Chapter 20

Laparoscopic Radiofrequency Ablation of Liver Tumors

Mirela Patricia Sîrb Boeti, Răzvan Grigorie and
Irinel Popescu

Additional information is available at the end of the chapter

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1. Introduction

The biological effects of radiofrequency (RF) waves were first reported on liver lesions by McGahan et al. in 1990 [1].

The early reports on the efficacy and safety of radiofrequency ablation (RFA) for liver tumors have encouraged rapid spreading of the technique for the treatment of unresectable or even resectable tumors. Nowadays RFA constitutes a wide-range therapeutical option for a variety of tumors. The vast majority of the reports about RFA refer to malignant liver tumors. There are only few authors who attest the efficiency of this in situ ablative method for benign liver tumors (e.g. hepatic cavernous hemangioma, hepatic adenoma). RFA must be integrated in a complex multimodal treatment for patient with liver tumors. Selected patients may also benefit of simultaneous and/or consecutive association of RFA with other treatments like surgery, chemotherapy, and other in situ ablation procedures.

All the authors concur to the fact that RFA is a technology-based treatment. However, the importance of operator experience in this treatment must not be alluded. Not only the complete knowledge of the RF armamentarium but also patient and approach selection for RFA are mandatory to certify this method as an effective and safe technique for treatment of the liver tumors [2].

It must be underscore that RFA is not just a simple technique of inserting a needle to "cook" the tumors but is a new technology in the treatment of liver tumors with a steep learning curve which may offer these patients a 50-95% chance of destroying these lesions [3].

While RFA is most commonly performed in the radiology departments through a percutaneous approach, our experience over 5 years determines us to advocate for the laparoscopic ablation of liver tumor using RF. Even if it is still a debate on the correlation of the different

RFA approaches with the results in terms of recurrence and survival, our recommendation is to use laparoscopic RFA (LRFA) whenever possible.

With this paper we intend to offer a review regarding the laparoscopic ablations with RF for patients suffering from liver tumors. We aim to describe the RF and ultrasound equipment, define the selection criteria of the patients for this kind of approach, present the ablation procedure, and the follow-up criteria, and discuss the LRFA outcomes in terms of procedural-related morbidity and mortality, tumor recurrence, and patient survival.

2. Methods

A review of relevant articles was undertaken based on a Medline search from January 1998 till January 2012.

2.1. Mechanism of RFA

When high-frequency (350-500 kHz) alternating current passes the tissues, polar molecules (e.g. water molecules) are orientated in conformity with the field polarity [4]. With every change of the polarity of the alternating current polar molecules are moving in attempt to follow its direction. Their ionic vibration results in dielectrical losses into tissues because of molecular friction. The dielectric losses generate heat (frictional heating) which causes thermal tissues injuries. The extension and type of the thermal lesions depend on the temperature and duration of current applications. These lesions begin at 42^0C. Above this level the time of lethal exposion drops progressively: 8 min at 46^0C, 4-5 min at 50ºC. At 60ºC the cellular death is inevitable due to irreversible lesions of mitochondrial and cytoplasmatic enzymes secondary to thermal protein denaturation [5]. Tissue desiccation occurs at 100ºC. But quick tissue heating over 100ºC has the disadvantage of fast increasing thetissue impedance due to charring, which consecutively restricts the heat propagation and eventually coagulation necrosis [5]. Malignant cells are more prone to damages due to hyperthermia than normal cells [6].

2.2. Indications of RFA

RFA is now gaining popularity as the preferred modality of local ablation for patients with malignant liver tumors who are not surgical candidates (table 1).

RFA is used to treat liver lesions considered unresectable due to their bulky volume, position near key vessels, multiplicity or insufficiency of remnant liver parenchyma.

In terms of the extend of hepatic disease we consider safe to perform LRFA on patients with total tumor volume less than 20% contrary with opinion of other authors who reported good results in patients with up to 50% total liver replacement [3].

RFA has an important role in converting nonresectable in resectable tumors and also in increasing resectability of multiple liver tumors. Resections of such tumors are feasible d'emblee or in two-stage procedure. RFA of the small and deeply situated tumor(s) in one

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hepatic lobe can be associated with resection of a large tumor or multiple tumors located in the controlateral lobe or with controlateral portal vein ligation. The procedure can also be performed before liver resection for tumors located in the section plane in order to obtain disease-free margins.

Patients with liver tumor but with general contraindications for hepatic resection or those who refuse the operation are also candidates for RFA.

Moreover, the application of RFA has now expanded to patients as a bridge to liver transplantation. RFA proved benefits for patients with cirrhotic and HCC who are within Milano criteria on the waiting list for liver transplantation. It also have been shown to result in down staging the HCC in cirrhotic patients beyound the Milano criteria and thus in listing these patients for liver transplantation.

Patient with primary or metastatic hepatic tumor(s) which are not candidates for hepatic resection Tumor characteristics multiple diffuse bilobar in association with hepatic resection in association with transarterial chemoembolization of hepatic artery deeply situated near the portal pedicles, hepatic veins, inferior vena cava recurrence after major hepatectomies small HCC on cirrhosis in patients (in Milan criteria) on waiting list for LTx large HCC on cirrhosis in patients (out of Milan criteria) to be included on the waiting list after downstaging large unresectable tumor for downstaging followed by hepatectomy number ≤ 5 (14) maximum diameter ≤ 5 (7, 8) cm Poor liver parenchyma function Patient with benign hepatic tumor Co-morbidities which increase the anesthesia-surgical risk Patient refusal of hepatic resection
Patient expectation survival ≥ 3 months
Other tumor localizations which can be treated
Written informed consent of the patient

Table 1. Indications of RFA.

Based on some studies there are authors who plead for RFA even as a substitute to hepatic resection for small liver tumors.

Patients with hepatic malignancies, except those with neuroendocrine tumors, should be approached with curative intent and the goal of extending survival. Curative intent means that similar to liver resection the ablation has to completely destroy not only the tumor but also at least 0.5-1 cm zone of normal liver parenchyma.

RFA was successfully used to treat patients with symptomatic and rapid-growth hepatic cavernous hemangioma [7]. Application of LRFA for the treatment of benign tumor proved to be safe and indicated also in patients with liver adenoma [8].

2.2.1. LRFA advantages

We advocate the laparoscopic approach to ablate the liver tumors with RF due to its advantages over the other two methods: percutaneous and open.

Laparoscopy represents a reliable diagnostic tool. Some authors consider that every liver resection must be preceded by abdominal laparoscopic assessment of the disease [9]. By identifying extrahepatic lesions, laparoscopy can up-stage the patients with cancer and can deem these as unresectable or untreatable with in situ ablation procedures (except those with neuroendocrine tumors).

Two third of the patients with advanced liver insufficiency being evaluated for orthotopic liver transplantation are restaged after exploratory laparoscopy, laparoscopic ultrasound (LUS) and Ultrasound-guided biopsy, half being downstaged and half upstaged [10]. This finding determines some authors to indicate laparoscopic staging followed by LRFA for patients with adenocirrhosis evaluated for liver transplantation unless there are unequivocal clinical data supporting the stage of hepatocellular carcinoma [10].

