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Ablative therapies: Advantages and disadvantages of radiofrequency, cryotherapy, microwave and electroporation methods, or how to choose the right method for an individual patient?

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Abstract Several ablation techniques are currently available. Except for electroporation, all of these methods cause fatal damage at a cellular level and irreversible architectural deconstruction at a tissue level by thermal effects. Ablation of a tumor using one of these techniques, whether thermal or otherwise, requires applicators to be positioned from which the energy is delivered in situ. Some techniques, however, require several applicators to be inserted (multibipolar radiofrequency, cryotherapy and electroporation) whereas a single applicator is often sufficient with other technologies (monopolar radiofrequency and microwave). These methods are conceptually very similar but are distinguished from each other in practice through the technologies they use. It is essential to understand these differences as they influence the advantages and limitations of each of the techniques. There is no such thing as the perfect multifunctional ablation device and choice is dictated on an individual patient basis depending on the aim of treatment, which itself depends on each patient’s clinical situation.

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Centrifugal radial ablation compared to convergent centripetal ablation: the difficult balance between simplicity and predictability

In situ destruction of a tumor has long been obtained using a centrifugal coverage method: energy dissipates towards the periphery from an applicator inserted into the center of the tumor target [1]. Ideally energy has to isotropically radiate with a minimum of loss in order to produce a fatal effect on the tumor, and beyond that over a targeted margin and a minimal thickness (Fig. 1). This centrifugal dispersive ablation strategy which is derived from the chemical ablation techniques is still the most widely used as it is the most simple to apply. It is the basis of techniques such as monopolar radiofrequency, microwave, laser and cryotherapy. Using these techniques, an overlapping ablation strategy is required for tumors over 3 cm in diameter (1.5 cm for laser and cryotherapy) in order to destroy the whole lesion with a sufficient margin. This may be achieved simultaneously if several applicators are used during the procedure (generally with laser and cryotherapy) [2]. Fundamentally, using several applicators with centrifugal dispersion methods does not change the operation of the procedure and final ablation is planned by simple summation of several overlapping centrifugal destructions caused by each of the applicators. If the applicators are sufficiently close together (which is essential to achieve continuous destruction between them) a more or less extensive synergistic effect occurs. It is important, however, to understand that each of the ablated regions created remains overall independent. As such, they represent areas of centrifugal radial destruction, the contribution of which to the success of the whole procedure is mostly influenced by the operator’s ability to implant the applicator in the center of each of the desired individual destruction zones (Fig. 1). The conceptual simplicity of ablations carried out using dispersion techniques is their main advantage. This is particularly apparent for monopolar radiofrequency and microwave ablation which can destroy a relatively wide range of tumors up to approximately 3 cm in diameter using a single applicator and therefore with a single puncture. This assumes, however, that the shape of the targets treated is as spherical as possible and that the assumption of isotropic energy propagation is observed. These two conditions are generally met for small tumors (<2.5 cm) although over this size, large deviations from the ideal centrifugal ablation model are seen because of the heterogeneous nature of tissue properties (electrical and thermal conduction, light absorption and micro- and macrocirculatory thermal convection). Because of the overall spherical expansion of the ablation zone it is desirable for the target treated to be remote from important structures in order to reduce the risks of complications due to collateral thermal damage.

Another ablation strategy involves convergence of energy from the periphery towards the center of the tumor. A minimum of two applicators are inserted into the periphery of the tumor in order to deliver the energy concentrically within the target. In practice at present, only radiofrequency and electroporation which deliver a bipolar RF current can use this strategy satisfactorily. The continuity of the treatment zone is governed by the distance between the electrodes: 3 cm for radiofrequency and 2.5 cm for electroporation are the distances beyond which the risk of discontinuity of the treated areas becomes high. For volumetric dosimetry reasons, targets over 2 cm in diameter need to be treated along several axes of energy delivered, similarly to the crossed beams in external conformational stereotactic radiotherapy methods. When these systems are used, it is recommended that at least three electrodes be implanted for "one shot" treatment of lesions with a diameter of between 2 and 3 cm and four to six electrodes for lesions between 3 and 5 cm in size (Fig. 1). Energy is always delivered in bipolar mode, although sequentially between each pair of electrodes and bipolar radiofrequency and electroporation have therefore attracted the description "'multibipolar'". Regardless of the number of electrodes used, they need to be implanted in the periphery of the targets and no longer in the center. Better still, if the tumor is sufficiently small it is even recommended that they be implanted outside of the tumor itself following the "'no touch''" ablation principle [3]. The main use of the multibipolar centripetal convergent ablation techniques is that they provide reliable and safe destruction over a continuous safety margin for tumors up to 4 cm in diameter. They also offer the possibility of adjusting the shape of the ablation zone to that of the tumor, at the same time taking account of its location (Fig. 2). The cost of this is greater procedural complexity which invariably requires several applicators to be implanted, and all along relatively well controlled directions and distances apart.

