CONTINUING EDUCATION PROGRAM: FOCUS...

Treatment of hepatic and pulmonary metastases with radiofrequency

T. de Baere*, F. Deschamps

Radiologie Interventionnelle, Institut Gustave-Roussy, 39, rue Camille-Desmoulins, 94805 Villejuif cedex, France

KEYWORDS
Radio-frequency;
Tumour;
Metastasis;
Hepatic

Abstract   Although metastatic disease indicates diffusion of a cancer at a distance from its site of origin, in some cases pulmonary and hepatic metastases are isolated and slowly progressive, making them suitable for local treatment. Thermo-ablation techniques are associated with low morbidity and reduced collateral parenchymal damage; they therefore play an important role in such patients, where the disease is slow and chronic, requiring repeated local treatments. Unlike radiotherapy, a second treatment is possible in the event of local failure.

© 2014 Published by Elsevier Masson SAS on behalf of the Éditions françaises de radiologie.

Principle

The current produced by radiofrequency (RF) is a sinusoidal current of 400 to 500 KHz. Tissues that are traversed by this current undergo ionic agitation, which generates heat through inter-particulate friction [1]. The aim is to expose the neoplastic cells to a temperature of more than 60 °C, which provokes almost immediate and irreversible cellular denaturation. The maximum diameter of the zone of tissue destruction induced by a simple needle electrode of RF is only 1 to 1.5 cm, which is not suitable for the treatment of hepatic tumours. Depending on the manufacturers, various techniques are used to increase this area of destruction:

* Corresponding author.
E-mail address: debaere@igr.fr (T. de Baere).

http://dx.doi.org/10.1016/j.diii.2014.04.017
2211-5684/© 2014 Published by Elsevier Masson SAS on behalf of the Éditions françaises de radiologie.
• a needle containing several electrodes (4–12), which are deployed after insertion in the target tumour (Figs. 1 and 2). The aim is to obtain as many single small RF lesions as electrodes, to create a larger area by summation. The size and shape of the final lesion therefore depends, among others, on the number of electrodes used, and of their disposition in space;
• cooling of the electrodes via circulation of cold liquid in the sheath of the electrode limits the accumulation of heat to the surrounding tissue, which makes it possible to deliver more electric energy without exceeding 100 °C in the tissues very close to the electrode which are subjected to greater RF energy than more distant tissues. We thus increase the maximal size of the RF lesion that one can induce;
• bipolar electrodes make the RF current circulate between two distinct parts of the same needle or between two different needles. There is therefore no need for grounding pads on the skin, unlike for all other monopolar systems. The electrical field is confined between the electrodes and can therefore be more intense. Finally, the generators can cope with several needles, therefore several poles to make the current circulate successively between different pairs of electrodes to cover a larger surface area and achieve a greater volume of destruction. This technique is therefore often (incorrectly) termed “multipolar”, whereas it is actually comprised of several successive bipolar applications. These make it possible to increase the size of the RF destruction zones.

**Indications**

Whether in the lung or liver, the majority of surgeons limit treatment to tumours under 5 cm in diameter, given that the ideal indication is for tumours under 3 cm, as the failure rate is higher above this [2–4]. The treatment of tumours that are larger than those that can be destroyed with a single dose of RF require overlapping impacts, which takes time and is always less effective than a single treatment. To understand this significant reduction in efficacy for a seemingly moderate increase in tumour size, it is important to understand that a 5 cm diameter tumour is approximately twice as voluminous as a 4 cm tumour, and likewise for a 4 cm tumour compared with a 3 cm tumour. Furthermore, although a RF system is capable of covering a sphere of tissue destruction of 4 cm in diameter in one impact, 6 RF impacts are required to cover a sphere of 5 cm.

The ideal localisation is at a distance from the hepatic capsule or pleura, and at a distance from the hiluses. Contact with a large vessel has been reported as a predictive factor for the failure of radiofrequency treatment of hepatic and pulmonary metastases [2–4]. This is due to the cooling by convection that is exerted close to the vessels.

![Figure 1](image1.png)  
**Figure 1.** 3D conebeam-CT image of a radiofrequency treatment using a deployable needle, of a metastasis close to the REX recess, during selective portal occlusion obtained via a left trans-hepatic approach with a balloon catheter.

