Expanding Local Control Rate in Liver Cancer Surgery – The Value of Radiofrequency Ablation

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1. Introduction

Hepatic resection still remains the golden standard treatment for patients with primary and metastatic liver cancer and offers the best chance for cure and survival (Agrawal & Belghiti, 2011). However the vast majority of the patients with malignant liver tumors are not suitable for hepatectomy due to number or distribution of the hepatic lesions relative to future liver remnant volume. Aiming to overcome these limitations various local tumor ablation techniques were developed. Among them radiofrequency ablation (RFA) gained popularity in the past decade and became the most used local ablation technique worldwide. The principles of RFA are well described and discussed elsewhere (Rhim et al, 2001; Ahmed & Goldberg, 2004; Chen et al, 2004). In brief - needle electrode/-s and high frequency electric current generator are used during RFA, in order to heat and coagulate neoplastic tissue (Figure 1).

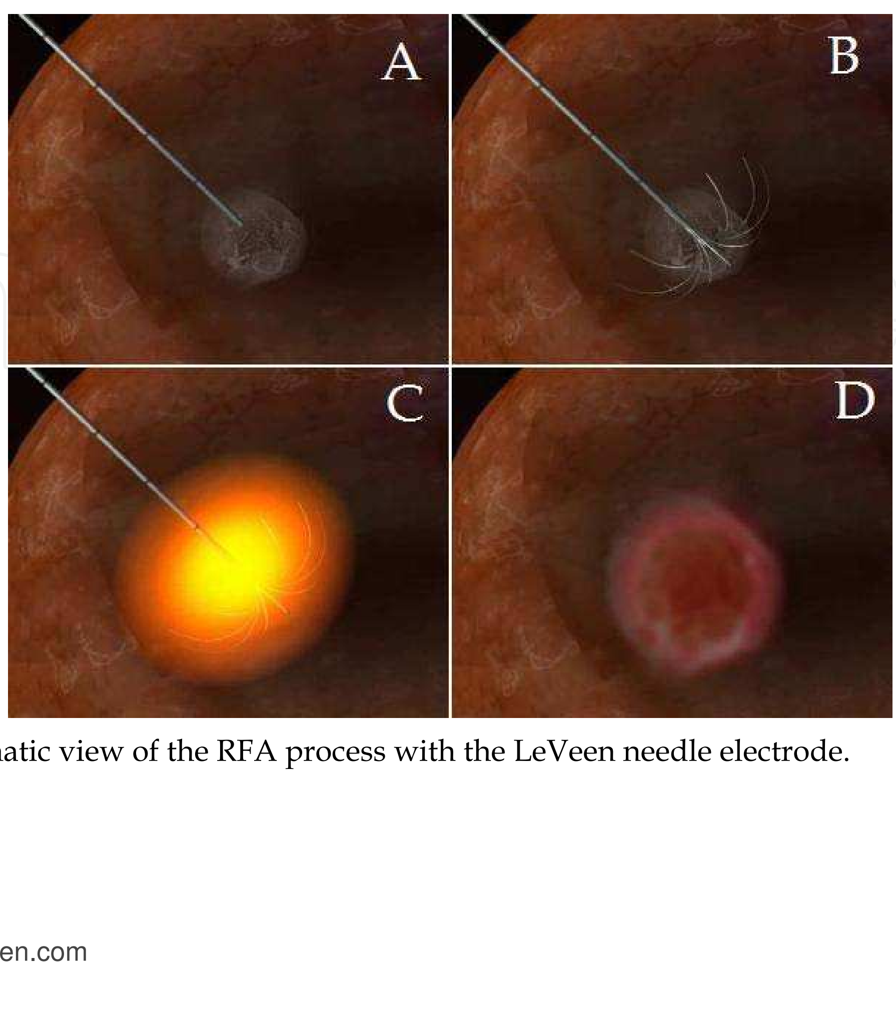

Fig. 1. Schematic view of the RFA process with the LeVeen needle electrode.

A sufficient rim of healthy liver parenchyma should also be destroyed as a safety margin. The size and geometry of created ablation zone depends mainly on the ablation protocol, electrodes used, tissue impedance and proximity of large vessels. Various RFA devices and electrodes are present on the market (Pereira et al, 2004), and they should be carefully evaluated before starting a clinical RFA program. Whenever possible the RFA devices should be tested in animal laboratory in order to become more familiar with the chosen technique before its clinical application. Clinical RFA of liver tumors currently is being performed percutaneously or during operation. Intraoperative RFA can be performed either as a sole procedure or (more frequently) as an adjunct to hepatic resection in order to control the functionally unresectable disease in the remnant liver (Figure 2). This chapter will discuss the rationale and technical aspects of intraoperative RFA in the treatment of patients with liver tumors.