The choice between a centrifugal radial approach and a centripetal convergent one depends on several clinical factors (Fig. 3). When several small targets need to be treated simultaneously (paucimultinodular disease) and/or at close time intervals (recurrent multicentric forms of disease), the simplicity and speed of conventional centrifugal ablative techniques emerge as essential benefits. Increasing the number of ablation sites (in one or more procedures) requires a functional parenchyma saving strategy combined with moderation in terms of the safety margins destroyed around each of the lesions treated (Fig. 4). Conversely, if following an ad hoc staging assessment the tumors appear to be single, centripetal convergent techniques are undoubtably preferable. It is essential to offer patients the greatest possible chances of recovery by ensuring the best possible ablation margins (Fig. 5). Tumor sites at risk of collateral damage or of complex shape (contours difficult to identify on imaging) also argue in favor of centripetal convergent techniques which offer more options to adjust the ablation zone in order to take account of specific local limitations (Fig. 2). The lung however is not conducive to centripetal convergent ablation technologies as the air contained within the lung parenchyma around the tumor acts as an insulator (infinite impedance) which drastically reduces energy transfer in multibipolar mode. In practice these techniques can only be considered for sufficiently bulky lung lesions (at least 3 cm in diameter) into which several separate electrodes can be inserted at least 1.5 cm apart. In the standard indications for lung nodules under 3 cm in size, multimopolar radiofrequency ablation techniques using deployable electrodes (umbrella or parasol) appear at present to be the most appropriate [4]. These allow excellent distribution of
energy delivery either through intranodular deployment of maximum active electrode surface area or by corbeling the target (edematous and hemorrhagic filling of alveoli around the tumor when the electrodes are deployed provides minimum conductivity).

**Electroporation: when thermo-ablation is too risky**

The recent (2006) emergence of electroporation onto the landscape of percutaneous ablation techniques offers the possibility of non-thermal destruction of tumors. Tens of RF pulses each of very high intensity (20–50A up to 5000V lasting a few μs) delivered between two electrodes (bipolar mode) produce irreversible changes in the membrane functions of cells exposed to pulsed EM fields [5]. Cell death occurs either immediately by coagulation necrosis or later by apoptosis. Supporting structures such as connective tissue, basal membranes and the lumens of blood vessels and ducts outside of the tumor however are relatively preserved (Fig. 6). Unlike the pure necrotic zones caused by thermo-ablation techniques, immunocompetent cells and macrophages can enter into the center of the electroporesed regions, explaining why these tend to retract rapidly during follow-up. Overall connective tissue

