

Surgical hepatic resection vs. ultrasonographic guided radiofrequency ablation in colorectal liver metastases: what should we choose?

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Abstract

Clinical evolution of the colorectal carcinoma occurs in up to 60% with colorectal liver metastases (CRLM). Although hepatic resection is considered to be the golden standard in CRLM, novel less invasive techniques have emerged, of which radiofrequency ablation has received a high credibility. When tumors are not eligible for surgery, guided radiofrequency ablation is considered an alternative. This method is appropriate when there are no more than 5 lesions with a diameter of less than 3 cm. While open surgery guarantees a more precise tumor excision, the effectiveness of ablation must be evaluated either by contrast-enhanced computer tomography, magnetic resonance, or ultrasound. This paper aims to review the current standings in radiofrequency ablation for CRLM and to compare the technique with surgical resection in order to find which one is the best treatment option.

Keywords: colorectal cancer, liver metastases, radiofrequency ablation, hepatic resection

Introduction

Colorectal cancer (CRC) is the most frequent digestive cancer, representing an important cause of morbidity and mortality worldwide [1,2]. Clinical evolution of CRC occurs in up to 60% with colorectal liver metastases (CRLM), and only 10-25% of these CRLM can be resected at the moment of the initial diagnosis. Although hepatic resection is considered to be the golden standard in CRLM, new less invasive techniques, such as transcatheter arterial chemoembolization, cryotherapy, microwave ablation therapy (MWA), laser induced thermotherapy (LITT), irreversible electroporation (IRE) and radiofrequency ablation (RFA), have been used for patients with unresectable hepatic tumors [3]. Among them, RFA has

received increased attention and is most widely used due to its advantages, such as minimal invasiveness, better safety profile, equivalent local control and survival rate as compared to liver resection.

Hepatectomy for CRLM has a morbidity of 17–37% and a mortality below 5% [4,5]. Recent reviews showed a 5-year overall survival rate after hepatic resection of 22–58% and a 10-year survival of up to 28% [6,7]. The local recurrence rate after resection varies between 1.2% and 10.4% [4]. Patients which are not eligible for resection, either because anatomy is making it impossible or due to other comorbidities, have a marginal survival, with only 0-2% being alive after 5 years [8,9]. Although systemic chemotherapy used for unresectable CRLM has improved overall survival with almost 2 years, only a few patients are still alive after 5 years. Several studies have described the use of RFA either percutaneously, laparoscopically or intraoperatively as a trustful possibility to extend the overall survival rate in patients with unresectable CRLM.

Recently, RFA has outdated other ablative therapies due to its low morbidity and mortality rates, as well as increased patient acceptance [10]. This paper will review the current standings in using RFA for CRLM and com-

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pare the technique with surgical resection, aiming to find the best treatment option which can extend the overall survival rate.

RFA principles

The principle of RFA is based on the property of inducing thermal injury to the tissue through electromagnetic energy deposition. Thus, the patient is placed in a closed loop circuit that includes an RF generator, an electrode needle, and a large dispersive electrode (ground pads) [11]. The principle of RF is based on the property of inducing thermal injury to the tissue through electromagnetic energy deposition. The patient is placed in a closed loop circuit that includes a RF generator, an electrode needle, and a large dispersive electrode (ground pads). Alternating current causes ionic agitation which leads the surrounding tissue to heat up. Thus, by increasing the current's amplitude thermal damage is produced leading to coagulation and cellular necrosis.

During the procedure certain aspects should be considered such as: tumor volume, ablation time, or effectiveness of ablation. The time is determined by the physician according to the tumor size and the used temperature. The volume directly influences the number of ablations needed, the so called overlap ablations which can be either spheroid or cylinder. Because in some situations tumors are not fully ablated, a short and long follow up using imaging indicators (ultrasound or angiographic studies, CT-scans) is required.

So far there are only four types of RFA systems available: two using deployable tines that expand into the tumor after an outer trocar is placed into the tumor or at the tumor edge [such as RITA Medical Systems (StarBurst XL - AngioDynamics) and RadioTherapeutics (RF Ablation System)] and two systems that commercialize straight-needle electrodes [Radionics (Cool-tip RF System) and Berchtold (Elektrotom 106 HFTT)]. The Radionics device uses active tips of different sizes so it may obtain different ablation volumes and requires a pump to supply cold saline through the hollow ports inside the needle in a closed system, while the Berchtold system infuses normal saline to increase the ablation area [12]. The RITA Medical Systems relies on direct temperature measurement throughout the tissue to prevent any electrode in a multi-tined configuration from exceeding 110°C. The needle electrodes of RITA consist of a 14-gauge insulated outer needle that houses retractable curved electrodes of various lengths [13]. When the electrodes are extended, with a length of about 4 cm, the device assumes the configuration of a Christmas tree with each of the prongs functioning as an antenna for disper-