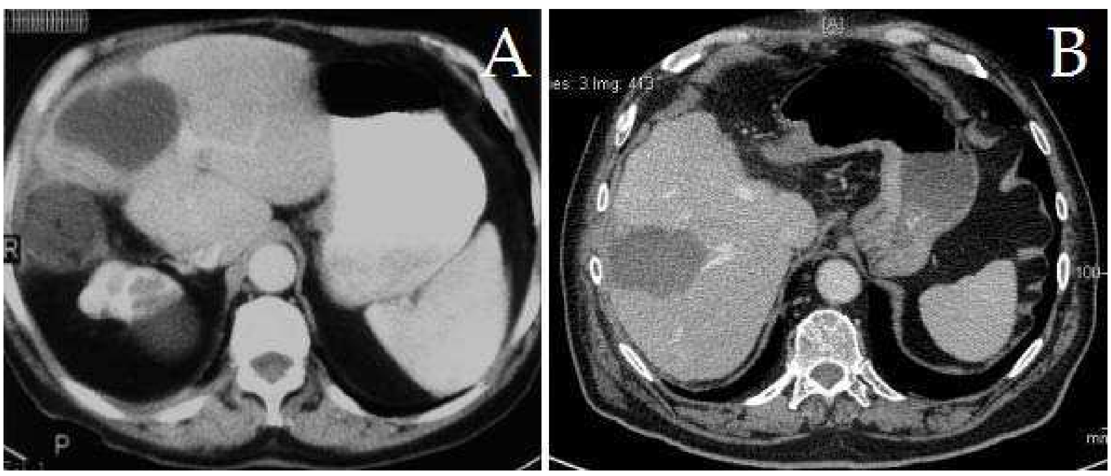

Fig. 2. Follow-up computed tomografy of patients after combined RFA and right hepatectomy (A) or left hepatectomy (B) for colorectal liver metastases.

2. Indications for RFA

Before considering RFA as a treatment option it should be remembered that hepatic resection still remains the standard treatment for patients with malignant liver tumors and offers the best chance for cure and survival. The volume of the liver remnant after resection is the most important factor when hepatic surgery is considered in a patient with liver cancer. Currently any hepatic involvement by a cancer is considered resectable if during surgery sufficient amount of tumor-free liver parenchyma can be spared, with preserved or reconstructed inflow, outflow and bile drainage. Otherwise RFA alone or in combination with resection can be performed to control the malignant disease in the liver.

2.1 Hepatocellular carcinoma

HCC in patients with viral hepatitis and/or cirrhosis is the most common indication for RFA. The limited hepatic functional reserve of a cirrhotic patient frequently is a cause of functional unresectability. In these patients RFA was proven as an effective treatment modality as well as a useful bridge to transplantation in transplant-candidates. Compared to various other local treatment modalities in both randomized and non-randomized studies RFA is more effective in terms of less recurrence of HCC or improved safety. However compared to liver resection RFA demonstrates significantly more recurrences and shorter time to recurrence (Sutherland et al, 2006). Important local factors, which influence the effectiveness of RFA of HCC, are the size and growth pattern of the tumor. For medium and large HCC, an infiltrating growth pattern (portal invasion, irregular margins, extranodal growth) is associated with higher risk of local recurrence than a noninfiltrating growth pattern (well-circumscribed margins or surrounded by a capsule). However some authors reported safe and effective, mainly intraoperative RFA of large HCC up to 8cm (Poon et al, 2004). For small HCC the presence or absence of a capsule did not influence the risk of local recurrence. There is an evidence from multivariate meta-analysis that RFA approach (percutaneous or intraoperative) influences significantly the effectiveness of ablation for both primary and metastatic liver malignancies regardless of the size of the tumor (Table 1, Mulier et al, 2005).

	Percutaneous RFA	RFA by laparotomy/laparoscopy
< 3 cm (small)	16.0	3.6
3-5 cm (medium)	25.9	21.7
> 5 cm (large)	60.0	50.0

Table 1. Local recurrence rates (in %) after RFA according to the approach.