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**Figure 1.** Strategies for in situ delivery of energy for tumor ablation: a: ablation of a 2-cm diameter spherical tumor with a mono-applicator radial centrifugal ablative device: in this diagram impact ideally produces spherical ablation of 3 cm providing a margin of 0.5 cm. Because of the rapid radial decrease in the amount of energy delivered to issues (by a factor of approximately d^2) the risk of falling outside of the lethal energy threshold increases with distance from the source (applicator positioned in the center). In other words, obtaining a continuous sufficiently wide safety margin becomes increasingly uncertain with increasing tumor diameter; b: ablation with the same radial centrifugal device of a 4-cm spherical tumor using the overlapped impacts technique (sequential or simultaneously): ideally, six ablations are required to achieve a 0.5-cm margin. In view of the exponential radial decrease in energy, the risk in this configuration of incomplete treatment (including a defective margin) is increased by a factor of six compared to the previous situation; c: with the same system, achieving a 0.5-cm ablation margin for a bulkier lesion requires the number of impacts to be increased. In this example, the tumor is elliptoid. In order to reduce the number of punctures the ablation needs to be performed ideally along the long axis of the tumor. It is then possible to ‘cover’ the tumor by repeating the ablation cycle after withdrawing the applicators a few centimeters (pull-back ablation); d: ablation of a 4-cm diameter tumor with a convergent centripetal device in multibipolar mode. As with the centrifugal radial system it is still necessary to perform six punctures in order to obtain a 0.5-cm margin. The applicators, however, are implanted into the periphery of the tumor closest to the margin (in this example, 5 in the periphery and 1 in the center for continuity). If the tumor is sufficiently small the peripheral electrodes can be implanted outside of the tumor directly into the desired margin (no touch ablation). The applicators are activated in pairs (bipolar mode) and sequentially in order to deliver the energy the whole tumor volume. Because of the peripheral arrangement of the applicators, high levels of energy are delivered directly into the margin, which considerably improves the predictability of ablation. The continuity of the ablation zone is influenced by the distance between the applicators (between two adjacent electrodes – maximum 3 cm for radiofrequency and 2.5 cm for electroporation) and the overlap of the individual ablation zones created between two applicators. For bulkier non-spherical or even infiltrating tumors, it is possible (as with centrifugal radial technologies, Fig. 1c) to increase the ablation zones by delivering additional cycles preferably using the pull-back technique but also if necessary by reimplanting some or all of the applicators. The overall predictability of the ablation limits and modeling of the area are still important as the energy fields created are orientated and delineated by the implantation of the applicators.
Figure 2. Multibipolar radiofrequency ablation of non-spherical liver tumor neighbouring gallbladder: a: axial computed tomography at arterial phase of intravenous contrast iodinate medium injection showing infiltrative hepatocellular carcinoma of segment 5. The treatment consisted to insert along long axis of segment in slightly convergent routes six electrodes, three in plan (full overlays) and three out of plan (hollow out overlays). Note the proximity of the peritoneum side of gallbladder wall; b: computed tomography at arterial phase one month after the procedure showing ablation zone covering all the infiltrative lesion including safety margin and fitting exactly the shape of the segment. Note the absence of injury of gallbladder.

Rationale bases for the choice between ablation techniques: *: monopolar radiofrequency, microwave (into the lungs for a small target as the non-conductivity of air considerably reduces the effectiveness of centripetal concentric multibipolar techniques. The applicators need to be implanted generally more than 1.5 cm apart); ±: multibipolar radiofrequency, electroporation (electroporation is the only non-thermal method and as such is useful to treat particularly hazardous sites); #: monomodal radiofrequency, cryotherapy, laser, microwave (cryotherapy and laser are centripetal radial methods which have the advantage of relatively precise per-procedure imaging visualization of expansion of the treatment zone: MRI for laser, all modalities and particularly CT for cryotherapy).

architecture is preserved and can be colonized little by little by division of healthy cells located in the margin of the treatment zone. This "gentle" ablation scenario allows treatment of tumors to be considered which until now have been contraindicated for all attempts at destruction using other thermal methods either because of their site, deemed to be hazardous (e.g.: a hilar tumor, etc.) or because of patient frailty (precocious organ function, etc.). A few qualifications however are necessary in terms of this ideal vision of electroporation ablation. Firstly, the energy delivered by electroproportion is an electromagnetic wave of the same wavelength as radiofrequency ablation. Biological tissues are by nature resistors and the Joule heating cannot therefore be zero. The rise in temperature caused by electroporation in an experimental study was up to 60 °C [6]. This level of hyperthermia however only occurs in the immediate proximity to the electrodes (fine, 19 G straight and not cooled) and only for a few tens of μs. Ultimately the "actual" thermal effect of electroporation is very limited and only affects tissues located in a radius of a few millimeters around the electrodes. Electroporation by necessity operates in non-coaxial bipolar mode (in its current version) and a minimum of two electrodes need to be inserted, no more than 2.5 cm apart. The limits of the effective treatment zone are approximately defined by the high intensity EM field created between the two electrodes and ablation of the tumor of over 1 cm as a general rule requires more than two electrodes to be inserted: three electrodes for up to 2 cm, four electrodes between 2 and 3 cm and five to six electrodes between 3 and 5 cm. In clinical practice, electroporation is therefore a multibipolar technique (Fig. 1). In addition, the use of high intensity RF pulses can cause myoclonia and severe arrhythmias. An electroporation procedure can therefore only be performed in patients in normal cardiac rhythm (or slow arrhythmias <100 bpm) in order to be able to deliver the energy only during the myocardial refractory period (the average length of the ECG ST segments is estimated automatically over several cycles by a cardiac synchronizer supplied with the generator). Integral muscle relaxation is also essential which implies the use of curare and by definition, general anesthesia. Limited severe collateral damage has been seen to date in patients generally selected on the basis of tumor sites deemed to be "at risk" for the other thermal methods [7,8].