Unsuspected intra-abdominal extrahepatic metastases can be noted in up to 26% of patients with colorectal liver metastases [11].

Moreove laparoscopy either alone or in association with intraoperative ultrasound examination can diagnose other liver lesions missed by the preoperative imaging examinations in up to 38% cases [12]. LUS can detect lesions less than 2 cm in diameter.

The laparoscopic approach proved to be safe for the treatment of subcapsular tumors due to the possibility of direct visualization and active protection of the surrounding structures (gallbladder, stomach, duodenum, colon, diaphragm) and possibility to control the potential bleeding from these lesions.

The pneumoperitoneum creates a working camera which not only removes the surrounding structures from the liver but also reduces the respiratory movements of the liver and thus facilitates the placement of the RF needle.

LRFA is also able to ablate deep-sited lesions difficult or impossible to be visualized by percutaneous US or to be punctured percutaneously. Some authors consider that for lesions located beneath the diaphragm laparoscopic approach can be associated [13] or even replaced with the thoracoscopic one [14, 15].

For treating patients with large or multiple liver tumors LRFA seems to be the first choice. Nevertheless, for tumors larger than 60 mm in diameter, tumors more than 5, and tumors close to the hepatic vein or inferior vena cava, some author consider RFA via laparotomy to be safer than LRFA [16].

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During LRFA the Pringle maneuver can be used if it is necessary. Pneumoperitoneum per se has the advantage to decrease the blood flow and increase the area of ablation [17].

In patients with multiple hepatic lesions surgeons with high expertise can performed LRFA in association with laparoscopic hepatic resection.

Comparing with the open technique, LRFA determines less intra-operative blood loss and fewer postoperative complications [16].

Due to its minimal surgical trauma, LRFA determines a fast recovery time and short hospital stay. It is our practice to discharge the patient 24-48 hours after the operation.

The benefits of LRFA in cirrhotic patients are certain when comparing with the open approach. First, preservation of the abdominal wall and lack of the need to mobilize the liver avoid interruption of large collateral veins and perihepatic ligaments, thus decreasing postoperative ascitic syndrome. Second, nonexposure of the viscera restricts the electrolytic and protein losses and hence the fluids requirements which secondary improves absorption of ascitis. Third, the laparoscopic approach is associated with lower intraoperative blood loss due to the haemostatic effect of the positive pressure of peritoneum, meticulous intraoperative manipulations of the tissue under magnification, and smaller abdominal incisions. It was reported that intraoperative blood loss is a major risk factor of postoperative morbidity and death [18].

For liver tumor recurrences, LRFA can be repeated as needed.

It is still not finally settled which is the best RFA approach in terms of recurrence and survival but we favor the laparoscopic one based on literature data and our experience.

2.2.2. Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and fourth in annual mortality. Its incidence continues to grow up secondary to the increasing prevalence of viral hepatitis [19]. Hepatic resection and liver transplantation are considered the mainstay of treatment of HCC being proven as the most effective treatments in means of disease-free interval and survival. However, less than 20% of HCC can be treated surgically because of multifocal diseases, proximity of the tumor to key vascular or biliary structures precluding a margin-negative resection, and inadequate functional hepatic reserve with cirrhosis. Usually, noncirrhotic or Child A cirrhotic patients with single small HCC (≤5 cm) or up to three lesions ≤3 cm are indicated for surgery.

2.2.2.1. Bridge to transplantation

The efficacy of RFA in wait-listed transplant candidates has been studied. Johnson et al. reported eight pretransplant patients treated solely by RFA and matched to a similar group by age, sex, Child-Turcotte-Pugh class, and Model for End-Stage Liver Disease (MELD) score who did not undergo treatment prior to transplant.[20] Patients pretreated with RFA were able to remain on the transplant list for longer periods of time than their matched counterparts. Dropout rates without RFA have been shown to be as high as 40%; however, the use of RFA has decreased them to as low as 20%. The use of RFA as a bridge to transplantation has proven to be an effective strategy. Control of tumor size and the theoretical prevention of metastatic disease formation allow patients to remain on the waiting list for longer periods, increasing their likelihood of obtaining a donor organ. RFA remains limited in its ability to provide complete necrosis of large tumors and should not be expected to do so in patients who are near the upper limits of transplant candidacy because of size criteria.

The need for an accurate intrahepatic staging is crucial for patients with HCC candidates to an aggressive surgical or ablative treatment. Combinations of resection and ablation may be required in certain cases, extending the indications for the laparoscopic approach to hepatocellular carcinoma in liver cirrhosis. Laparoscopy with LUS seems to be useful to identify unsuspected new nodules and to help in choosing the most suitable treatment. Laparoscopy with LUS could represent a sound preliminary examination in patients who are candidates to liver transplantation in order to both improve the staging and guide an interstitial therapy as a bridge to the transplantation itself [21].

2.2.2.2. Resection versus RFA

Surgical resection is the gold standard of treatment for HCC in noncirrhotic and cirrhotic patients who can tolerate hepatic resection. Noncirrhotic patients with HCC can usually undergo resection. However, patients with underlying cirrhosis are rarely candidates for resection and often face a dismal prognosis. As a result, prospective studies comparing patients who are surgical candidates and underwent RFA with those who underwent resection are fairly limited.

2.2.2.3. The use of RFA in nonsurgical candidates

The reported rate of resectable HCC is low and ranges from 9% to 27%. It is limited by the proximity of the tumor to major vascular and biliary structures that would preclude negative resection margins, but more importantly by the degree of underlying liver disease and Ability of the patient to tolerate hepatectomy. Small tumors are generally best suited for RFA and provide the best results. However, larger lesions have also been ablated with mixed success, occasionally even providing overall long-term survival of some patients with HCC. Small lesions are generally considered those that are <3–3.5 cm in diameter.

Larger lesions are known to be more difficult to treat using RFA. Tumors >3 cm may require repositioning of the electrode or multiple treatment sessions in order to obtain clear margins. However, even using a more aggressive approach, the efficacy of RFA has been proven to be limited by tumor size. Lesions measuring >5 cm have at best only a 50% chance of being completely ablated.

Therefore, most authors do not recommend the use of RFA for tumors >5–6 cm because of the technical limitations of the current used equipment and their inability to provide complete coagulative necrosis.

Despite the tumor size limitations of RFA, its use in unresectable HCC is significant. Those who are not transplant candidates or are unable to undergo resection face a dismal progno-

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sis, and RFA provides a chance for survival, especially for patients with smaller lesions. However, the use of RFA should be discouraged in patients with large lesions or those who have evidence of metastatic disease, because these groups have such a poor outcome that RFA is unlikely to provide any tangible benefit.

