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New tumor ablation techniques for cancer treatment (microwave, electroporation)

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Abstract Since the introduction of radiofrequency ablation (RFA) for the treatment of liver tumors at the end of the 1990s, indications for local ablation techniques have been extended to other organs, in particular, the lungs, kidneys and bones. These techniques have also been improved, in particular to try and overcome the limitations of radiofrequency techniques, especially the significant decrease in complete ablation rates for tumors larger than 3 cm and tumors that are contiguous to vessels larger than 3 mm. Microwave ablation is a rapidly developing thermal ablation technique similar to RFA but with numerous differences. Electroporation, a non-thermal ablation technique with other possibilities, is in earlier stages of clinical development.

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Microwaves

Principal

Microwave ablation involves the thermal destruction of tissue and is based on three different phenomena:
- thermal production, which is proportional to the amount of energy delivered to the tissue and the interaction of this energy with the tissue. This interaction rapidly decreases as the distance from the microwave needle applicator increases;
- thermal conduction is the way the heat is obtained via diffuse energy that spreads to neighboring tissue. Different tissues have different conduction properties;

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• thermal convection is the dissipation of heat when it is transported by a fluid that crosses heated tissues. In the liver, convection is mainly due to vascularization, while in the lungs, it involves vascularization as well as bronchoaveolar structures. More precisely, the effects of convection can be distinguished in relation to the microcirculation or macrocirculation. For the microcirculation, the well-known "heat sink effect", which has been reported and identified in numerous publications, is the reason that it is difficult to destroy tumors that are contiguous to vessels that measure more than 2 to 3 mm. The microcirculation is responsible for convection and explains why the volume of thermal ablation obtained ex-vivo, (in non-vascularized tissue) is always larger than that obtained in vivo (in vascularized tissue);

Overall, these three phenomena are the cause of the thermal equilibrium, which depends on the distance from the electrode, the type and quantity of energy delivered, and the length of treatment and type of tissue as well as its vascularization.

Microwaves cause thermal destruction that is not specific for the tumor. The goal is to heat tissues to temperatures above 60 °C.

Microwave frequencies used for medical applications vary between 915 MHz and 2450 MHz (Table 1). These frequencies are much higher than radiofrequency ablation (400 kHz, resulting in a shorter wavelength of approximately 30 cm), which allows microwave antennas to emit in the body without ground pads. The physical property that controls microwave penetration in tissue is permittivity. Permittivity has been found to be greater and therefore result in better diffusion of microwaves in tumoral tissue than in normal tissue [1]. Organs that seem to respond best to microwave ablation are those with marked differences in permittivity between tumors and the surrounding tissue. For example, this is true for breast tissue with the fat that surrounds the tumors and lungs with the air that surrounds the tumors.

When microwaves are applied, the electric dipole moment of the water molecules in tissue are agitated and seek to realign with the rapidly changing electric field, resulting in heating by friction. With microwave tissues in contact with the needle antenna reach temperatures of 160 °C to 180 °C, which is higher than that obtained with radiofrequency because they are limited to the boiling temperature of tissue, or slightly above 100 °C [2]. The increase in temperature is also faster with microwave than with radiofrequency, even bipolar [3]. The temperature 5 mm away from the microwave antenna is 100 °C while it is only 70 °C with radiofrequency [2]. Because of this improved thermal profile, much of the microwave energy is obtained by thermal heating and there is less room left for diffusion than during radiofrequency. Thus, in experimental animal models in vivo, thermal convection has less effect on zones of microwave ablation than zones of radiofrequency ablation. However, there is still loss of convection because an experimental study in healthy animal lungs showed a moderate heat sink effect in 30% of the vessels smaller than 6 mm, in 12% of the vessels between 3 and 6 mm and in 10% of the vessels smaller than 3 mm [4].

Because of the rapid heating along the entire length of the antenna, the use of microwave is limited to 60 W to avoid burns along the needle path. For this reason, most existing systems have a cooled shaft antenna with heating of the active distal tip of the needle. In addition, certain systems have a choke between the active distal tip and the proximal parts of the needle to limit reflection of energy from the heated tip. Cooled shaft antennas have been shown to be more effective because non-cooled shaft antennas cannot deliver more than 60 W of power in 10 min, while cooled shafts can deliver 60 W for at least 20 min [2]. Moreover, the ablation zones obtained with cooled shaft antennas seem to be more spherical [5].

All of these improvements have increased the ablation zone volumes than can be obtained with a single microwave session to reach a transverse diameter of approximately 3.5 cm. It has not been determined whether the best frequency for medical microwave use is 915 MHz or 2450 MHz. Although existing systems can deliver 100 W for several minutes, there are very few published results evaluating this amount of power.

