Case Report

Aggressive Recurrence after Radiofrequency Ablation of Liver Neoplasms

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SUMMARY

Radiofrequency ablation is considered safe for inoperable liver neoplasms; with small lesions the rate of success is very high, the local recurrence is marginal and generally suitable for a retreatment. We have little information about the possibility of rapid regrowth of the tumor after a response judged as complete.

We present four patients, affected by primary (3 patients) and metastatic (1 patient) uninodular cancer. All the lesions were small, superficial and well suited for surgery, but were treated by radiofrequency ablation elsewhere. The early instrumental evaluations stated a complete result in all the patients

Cancer regrowth was diagnosed at 3, 4, 6 and 12 months after radiofrequency ablation, always starting from the treated lesion. In case 1 the whole right lobe was involved together with a controlateral multinodular recurrence; cases 2 and 3 presented an extensive liver and parietal wall involvement; while in the fourth patient a diffuse biliary colonization was observed. Only 1 patient was suitable for surgery; the others died 6, 2 and 4 months, respectively, after recurrence.

Recurrence after radiofrequency ablation may show an aggressive evolution precluding any possibility of cure. Radiofrequency ablation must not be considered a suitable alternative to surgery in patients with a low surgical risk.

KEY WORDS:
Liver neoplasm; Radiofrequency ablation; Hepatic cancer recurrence

ABBREVIATIONS:
Radiofrequency Ablation (RFA); Percutaneous Ethanol Injection (PEI); Computed Tomography (CT); Hepatitis C Virus (HCV); Hepatocellular Carcinoma (HCC); Hepatitis B Virus (HBV); Alpha-Fetoprotein (AFP); Magnetic Resonance Imaging (MRI)

INTRODUCTION

Surgery is considered as the only known curative treatment for malignant tumors of the liver. Nonetheless, especially for primary cancer, other therapeutic options will be validated not only for palliative reasons, but also with a curative intent. Many reports suggest the same life expectancy both for surgery and for percutaneous ethanol injection (PEI) (1,2) or radiofrequency ablation (RFA) (3). Thanks to a lower immediate risk, these non-surgical procedures have been considered as first choice treatment even for patients suitable for liver resection (3).

Experience in the treatment of liver cancer by RFA is quite recent, therefore there is a lack of data concerning long-term results after RFA. In the reported experiences follow-up is generally short and the therapeutic effect mostly assessed by computed tomography (CT) evaluation at 1-3 months rather than with the help of histological analysis (4,5).

At this evaluation the recurrence of cancer after RFA is generally described as a thin area of vital tissue surrounding the necrotic area and is not considered as a definitive treatment failure, it being possible to complete the therapeutic effect with subsequent sessions (4,6).

No report clearly claims the possibility of an ominous evolution consequent to an incomplete response to local treatment.

Neoplastic liver lesions are frequently observed and treated in our surgical department as there is a particularly high incidence of this neoplasm in our province (7).

Patients are referred to our department for the first treatment or after failure of primary treatments performed in other departments or institutions.

Some recent and significant observations of small lesions treated by RFA and followed by unusually rapid and aggressive recurrence suggest the need to describe these events and discuss the consequent physiopathological and clinical implications.

CASE REPORTS

Case 1

A 68-year-old woman, treated in 1994 for a retroperitoneal leiomyosarcoma; three years later echography showed a hepatic metastasis measuring 2.5cm located in the 7th segment. At CT no other recurrence was noted either in the liver, with normal morphology and function, or in the retroperitoneal area **(Figure 1a)**. The patient was proposed for a cycle of percutaneous RFA. The first CT, two months after RFA, showed no enrichment after contrast injection, thus suggesting a complete therapeutic result. Multiple small recurrences at the margin of the necrotic area were suspected 6 months later **(Figure 1b)** and were treated with another cycle of RFA. Again, the one-month control CT showed complete necrosis, the ablated zone being larger than the resid-

