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Laser ablation: an alternative to radiofrequency ablation for hepatocellular carcinoma in cirrhotic patients?

Hepatic Oncology

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Hepatocellular carcinoma (HCC) is a global clinical and social problem whose management is planned according to the evidence-based recommendations of international societies [1]. An array of management choices has gradually been introduced into clinical practice over the last two decades, with definite advantages for cirrhotic patients with HCC. Thanks to the development of clinically based systems such as Barcelona clinical liver cancer (BCLC) classifications, which stratifies patients according to tumor stage and underlying cirrhosis, radical therapies such as hepatic resection (HR), liver transplantation (LT) and percutaneous locoregional ablation are recommended in patients with early-stage tumors (BCLC 0 and A). These indications are based essentially on tumor volume, the status of the underlying liver disease and the performance status, but the presence of comorbidities, and the patient's age may influence clinician's choice [1].

For percutaneous ablation therapies (PATs), the guidelines recommend radiofrequency (RF) for lesions that can be safely treated with this procedure as it is more predictable and effective than percutaneous ethanol injection (PEI).

Some meta-analyses of prospective randomized controlled trials (RCTs) demonstrated that RF is superior to PEI both in terms of survival and in terms of local recurrence [2]. The risk of complications and/or reduced effectiveness for lesions at risk sites or the presence of minimal residual viable tissue are frequent in cases treated with RF compared with PEI, indicated as an alternative to RF when this latter cannot be performed for technical reasons. Therefore, RF is the first-line treatment of choice for single nodules of ≤ 2 cm (very early), when appropriate, even though for lesions in this stage both RF and PEI achieve complete response in over 90% of cases. Some authors feel that for better local disease control, especially in cases of high levels of AFP and/or advanced grading, anatomic resection should be preferred to RF. In cases of single nodules measuring between 2 and 3 cm or up to three nodules of less than 3 cm, the choice between HR and RF must be on a case-by-case basis using a multidisciplinary approach; age, any associated comorbidities and nodules location must be taken into account [2]. Percutaneous thermal ablation may be the first-line choice

KEYWORDS:

- cirrhotic disease
- hepatocellular carcinoma
- laser ablation
- percutaneous locoregional therapies
- radiofrequency ablation

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only in patients not candidate to resection or transplant as patients in this stage in Child-Pugh A resection have been demonstrated to achieve both better survival and reduced recurrence rate [3]. For nodules greater than 3 cm or multifocal nodules, the preferred choice is resection since the failure rate with incomplete response with RF increases even in lesions only slightly under 3 cm. Combined radiological treatments or sequential transarterial chemoembolization (TACE) plus RF or PEI can be considered only in cases of nonresectability [4], although available studies do not yet permit drawing robust conclusions due to a nonoptimal selection of patients to undergo treatment. We do not yet know what population of patients may benefit from these combined therapies. This brief summary on PATs is based on data reported by well-designed, high-powered randomized controlled trials performed on cohorts of patients with an optimal clinical profile both for ablation and for surgery (single nodules up to 3 cm with no clinical signs of portal hypertension). The data currently available come from RCTs between RF and PEI [2], between these two and surgical resection [3], and between RF and TACE [4]. There are very few data on the comparison between the three hyperthermic ablative techniques: RF, laser and microwaves (MW). The only available RCT, from 2002, compares RF and MW; it does not, however, include clinical data on survival, and the comparison was made only in terms of local control of the tumor [5]. Therapeutic equivalence should be confirmed by means of an RCT on a larger sample, with a longer and more appropriate follow up, and with standardized RF and microwave devices. It must be underlined that the results of this study should be seen as a snapshot of the time when the study was done and cannot therefore be interpreted as indicating the potential effectiveness of the entire range of possible technologies (i.e., other RF or MW devices). In other words, technological progress has rendered the comparison between the two techniques by Shibata *et al.* [5] in 2002 obsolete.

The purpose of thermal techniques is to induce irreversible cellular damage by increasing or decreasing the local temperature in the designated target. Hyperthermic therapies use high temperatures (>50°C) around the applicators positioned in the center of the tumor. The extension of the area of irreversible damage is influenced by multiple factors: the technical characteristics, the shape and size of the

applicators, how the energy from the source is applied in the target area, the structure of the irradiated tissue itself and, to a lesser degree, how the thermal energy is produced. Thus far, the source of percutaneous ablation most studied and most clinically tested (and, in our view, supported by major vendors) is RF energy source. Systems based on RF energy, therefore, are a useful point of reference when reasoning on ablation techniques in general and when studying specific improvements that can be made to other thermal technologies. It must be noted that currently there are no data that support the superiority of RF energy and technique over other hyperthermic agents and their technology, neither in terms of local control nor in terms of long-term response, in the survival of small HCC patients. In other words, the differences in terms of results are modest [6,7].