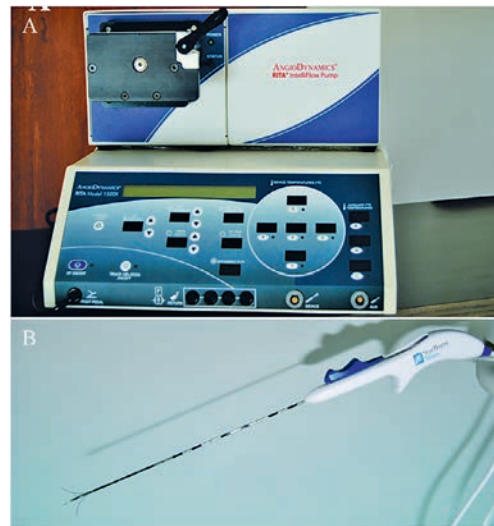


Fig 1. A). AngioDynamics RITA Model 1500X RF Generator; B) StarBurst® Talon RFA with an IntelliFlow pump with saline infusion; Device length 25 cm, outer diameter 14 gauge/6.4 french with 4 deployable tines which creates 4 cm ablation

sion of current. As ablation begins, the areas surrounding each prong coalesce, increasing the ablation area. The Model 1500X Electrosurgical Radiofrequency Generator is capable of delivering up to 250 W of RF power (fig 1). A good sign of complete ablation is at the end of the procedure when temperatures must be above 70°C, otherwise more ablation might be necessary so that the procedure could be considered accurate. Several sessions may be performed using overlapping ablations as the size of the tumor may not be sufficiently covered.

The Radionics and Radiotherapeutics devices rely on an electrical measurement of tissue impedance to determine that tissue boiling is taking place. These impedance rises can be detected by the generator, which then can reduce the current output to a preset level [14]. The Radiotherapeutics RFA device (LeVeen Needle Electrode) was introduced in 1997 and consists of an insulated 17-gauge outer needle that has 10 separated prongs deployable from the needle tip that, when extended, seem to resemble an umbrella [15]. The diameter when extended varies from 2 to 4 cm. The ablation protocol is not based on tissue temperature as in the case of RITA devices, but on tissue impedance and an ablation is considered successful if the device impedes out.

Treatment Algorithms for Liver Tumors Using RFA

Conventional transabdominal ultrasound has been successfully used in detecting liver masses and has cer-

tainly improved over the past years by introducing microbubble ultrasound contrast agents (UCA), that provide a more specific diagnostic and characterization of liver tumors [16]. As a guiding procedure for RFA, US examinations still have its advantages as compared to computer tomography (CT) or magnetic resonance (MR), based on the worldwide availability, ease of use, no radiation exposure and low cost characteristics. Nevertheless, for the assessment of complete ablation and follow-up, contrast-enhanced CT or MR examinations are still preferred.

Both intraoperative (IOUS) and laparoscopic ultrasound (LRUS) are considered to have better accuracy than transabdominal US, as they obtain a better scan of the liver due to the direct contact. For example, IOUS performed on 561 malignant lesions revealed a lesion detection of 95.1% [17]. LRUS is used more often for superficial lesions or tumors in the vicinity of other organs, as well as if percutaneous approach might be difficult [18,19]. However, a study published by Loss, which used contrast enhanced intraoperative ultrasound (CE-IOUS) right before surgery or RFA has turned out to be game-changer as additional tumor lesions were found. From the 50 patients, who had CE-CT, CE-MR and/or PET-CT scans, 56% were found with more lesions after CE-IOUS which led to a completely different approach than was initially decided [20].

With CEUS techniques developing, detecting and delimiting liver tumors has improved allowing real time evaluation of blood flow, perfusion of normal and pathological tissue [21]. Some studies have shown even a more biodisponibility of CEUS than enhanced helical CT in detecting small hypovascular tumors and therefore changing perspective in prognosis and therapy [22]. Performing CEUS while guiding the RFA needle allows a real-time evaluation of colorectal liver metastases and stands as a more precise procedure since the needle insertion may be done during the portal phase. Hypovas-

cular metastases appear as dark defects in contrast with the enhanced surrounded tissue [23]. While RFA is performed, a hyperechogenic region appears and progressively increases in dimensions corresponding to gas microbubble formatting a coagulated tissue. A recent study which compared the efficacy of US vs CEUS for RFA in liver metastases revealed a higher early tumor necrosis and lower intrahepatic recurrence in CEUS procedures. Thus, 136 patients were examined with CEUS, with a total of 236 hepatic metastases, concluding that patients with tumors larger than 2 cm or with single metastases had a higher survival rate than in the US group [24].