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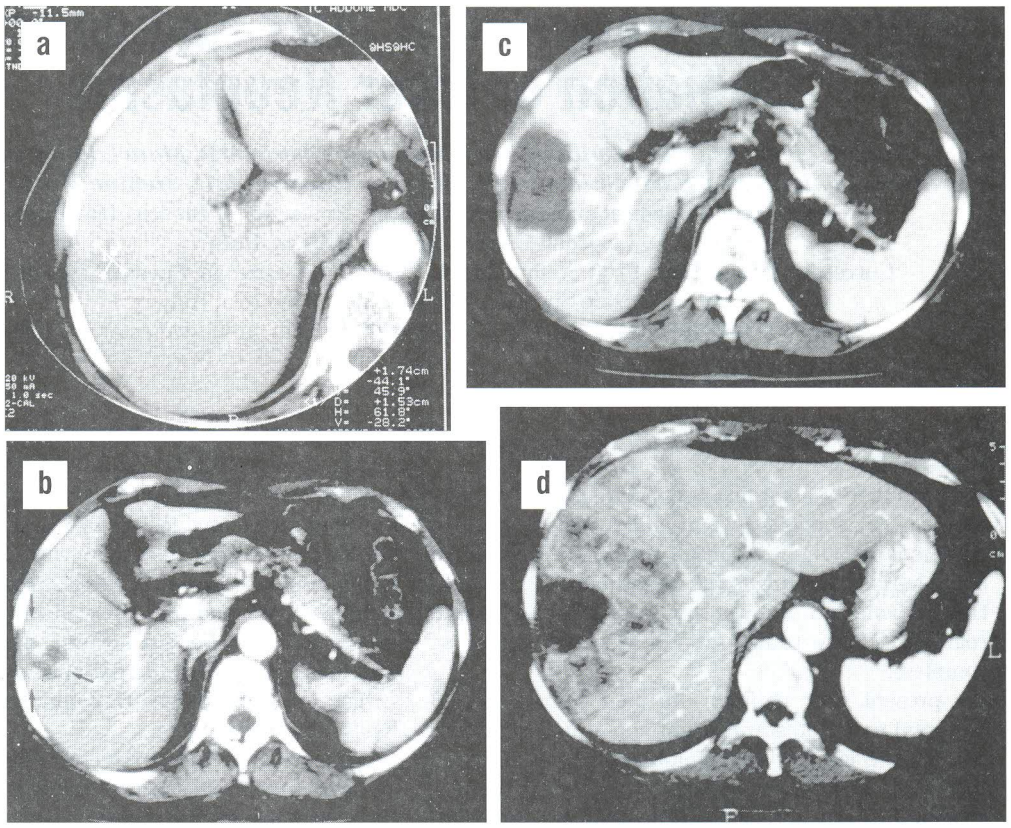

FIGURE 1
A 68-year-old woman with a small metastasis (retroperitoneal leiomyosarcoma).
(a) CT scan shows a solitary lesion in the 7th segment.
(b) Control CT 6 months after RFA: a local recurrence all around and inside the nodule is marked by enrichment in the arterial phase (black arrows).
(c) One-month follow-up CT scan after a second cycle of RFA; the image suggests complete ablation of the tumor, the necrotic area being wider than the original tumor.
(d) Control CT 4 months after the previous one: massive liver involvement due to an infiltrative cancer regrowth surrounding the RFA lesion.

ual tumor **(Figure 1c)**. Four months later, at the control CT, the entire right lobe had been replaced by an infiltrative cancer apparently arising from the primary treated lesion **(Figure 1d)**; two small nodules were present in the left lobe. At laparotomy, the right lobe was totally involved by the recurrence; i.o. echography showed more than 12 small nodules in the left lobe. Despite chemotherapy, the patient died 6 months later.