![Figure 2](image2.png)  
**Figure 2.** Pulmonary metastasis of the lower right pulmonary lobe within which a radiofrequency needle has been deployed (a). The CT scan taken 10 min after radiofrequency treatment shows the tumour surrounded by a zone of alveolar condensation, which corresponds to the zone of destruction (b). The pneumothorax visible on this image has been punctured and will be aspirated. No drain will be left in place as this pneumothorax will not recur after aspiration. On the CT scan obtained 2 months after the radiofrequency, there is a zone of condensation that will slowly decrease over time (c).
The means of guidance varies as a function of the organs and of the visibility of the target tumour. For the lung, treatment is always percutaneous and guided by CT scan (Fig. 2). For the liver, RF can be used percutaneously or perioperatively (laparotomy or laparoscopy) under ultrasound guidance. CT scans are usually reserved for cases that are not accessible with ultrasound. If RF needs to be used in an isolated manner, then, the percutaneous route is preferable since it is usually less invasive. Laparoscopy or laparotomy is only proposed when the percutaneous route is not available or when the peritoneal area or lymph nodes need to be "checked".

Result

Hepatic metastases

In a recent literary review, the rate of complete ablation for hepatic radiofrequency varies between 58% and 95%; in the majority of publications [5], the success rate was related to the size of the tumour, as described above. For Elias et al. [3], in the liver, this failure rate increases from 3%, when the tumour is not in contact with vessels, to 23% when it is, and for Lu et al. from 12% to 53% [6].

We recently demonstrated that the occlusion of vessels in contact with the tumour using a balloon results in success rates for radiofrequency that are equivalent for tumours that are in contact or at a distance from vessels with 89% and 91% success, respectively; this applies to tumours that are under 35 mm [7] (Fig. 1).

In terms of local efficacy, the comparison between radiofrequency and metastasectomy performed by Elias et al. shows a similar failure rate, 6% for radiofrequency and 7.3% for metastasectomy [3]. Due to the lack of randomised studies, studies that compare radiofrequency and surgery comprise numerous biases by often including very different patients. In many studies, radiofrequency is reserved for non-surgical patients and sometimes even for patients who have tumours in contact with vessels and vascular structures. They are the worst indications for radiofrequency due to the dispersion of heat by convection engendered by the vessels. Berber et al.’s study, published in 2008, compared extremely different groups with more extrahepatic diseases in the radiofrequency group and a more altered WHO state [8]. If one compares surgical resection and radiofrequency in patients who do not have extrahepatic disease, there is still a significant difference, with a median survival of 59 months for surgery and 40 months for radiofrequency, but if one compares patients with equivalent ASA stages, then radiofrequency is equivalent to surgery.

It is difficult to evaluate the results of radiofrequency in terms of survival as this technique is proposed in very different situations in patients with hepatic colorectal metastases. Indeed, this treatment is proposed at different stages of the disease, sometimes as a last resort treatment for progressive disease after chemotherapy or sometimes very early in the disease before chemotherapy. To illustrate this difficulty, Machi et al. report a median survival of 48 months in patients that had not received chemotherapy and a median of 22 months in those who had [9].

Experience in hepatic surgery shows that the prognosis for local treatment in patients who are progressive under chemotherapy is not as good as that of patients who respond to treatment or are stabilised by the treatment [10]. Ideally, it would be better to treat hepatic metastases that have responded or have been stabilised by chemotherapy.

Gillams et al. report that patients, with fewer than 5 tumours of under 5 cm, have a survival rate of 30% at 5 years, whilst survival is under 5% for more voluminous or numerous tumours [11]. For patients with a single hepatic metastasis of under 4 cm, the survival rates at 1, 3, and 5 years are 97%, 84%, and 40%, respectively with a median survival time of 50 months [12]. The latter results are quite similar to those reported in the surgical literature. These are the best results ever published for hepatic radiofrequency treatment, but the population is extremely selective with a single tumour of less than 4 cm (mean = 2.3 cm) and without extrahepatic disease.

A novel approach explores the use of palliative radiofrequency for reduction in tumour size. This randomised Dutch study compares chemotherapy alone versus radiofrequency and chemotherapy in 152 patients, who had up to 10 hepatic metastases of less than 4 cm [13]. Survival without progression is significantly different between the two groups with 10 months in the chemotherapy alone group and 16.8 months in the radiofrequency plus chemotherapy groups. There was no difference in overall survival at 30 months, but the curves seem to separate late and the follow-up of these patients will be continued before publication of the study.

Pulmonary metastases

The rate of sterilisation of pulmonary tumours using radiofrequency clearly also depends on the size of the tumours treated, but overall the majority of current publications agree on a success rate of 80 to 90% for metastases of less 2 cm [2].

In the lung, contact with a vessel larger than 3 mm increases the failure rate from 23% to 58% in the lung for Gillams et al. and from 22% to 35% for Iraki et al. [4,14].