2.2.2.4. Surgical resection in combination with LRFA

Patients with multifocal disease may be treated by a combined approach using both surgical resection and RFA. The bulk of the tumor burden is initially resected, and RFA is then performed on any remaining unresectable lesions. However, there are few data to support this approach, especially in the setting of HCC. Most agree that if HCC has progressed so extensively, the patient is unlikely to be cured even by aggressive combined modalities of this nature. Additionally, although well tolerated intraoperatively, RFA combined with hepatic resection does place the patient at a higher risk for postoperative liver failure and death. This is especially true in the cirrhotic patient with poor hepatic reserve prior to intervention. Therefore, the role of LRFA in conjunction with resection must be used judiciously and mandates further reviews before it can be recommended in the treatment of HCC.

2.2.3. Metastatic colorectal cancer

The liver is the most common site of distant metastases second only to lymph nodes [22]. Initially considered to be a terminal diagnosis, treatment of these lesions has provided significantly better outcomes for many of these patients, in comparision to those untreated.

Akin with the primary liver masses, surgical resection remains the gold standard therapy for liver metastases from colorectal cancer.

Colorectal cancer is the leading cause of cancer death in US. At the time of exploration for their primary tumor 16-25% of patients have liver metastases and about 25% will develop such lesions in the disease course.

Colorectal cancer is responsible for up to 75% of liver metastases that undergo surgical treatment. For those who undergo resection of isolated liver metastases, the 5-year survival rate has recently been shown to be as high as 58% [23]. Prospective studies that compare RFA with Resection in operative candidates are extremely limited.

Unfortunately, up to 80% of the patients diagnosed with stage IV disease are not candidates for resection. For unresectable liver metastases, alternative options, such as RFA alone or in conjunction with other therapeutic modalities, are being explored to further improve survival [24]. Criteria for unresectable metastases include bilobar disease that cannot be completely excised, proximity to major vasculature structures precluding margin-negative resection, and comorbid conditions that preclude surgery [25]. For these untreated patients, survival is <5%–10% at 5 years [26].

Large trials evaluating the combination of RFA and resection are limited, and therefore it is difficult to draw definitive conclusions regarding its efficacy and safety. As larger portions of hepatic parenchyma are resected or ablated, the risk for liver failure increases, making it difficult to support the use of a combined approach without achieving a survival benefit. At this time, there are few data to support combining RFA with surgical resection.

2.2.4. Liver metastasis from neuroendocrine tumors

Liver metastases occur in 5-90% of patients with neuroendocrine tumors and the specific pattern of these is an indolent course, which may be dominated by symptoms related to hormonal secretion.

The goal of surgical resection and RFA in most cases of both primary and metastatic liver disease is curative. However, neuroendocrine tumors represent a unique group of slowly growing, often highly symptomatic tumors that are unlikely to be cured by resection. The untreated patients with unresectable neuroendocrine liver metastases have a 5-year survival rate of 25-38%.[27] In patients with metastatic neuroendocrine tumors who are unlikely to be cured by surgery or unable to tolerate an invasive form of treatment, RFA has been shown to ameliorate the symptoms (95%), significantly or completely control the symptoms (80%), and partially or significantly decrease the circulating hormone levels (65%) [28, 29]. LRFA seems appealing for these patients because the recurrence rate after resection is >80% at 5 years. Moreover, in case of liver recurrence, LRFA can be repeated for maintaining tumor control in the liver without increasing morbidity.

2.2.5. Liver metastasis from nonneuroendocrine and noncolorectal tumors

Regarding the nonneuroendocrine and noncolorectal liver metastases there are few reports on the utility of RFA to treat them. Patients with liver metastases from sarcoma, breast cancer, gastric cancer, pancreatic adenocarcinoma, or malignant melanoma are predicted to have a short survival due to the rapid diffusely disseminated disease. The overall median survival for these patients is 33 months. The aim for these patients is to prolong life with treatments which have low side effects and offer a good quality of life. Notwithstanding the curative intention of the treatments, most of them are ultimately proven to be palliative due to the progression of the disease. For these patients LRFA has not only curative but also debulking target. For the patients with nonresectable liver metastases, LRFA offers an overall median survival of more than 51 months [30].

2.3. Contraindications of LRFA

These contraindication are:

- Patients ≤ 18 years-old or ≥ 80 years-old,
- Sever coagulopathy (PLT <50.000/mm3, PT, APTT >1,5N),
- Renal failure (serum creatinin > 2,5 mg/dl),
- Jaundice (bilirubinemia > 3 mg/dl, bile duct dilatation),
- Acute infection,
- Tumor vascular or organ invasion,

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- Patients with cardiac pacemaker, implanted metallic pieces,
- Sever mental disturbances,
- Pregnancy and breast feeding.

2.4. Patient preparation for LRFA

For all patients admitted for LRFA a baseline evaluation has to be done within one week before the procedure. Besides history and clinical examinations, there are some mandatory laboratory tests and imaging examinations.

Laboratory tests consist of complete blood cell counts, coagulation profile, renal and liver panel, and appropriate serum tumor markers.

Imaging examinations include percutaneous abdominal ultrasound, computer tomography, magnetic resonance imaging (MRI), chest Rx, and, in selected cases, positron emission tomography using ^{18}FDG [12].

The patients known with cardiac problems should have a pretreatment cardiologic assessment in order to prevent the possible arrhythmia due to RFA. Without being an absolute contraindication, patients with implanted cardiac pacemakers need special attention before, during and after the procedure.

Due to the great risk of biliary injury during RFA of the central liver tumors, some authors place preoperative prophylactic biliary stents in patients with such lesions [12].

A dose of intravenous antibiotics is given just before RFA. The duration of administration depends on the various protocol used, being up to 5 days [2].

Informed consent of the patient is obtained before the procedure.

For LRFA the most used is the supine position of the patient. Only when there is a predominance of the disease in the posterior segments of the liver the patient is put on the operating table in left lateral position [31].

The LRFA is performed under general anesthesia.

2.5. The RF-equipment

2.5.1. The RF-equipment

Historically, the major impediment on RFA has been the size of the area to be ablated which could be the explanation of the Achilles' heel of this procedure: local tumor recurrence. In order to improve the results, RF equipments have been continuously perfected.

The rapid increase of temperature (above 100°C) during RFA, leading to charring of the tissue and increase of impedance, was shown to be the main cause of the small coagulation volumes. Many electrodes have been designed to improve energy deposition on tissue and further increase coagulation volume. Nowadays there are various single or combined type of electrodes. The main types are: single, cluster, multitined expandable, spiral expandable, cooled, wet (perfused), monopolar or bipolar electrodes (table 2).[32]

RF system	Rita Model 1500x	**Cool –tip**	Boston RF 3000	**Berchtold**	**Surtron**	Celon Power-Olympus
Power	250 W	200 W	200 W	60 W	200W	250 W
Frequency	460 kHz	480 kHz	480 kHz	375 kHz	480kHz	470 kHz
Ablation control	Impedance and temperature	Impedance	Impedance	Impedance	Impedance	Impedance
Energy delivery	Monopolar bipolar	Monopolar	Monopolar	Monopolar	Monopolar	Bipolar multipolar
Electrode diameter	2.2 mm	1.6mm/ 3x1.6mm	2.5 mm	1.7 mm		1.8 mm
Electrode geometry	"Christmas tree"	Single, Cluster	"Umbrella"	Single, Cluster	Single	Single
Active part of the electrode	5cm/7cm	Single/ Cluster 3cm/2,5cm	4 cm	1.5 cm		4 cm
Electrode	Expended± wet ±flexible	Cooled single/cluster	Expended	Wet		Cooled
MRI	Yes (XL)	Yes (single or cluster)	Yes (3.5cm)	Yes	Yes	Yes (mono/ multipolar)

Table 2. Different characteristics of RF equipments and probes.