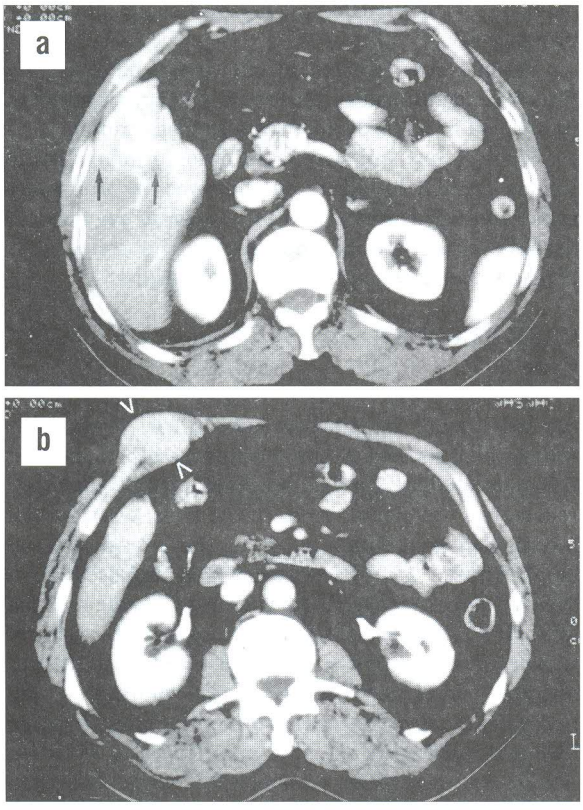

FIGURE 2
A 67-year-old man suffering from HCV-related cirrhosis complicated by a 2-cm HCC in the 5th segment.
(a) One year after RFA control, enhanced CT scan shows a multinodular confluent recurrence, 7x6cm in size, including the entire 5th segment (black arrows).
(b) Neoplastic seeding in the parietal wall is also present (white arrowheads), the size of the mass doubling in one month of observation.

Case 2

In a 67-year-old man followed for chronic hepatitis C virus (HCV)-related hepatitis, echography in 1997 showed a small (2cm) nodule of hepatocellular carcinoma (HCC); the lesion was located superficially in the 5th segment, far from the vascular tree. The patient was in good clinical condition, with normal liver function (Child A). In the absence of any contraindication for resective surgery, he was treated with RFA. One year later, multiple confluent nodular formations appeared at the site of thermoablation, forming a 7x6-cm mass associated with a new nodule in the 8th segment **(Figure 2a)**; a mass was noted in the abdominal wall along the exact trajectory of the needle with a clear increase in size during 1-month observation **(Figure 2b)**. We performed a wide resection of the parietal wall, associated with segmentectomy of the 5th segment and intraoperative ethanol injection for the small deep lesion located in the 8th segment.

The patient died from liver failure fifteen months later.