New 3D imaging techniques are evolving and may be an even better option for applying RFA. Leen et al had a more accurate planning and guidance of needle electrodes and were more successful in the assessment of residual or recurrent disease, while performing guided RFA with contrast enhanced 3D ultrasound (CE-3DUS) in liver tumors. CE-3DUS allows both tumor shape and geometry to be determined, highlights adjacent vessels and may easily allow another RFA procedure after assessing the initial response within 10 minutes, if a residual viable tumor tissue is suspected [25].

Clinical trials using Acoustic Radiation Force Impulse (ARFI) imaging with RFA procedures on liver masses have been studied for the past years. Real-time ARFI imaging pre-procedure, during and post-procedure may influence the efficacy of RFA. Comparing sections before and after ablation, may identify if the entire tumor has been coagulated and the safety margin area was reached. However CT or MR scans are still considered necessary [26]. Real Time Sono-Elastography (RTSE) as well, may be a possible procedure for monitoring and assessing the RFA process. An in vivo study suggested that real time elastic-changing tissue can predict the tissue necrosis within RFA procedures [27]. While comparing RTSE to CEUS examination during ablation, there was

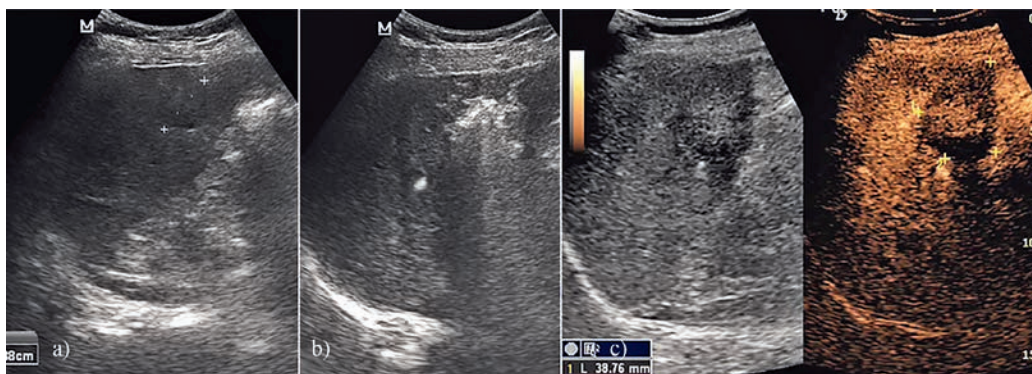


Fig 2. Solitary liver colorectal cancer metastases of 2.88 cm in diameter; CEUS after one month revealed a RFA area of about 3.9 cm/4.5 cm; a) before RFA; b) after RFA; c) CEUS one month after RFA

no major inaccuracy in appreciating tumors size, thus placing RTSE as a possible future competitor for evaluating tumor ablation [28] (fig 2). Nevertheless more studies are to be taken in consideration.

Although plain criteria have not been established so far in using RFA on liver tumors is more likely to be recommended to patients that are not candidates for curative resection. Treatment recommendations in Japan, North America and Europe are slightly different, but RFA may be appropriate for the following [29-31]:

- A number of less than 5 lesions are preferred when treating CRLM
- Complete ablation is better achieved when hepatic masses have a diameter less than 3 cm
- Tumor location and their relation with the surrounding tissue should be well known before the procedure. Surface lesions are sustainable for RFA, but complications may be still encountered. Masses located near the gastrointestinal tract are to be avoided due to high risk of injuring either the gastric or bowel's wall. Also, lesions in the proximity of the hepatic hilum and hepatic vessels may have its contraindications.
- General contraindications for RFA are considered intrahepatic bile duct dilatation, coagulopathies as well as bilioenteric anastomoses.