2.5.2. The ultrasound equipment

The ultrasound equipment used for ablation must have either a fixed or flexible linear laparoscopic ultrasound probe (figure 1A) or a fixed forward-viewing convex-array transducer (figure 2B) and the possibility of Doppler imaging.

For improvement of tumor visualization and targeting for RFA, a prototype tracked ultrasound-guided laparoscopic surgery system was design and used in clinical practice by some authors [33]. By tracking two-dimensional ultrasound images in physical space, the system generates three-dimensional ultrasound volumes. Once the tumor is manually identified in this volume, a targeting system is used to guide the tip of the RFA probe inside the tumor [33].

A picture-in-picture box with the quarter-size laparoscopic image superimposed over the full-sized ultrasound image is of paramount importance for the coordination of the movement of the instruments.

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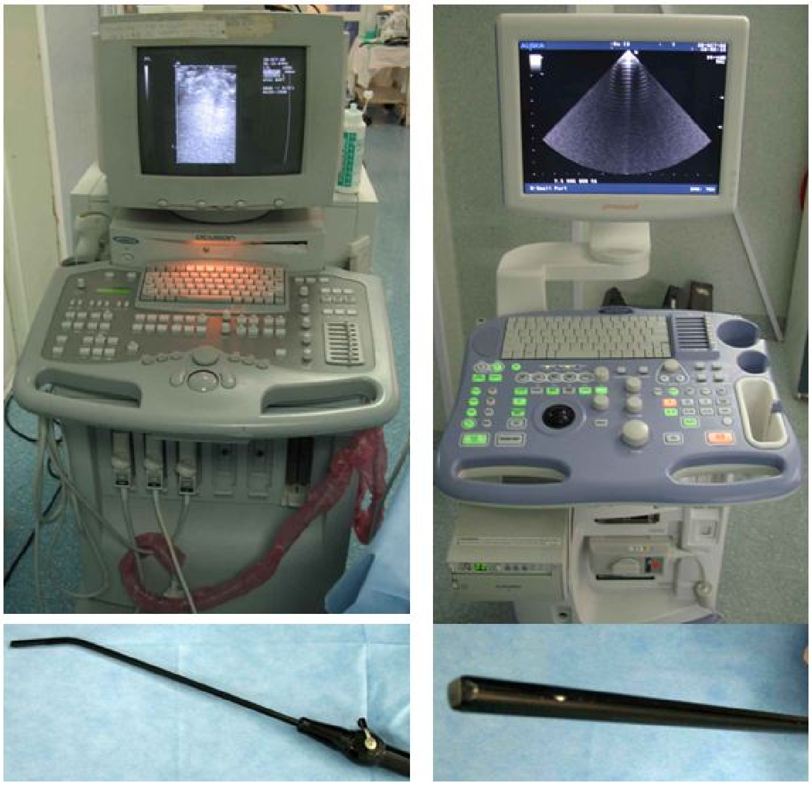

Figure 1. Ultrasound equipment. A. Ultrasound machine with flexible liniar transductor for laparoscopy. B. Ultrasound machine with fixed convex transductor for laparoscopy

2.6. LRFA technique

2.6.1. Pneumoperitoneum induction

In many centers the Veress technique remains the most widespread method of induction of peritoneum. Because the most common complications of laparoscopic surgery are related to insertion of the Veress needle and the first trocar, alternatives such Hasson's open method or optical access trocar-insertion emerged. These alternative methods are especially useful in patients with previous operations and intraabdominal adhesions.

The Hasson's open method implies the transversing of the tissue planes under direct view and carries the disadvantages of continuous air leaks and prolonged operating time. Besides it can be cumbersome in obese patients.

The optical access trocars have been developed as an alternative means of transversing the tissue planes under direct view. We advocate the use of optical access trocar which in our department is the standard device for obtaining abdominal access in laparoscopic practice since 1995 [34]. The method consists in introduction into abdomen of a 12-mm disposable Optiview® trocar (Ethicon Endo-surgery Cincinnati, OH) or a 5-12 mm Visiport™ Plus Optical trocar (Covidien)with an inserted 0^0 laparoscope.

2.6.2. Trocar insertion

Most of the patients submitted for LRFA can be treated with placement of two right subcostal ports. The umbilical placement of one trocar represents an impediment to reach the dome of the liver from such a location.

Selected patients need insertion of the third or fourth trocar (figure 2). The additional trocars may be needed for dissection of the intra-abdominal adhesions, performing cholecystectomy, retraction of the adjacent organs, or multiple needle insertion for treating multiple tumors.

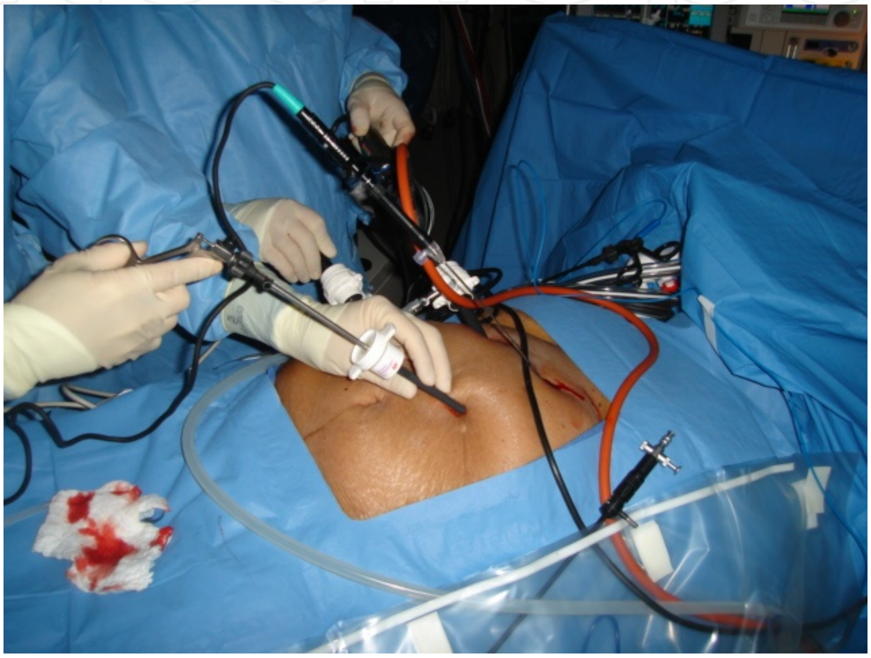

Figure 2. Patient with previous laparotomy, placed in supine position for LRFA of bilateral liver metastases. Three trocars are inserted: one for video, one for ultrasound transductor, and one aditional trocar for forceps. The RF probe is percutaneously introduced.