In terms of survival, 4 series published in 2006/2007 reported comparable survival rates ranging from 84% to 90% at one year, and from 62% to 78% at 2 years [2,15–17]. These figures are close to historical surgical series, but there again, the populations are extremely different, and the surgical series are often old and did not benefit from recent medical advances in the management of cancer.

Follow-up imaging

Hepatic metastases

The aim of treatment via direct puncture is to destroy the tumour, but also a ring of healthy tissue to obtain "safety margins" or "ablation margins". These destroyed tissues will obviously stay in place and form a "scar". This scar is therefore initially larger than the tumour (tumour + safety margins) and only gets smaller late on. It is therefore impossible to use the usual WHO criteria for the evaluation of tumour response based on the reduction in size of the tumour. The scar left behind after treatment is composed
of necrotic tissue, fibrosis, inflammatory tissue, granulation tissue, and viable tumour if the treatment was incomplete. The aim of follow-up imaging is to identify the presence of this viable tumour within the scar. CT scan and MRI are the most commonly used techniques for this follow-up. They enable rapidly repeatable acquisitions over time after injection of contrast medium, to look for zones with early opacification, corresponding in most cases to the tumour [18]. However, iconographic follow-up should not be performed too early, at the risk of incorrectly interpreting the richly vascularised granulation tissue resulting from treatment as tumour residue, this develops principally in the periphery of the destroyed zone, and persists for at least 4 to 6 weeks. This is why it is usually recommended to start follow-up imaging around 8 weeks after treatment, unless a complication is suspected or the treatment is considered as clearly incomplete by the surgeon during the RF procedure. The scar begins to shrink a few moths after treatment, but this post-RF scar usually persists for many years. Two particular post-therapeutic aspects should be recognised and not confused with contrast uptake by residual tumour tissue. The first is the presence of a fine ring (<1 mm) of contrast uptake (visible on CT and MRI) surrounding the entire circumference of the necrotic zone. This contrast uptake is progressive, absent in the arterial phase and maximal in the late phase. It is present in 32% of cases in our series and on histology, it corresponds to non-neoplastic inflammatory granulation tissue in the hepatic parenchyma next to the coagulation necrosis [18]. The second is the presence of triangular areas of contrast uptake with clear contours, visible in the arterial phase, at the periphery of the post-RF necrotic zones. These correspond to perfusion anomalies induced by the treatment. They are present in 12% of cases in our series.

Pulmonary metastases

The rate of complete ablation actually depends on the volume of ablation relative to the volume of the tumour; the margins of ablation are therefore a significant predictive factor [2,14]. We have described, for pulmonary metastases, that a ground glass opacity that shows an ablation zone that is four times as large as the tumour is a predictive factor for success with 96% destruction, compared with 80% destruction when this objective is not attained. Similarly, it has been reported that the margins of ablation were absent in 85% of cases of tumours that relapsed; in the same study, an ROC analysis constructed from relapse as a function of minimal ground glass opacity after ablation confirms that if a 4.5 cm margin of ablation is obtained all the way around the tumour, the success rate for destruction is 100%.

It is therefore very important to make the zones of ablation larger than the size of the tumours to increase the success rate (Fig. 2).

The PET scanner is extremely interesting for monitoring pulmonary metastases treated with radiofrequency since it is capable of detecting a local relapse on the treatment site with more sensitivity than conventional CT scan, and above all, it is capable of detecting local recurrences earlier [19]. Indeed, we demonstrated that PET, at 3 months, has a very high sensitivity whilst it was unusual to discover incomplete treatment between 6 months and 1 year after treatment.

The advantage of PET in pre-treatment is to alter the therapeutic attitude in 30% of cases with either an association of other RF sites, or association of surgical treatment, or abandon of local treatment as the disease is diffuse. This benefit has not yet been clearly demonstrated for the evaluation of hepatic metastases.

Tolerance

Radiofrequency was initially proposed for cases with a contraindication for surgery: it was only used in patients that were inoperable. This is true in the liver, notably for hepatocellular carcinoma, but also in the lung for primary bronchial cancers combined with advanced COPD or for metastases in patients who have already undergone several surgeries or who have significant co-morbidities.

RF preserves the healthy parenchyma and thus, the function of the organ since the volumes of parenchymal destruction are extremely low. This is demonstrated by an absence of alteration in respiratory function after treatment, with notably preservation of the FEV1 in several studies [2,20]. As such, the lower limit of the FEV1 and respiratory function for patients in whom this technique can be proposed has not been defined. A recent publication shows that this treatment can be used with relative safety in patients with a single lung, although it is important to remember that in this context, this treatment presents obvious life-threatening risks, which have been elsewhere [21].

