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Laser Ablation for Hepatocellular Carcinoma

The Advent of a Novel Needle Guide System: Toward a Patient-Tailored Approach with Nodules between 3 and 5 cm.

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So far, the source of percutaneous ablation most studied and most clinically tested and supported by major vendors is RF energy. It should be noted that, to date, there are no data that support the superiority of RF energy source and their technology compared to other hyperthermic agents, neither in terms of local response nor in terms of long-term outcome in treating of small HCC. The differences in terms of results in the survival of small HCC patients are modest[1-8].

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. 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 calibre (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[9-13]. Laser beams are transmitted from the source to the tumour tissue of the patient by means of flexible quartz fibres. The flat tip fibre is the type most commonly used, with thin (<1 mm-gauge) applicators[6, 14, 15].

Many studies have demonstrated that the size of the nodule is the most important parameter in predicting ablation success[16, 17].

The ablation of the tumour by means of hyperthermic techniques is achieved by heating the entire tumour volume to cytotoxic temperatures of 50°C-54°C for 4-6 minutes[9, 18, 19].

Local control is achieved in 80%-90% of cases, as well as in smaller tumours of less than 2.5 cm in diameter regardless of the technique used. For slow-growing lesions, as in HCC, there are no differences in survival as once the lesion has been completely destroyed, other factors such as new lesions and underlying cirrhosis will be important in determining survival compared to persistent minimal foci of still viable tissue not treated. The differences in tissue heating between the different types of RF electrodes and some models of laser applicators[13, 20, 21] cancel each other out in the case of small lesions[16]. 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[5, 6, 17].

The recent randomized trial in patients with cirrhosis and HCC within Milan criteria confirmed the effectiveness and clinical equivalence between the two techniques[8].

However, clear differences between the various percutaneous techniques and different methods emerge in the case of larger HCC[22].

An important factor that limits the extension of the necrosis and of the amount of tumour destruction is the non-homogeneous 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 are necessary, or the simultaneous use of a number of applicators, to successfully treat the entire tumour with sufficient ablative margin[23], even if accurate targeting and correct applicator positioning can be very difficult[9, 24, 25].

As RF effectiveness is size-dependent, to obtain complete destruction the upper limits must not exceed 2.5-3.0 cm[26-28].

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To overcome this limitations and obtain larger volumes of necrosis, a variety of devices[29, 30] of different shapes and designs[31, 32], used with different algorithms[33] or activated in different ways (consecutive, switching, or simultaneous) has been developed[34-37].

In the treatment of large HCC (≥ 5 cm), conventional RF is limited mainly by incomplete ablation, with reported complete ablation rate of 74% after a single session in lesions between 3 and 5 cm and 62% in nodules >5cm after multiple sessions[38].

Using three internally cooled bipolar electrodes complete ablation rates was 81% in patients with large HCC[39].

The recent availability of the new RF devices would seem to ensure larger area of coagulation thereby modifying these data; however, these novel probes needs to be validated[40].

In addition, percutaneous RF ablation is limited 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).

In all of these cases, specific protection systems must be used with RF to avoid damaging contiguous vital structures[41].

different sites in the same session (i.e. 2 nodules of 2 cm in size simultaneously in four minutes)[42].

If then we take in consideration other parameters such as the ease to use of the technique chosen in treating the lesions in order to obtain a complete ablation in the shortest possible time (a major focus of research in all these years has been on the development of techniques for achieving in a single-session large volume tissue necrosis in a safe and fast manner), the time required for a single session to destroy completely a nodule of HCC of 2.5 cm with fine needle technique is shorter than that of an RF treatment session (4-6 minutes vs 12 minutes, respectively)[8, 14].

We think, however, that ease of use in many cases is subjective and depend of clinical circumstances[1, 16].

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.

Further, in the case of RF devices used with the sequential or with the switching technique, times are longer, besides being cumbersome and more complicated [39, 44].

Therefore, the LA technique may be used to obtain high

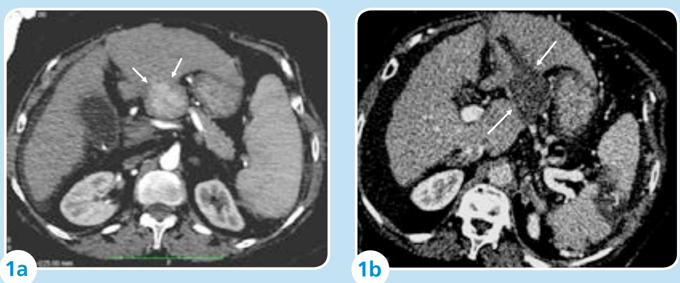

Figure 1. Representative case of exophithic HCC 3.5-cm-diameter in S 2 adjacent to the pancreas, stomach wall and celiac tripod **a)** before laser session and **b)** after laser treatment.

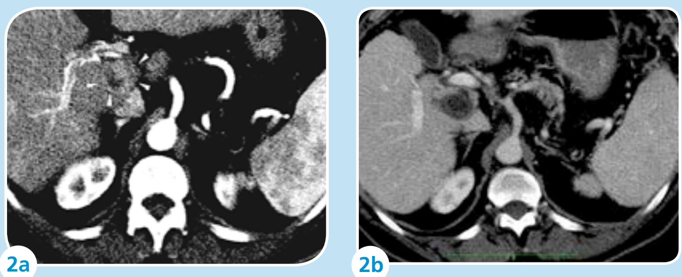

Figure 2. Representative HCC 2.5-cm-diameter hard-to-reach in caudate lobe. **a)** before ablation and **b)** after complete ablation.