2.6.3. Abdominal exploration

All adhesions that interfere with proper exploration of the abdomen are taken down. A systematic and thorough visual exploration of the abdominal cavity is performed, and all peritoneal surfaces are carefully examined for possible deposits, paying special attention to the undersurface of the diaphragm, the hepatic round ligament, and the omentum. Lymph nodes in the hepatoduodenal ligament are examined for enlargement. The quality of the liver parenchyma with regard to the degree of cirrhosis or steatosis is also assessed.

Laparoscopic ultrasound is performed systematically in a longitudinal fashion, different from the transverse orientation in intraoperative ultrasound. For laparoscopic ultrasound liver scanning, most authors use the linear probe. For a better visualization of the upper segments or caudate lobe some authors favor the use of others probes. In some cases for a better contact between the convex liver surface and the probe, instillation of normal saline solution into peritoneum can be very helpful to provide an acoustic window. Sometimes the abdomen need to be desufflated to improve contact with the liver. The laparoscope and LUS probe can be interchanged between the ports to provide different views of the liver and to enable varying placements of the probe on the liver surface. Generally it is not needed to take down the falciform ligament but the creation of a window in the falciform ligament allows the exploration of the liver in patients with dense midline adhesions. Maintaining visual guidance of the probe's position on the liver with the laparoscope aids in orientation. Scanning is started with visualization of the point at which the three liver veins drain into the inferior caval vein. The number and size of hepatic lesions and their segmental locations are carefully documented. The exact location of the liver masses relative to the central vascular structures is aided by color Doppler, and the distance to the vessels is measured in centimeters, considering a safe margin for ablation of 1 cm. Color Doppler is also used to assess the vascularity of the hepatic lesions. The distance between hepatic lesion and surrounding viscera is evaluated in order to plan the ablation process.

2.6.4. Tumor biopsy

Once the lesions are mapped in the liver, a core biopsy is performed under ultrasound guidance using an 18-gauge spring-loaded biopsy gun (Microinvasive) and sent for frozen section to confirm malignancy. In some HHC, obtaining of proper amount of tumoral tissue is difficult due to its inconsistency and repeated biopsy are needed. The tumor biopsy can also be Obtained after the RFA having the advantage of harvesting a more consistent tissue fragment and avoiding the possible bleeding from liver puncture site. Tissue samples are taken only from representative tumors and not from all.

2.6.5. RF needle insertion

Laparoscopic introduction of the RF electrodes into the liver tumors are ultrasound guided and the operator has to plan very carefully the insertions. This represents the most difficult part of the procedure, and most beginners under treat due to this.

Introduction of the electrodes especially to ablate large tumors, tumors near great vessels or poor visualized tumor is very demanding using the fix or flexible linear-type ultrasound probe (figure 1A). Often small and deep-seated tumors necessitate repeated trial-and-error insertions of the RF electrode. The safety and the complete necrosis of ablation is very much dependent on the RF electrode positioning.

For ablation of liver tumors under the guidance of a linear-type probe, the RF electrode must be inserted from the abdominal wall cranially and parallel to the ultrasound probe. For accurate tumoral insertion of the RF probe operator has to mentally establish in three dimensions the insertion site and angle on the abdominal wall and also on the surface of the liver. For small and deep-seated tumors, insertion of the electrode can be very difficult due to the impossibility to observe the needle on a single image. Therefore, the ultrasound probe has to be moved according to the position of the needle tip.

Continuous monitorization of the position of the needle tip on the ultrasound image immediately after puncturing the liver is possible using the laparoscopic system with a fixed forward-viewing convex-array transducer, with a guide groove on the back of the shaft (figure 1B) [35]. Perpendicular direction of scanning of this transducer enable the easy and accurate puncture of the deep-seated tumors. Unlike with other conventional linear-type, it is not necessary to consider the insertion site on the abdominal wall and surface of the liver. This transducer facilitates the needle insertion in tumors situated in segment VII, VIII, for which scanning by linear-type probes is more difficult [35]. Some authors advocate the use of the forward-viewing convex-array probe for lesions situated in segment I arguing that this US-probe makes not only the imaging of the caudate lobe easily but also avoid the insertion of the needle through segment IV which has the risk to damage major vessels and biliary ducts [36].

Positioning the needle tip depends on the type of the electrode used. If a straight (nonexpendable) electrode is used then it is advanced under US-guidance until its tip reaches and passes the deep margin of the lesion in order to obtain a safe oncological rim of normal parenchyma. Depending on the tumor size and noninsulated distance of the electrode it might take more than one application to complete the lesion ablation. Repositioning the electrode is performed to obtain overlapping spherical or cylindrical ablations.

If the electrode has Christmas tree-type deployment then the tip of the electrode is positioned also in correlation with the tumor diameter and the active size of the electrode. If only one ablation is planned the tip of the electrode is advanced till it reaches the superficial margin and the prongs are progressively deployed. If more than one ablation is intended then the tip of the electrode is positioned into the tumor considering the dimension of the prongs. After completing the first ablation, the prongs are undeployed, the electrode is retracted by 2-2.5 cm, the prongs are again deployed, and ablation reinitiated.

If one considers the use of an umbrella-type expandable electrode, the tip of the electrode usually targets the center of the tumor. In case of a large tumor, the positioning of the electrode is similar with the previous expandable type.

Using the first-generation RITA Medical System model 30 (4 arrays) or model 70 (7 arrays), a single ablation cycle is enough to destroy a tumor <3 cm. For tumors >3 cm overlapping ablations are necessary using these probes. Using the second-generation of probes - RITA Medical System Starburst XL (9 arrays, 5 cm) - the tumors <3 cm are ablated with a single 3 cm ablation, those of 3-4 cm with a single 4 cm ablation, those of 4-5 cm with one cycle of a 5 cm ablation and those of >5 cm with application of 2-4 cycles of ablation to obtain adequate margins [29]. The new RITA System Starburst XLi enhanced permits ablation of the 5-7 cm sized tumors with a single ablation cycle.

In patients with multiple lesions the duration of the ablation process can be shorten using simultaneously two RF needles. However these simultaneous ablations are very demanding due to real-time monitorization. In case of performing these, care must be taken to place the needles apart otherwise much larger ablation area can result.

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Withdrawal of the RF needle after the ablation needs some consideration to discuss. RFA of the needle track is needed not only to control the bleeding but also to avoid recurrences along it. Bleeding from the needle track is seldom a problem but it might be cumbersome in cirrhotic patients. Generally RF ablation with application of a 20-30W power suffices. If not, laparoscopy permits us to control the bleeding by other means: electrocautery, haemostatics, argon application.