To date, we have treated over 50 patients with abdominal tumors located in a difficult site and/or in very frail patients without seeing serious complications (Figs. 3 and 6). This very specific profile makes it a promising treatment for very confined organs such as the pancreas or prostate which are not very suitable for the other thermal methods [9]. Conversely, the few pilot series available on electroporation of small lung tumors are not yet conclusive [10]. The current design of the electrodes for the electroporation system is not suitable for as badly a conducting environment as the
aerated lung parenchyma around the tumor (cf. paragraph above). One in vivo experimental study on pig vertebra has suggested that electroportion could be effective without producing neurotoxicity [11].

**Other factors guiding the choice of an ablation technology**

It is conventional to compare ablation technologies with each other in terms of a number of concomitant criteria which provide an approximation about the effectiveness and tolerability of the procedures.

**Monopolar radiofrequency compared to microwave mono-applicator radiating centrifugal ablations**

Monopolar radiofrequency ablation is assumed to have less destructive capacity compared to microwave as the temperatures achieved do not exceed 100 °C with radiofrequency ablation whereas temperatures of over 150 °C are regularly produced by microwaves [12]. In addition, the temperature peaks are achieved significantly faster with microwave than by radiofrequency ablation. It is important, however, to remember that these measurements which have been carried out in vitro, a few millimeters from the applicators, are not sufficient to allow any conclusion to be made that microwave is clinically superior in terms of the volume of destruction produced or its ability to overcome the effects of flow-related cooling. In view of the size of tumors usually treated clinically (3 cm is the upper limit for most groups) the effectiveness of an ablation technology cannot be measured or even estimated 5 mm from the applicators. To date, the theoretical superiority of microwave has not resulted in fundamentally different results from those already reported for radiofrequency ablation: tumor diameter (>3 cm) and proximity to a large vessel remain factors associated with a higher incidence of incomplete treatment (primary or secondary) [13]. Only correctly conducted clinical studies (ideally randomized) will be able to demonstrate it.
the superiority of one method over the other. We should also note that microwave ablations cannot at present be monitored by any tissue feedback, unlike radiofrequency ablation, the process for which can be modulated robustly by continuous measurement of tissue impedance.

Risk of complications associated with the diameter and number of applicators

A clear relationship exists for a given organ between the risk of hemorrhage after biopsy and both the diameter of needles used and the number of needle insertions made. Although there have been no specific studies on ablation procedures, it is tempting to liken the same type of risk to the applicators used for each of the technologies. Hemorrhage is one of the main complications of percutaneous ablation techniques although collateral damage and abscess formation in the ablation zones which occur in equal incidence are usually more serious. These are mostly related to the necrosis volume and the ability to predict its boundaries than to the number and diameter of applicators used. In this context and as described above, the multipolar electroporation or radiofrequency technologies which simultaneously use several electrodes (up to 6), cause predictable and modulable zones of destruction depending on the volume, shape and site of the tumors. In this sense, they are very safe to treat tumors located in a hazardous site (Figs. 1, 2 and 6). This is particularly true for electroporation, the lethal effect of which stops at the boundaries of the high intensity electric fields, which can easily modeled from a given configuration of electrodes. It is interesting to note that monopolar radiofrequency systems which use single deployable electrodes carry an undoubtedly greater risk of collateral damage as it is not possible to monitor all of the paths of the electrodes by imaging as they are deployed.

Conversely, in the same way as for hemorrhage, the risk of seeding of malignant cells along the puncture tracts is related to the number of punctures performed. As these are ablative techniques it is reasonable to consider that those which can be used to produce straightforward ablation of the puncture tracts such as radiofrequency and microwave ablation (although hot withdrawal is more difficult to control with the second of these techniques because of the possibility of rapid skin burns) the risks of hemorrhage and seeding would be reduced. With other techniques such as laser illumination, cryotherapy and electroporation, for which there is currently no treatment for the puncture tracts, the risk of seeding is probably higher, particularly as these involve multi-applicator techniques [10]. Paradoxically, increasing the number of puncture tracts with electroporation does not appear to carry a particularly high risk of hemorrhage, probably due to the fact that the electrodes are particularly