4. RFA vs. liver resection

Many studies have compared the recurrence and outcome of RFA alone, hepatic resection or hepatic resection followed by RFA in the treatment of CLRM, showing variable results. RFA was proven to be efficient in patients with unresectable CLRM, patients gaining a longer survival rate, but with doubtful results for patients with resectable metastases, where liver surgery has proven to be more efficient. While resection is still considered a standard of care for resectable CRLM, it is hard for other therapies to prove worthy to replace this procedure [32,33]. A recently published meta-analysis indicated that in the treatment of CRLM, liver resection was superior to RFA. Liver resection had a significantly higher survival rate at 3 and 5 years, as well as disease-free survival rate at 3 and 5 years. It was reported that better prognosis was achieved after RFA when maximal size of the tumors was less than 3 cm as consequence of the disease free margins [34]. The authors suggested that the tumor should not exceed 3.5 cm in its longest axis in order to obtain a safety margin of 1 cm all around the lesion [35,36].

Because liver resection is still the fundamental treatment, RFA continues to be used in patients with poor prognostic factors. However, in some cases the patient's

disease itself influences the survival rate, no matter what type of treatment is used. RFA used in advanced stages with multiple tumors, larger lesions, or associated comorbidities, may not always have a superior outcome, as the disease is very aggressive. Thus, survival for patients undergoing ablation may be more a consequence of tumor characteristics rather than of the therapeutic response [37-40]. Hyuk et al published a comparative study on 67 patients (42 liver resection vs 25 RFA) concerning the optimal treatment for solitary metastases, with results again in favor of liver resection. Survival at 3 and 5 years was superior in liver resection compared to RFA, regardless of the tumor size (<3 cm vs >3 cm), type (synchronous vs metachronous), location of liver metastases (central vs peripheral), postoperative chemotherapy or even recurrence rate [41].

Discussions about combining therapies or using them alone for unresectable CRLM demonstrate an interesting perspective. Whereas RFA is used especially in cases with unresectable CRLM, combining chemotherapy, hepatic resection and RFA may prove to be a more successful approach. This therapeutic strategy, using first chemotherapy that can lead to tumor downstaging, and adding liver resection and RFA, had a higher survival rate and lower recurrence rate as compared to each of them used as individual treatments [42,43].

In order to be able to really compare the efficacy of RFA, complete ablation must be achieved. Assessment of tumor growth after ablation is rather important as tumor reappearing at the site of previous RFA might be either a new tumor or an outgrowth of remaining cells from incomplete ablation. While open surgery may guarantee a more precise excision of the tumor, the effectiveness of ablation must be evaluated either by contrast-enhanced CT, MR or US, even though they may have their limitations in identifying the safety margins. For a tumor to be considered successfully ablated there has to be at least a 0.5 cm margin of apparently normal hepatic tissue surrounding the tumor during the portal phase [44-46]. Both CT and MR imaging are considered to be more reliable [47-50].

Wong et al [51] concluded in his review that local tumor recurrence rates after RFA varied from 6% to 40%, and was associated to the size, location, and number of lesions. The pattern of recurrence between resection and ablation proved to be different. Thus, RFA patients were more likely to recur near the RFA site due to incomplete ablation of lesion size, heat sink effect, or limitations of the technique. On the other hand, removing the hepatic parenchyma proved to be more clinically effective [52]. Sanghwa Ko et al [53] presented as well a retrospective study of 29 patients suggesting that RFA is significantly

inferior to surgical resection in patients with tumor size higher than 3 cm. A recent study highlighted that the proper way to evaluate local site recurrences after RFA is by using a fluorine-18 deoxyglucose positron emission tomography (FDG) PET-CT within one year from the procedure. Thus, the patient may be subjected to another ablation procedure.

Nowadays, new methods are being developed in order to enhance the ablation area or to make the procedure safer. Enhancing the procedure, with continuous infusion of diluted HCl during RFA [14] or, RFA combined with superselective bland transcatheter arterial chemoembolization (TACE) using 40 µm microspheres [54] have proven to give good results, in experimental conditions. Using these calibrated microspheres before RFA could provide a certain grade of ischemia, as they may occlude vessels that induce the dissemination of cancer cells.

Conclusions

So far, when evaluating the effectiveness of liver resection and guided-RFA on CRLM, the odds for curative treatment are in favor of surgical interventions. While comparing these two types of therapies we conclude that ablation might be more useful as an adjunct therapy or with palliative purposes for unresectable CRLM, due to the higher hepatic recurrence rate in case of an incomplete procedure or because of surgery risks. RFA might be a less invasive procedure, but it remains in the shadow of liver resection which still stands as the main option in the treatment of CRLM. Improvement of RFA techniques is certainly needed and other technical developments should be sought in order to improve survival and quality of life for advanced colorectal cancer patients.

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