2.6.6. Real-time monitoring of the ablation process

The ablation process is assessed in three ways:

1. monitoring the thermocouples temperatures,
2. observing the ablation effect by ultrasound,
3. checking the absence of the Doppler signal into the previously vascularized tumors.

Except of RITA generators all the others deliver energy to tissues automatically based on impedance feed-back control. Because the damages of the tissues are well established at certain temperatures, we favor the use of RITA generators which control the ablation process using the thermocouple temperature. The device can be manually preset to the target temperature. We use for ablation a preset 105^0C temperature at thermocouples. During the ablation procedure the temperatures of the thermocouples are monitorized and visualized on the display of the device. The process can also be registered on a notebook connected to the system.

Aiming the enlargement of the ablation area, many authors have developed their own protocol of ablation [37]. Due to animal experimental studies and our clinical experience, LRFA has become a standardized operation. The time of ablation process depends on the tumor volume. The mainstay is to achieve the target temperature progressively till the full deployment appropriate to the tumor diameter. Our protocol is to deploy progressively the prongs of the RF needle. The prongs are deployed at 2 cm and subsequently to 3 cm until target temperature of 105^0C is reached at all thermocouples. Then the catheter is advanced to 4 cm and consecutively to 5 cm and maintain for 7 min at each deployment [37]. If the target temperatures cannot be achieved the prongs are completely retracted and the catheter rotated with 45^0 and then the prongs redeployed. While advancing the deployment of the prongs, the temperature of the thermocouples decreases and then progressively increases. Sometimes the reposition of the needle is needed to avoid the vicinity of the great vessels or to maintain the prongs inside the liver parenchyma. Even when one to three prongs cannot reach the highest temperature, the ablation procedure is continued taking them out of equation.

After the ablation is ceased, the monitoring of the thermocouples temperature is observed and it should be noticed that it drops rapidly over the 10-20 s and slower after. The temperatures higher then 60-70^0C at 1 min after ablation are considered relevant to a successful ablation. In case of uncertain ablation, the needle is 45^0 rotated and the tines are again fully deployed. If the temperatures are above 60^0C the ablation is well done. If not, the ablation is repeated.

The ultrasound visualization of the tumor ablation is possible due to the microbubbles formation into the tissue. These are caused by out gassing of dissolved nitrogen. The area of the tumor becomes progressively hypoechoic and due to the gas shadow the deep edge of the tumor is obscured (figure 3). This justify the planning of the ablation process from the deepest tumor area to the superficial one. In about 10 min the gas is reabsorbed and the tumor regains the initial aspect with the exception of some amount of gas and the needle track.

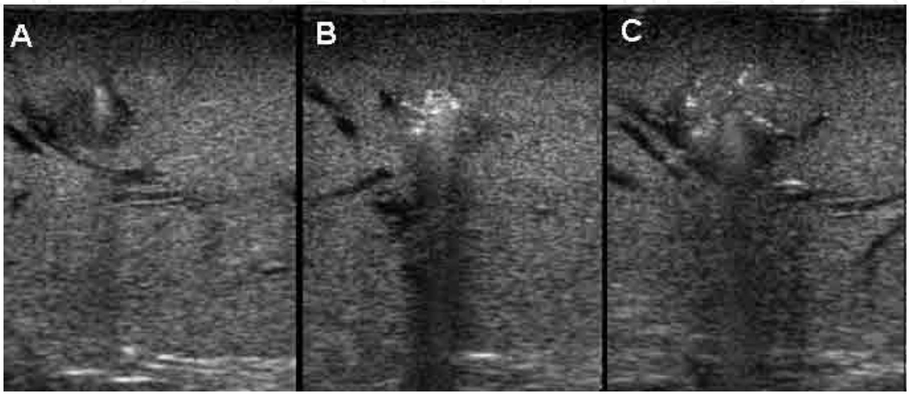

Figure 3. RFA ablation of HCC. A. Positioning the tip of the electrode in the hepatic tumor. B. RFA is started and microbubbles of gas determine appearance of hyperechoic images in the tumor. C. The extension of ablated tissue obscures the deep edge of the tumor. From image collection of Dr. Boros Mirela.

Doppler control of the ablation process is useful in case of vascularized tumors to certify the disappearance of the flow. Usage of the micro bubble contrast agents (e.g. SonoVue ® Bracco International B.V., Holland) can add more help in assessment of the liver blood flow.

Fluorescence spectroscopy was tried in porcine models aiming to detect hepatocellular thermal damage in real time and hence ensure adequate tumor ablation [38].

Due to the skin burn complications reported after RFA, the monitorization of the skin temperature under the grounding pads needs to be mentioned. Especially in patients with large or multiple tumors the position of the grounding pads is essential. The common position is at the same distance on the anterior surface of the tights. These neutral electrodes are needed only when RF monopolar electrodes are used. The bipolar electrodes do not necessitate these pads. It was showed that placing the ground pad over the patient's back resulted in delivering an increased power to the tumor itself and decreasing the time to reach the target temperature [31]. When planning to use two needles two pair of grounding pad are mounted on the patient's back and tight. After completing the ablation the peripheral small tumors become volcanic crater-like and the larger ones appear as a depressed mass.

2.2.7. Useful intraoperative maneuvers

2.6.7.1. Saline-enhanced LRFA

Hypertonic saline injected through a side port on the shaft of the electrode prior to ablation can be uniformly distributed within an encapsulated HCC and thus increase ionicity and conduction within the tumor. The result is an increased volume of ablation up to 6-7 cm diameter. On the contrary, this method is not safe for patients with scirrhous colorectal liver metastases due to the unpredictability distribution of hypertonic saline.

2.6.7.2. Saline infusion systems

The electrodes designed with tiny channels can be used to infuse small volumes of saline into tumor during ablation process in order to prevent desiccation and charring of the tumor that would otherwise prevent conductivity and limit the ablation volume.

2.6.7.3. Vascular occlusion

The application of the Pringle maneuver for limited amounts of time has been shown by some authors [39] to increase ablation volumes but was found inefficient by others [40]. The vascular pedicle occlusion might be justified due to reduction of the heat-sink effect [41]. Total vascular exclusion of the liver was shown to result in the greatest increase in necrosis volume when compared to no occlusion or Pringle maneuver [42].

The possibility of vessel damage or thrombosis secondary to RFA with vascular inflow occlusion was pointed out by some authors [43]. These vascular side effects could be increased in such cases when one or more of electrode prongs are placed in the lumen of a vessel [44]. Moreover, increased ablation secondary to Pringle maneuver carries with it an associated risk of biliary, portal, or parenchymal injury [45].

We consider reasonable not to perform Pringle maneuver also because laparoscopy results in a 30-40% reduction of the blood flow as it was stated by other authors [46].