Case 3

A 66-year-old female was in follow-up for chronic

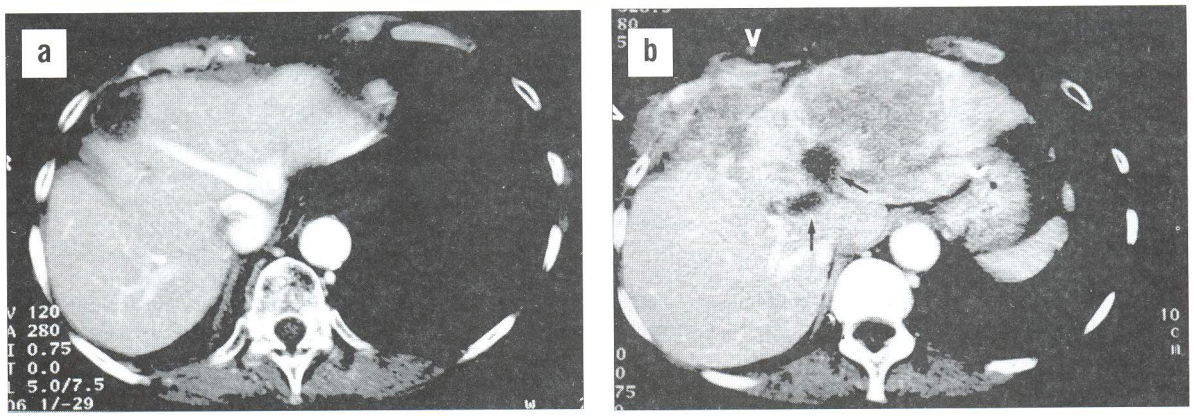

FIGURE 3 A 66-year-old patient, affected by HBV-related chronic liver disease. **(a)** One month CT scan after RFA of a small recurrent nodule of HCC in the 4th segment; a wide area of complete necrosis is showed surrounding the middle suprahepatic vein. **(b)** Three months later, a wide recurrence in the left lobe was present; a complete neoplastic portal thrombosis (black arrows) was evident as well as a large parietal recurrence involving the costal plane and connected with a tumoral involvement of the 4th segment (white arrowheads).

HCV-related hepatitis. In February 1995, due to the onset of HCC (2cm in the 7th segment) in the absence of overt cirrhosis we performed a limited hepatic resection, and a second liver resection 6 months later due to the presence of a new hepatic nodule in the 8th segment at a certain distance from the first one. In subsequent years new small PEI-treated nodules appeared in other liver segments with a good clinical result. A subcutaneous metastasis measuring 1cm was removed along the trajectory of PEI.

In 1998 a nodular lesion was highlighted by a CT scan of the thorax; percutaneous needle biopsy was