The possibilities for more precise placement of the electrodes and for obtaining both inflow and outflow vascular control are among the most important factors contributing to the superiority of surgical RFA (Julianov et al, 2008, Julianov, 2009) (Figure 3).

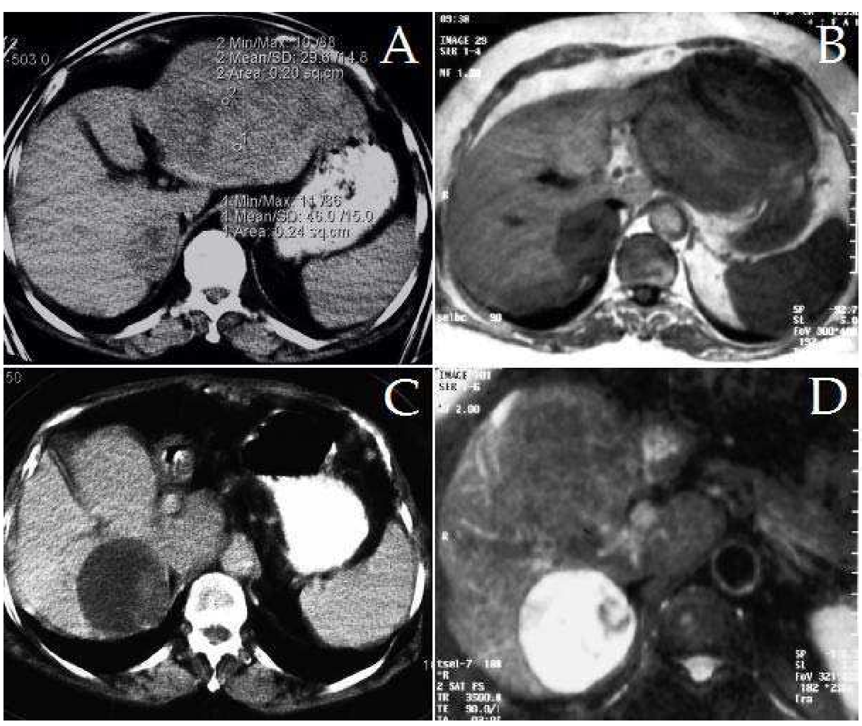

Fig. 3. Preoperative CT (A) and MRI (B) images of a patient with bilobar HCC. Follow-up CT (C) and MRI (D) five years after combined operation – RFA of a right-sided lesion which was adjacent to vena cava and resection of the dominant left-sided tumor, demonstrates control of the disease.

The route of application also influences the safety of the RFA. Although the morbidity is insignificantly higher in more invasive surgical approaches (by laparotomy/laparoscopy), the possibility to control complications during treatment, results in virtually no mortality from intraoperative RFA for both primary and metastatic liver cancer (Table 2, Mulier et al, 2002).

	percutaneous RFA	RFA by laparotomy	RFA by laparoscopy
Morbidity	7.2	9.5	9.9
Mortality	0.5	0	0

Table 2. Morbidity and mortality rates (in %) after RFA according to the approach.

Short- and intermediate-term survival rates after RFA for small HCC are as high as 100% and 98% for 1- and 2-years, with corresponding local recurrence-free rates of 98% and 96% respectively (Lencioni et al, 2003). However with time progression and for medium- and large-sized HCC the results worsened sharply. Except from the lower complete ablation rates obtained in larger lesions, this situation is explained by the frequent presence of microscopic satellite tumor nodules in HCC. In small HCC microscopic tumor extends more than 1 cm beyond visible tumor borders in 60% of patients. In larger lesions this microscopic extension is more than 2 cm in 67% (Lai et al, 1993). It is important to note also that even in early HCC < 2 cm microscopic portal vein invasion is present in 25% of lesions (Kojiro, 2002). According to the above data it is reasonable to recommend RFA with at least 1.5 cm security ablation margin for small HCC and with ≥2.5 cm margin for larger lesions, with concomitant inflow- and/or outflow control during ablation. In cases with bilobar/multiple tumors RFA can be recommended as an adjunct to surgical resection or as an alternative treatment option if the disease is deemed inoperable at laparotomy/laparoscopy. RFA can be a valuable treatment option for patients with unresectable HCC up to 8 cm. Surgical approach offers significantly better local control rates compared with percutaneous RFA independent of tumor size. Thus percutaneous RFA should be reserved for patients who refuse or cannot tolerate surgery.