2.6.7.4. Cooling of the biliary tract

Despite the major vessels, major biliary ducts are deemed to be vulnerable to hyperthermia. Damage of these ducts were reported to occur when the RF needle was located less than 5 mm apart from these [36]. As with the biliary ducts, gallbladder is submitted to damages during and after the ablation process. For tumors situated in segment I, IV, V, in the proximity of the gallbladder cholecystectomy may be recommended before starting the ablation in order to avoid organ perforation or inflammation. The method to prevent the occurrence of biliary system damages is cooling it by pouring cold saline solution onto the surface of the bile duct and gallbladder [36] or by infusing a 4^0 C saline solution quickly through a catheter placed in the bile duct via choledochotomy [47].

3. Results

3.1. Follow-up

Postablation syndrome is a self-limited flu-like syndrome. This systemic inflammatory reaction occurs in one third of patients after RFA and usually depends on the extension of the ablated lesion(s) and ablation time. Its clinical manifestations are milder compared with cryotherapy and consist in transient fever, pain, malaise, myalgia, nausea, and vomiting [48]. The laboratory tests which attest the inflammation are leukocytosis, elevation of serum transaminases, and bilirubin level. The laboratory analysis are performed in the first day after ablation. The WBC count increases more in patients with normal livers and less in patients with previous chemotherapy and cirrhosis [49]. The most dramatic elevations are noticed with AST (14-fold) and ALT (10-fold) but with a fast return to baseline within a week. Serum bilirubin, alkaline phosphatase, and GGT also increase immediately after ablation but with a slower return to baseline up to 3 months. The degree of these elevations is more pronounced in patients with normal hepatic parenchyma than in patients with hepatic steatosis, fibrosis, or cirrhosis [49]. Despite what it would be expected because of the cell death, serum potassium and lactate dehydrogenase levels remain stable after RFA.

To test the tumor markers, blood sample is obtained 1 week after ablation, every 3 months for 2 years, and every 6 months thereafter.

Grayscale ultrasonography of LRFA ablated liver tumor may show hypoechoic, hyperechoic, or mixed appearance. It can be used to early diagnose the hepatic abscess as complication of RFA.

The triphasic (noncontrast, arterial, portal-venous) CT scan is performed to establish a baseline at 1 week postablation and on regular basis every 3 months for 2 years, 6 months for 2 years and yearly thereafter (figure 4).

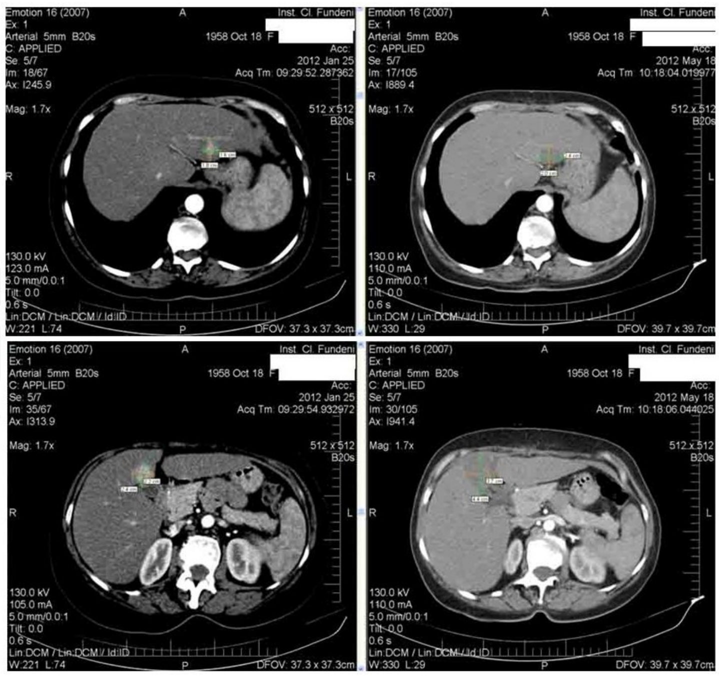

Figure 4. LRFA of a multicentric HCC on cirrhotic liver. The upper images show a hepatic tumor in segment II pre and postablation. The lower images show a hepatic tumor in segment IV pre and postablation. Tactic cholecystectomy was performed during the same operation. There is no tumor recurrence after 3 months postablation.

In the first week postablation, the destroyed tumors appear on contrast-enhanced CT (CECT) with low attenuation when comparing to the normal liver tissue. CECT scan performed in the first 2 weeks postablation may underestimate the actual result due to the presence of granulomatous hypervascularized healing around necrosis which can be misinterpreted as residual viable tumor.

The small ablated lesions have a spherical, "punched out" shape contrary to the large ablated lesions which have a more irregular shape. The success of ablation is announced by CT demonstration of a larger lesion due to the ablation of a rim of nontumoral hepatic parenchyma (figure 5). On further CT scanning the lesion will decrease in size. Any increase in lesion size, irregularity of the edges, or contrast enhancement diagnoses either the incomplete necrosis or local recurrence. Sometimes the appreciation of the contrast enhancement of the lesion might be very difficult especially when comparing the pre- and postablation hypodense liver masses. The assessment of CT Hounsfield unit of the preablated liver lesion was shown to be very reliable in assessment of its evolution. The quantitative measurement of tissue density expressed in Hounsfield unit scale is reproducible over time and is machine independent. In successfully ablated lesions there is a measurable decrease in contrast uptake, which is indicated by the minimal increase in Hounsfield unit density following the administration of contrast in postablation scans [50].

Contrast-enhanced ultrasonography (CEUS) is also useful to provide information regarding ablated lesion but has low sensitivity in identifying the safety margin and incomplete coverage of the liver in patients at high risk of developing new hepatic tumors.

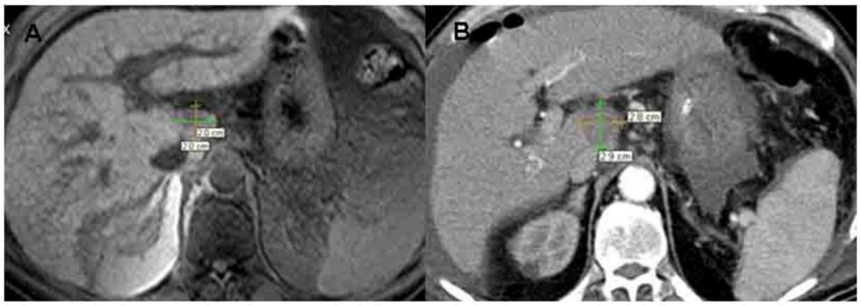

Figure 5. Follow-up of HCC with LFRA. A. RMI is diagnostic for a 2 cm sized tumor situated in caudate lobe. B. Two months after LRFA the tumor is hypodense on CECT and a little larger than prior ablation with a diameter of 2.8 cm. The ablation was successfully completed.

If the CT imaging is doubtful, MRI or PET is indicated. Unenhanced or contrast-enhanced MRI can be used post-LRFA. MRI has a higher sensitivity than CT for detection of recurrences at 2 months (89% vs. 44%) [51] but at 4 months there is no difference between them.

Despite its higher sensitivity for local recurrence comparing with multidetector CT (MDCT), radiolabeled deoxyglucose ([18F]FDG) PET/CT is limited to few centers.