Briefly, during RF ablation the electrical current oscillates between two electrodes through ion channels present in most biologic tissues. The flow of electrical current is influenced by the presence of high blood flow in the application site (heat-sink effect) or by the low electrical conductivity (electrical impedance) of the irradiated tissue, requiring an electrical switching for effective multiple-applicator use. In other words, to achieve necrosis that is broader than what is usually possible with a single source, we can activate the RF sources of a multiple applicator more easily with a sequential or consecutive technique than with a simultaneous technique. The most widespread RF ablation technique in clinical practice uses straight, monopolar, internally cooled small-gauge electrodes (17 gauge, 1.5-mm diameter) with a 2–4-cm long exposed metal tip [8]. Much less frequently used, probably because they are much more invasive, are systems with expandable electrodes which deploy from a single needle shaft with a 14-gauge caliber (2.1-mm diameter) a star-shaped array of four, nine or twelve tines or umbrella-shaped arrays of ten tines from a 13-gauge needle [8]. Laser energy, like RF and microwave energy, induces electromagnetic heating to raise the temperature of tissues to lethal levels. It is a fast, precise and relatively tissue-insensitive technique, and can be delivered very easily and safely with simultaneous technique to obtain large areas of coagulation. Laser energy generators are very common worldwide given their many clinical applications in numerous fields of medicine, while percutaneous ablation devices are far less common [7–9].

Laser beams are transmitted from the source to the tumor tissue of the patient by means of flexible quartz fibers, which are inherently magnetic resonance (MR) imaging compatible. The flat tip fiber is the type most commonly used, with thin (<1 mm-gauge) applicators [6]. Instead, water-cooled 3-mm-diameter applicators, which require a large bore cannula (9-gauge, 3.8-mm diameter) to be positioned in the designated area, are less frequently used for HCC treatment [7].

Numerous studies have demonstrated that the size of the nodule is the most important parameter in predicting ablation success (the cutoff is around 3 cm in diameter) [1,10,11]. The destruction of the tumor by means of hyperthermic techniques is achieved by heating the entire tumor volume to cytotoxic temperatures of 50–54°C for 4–6 min [8]. Local control is achieved in 80–90% of cases, as well as in smaller tumors of less than 2.5 cm in diameter regardless of the technique used [5]. The biological characteristics of the tumor (i.e., tumor presentation and growth rate) most likely play no less important a role than does our ability to use specific ablative technologies to completely eradicate the nodule. For slow-growing lesions, as in HCC, there are no differences in survival as once the lesion has been completely or almost completely eradicated, other factors such as new lesions and underlying cirrhosis will be important in determining survival compared with persistent minimal foci of residual tissue not treated. The differences in tissue heating between the different types of RF electrodes and some models of laser applicators cancel each other out in the case of small lesions [10]. Thus, the two techniques (MW can also be included in this equivalence) obtain equivalent results in the case of small lesions and slow-growing lesions, which are easily treatable [6,11,12]. However, clear differences between the various minimally invasive percutaneous techniques and different methods emerge in the case of larger HCC or infiltrating HCC [13]. An important factor that limits the extension of the coagulation zone and of the amount of tumor destruction is the nonhomogeneous distribution pattern of heat inside the treated tissue. This means that in the case of larger lesions (defined as over 3 cm in diameter), a single treatment session does not suffice to cover the entire target volume. In these cases, multiple overlapping ablations or the simultaneous use of a number of applicators are necessary to successfully treat the entire tumor with sufficient ablative margin,

even if accurate targeting and correct applicator positioning can be very difficult. In these cases, the RF technique has evident limits and appears to be difficult to apply [14]. A variety of devices of different shapes and designs, used with different algorithms or activated in different ways (consecutive, switching or simultaneous), obtain rates from 62 to 81% in large lesions (≥ 5 cm) or in tumors greater than 5 cm both in single and in multiple sessions [7,15]. Additionally, percutaneous RF ablation is limited, in some cases, by complex anatomy and difficult access or by lesions in high-risk site (i.e., near gallbladder, main biliary duct, hepatic hilum, adjacent hollow viscera or exophytic location) and/or hard-to-reach locations (e.g., in the dome of the liver, in the caudate lobe) [16]. In all of these cases, specific protection systems must be used with RF to avoid damaging contiguous vital structures [16]; alternately, PEI should be used, as recommended by the guidelines [1]. Instead, in our view, LA, thanks to the recent introduction into clinical practice of a novel guide system which facilitates both the parallel insertion of multiple thin needles and their positioning in geometrical configurations to maximize the ablative effect, is more effective in all these cases in achieving with safety large volumes of necrosis [17] and in treating at-risk lesions without resorting to specific methods to protect vital structures [18]. For lesions ≥ 5 cm, complete response can be obtained in about 90% of cases. Proof of the wide flexibility of laser technology is the interesting possibility of effectively and safely treating multiple lesions of different sizes in different sites in the same session. Actually, this is possible only using the laser technology that allows the activation of four fibers at the same time: for example two nodules of 2 cm in size can be simultaneously ablated in 4 min [17].