2.2 Liver metastases

The liver is a common site for metastases from almost all solid malignancies. Hepatic resection is the standard treatment for liver metastases from various primary sites. However curative resection is frequently precluded by insufficient volume of the planned future liver remnant. Hepatectomy is not useful also in patients in poor general condition or in those who refuse liver resection. In these circumstances RFA was intensely explored as a treatment option for metastatic liver disease in unresectable cases. Currently RFA is used for treatment of unresectable liver metastases from different primaries including colorectal, neuroendocrine, sarcoma, breast etc. (Livraghi et al, 2003; Pawlik et al, 2006; Sutherland et al, 2006). Almost all of the published clinical data show that RFA can improve survival in patients with metastatic liver cancer compared with chemotherapy alone. In our study in 130 patients, RFA as an adjunct to surgical resection significantly improves both the local control and survival rate in primary and metastatic liver cancer (Julianov, 2009). However there is no a randomized controlled trial comparing RFA with liver resection for metastatic liver disease. For many reasons such a trial does not seem ethical to be conducted in a near future (Julianov & Karashmalakov, 2011). It is clear that RFA still cannot replace hepatic resection in the treatment of the liver metastases. For example - incomplete necrosis rates after percutaneous RFA for colorectal liver metastases reach 40% even in the treatment of small lesions <3 cm by most experienced hands (Livraghi et al., 2003). Moreover, the MD Anderson Cancer Center group reports stressing and still poorly explained data: no 5-year disease-free survivors in the RFA-treated group of 30 patients with solitary colorectal liver metastasis, even among patients with lesions < 3 cm. The comparison with the results of the liver resection in the same report clearly demonstrates that resection determines the outcome—5-year overall- and disease-free survival 27% and 0% for RFA versus 71% and 50% for resection, respectively (Aloia et al, 2006). Regarding the route of application of RFA (percutaneous or surgical) there is evidence that short-term benefits of lower invasiveness of percutaneous RFA for liver tumors do not outweigh the longer-term higher risk of local recurrence. As mentioned above – surgical RFA results in superior local control, independent of tumor size, and percutaneous RFA should be reserved for patients who cannot tolerate laparoscopy or laparotomy (Mulier et al, 2005).

3. Technique of intraoperative RFA

3.1 General considerations

Irrespective whether RFA is planned or not, any operation for liver tumor begins with through exploration of abdominal cavity for presence of previously unrecognized extrahepatic disease. Exploration of the liver with intraoperative ultrasound (IOUS) is a key step of the operation. All of the current imaging studies, including PET-CT, have well known limits to detect small hepatic and extrahepatic lesions compared with intraoperative staging, which includes IOUS. The latter fact ultimately adds unpredictable bias in estimating "new" lesions in any study of percutaneous RFA of liver metastases (Elias et al, 2005). In our study, as in many others IOUS demonstrates significantly higher sensitivity compared with other diagnostic methods for detection of hepatic lesions (Table 3; Julianov, 2008). More than 90% of the missed lesions are < 1cm and frequently had subcapsular location.

Diagnostic method used	Sensitivity	p
Preoperatively		
US	64 %	0,001
CT	79 %	0,001
US + CT	82 %	0,001
Intraoperatively		
Inspection & palpation	78 %	0,01
IOUS	92 %	0,01

Table 3. Sensitivity of different diagnostic methods for detection of hepatic tumors.

Resectable extrahepatic disease is not longer considered as a contraindication for liver surgery. However in most cases the presence of unresectable extrahepatic disease is a contraindication for a liver-directed procedure. Currently the exception from this rule can be made for some patients with peritoneal carcinomatosis, if cytoreductive surgery plus intraperitoneal chemotherapy can be performed simultaneously with the liver-directed surgical treatment. In every case any attempt should be made initially for R0 resection even as a staged procedure. Survival rates following two-step hepatectomy for liver metastases still are better than those of combined RFA+liver resection procedures. RFA is recommended in some cases before portal vein embolisation to control small centrally placed lesion in the planned future liver remnant. When R0 hepatectomy deemed impossible RFA+resection can be considered. The aim of the procedure is to resect as much as possible of the lesions, treating smaller and centrally placed ones with RFA in order to preserve sufficient amount of residual healthy liver. However in patients with unresectable recurrence after liver resection, in high-risk patients with severe comorbidities or in those refusing hepatic resection RFA is a treatment option as a sole procedure (Figure 4).