Pneumothorax occurs after 50% of pulmonary punctures via radiofrequency. It is usually drained in between 8 and 15% of cases, and constitutes more of an expected secondary effect of radiofrequency than an actual complication. True complications include pulmonary haemorrhage and infection, occurring in fewer than 1 and 3% of treatments, respectively. Infection is most common in patients with primary bronchial cancer as the latter often develops on an altered pulmonary parenchyma, which is more susceptible to infection.

A legitimate concern is the production of gas during the boiling of pulmonary tumours, which could be evacuated via the pulmonary veins. During pulmonary radiofrequency, gas bubbles have been detected in the carotid artery, but until now, only one neurological complication has been reported following radiofrequency out of several thousand published cases [22]. More difficult to avoid, although extremely rare, is gas embolism caused by inspired air in the lung: two separate cases have been reported in the literature [23,24]. It should be noted that these cases occurred even before the participation of radiofrequency and that they were caused by needle placement and tearing of the parenchyma. In one case, the patient had undergone extensive radiotherapy and the needle was difficult to insert due to the extremely friable and fibrous parenchyma.

Conclusion

Radiofrequency is a promising treatment that originally arose out of the contraindications for surgery, and should in
the future replace surgery in certain indications with small tumours.

As a curative treatment of small tumours, it will be in competition with conformational radiotherapy techniques (tomotherapy and gamma knife). Are these techniques competitors or could they be proposed as a combined treatment to improve results? Ideally, randomised trials are needed in the treatment of small pulmonary and hepatic metastases for comparison with surgery. In practice, such trials are extremely difficult to implement, firstly due to patient consent and secondly due to the fact that “good candidates” for surgery are usually poor candidates for radiofrequency and vice versa.

A recent study into cytoreductive radiofrequency reveals a new field of investigation for radiofrequency that could be used for palliative therapy.

Finally, the treatment of tumours over 3 cm will certainly involve other techniques, such as microwaves, which are under development.

**TAKE-HOME MESSAGES**

- The ideal indications for pulmonary and hepatic radiofrequency are tumours under 3 cm.
- The ideal localisation of the tumour is at a distance from any large vessels, which multiply the failure rate four-fold due to their cooling effect.
- Comparison between hepatic radiofrequency and metastasectomy shows a failure rate of 6% and 7.3%, respectively for tumours of 25 mm or under.
- Radiofrequency of a single hepatic metastasis of under 4 cm enables survival at 1, 3, and 5 years of 97%, 84%, and 40%, respectively.
- CT scan and MRI are the most commonly used techniques for the follow-up of hepatic radiofrequencies. They are used to look for zones of tumour persistence, which show early increased uptake.
- On these examinations, a fine ring (<1 mm) of contrast uptake surrounding the entire circumference of the necrotic zone and the presence of triangular areas of contrast uptake with sharp borders, visible in the arterial phase, are not a sign of recurrence but of inflammation or arterio-portal fistula.
- A ground glass opacity with an area that is four times greater than the targeted pulmonary tumour, is a predictive factor for success.
- A PET scan is the best method for monitoring pulmonary metastases that have been treated with radiofrequency.

3 is responsible for reducing the efficacy of radiofrequency close to vessels.
4 promotes complete ablation.

2) Pulmonary radiofrequency:
1 is the treatment of choice for pulmonary metastases of under 2 cm.
2 it can be proposed for the treatment of pulmonary metastases under 4 cm.
3 is more effective locally than stereotactic radiotherapy.
4 destroys around 99% of tumours under 2 cm.

3) Pulmonary radiofrequency:
1 is guided under fluoroscopy.
2 is guided by CT scan.
3 induces around 40% pneumothorax, and 10% pneumothorax to be drained.
4 involves the imperative use of deployable needles.

4) Hepatic radiofrequency:
1 is guided under ultrasound only.
2 is more effective than alcoholisation for the treatment of metastases.
3 requires coagulation of the trajectory of the needle to reduce tumour seeding.
4 involves the imperative use of deployable needles.

5) Pulmonary radiofrequency:
1 is more effective than stereotactic radiotherapy.
2 destroys around 80% of metastases under 2 cm.
3 prolongs the survival of treated patients.
4 induces around 70% survival at 3 years.

6) Follow-up imaging after percutaneous ablation with hepatic radiofrequency:
1 is not necessary as the tumour has been destroyed.
2 initially reveals a treatment zone that is larger than the tumour.
3 does not need to be continued beyond 9 months.
4 can be performed by CT scan, but MRI enables earlier detection of possible incomplete treatments.

**Answers**

1) Correct: 1, 3.
2) Correct: 2, 4.
3) Correct: 2, 3.
4) Correct: 2, 3.
5) Correct: 2, 4.
6) Correct: 2, 4.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

**References**