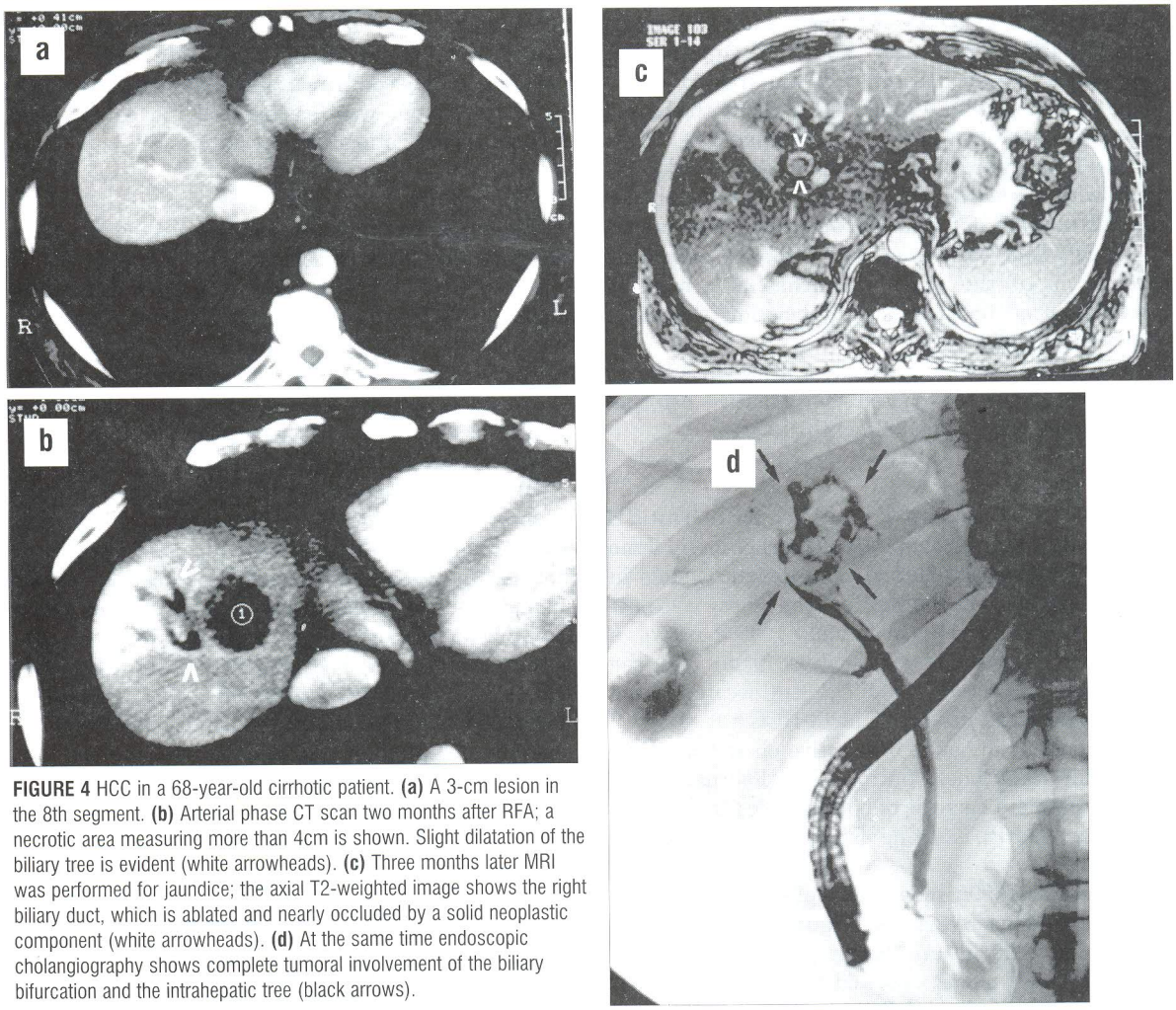

FIGURE 4 HCC in a 68-year-old cirrhotic patient. **(a)** A 3-cm lesion in the 8th segment. **(b)** Arterial phase CT scan two months after RFA; a necrotic area measuring more than 4cm is shown. Slight dilatation of the biliary tree is evident (white arrowheads). **(c)** Three months later MRI was performed for jaundice; the axial T2-weighted image shows the right biliary duct, which is ablated and nearly occluded by a solid neoplastic component (white arrowheads). **(d)** At the same time endoscopic cholangiography shows complete tumoral involvement of the biliary bifurcation and the intrahepatic tree (black arrows).

TABLE 1 RFA and Tumor Characteristics in Four Recurrent Patients with Primary and Metastatic Liver Neoplasms

		Tumor		RFA procedure			Pattern of recurrence		
Patient sex, age	size cm	location	vascular contiguity	approach	needle(s)	no. of sessions	delay (months)	site	type
1) M.G.M., fem, 68	2.5	VII subcapsular	no	percutaneous	single cooled type	2	6	bilobar	infiltrative
2) R.S., male, 67	2	V subcapsular	no	percutaneous	single cooled type	1	12	V-VIII segments abdominal wall	confluent nodules parietal recurrence
3) B.G., fem, 66	2	IV subcapsular	middle suprahepatic vein	percutaneous	single cooled type	1	3	left liver thoracic wall	wide hepatic recurrence portal thrombosis parietal recurrence
4) P.F., male, 68	3	VIII subcapsular	biliary contiguity	percutaneous	cluster (3 needles) cooled type	1	4	bilobar	massive metastatic colonization of biliary tree

positive for metastasis. We performed a wedge resection of the inferior right lobe; one year later, a right inferior lobectomy was carried out for a single metachronous metastasis. Between these two operations, a 1-cm subcutaneous metastasis at the site of percutaneous pulmonary biopsy was removed.

A further liver recurrence (measuring 2cm, located in the 4th segment near the middle suprahepatic vein) appeared 4 months later. It was treated with a single session of RFA. Control CT at 1 month showed a complete necrosis 5cm in size **(Figure 3a)**. Three months later the patient was admitted to our department with a clearly palpable mass in the anterior intercostal space. CT scan showed a wide recurrence in the left liver associated with complete neoplastic thrombosis of the portal branches and massive involvement of the thoracic wall including the costal plane **(Figure 3b)**.

The patient, who had already undergone systemic chemotherapy, was proposed for palliative external radiotherapy but she died 2 months later.