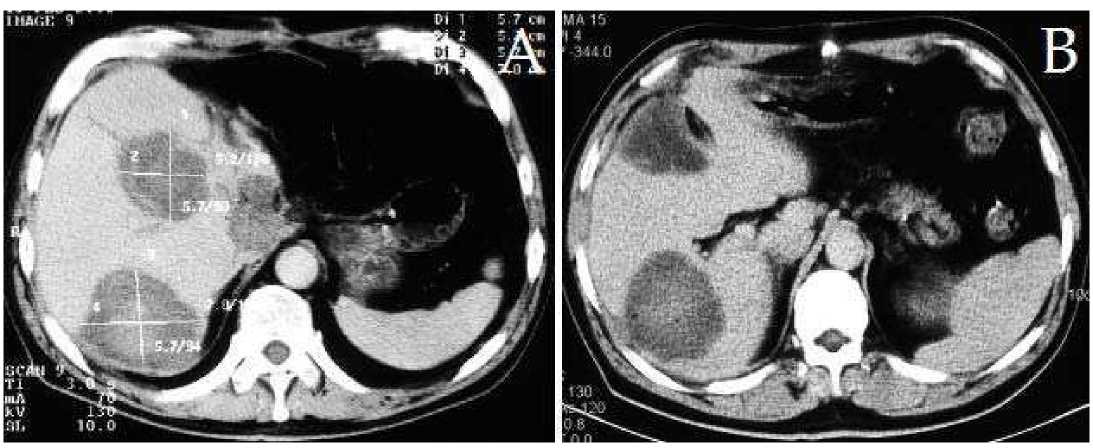

Fig. 4. Follow-up CT after intraoperative RFA of recurrent colorectal liver metastases after previous resection (A), and of colorectal metastases in a high-risk patient (B) .

In selected patients with synchronous bilobar metastases and resectable extrahepatic disease simultaneous RFA plus liver and extrahepatic resection can be safely performed (Julianov et al, 2004, 2006). A substantial survival advantage can be expected in patients in whom local control is achieved with RFA/RFA+resection, compared with those patients treated with chemotherapy only. In our study of patients with liver metastases there were no 2-year survivors between patients deemed unresectable at operation and further treated with chemotherapy only. For comparison - the 3-year survival rate for patients treated with liver resection alone was 71% vs. 34% for those treated with combined RFA+resection or RFA alone. However the mean number of liver metastases was 2.5 in the resection group vs. 5 in the combined treatment group (Julianov, 2009).

3.2 Technique of intraoperative RFA in different situations

When performing intraoperative RFA some principal rules should be followed. IOUS guidance is mandatory for proper positioning of the RFA probe. A free-hand puncture technique usually allows more freedom to manipulate when compared to the puncture through guide, attached to the US-transducer. Mobilization of the liver is not mandatory but is sometimes necessary in order to achieve more comfortable positioning of the RFA electrode, to isolate the liver from adjacent organs/structures in order to protect them from thermal injury, or for the purposes of outflow vascular control. The most deep and closest to the major vessel part of the lesion is treated first, to eliminate further cooling effect ("heat sink") of the blood flow on ablation process. During RFA we always apply Pringle-maneuver, starting at 5 minutes after beginning of each ablation cycle till its end. Finally the probe is cauterized before removing it from the liver, in order to minimize the risk of needle-tract seeding of viable tumor cells.

RFA near major blood vessels. Proximity of a major vessel was identified as an independent limiting factor for successful hepatic RFA (Mulier et al, 2005). In animal experiments with RFA a rim of viable tissue has been always observed around the large vessels >5mm (Lu et al, 2002). Thus vascular control becomes important adjunct to RFA procedure, when tumors near major vessels are treated in both normal and cirrhotic livers (Rossi et al, 2000; De Baere et al, 2002; Washburn et al, 2003). Pringle-maneuver is sufficient vascular control technique for lesions located near inflow vessels. However inflow occlusion does not eliminate the "heat sink" when the tumor located near major hepatic vein is treated. In this situation the backflow cooling from the hepatic vein can be simply controlled by finding with IOUS the respective vein confluence to the inferior vena cava, and compressing the vein with the transducer until its lumen disappears on IOUS-screen (Julianov, 2008, 2009). Even the lesions adjacent to the vena cava can be successfully treated if proper vascular control techniques are used during RFA (Julianov et al, 2008; Figure 3).