Whatever the ablation zone volume that can be obtained with a single microwave antenna, one of the interests of this type of energy is the possibility of activating several antennas (Figs. 1 and 2) at the same time (as long as several generators are available), which is not possible with radiofrequency devices. It has been shown that simultaneous activation of 3 microwave antennas results in greater ablation volumes than sequential activation. Indeed, simultaneous activation produces an ablation zone volume of 43.1 ± 4.3 cm³ while sequential activation results in a volume of 14.6 ± 5.2 cm³ [6]. Studies are ongoing to determine the ideal distance between probes, but between 1.7 and 2 cm seems to be the most effective distance [6]. It appears that the greater the amount of energy delivered, the more the antennas can be separated without having non-coagulated areas between the antennas.

Clinical results

Hepatocellular carcinoma

In 2002, a series comparing radiofrequency and percutaneous microwave coagulation ablation in the treatment of 99 hepatocellular carcinomas between 1 and 3 cm in diameter (=2.2) showed complete ablation in 96% of the tumors with radiofrequency and 89% with microwave ablation (P=0.26) [7]. Three years later, a very recent series using a more effective microwave device treated HCC of between 3–5 cm in 89 patients and 5–7 cm in 20 patients using either radiofrequency or microwave ablation. The size of the tumors remained a predictive factor whatever the technique. There was no significant difference between the rate of complete ablation with radiofrequency ablation (89.8%) and microwave ablation (95.9%) [8]. In that study, complete tumor ablation, recurrence and alpha-fetoprotein above 1200 ng/mL were independent predictive factors with a hazards ratio of 4.15, 1.56 and 1.59, respectively.

Liver metastases

There are very few results in the literature with the most recent generation microwave cooled shaft antennas. Ten
tumors with a mean diameter of 4.4 cm (2–5.7 cm) were treated with a triple antenna system using 45 W for 10 min before surgical resection. The mean maximum ablation zone diameter was 5.5 cm, and the ablation zone produced by 3 antennas had fused to create a large ablation zone volume \[9\]. There were no histological signs of the tumor.

The same device was used with the same parameters in a phase II study in patients for 94 ablations in 224 liver tumors. The mean size of the tumors was 3.6 cm (0.5–9 cm) \[10\]. The mean ablation zone volume obtained with one antenna was 10 mL (7.8–14.0 mL) and with 3 simultaneous antennas was 50 mL (range 21–146.5 mL). The local recurrence rate was 2.7%.

Eighty watts of power for 26 min resulted in an ablation rate of 94% in tumors less than 3 cm, 91% in tumors between 3 and 5 cm and 92% in tumors between 5 and 8 cm \[11\]. The mean long axis ablation zone diameter was 8 cm and the short axis ablation zone diameter was 6.1 cm.

**Figure 1.** Microwave treatment of pulmonary metastases. CT scan of a 38 mm left pulmonary colorectal metastases in which 2 microwave antennas were placed (a). CT Scan 20 min after microwave treatment shows a tumor surrounded by a zone of aveolar condensation and a cavity in the center due to the very high temperatures of the microwave; a slight pneumothorax should be noted (b). CT Scan 1 month after treatment shows an ablation zone, which largely covers the area of the tumor associated with reactive pleural effusion (c). Three months after treatment, regression of the ablation zone volume and persistent pleural effusion (d).
The largest published series included 100 patients with 270 tumors (50% colorectal metastases, 17% hepatocellular carcinomas, 12% carcinoid metastases and 22% others). The only complication was a liver abscess and after 36 months of follow-up, ablation of the target tumor was only incomplete in 7% of patients [12].

A series of 1136 patients with 1928 treated tumors reported 5 cases of liver abscess, 2 cases of biliary injury, 2 perforated colons, 5 needle path seedings and 3 skin burns [13].

**Pulmonary metastases**

There are very few published results on the use of microwave ablation for the treatment of lung cancer. Results of a small series are promising and the largest series reported results in 50 patients treated by microwave, including 30 with primary non-small cell lung cancer. Sixty-six treatment sessions were performed in tumors less than 5 cm (med + SD = 3.5 cm ± 1.6) [14]. Only one antenna was used in tumors less than 2 cm (53%), 2 antennas were used in 5% of the cases, 3 antennas in 27%, and 4 antennas in 9%, and a needle with 3 rounded deployable antennas in 6%. Local tumor control was obtained in 74%, with a significantly higher rate of local recurrence in tumors larger than 3 cm ($P=0.01$). It should be noted that after microwave treatment, 43% of the patients developed cavitation in the tumor region treated by microwave, and that 6% of the population developed an infectious complication, including one abscess and one pneumopathy. The abscess caused erosion of the wall of the pulmonary artery and resulted in death by hemoptysis. On the other hand, survival was improved in patients who presented with cavitation following ablation.