A recent noninferiority randomized trial in patients with cirrhosis and HCC within Milan criteria demonstrated clinically favorable equivalent efficacy when RF and laser ablation techniques were compared [19]. Overall complete ablation obtained with both techniques was greater than 90%. The mean time to local progression (TTLP) was comparable between RF group (42.0 months) and laser group (46.7 months). The mean local progression-free survival was 35.7 and 35.5 months in RF and laser groups, respectively. The mean overall survival (OS) was 42 months in both groups and survival probability at 1 and 3 years was

94 and 89% in RF group, and 94 and 80% in laser group. There were no substantial differences between the two techniques with regard to the type and rate of complications (one case per group of subcutaneous tumor seeding, both surgically removed). The authors also report a brief preliminary analysis of the cost of applicators: laser devices cost 40–70% less than RF system. Despite the number of patients enrolled (70 per group) – relatively small but sufficient for the noninferiority study – and that the trial was conducted in only one center, the results validate, at least partly, what has been discussed and claimed prior regarding the absence of any difference between the two techniques in treating small HCC. It must be noted that the comparison was between standardized RF and laser devices, validated and most commonly used (17-G cooled tip RF electrode and laser applicator with a caliber <1 mm).

Given the high rates of complete ablation in small HCC associated with low complication rates, other factors such as ease of use may be taken into consideration when choosing which energy source to adopt. For example, the reduced number of sessions required by RF to completely destroy an HCC of a given size was the determining factor in substituting PEI with RF ablation in treating most patients with small HCC [10] and the main reason why authors such as Shibata *et al.* [5] believed that RF was easier to use than MW. However, the time required to perform an ablation session with either PEI or MW is shorter than that required by RF [5,10]. Thus, ease of use in many cases is subjective and depends on clinical circumstances. In lesions up to 2.5 cm, the time required for a single session with fine needle technique is shorter than that of an RF treatment session (4–6 min vs 12 min, respectively) [19]. In the case of larger lesions, more time is required for both techniques, but the size of the probes may affect the ease of use of the system adopted. Targeting and the correct positioning of the devices appear easier with the fine needles of the laser technique than with the larger RF devices. In both cases, the methods are operator-dependent; the spatial configuration of the devices, however, is undoubtedly affected more by the caliber and the spatial positioning of the probes than by the time needed to correctly perform the ablative maneuver. Further, in the case of RF devices used with the sequential or with the switching technique, times are longer [15]. We believe that

the operator's experience and skills affect the results more than the ablative device or system used. For instance, to increase the amount of heat, a number of applicators of one type of source can be used rather than changing the energy source. While some energy sources are more appropriate for certain applications, none has been clearly demonstrated to be appropriate for all applications. The availability of a number of systems may favor one choice rather than another based on the type, site and size of the lesion that the operator must treat. In general, the operator should have an array of applicators available and a set of ablative systems so as to increase the ablation area without increasing the duration, complexity or invasiveness of the procedure. In short, the thermal ablation's success depends on the operator's skill, on the technique chosen and on the biological characteristics of the tumor.

In light of what has been discussed thus far, we believe that the LA technique may be used to treat high-risk lesions safely and effectively and to obtain high rates of complete response in lesions up to 6 cm without having to resort to sequential combined treatments [20]. Thus, in BCLAA patients not candidates for resection but for thermal ablation, with nodules whose size is between 3 and 5 cm where there is a high risk of satellite nodules, laser energy technique with fine multiple applicators that can enlarge the ablation field can be used in place of combined TACE followed by RF [4] or PAT followed by TACE [20]. The recent availability of the novel RF devices would seem to ensure larger area of coagulation thereby modifying these indications; however, these novel probes need to be validated.

In our view, the technological advances underway may have a positive effect on an increasing number of patients. Rigorous, well-controlled, preferably multicenter trials comparing the various techniques available, like the one mentioned before by Di Costanzo *et al.* [19], are needed. It is likely that many of the devices being studied and validated will facilitate similar therapeutic results due to the tumor's underlying biological characteristics. Further, other clinical trials are needed to determine who the most suitable candidates for these therapies are and to match the best technologies with specific pathologies. Research should focus on and optimize devices so as to improve the delivery of energy to specific organs or to specific types of tumors [7–9].

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes

employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

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