Figure 6. Irreversible electroporation of a single perivascular liver nodule in frail patient: a: T1-weighted resonance magnetic image at arterial phase of intravenous gadolinium contrast medium injection showing 2 cm hepatocellular carcinoma located at the junction of segments 5 and 8 abutting right portal branch. Note the presence of ascites in this patient with cirrhosis Child-Pugh B. The treatment consisted in insertion of three electrodes, two in the plan (full overlays) and one out of the plan (hollow out overlay); b: T1-weighted image before intravenous gadolinium contrast medium injection one month after the procedure showing hypo-intense electroporated zone including in the center a hyper-intense tumor ghost image (probably related to coagulative necrotic changes); c and d: T1-weighted images at arterial (c) and portal (d) phases of intravenous gadolinium contrast medium injection showing gradual delayed enhancement of the periphery of electroporated zone (no complete destructive effect on liver microcirculation) while the tumor ghost image and the linear areas which abutted the electrodes remain unenhanced (necrotic areas). Note the absence of damage biliary ducts and right portal branch.
fine (19 G) and that also as this is a non-thermal method, there is no back diffusion of heat along the puncture tracts and therefore little risk of secondary bleeding or peritonitis due to healing tissue sloughing off if any of the tracts pass through the gastroduodenal system. Overall, the number and diameter of applicators used does not appear to have a major impact on the risk of complications of percutaneous ablations, probably because the puncture procedure performed by trained operators in reality carry a lower relative risk of complications than that of the ablations themselves.

Per-procedure visibility of ablation zones produced

Being able to accurately see expansion of the ablation zone during the procedure is a considerable benefit, both in terms of the effectiveness and the safety of the procedures themselves. Laser illumination ablations are completely compatible with MRI imaging and can therefore be monitored in real time by thermal mapping. This ablation technique is therefore particularly appropriate to treat central nervous system tumors which require great precision [14]. Cryotherapy is very widely used nowadays to treat renal and locomotor system tumors, as this technology has the major advantage of allowing operators relatively accurate monitoring of ice formation with any imaging modality and particularly with unenhanced computed tomography. This undeniably increases the safety of the procedures particularly when the tumors are located in anatomical regions at high risk of collateral damage [15].

Conclusion

Like the surgical scalpel, there is no such thing as the universal ablation technique in interventional radiology. The advantages of a given technology are often consubstantial with its limitations. Each method can offer the best benefit/risk balance in a specific clinical situation and for reason any practitioners wishing to become fully involved in this type of care needs to understand the fundamental principles and technical features of ablative methods. The challenge is to actively contribute to the necessarily multidisciplinary treatment strategy in oncology.

Take-home messages

**General points**

- No universal ablation method exists.
- The choice depends less on the type of energy used than on the spatial energy delivery distribution strategy.
- From this perspective radial centrifugal techniques which may be mono- or multi-applicator (monopolar radiofrequency, microwave, lasers and cryotherapy) should be distinguished from convergent centripetal techniques which are currently all multi-applicator and multibipolar (multibipolar radiofrequency and electroporation).
- Centrifugal radial techniques are simpler to use but are less predictable in terms of the ablation limits they produce.

- Centripetal convergent techniques are more complicated to use but offer the possibility of more conformational treatments as the ablation limits are to some extent limited by the implantation of applicators in the periphery of the tumor targets. Rationale for the choice of an ablation technique
- This depends on the size, shape and site of the tumors and also on the state of advancement of the malignancy (solid tumor/multiple sites, previously untreated/relapsed patient).
- Multiple oligonodular or recurrent small tumor disease can be beneficially treated with centrifugal radial methods. These are simple and well tolerated and can be used repeatedly in order to control tumor growth for as long as possible.
- With single tumors, where radial ablation offers a serious chance of cure to the patient, convergent centripetal techniques offer the advantage of better predictability of margins over a wide range of diameters (at least 4 cm), shape and site of the tumor (apart from the lungs which are poor conductors).
- Electroporation is the only non-thermal ablation method. From this perspective, apart from the fact that it is a convergent centripetal technique it is promising for hazardous sites or in frail patients (apart from pulmonary sites).
- Because of the real time visibility of expansion of the ablation zones on imaging such as MRI with laser or unenhanced CT for cryotherapy, some methods appear particularly suitable to treat tumors in a critical anatomical location such as the central nervous system (laser) or kidneys (cryotherapy).

Disclosure of interest

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References