RFA near hilar bile ducts. RFA for a lesion near the hepatic hilum is considered dangerous because of the high risk from thermal injury and subsequent stricture of hilar bile ducts. However successful and safe RFA of a hepatic tumor near the hepatic hilum can be performed (Figure 5).

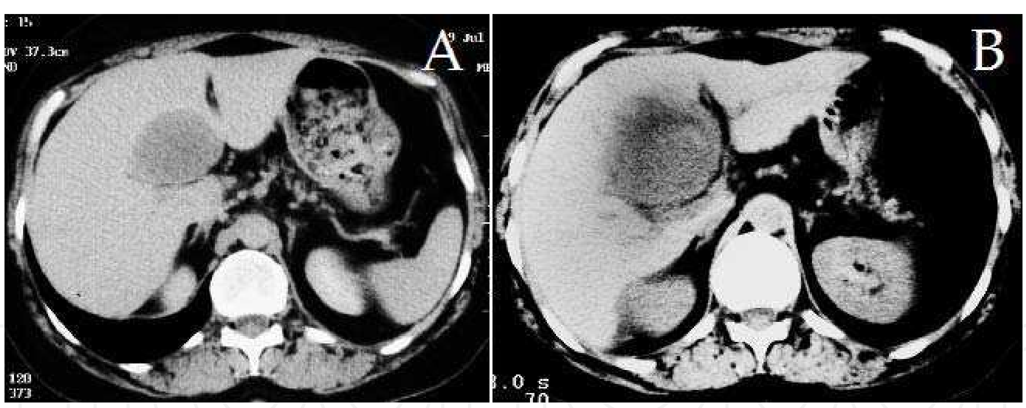

Fig. 5. Computed tomography of a patient with liver metastasis from gastrointestinal stromal tumor (A). RFA with cooling of bile ducts was performed (B).

For this purpose the left and right main duct should be protected. One option is to place the stents in both ducts through ERCP. Another option proven in both experimental and clinical setting is to cool the bile ducts during ablation. Our preferred option is to cool the biliary tree by perfusion of cold 5% isotonic glucose solution in the bile ducts using catheters inserted through small incision of the common bile duct, as proposed by D. Elias (Elias et al, 2001).

Large-volume RFA. For large lesions, more than a single positioning of the RFA probe is frequently necessary to control the tumor with appropriate safety margin. In such cases it is important to plan the whole RFA procedure with all positions of the electrode before starting the ablation. RFA causes changes in the coagulated liver parenchyma, which will affect further proper positioning of the probe under US-guidance (Figure 6). The geometry of overlapping ablations can vary widely, and they should be planned with respect of the size of the target lesion. A well-designed protocol for RFA of larger lesions should be used in order to ensure high success rate of complete ablation (Chen et al, 2004).

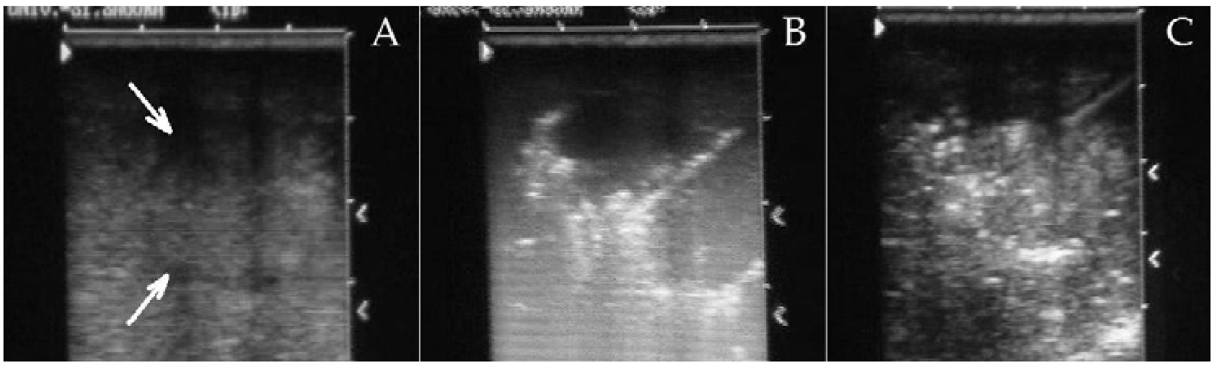

Fig. 6. IOUS images. Isoechoic liver metastasis with hypoechoic rim before treatment (A). The lesion is punctured with the LeVeen needle electrode and ablation started (B). The RFA cycle is finished (C).