Case 4

A 68-year-old patient was followed for hepatitis B virus (HBV) and alcohol-related cirrhosis. In June 1998 echography revealed a small hepatic nodule in the 4th segment, but the result of the biopsy was negative for neoplastic cells. In January 1999 there was a volumetric increase of the nodule (3cm) and the appearance of a second nodule (2.8cm) located in the 8th segment, both compatible with HCC.

The patient underwent selective chemoembolization of the right lobe. Control CT in February 1999 showed complete necrosis of both nodules. The alpha-fetoprotein (AFP), starting from 413, decreased to 12ng/mL.

In October 1999 a medial area of the nodule in the 8th segment appeared viable **(Figure 4a)**.

In June 2000 he underwent percutaneous RFA. Control CT at 2 months showed a necrotic area measuring 4cm under the glissonian capsule without enrichment after contrast injection, thus suggesting a good therapeutic result; slight dilatation of the biliary tree was evident **(Figure 4b)**.

In September 2000 the patient was admitted to our department with obstructive jaundice: magnetic resonance imaging (MRI) showed massive metastatic colonization of the biliary tree, from the previously treated lesion to the hilum **(Figure 4c)**; endoscopic cholangiography confirmed this finding **(Figure 4d)**.

No treatment was feasible and the patient died during hospitalization for liver failure.

DISCUSSION

Radiofrequency ablation is now accepted as a curative procedure for liver neoplasms.

After 15-30 minutes of treatment, intratumoral application of RF causes a coagulative necrosis in a 2.5 to 5-cm sphere (8); in order to guarantee a good oncological result, this area has to include a margin of cancer-free hepatic tissue at least 1cm beyond the tumor.

The procedure is now in widespread use, but an adequate analysis of long-term results is still lacking.

Although sonography is the most commonly used imaging device for monitoring percutaneous RFA, it is only a rough guide for defining the exact margin of thermal injury (6,9). Echogenic modifications consequent to the treatment are not closely related to the extent of the necrosis, as shown by Goldberg in some patients undergoing liver resection after RFA (10). The result may be better assessed by CT or MRI one month or more after the treatment. CT and MRI are generally accepted as gold standard techniques, but their imaging resolution may not be sufficient to detect small residual foci at the margin of the tumor (10) or within the necrotic area (11).

If any portion of the tumor is missed, recurrence is inevitable. This is more likely to occur in large neoplasms, especially if located near to the hepatic vessels or when an unfavorable geometry of the lesion results in an incorrect overlapping of the spherical zone of action of RF (5,6).

In case of local recurrence of limited extension, retreatment may be feasible and effective. The evolution of the lesion, however, is generally slow or at least comparable to the previous growth pathway of the tumor.

In contrast with this, our report suggests that cancer recurrence may be much more aggressive after RFA **(Table 1)**.

Observation of case 1 clearly highlights the possibility of a treated lesion suddenly increasing: whole liver involvement was demonstrated in a 4-month period following RFA, starting from a small area of recurrence after the first treatment and showing an infiltrative radial pattern, probably related to massive vascular involvement. This type of growth is unusual for a metastasis, suggesting a direct negative effect of the procedure.

Cases 2 and 3, both hepatocellular tumors, also present a sudden massive involvement of the liver after RFA, showing an evident change when compared to the previous history of the tumor, marked by a clear tendency to persist and relapse, but with slow growth. Also, the rapid and massive colonization of the portal vein seen in case 3 is extremely rare for a small lesion located far from the main lobar portal trunk.

To our knowledge, massive biliary cancer involvement after RFA application (case 4) has never been described. Cautionary utilization of the procedure for centrally located lesions is usually motivated by the fear of biliary injury, with subsequent choleperitoneum and liver biloma or abscess, rather than by the possibility of cancer dissemination (12,13).