In case of further uncertain imaging results for tumor recurrence, percutaneous biopsy or exploratory laparoscopy with LUS examination and biopsy may be needed [52]. In case of positive malignant fresh sections, the tumor recurrence must be reablated including the whole previous lesion due to the 23% risk of viable tumoral cells in the core of the lesion and respecting 0.5-1 cm edge of oncological safety.[52]

Quality of life is assessed pre- and postablation using different questionnaires.

3.2. Morbidity and mortality

The type of complications after LRFA are mainly the same with those encountered after percutaneous or open approach but with an intermediate rate. The specific complications for the laparoscopic approach are those linked to the introduction of Veress needle and trocars. In LRFA there have not been reported thermal damages of the neighboring organs. The rate of complications seems to be non-related with the histological pattern of the tumor. It has also been proven on large cohort of patients that the rates of complications are comparable if it is the first RFA (5%), repeated RFA (1%), or RFA combined with other procedures (3%) [49].

Hepatic abscess represents the most common complication registered after RFA and is related mostly to large area of necrotic tissue. One explanation for development of hepatic abscess is the retrograde enteric bacterial contamination of the biliary tract from bilioenteric anastomosis or Oddi sphincterectomy. In patients with previous Whipple procedure the incidence of the liver abscess is 40% much more higher than in patients without bilioenteric anastomosis (0.4%) [49]. Considering these, some authors avoid performance of RFA on such patients [2]. In case of performing LRFA for the patients with bilioenteric anastomosis, there should be a close follow-up aiming the early diagnosis and treatment of this complication and a longer antibioprofilaxy. The hepatic abscess can be treated with antibiotics and percutaneous drainage.

Other possible complications are ascitis, liver failure, and respiratory complications.

Thrombocytopenia (excluding patients with preexisting thrombocytemia) and gross mioglobinuria are seldom encountered, being related to the extensive procedure for large or multiple tumors. Acute renal failure due to mioglobinuria is much less encountered as a complication of RFA than cryotherapy and it can be prevented with high hydration of the patient during and after the procedure.

Skin burns are a rare complication with LRFA.

Overall, LRFA is safe and well tolerated, with a per procedure mortality of less than 1%.

3.3. Parietal seeding

Parietal seeding is less a problem in laparoscopic than in percutaneous RFA and can be coped with the aid of a 14 G venous needle or a 2 mm trocar placed through the abdominal wall. The RF electrode is introduced through these large sheaths [53]. For cluster needle such a precaution is not feasible.

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3.4. Local recurrence

Local recurrence is defined if the lesion is within 2 cm of the ablated tumor. Remote or distal recurrence is defined when the lesion is at least 2 cm far from the ablated tumor. [53]. Local recurrence is the best measure to assess the technical success of RFA.

Theoretically, the recurrent lesions are due to viable malignant cells that escaped thermal injury during the ablative procedure. This could be the explanation of the recurrences which mainly occur at the periphery of the lesions [50].

The wide range of local recurrence after RFA between 1.8% and 60% reflects difference in tumor type, size, number, liver segmental location, approach, ablation margin, blood vessel proximity, operator experience, and - last but not least - type of RF probe and generator used [54, 55].

The higher rates of recurrence seen within certain tumor histology types are likely a reflection of tumor biology (e.g. density, vascularity, heat conduction) but also of parenchymal milieu (e.g. cirrhosis) [55]. Patients with metastases from colorectal cancer, hepatocellular carcinoma, and melanoma have higher rates of local recurrence comparing with other malignant liver tumors [56].

LRFA results In a tumoral recurrence of 5.8% which is similar with 4.4% obtained in open approach but significant lesser comparing with 16.4% reported with the percutaneous approach [55].

In case of limited hepatic recurrences after other ablative procedures or in selected cases after liver resection, it is our believe that LRFA deserves to be the first-choice treatment. In case of multiple hepatic recurrences, transarterial chemoembolization (TACE) is needed in association with LRFA performed for the larger lesions [57].

3.5. Association of LRFA with other therapeutic methods

In patients with multiple liver masses, LRFA can be performed in association with laparoscopic liver resections [58]. LRFA is indicated for deep-situated (<3 cm) tumors while resection is feasible and safety for exophitic/subcapsular tumors. The association of resection with RFA was found to be a safe procedure with long term outcomes better than the ablation but poorer than resection alone [59].

Due to the progression of the malignant disease most of the patients will develop recurrences after LRFA [53, 60]. Because better survival rates have been obtained with the association of regional chemotherapy, some authors recommend the placement of hepatic arterial infusion pump (HAIP) in all patients who undergo RFA [61]. Concomitant LRFA and HAIP are safe and feasible [62].

LRFA is a therapeutic option for the patients with primary digestive cancer and synchronic liver metastases. A rule of thumb is to perform surgery for the primary indication that brings the patient to the operation (i.e. colorectal, pancreas resection, ileostomy reversal). The surgery for digestive tract can be performed either by laparoscopy or laparotomy and is followed by LRFA. A laparotomy should be converted for LRFA because laparoscopic approach facilitates accurate needle placement [63]. Moreover, LRFA avoids the need of large incision for liver access. For selected cases with colorectal tumors and liver dissemination in which liver resection might increase the operative risk, the ablation of the hepatic lesions is recommended to be performed laparoscopically in the same operative session. The tumor ablation combined with other operative procedures was shown to be safe and not to increase the risk of morbidity and hospital stay [63].

4. Conclusion

Laparoscopic exploration and intraoperative ultrasound permit an accurate staging of malignant disease. In unresectable malignant liver tumors, LRFA represents a safe and effective treatment especially when percutaneus approach to the lesions is deemed difficult. LRFA can also be a substitute for hepatic resection in patients with small malignant tumors or benign liver tumors. LRFA proved to be safe for the treatment of subcapsular tumors due to the possibility of direct visualization, active protection of the surrounding structures, and control of the potential bleeding from these lesions. Deep-situated lesions difficult or impossible to be visualized by percutaneous US and/or punctured percutaneously can be successfully ablated by laparoscopy. Laparoscopic approach is the first choice for ablation of large or multiple liver tumors with possible association of surgical resection or portal vein ligation. LRFA represents a good bridge therapy for prevention of tumor progression and downstaging of multiple lesions for patients with HCC and cirrhosis on the waiting list for liver transplantation. LRFA is associated with less intraoperative blood loss and fewer postoperative complications when compared with open procedure. Due to its minimal surgical trauma, this procedure determines a fast recovery time and short hospital stay. Tumoral recurrence after LRFA is similar to the open approach but significant lesser comparing with percutaneous one. In case of incomplete thermal ablation or tumor recurrence, LRFA can be repeated or followed by transarterial chemoembolization.

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Author details

Mirela Patricia Sîrb Boeti[1,2*], Răzvan Grigorie[2] and Irinel Popescu[1,2]

*Address all correspondence to: paboet@yahoo.com

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1 University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania

2 Fundeni Clinical Institute, Department of General Surgery and Liver Transplantation, Buchares, Romania

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