progression was observed after the procedure.[26] It is possible that LAT induced a morphological change in the tumor cells, exaggerating their biological malignancy.[24] Thermal stress may change the phenotypic expressions of cancer cells; therefore, insufficient LAT may induce the rapid progression of HCC.[30] It is reported that thermal stress increases oxidative DNA modifications and induces chromosomal gains and/or losses in vitro, and thermal ablation strongly promotes the growth of residual cancer cells.[31–33] LAT stimulates liver proliferation adjacent to the treatment site, and promotes the progression of tumor micrometastasis.[34] Based on these findings, LAT can probably cause IHD, although the incidence of IHD after LAT is not very high.

In conclusion, LAT for HCCs adjacent less than 5 mm to major portal veins or branches can promote IHD, with a very poor prognosis, even in patients with small tumors (less than 3 cm). The diagnosis of IHD is sometimes difficult because of the sectional attenuation on enhanced CT or MRI. The late diagnosis of IHD can worsen the prognosis of IHD.

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