To date the physiologic response of large-volume RFA (Figure 7), has not reported to be different from the more limited "usual" ablation volumes in clinical practice. However the safety limit of clinical RFA of the liver remains unknown.

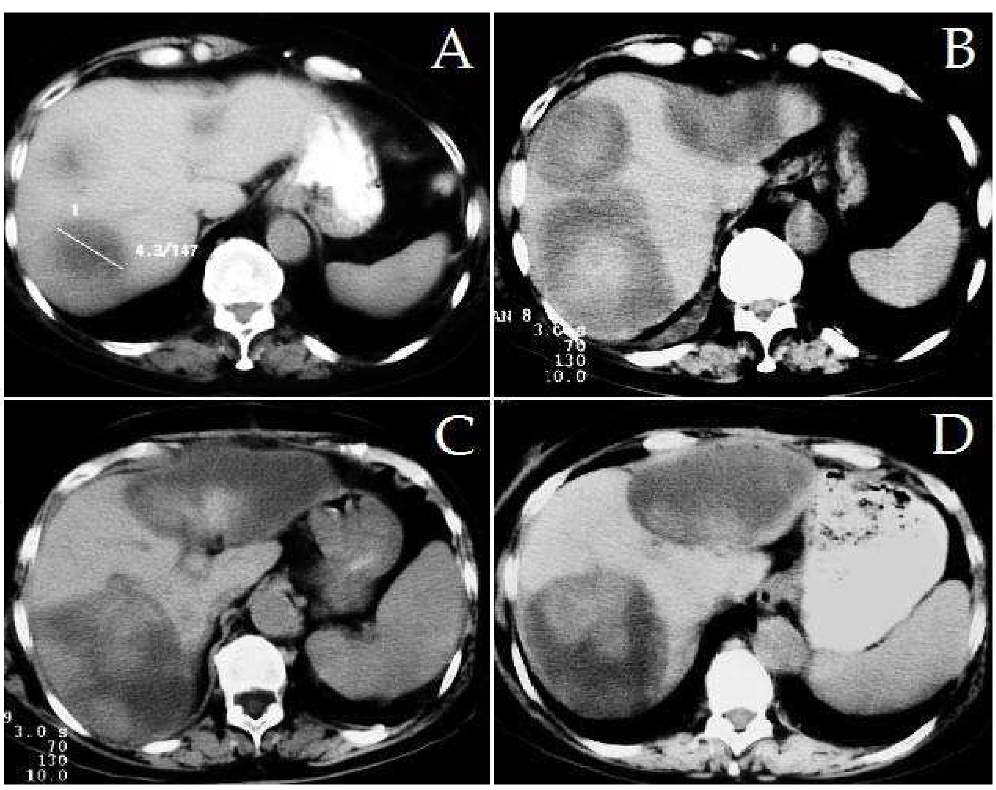

Fig. 7. Computed tomography of a patient with colorectal liver metastases before (A) and one week after large-volume RFA (B). Posttreatment follow-up CT of a patient two weeks (C) and 6 months (D) after large volume RFA.

In animal model of RFA a 40% of the liver volume is ablated without mortality in healthy livers whereas in cirrhotic liver up to 20% can be ablated safely, without significant systemic inflammatory response (Ng et al, 2006). It is not clear whether these data are applicable in clinical setting. In our experience, the posttreatment course of patients with even very large volumes of hepatic RFA does not show any specific difference from more "usual" cases.

3.3 Complications after RFA

The postoperative care after RFA does not require specific treatment, irrespective whether RFA is performed as a sole procedure or simultaneously with various hepatic and/or extrahepatic resections. However the possibility of a potential life-threatening complication after RFA should always be kept in mind (Figure 8).