The two observations of extrahepatic tumor seeding described in this collection (cases 2 and 3) also need commenting on. Only a few experiences on this subject have been published so far (14-16). In a collection of more than 1100 patients from Italian centers, Livraghi reported a mere 4 cases of peritoneal or subcutaneous seeding, but no details of the clinical evolution were provided. Recently, the incidence of this complication was reported to be as high as 12.5% (4 out of 32 cases) after RFA for HCC and 12% by Llovet in secondary liver neoplasms; again data on the clinical significance of this complication are lacking. In our experience, the type of presentation of tumoral seeding appears different from the trend described after PEI (17-19), where this event is considered extremely uncommon (16) and generally of limited clinical value due to the small size and slow growth of the tumoral infiltration. In the cases presented here the rapid increase in size of the mass infiltrating the parietal wall was surprising. The different pattern of growth of subcutaneous seeding after PEI or RFA was clearly evident in case 3, where the two types of implantation were subsequently observed in the same patient.

Following these observations we assume that cancer growth at the site of unsuccessful RFA can be very aggressive and that subsequent resective surgery for curative purposes may rarely be feasible.

In the patients described in this report the primary lesion was single and small; three lesions had been treated in a single RFA session, and only in one patient was the lesion close to a vascular pedicle. In all cases the ablated zone was larger than the tumor and no enrichment was noted at the arterial CT phase performed more than 1 month after the treatment. Furthermore, all the patients had been treated by radiologists with specific experience in the percutaneous treatment of liver neoplasms, particularly RFA. Therefore, in the presented cases we exclude conditions known to be related to an increased risk of local failure or spread of cancer.

To our knowledge this report is the first to provide a complete definition of the evolution and the clinical history of recurrent lesions after RFA, so different in expression yet always of the maximum severity. Seki recently presented a single observation of a rapid cancer recurrence with aggressive behavior but the patient had undergone a combined treatment (transcatheter arterial chemoembolization and RFA) (20). Nowadays, in published experiences presenting clinical results, cancer recurrence after RFA is generally recorded as local, i.e., in the area of treatment, or remote in the liver, but there are no details of the extension or evolution of the recurrence and no mention of the possibility that the failure of local control may be related to cancer diffusion (13,21,22).

While new-generation probes and generators are studied and created to allow the ablation of larger lesions, thereby increasing the potential application of RFA and reducing the possibility of incomplete treatment, no attention seems to be paid to the risks of diffusion, potentially related to the procedure itself, nor to the causes of this severe negative effect and to the technological and methodological modifications apt to prevent it.

We can suggest some factors that may favor the neoplastic diffusion connected with the procedure. First is the powerful thermal energy emitted by the instrument inside the nodule; this can induce a condition of local hypertension with fracture of the pseudocapsule, if present (15), diffusion of vital neoplastic cells in the perilesional liver parenchyma or directly into the blood vessels or biliary ducts. At the periphery of the treated nodule a zone of contact of the partially necrotic neoplastic tissue and the normal vascularized parenchyma may arise. Furthermore, hyperemic perilesional reaction can favor cancer regrowth (6). The echographic and CT demonstration of an inflammatory response to the treatment with formation of microbubbles of gas in the heated tissue is a clear macroscopic expression of this tissutal reaction to the procedure (23).

Although the long-term survival of patients affected by tumors of the liver is essentially dependent on the biology of the cancer and the evolution of the chronic liver disease, if present, rather than on the type of treatment, local control of the tumor is a critical factor (24); therefore the type and the rate of local recurrences of the tumor are of primary value in assessing the validity of a new therapeutic procedure.

The impact of the complications reported here can taper the optimistic outcomes reported in some initial series (13), suggesting caution in the indications and

application of RFA, particularly in patients otherwise suitable for surgery. In such patients the advantage of low mortality and morbidity may be reduced by the possibility of a non-curative treatment leading to cancer progression. The incidence of local failure after RFA, reported as low as 1.8 by Curley (13), reaches 12-18% according to other extensive experiences (25,26).

The possibility of aggressive recurrence after RFA - though in a limited number of cases - must be considered when assessing the different options in treating hepatic neoplasms, and cannot be ignored when RFA is proposed, for example, as a preliminary procedure for treating this type of neoplasm in patients included in a waiting list for liver transplantation (27).

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