**Electroporation**

Electroporation is a technique whose preliminary results will be described because there are no published clinical trials for the treatment of liver and lung tumors. Electroporation is a technique that opens the pores of the cell membranes by applying a high intensity electric field. This effect is obtained by an interaction with the electric field of the electrically charged phospholipid membrane. This technique includes reversible and irreversible electroporation. Reversible electroporation, which is also called electrochemotherapy, opens the pores of the cell temporarily to allow entry of the chemotherapy drug, which though effective, cannot penetrate the cell unless this electric current is applied. Cell death is then induced by the drug [15]. This results in destruction of targeted tumor cells alone, because after electroporation, healthy cells receive a drug that is not lethal to them. It should be noted that this method was first used to incorporate and insert foreign genes into the cell [16]. Irreversible electroporation, which has begun to be used in interventional radiology, opens the cell pores permanently and causes cell lysis without the use of cytotoxic drugs [17]. There is no specificity for tumor or healthy cells with irreversible electroporation. Irreversible electroporation can be performed by placing two electrodes on the same antenna, but it is usually performed with two electroporation antennas placed apart in the tissue. With existing devices between 1000 and 3000 V/cm of power are needed and the antennas must be no more than 2 cm apart.

Thus, electroporation produces fairly small ablation zones or requires numerous antennas. For example, 4 or 5 antennas could be needed to treat a 3—3.5 cm tumor. Electroporation is interesting because it is non-thermal and therefore avoids the destruction of tissue contiguous large vessels (Fig. 3). Moreover, it probably preserves the fibrous and collagen elements of ductal and vascular structures. Indeed, in experimental models, vessels, bronchial and probably biliary structures appear to be perfectly well preserved [18—21]. Finally, at the periphery of the irreversible electroporation zone, there may be a zone of reversible electroporation, which could be taken advantage of for associated drug treatments.

**Figure 2.** PET-scan image of a calcified metastases of the liver dome showing intense contrast enhancement (a). MIP reconstruction of the 3 microwave antennas placed relatively parallel for treatment (b). CT scan the day after microwave treatment. There is an ablation zone that measures approximately 55 mm long along the long axis showing the calcified metastases (c).
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Figure 3. Macroscopic view of a pig liver after electroporation ablation in contact with a large suprahepatic vein. The ablation zone is brown and surrounds the large suprahepatic vein. There is no healthy tissue left between the vessel wall and the ablation zone. There was no convection induced heat loss.

Because of the power of the electrical stimulus during electroporation, this technique should be performed during the milliseconds of the so-called ECG refractory period (after the Q wave). Electroporation systems are therefore dependent upon an ECG to avoid inducing cardiac arrhythmias. Finally, a neurological simulation must be performed on the entire body requiring general anaesthesia with curarization [22]. There is an ongoing European trial for hepatocellular carcinoma smaller than 3 cm.

**TAKE-HOME MESSAGES**

- Microwave ablation of tumors is a thermal ablation technique guided by imaging, like radiofrequency ablation, that uses a frequency of between 915 MHz and 2450 MHz (400 KHz for radiofrequency).
- Microwaves do not require a ground pad and they induce temperatures of 160–180°C from contact with the needle antenna in a relatively short time (≤100°C for radiofrequency).
- Microwaves are less sensitive to thermal convection of large diameter vessels.
- Simultaneous activation of several microwave antennas produces much larger ablation zone volumes than sequential antennas.
- There is no significant difference between the rate of total ablation of HCC with radiofrequency (89.8%) and microwave (95.9%).
- For liver metastases, 80 W of power for 26 min resulted in an ablation rate of 94% for tumors smaller than 3 cm, 91% for tumors between 3 and 5 cm and 92% for tumors between 5 and 8 cm. Ablation zone diameters were 8 cm for the long axis and 6.1 cm for the short axis.
- Electroporation opens the pores of the cell membranes by applying a high intensity electric field that interacts with the phospholipid membrane.
- Electroporation is a non-thermal ablation technique that overcomes the complication of the destruction of tissue in contact with large vessels.

**Clinical case**

**Questions**

1. The "heat sink effect":
   a) is thermal loss by convection.
   b) is thermal loss by conduction.
   c) is the cause of the reduced efficacy of radiofrequency ablation near vessels.
   d) is minimal or absent with microwave.

2. Pulmonary microwave ablation:
   a) is the reference technique for local ablation of metastases.
   b) results in less heat loss than radiofrequency.
   c) has a lower complication rate than radiofrequency.
   d) can result in larger ablation volumes than radiofrequency.

3. Cryotherapy:
   a) is based on decompression (Joule/Thomson effect) of gases.
   b) is not a thermal destruction technique.
   c) is lethal for cells at 0°C isotherm.
   d) is often less painful than radiofrequency.

4. Cryotherapy:
   a) cannot be used in the lungs.
   b) always requires several probes.
   c) has longer treatment cycles than microwave.
   d) uses helium to reheat tissue.

5. Irreversible electroporation:
   a) is a non-thermal ablation technique.
   b) has replaced radiofrequency in the treatment of liver metastases.
   c) seems to preserve the biliary tract that is included in the ablation zone.
   d) is technically simpler to perform than radiofrequency.

6. Imaging following percutaneous microwave ablation:
   a) is not necessary because the tumor has been destroyed.
   b) initially shows an ablation zone that is larger than the tumor.
   c) is not necessary more than 9 months after surgery.
   d) CT scan can be used, but PET-scan shows any incomplete treatment earlier.

**Answers**

1. a), c), d).
2. b), d).
3. a), d).
4. b), d).
5. a), c).
6. b), d).

**Disclosure of interest**

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