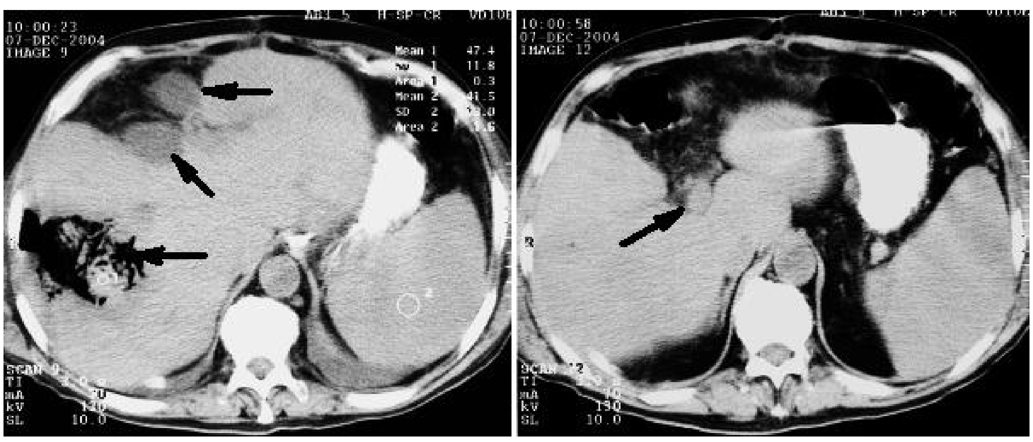

Fig. 8. Computed tomography of a patient after simultaneously performed bowel and liver resection plus RFA. Hepatic abscesses occurred at resection- and RFA sites (arrows).

Although RFA of the liver is a well-tolerated and safe procedure, complications and rarely death may occur after RFA-treatment. The most common complications after RFA of the liver are bleeding, abscessus and biloma formation and they sometimes may be fatal (Enne et al, 2003). The life-threatening complications from the thermal injury of organs adjacent to the liver were reported mainly for percutaneous RFA. Surgical approaches permit protection and isolation of endangered organs from inadvertent burn injury during hepatic RFA. In patients with cirrhosis, delayed portal vein thrombosis can occur after RFA near the main portal vein branches. Rare complication as a gas gangrene after RFA was also reported (Kvitting et al, 2006). Any complication after hepatic RFA require immediate treatment and when necessary interventions (surgical or image-guided) should be regarded as life saving and performed without delay. This approach permits avoiding mortality even in most critical situations (Julianov, 2008)

4. Conclusions

The two crucial questions must be always addressed when considering RFA as a treatment option in a patient with primary or metastatic liver cancer: 1. Whether RFA is equal in curability to surgical resection for resectable malignant liver tumor, and 2. What additional survival benefit does RFA has over modern systemic therapies in the treatment of unresectable disease? The long-term results from clinical studies to date showed significantly better survival obtained from surgical resection for all types of resectable malignant liver tumors. Thus RFA cannot be regarded as an equally effective alternative of liver resection. On the other hand, if compared with systemic treatment alone there is enough clinical data to demonstrate that when local control is achieved by RFA it offers survival advantage (and even cure) for patients with unresectable disease. Unfortunately these facts are frequently misinterpreted and lead to misuse or abuse with RFA. In a survey from Germany 25.9% of patients undergoing RFA had a resectable tumor (Birth et al, 2004). This is partly because of the public pressure on physicians to refer their patients for minimally invasive treatment, rather than for major surgery, becomes heavier today. As a consequence many radiologists and gastroenterologists start to treat with percutaneous RFA patients with resectable tumors. On the other hand, surgeons that have no experience with hepatic surgery start to perform RFA as an alternative to resection in resectable cases, rather than referring these patients to the experienced liver surgeon. As the philosopher Abraham Maslow once said, "If the only tool you have is a hammer, then you tend to see every problem as a nail." However, when RFA is properly used in patients with primary and metastatic liver cancer its clinical benefits in terms of prolonged survival and even cure are indisputed. Today the RFA-device clearly is a necessary tool in the armamentarium of a liver surgeon.

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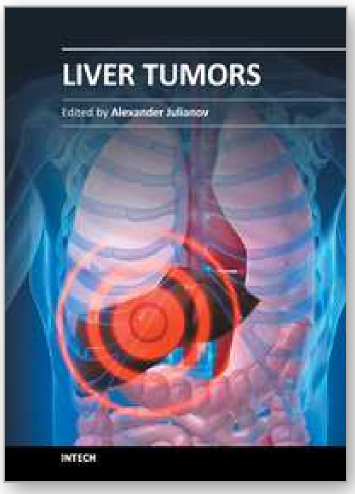

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This book is oriented towards clinicians and scientists in the field of the management of patients with liver tumors. As many unresolved problems regarding primary and metastatic liver cancer still await investigation, I hope this book can serve as a tiny step on a long way that we need to run on the battlefield of liver tumors.