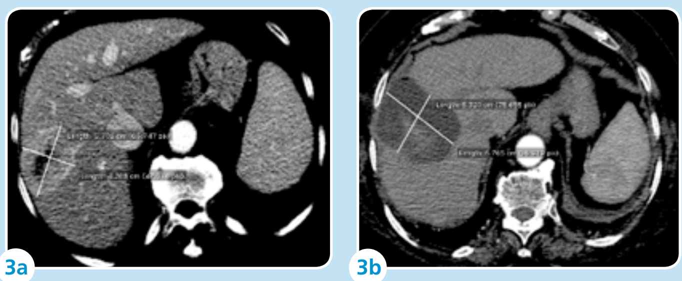

Figure 3. Representative large HCC 5.7-cm in maximum diameter in S5. **a)** before ablation and **b)** after complete ablation.

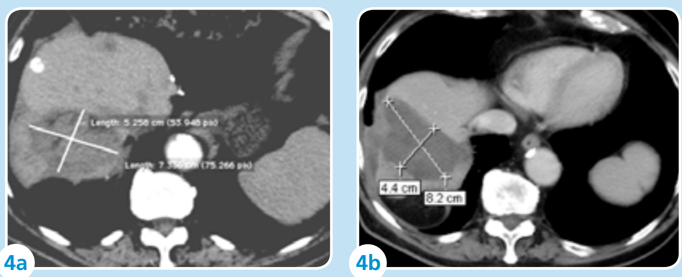

Figure 4. Representative large HCC 7.4-cm in maximum diameter located in the dome of the liver in S7-8. **a)** before laser session and **b)** after complete ablation. Note the large coagulation zone.

Instead, in our view, laser ablation (LA) technology, thanks to the recent introduction into clinical practice of a novel guide system which facilitates the parallel insertion of multiple thin needles, is more effective in achieving with safety large volumes of necrosis[42] and in treating at-risk lesions without resorting to specific methods to protect vital structures[42, 43] (Figs 1a, b and 2 a, b). For lesions ≥ 5 cm, complete response can be obtained in about 90% of cases (Figs 3 a, b)[15, 42].

Additionally, only using the laser technology that allows the activation of four fibers at the same time, it is possible to treat effectively and safely multiple lesions of different sizes in

rates of complete response in lesions up to 6 cm (Fig. 4 a, b) without having to resort to sequential combined treatments (TACE+RF or LA+TACE)[45, 46].

Thus, in BCLA A 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 treatments[47].

Finally, it would be appropriate to complete this brief comment with some notes to the cooled laser systems. So far, has been used successfully by German authors a large cross-sectional water-cooled probe diameter (3 mm) that requires a large bore cannula (9-gauge, 3.8 mm diameter) for HCC treatment.

This laser system, in the last two decades, were less frequently used for HCC treatment while achieving excellent outcome with high percentage of complete response and low local recurrence[48].

The recent introduction in clinical practice of a novel ablation laser diode system with flexible diffusing-tipped fibre optic and 17-gauge internally cooled catheter represents a real novelty. This device can achieve a large well-circumscribed ellipsoid ablation zone up to 3-cm in a single application in about three minutes. Due to its characteristics it has been applied so far to focal malignant lesions of the prostate and brain, but research and clinical applications on hepatic focal lesions and lung metastatic disease are ongoing[49, 50].

The limitations of the previous system which used high-calibre devices can be overcome by this technical solution. Further, the execution time of the entire manoeuvre can be shortened significantly by using real-time RM guidance in positioning the water-cooled devices, in monitoring and controlling during ablation, and in final assessment of the efficacy[49].

Therefore, with laser technical improvements such as the novel needle guide system or the new small cylindrical water-cooled diffuser, it possible to employ an array of applicators to increase the ablation zone without increasing invasiveness, procedural complexity, times of ablation, or costs[8].

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Laser and Radiofrequency Ablation in the treatment of benign Thyroid Nodules

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Background

Image-guided ablations have been increasingly using as an alternative treatment to surgery in the management of clinically relevant benign thyroid nodules. Some different ablative techniques are nowadays available for this kind of treatment, such as radiofrequency ablation (RFA) [3,8,9], laser ablation (LA) [5,6,10] and microwave ablation (MWA) [11,12]. All these methods have been proven feasible and clinically effective, with similar results in terms of nodule shrinkage.

The two most widely used techniques for benign nodule image guided thermal ablation are **RFA** and **LA. RFA** was the first technique used to perform image-guided tumor ablation [2,4,7].

Traditionally used in the liver, RFA is applied through an electrode (i.e., the needle) under imaging guidance to induce focal high-temperature cytotoxic heating in target tumors.

The patient is part of a closed-loop circuit made by the needle, the power generator, and a ground pad. This allows for having an alternated electric field within the tissue of the patient. As biological tissues are poor electricity conductors, ionic friction takes place and leads to heat generation (i.e., the Joule effect).

The discrepancy between surface of the needle and of the ground pad allows for concentrating most heating power around the needle itself. High temperature implies tissue dehydration and water vaporization, thus leading to coagulative necrosis. Differently from application in other organs, such as the liver, where the aim is to destroy the whole tumor with a reasonable safety margin, in thyroid the aim of the treatment is to destroy the majority of the nodule avoiding damaging the surrounding critical structures (e.g. skin, vessels, nerves). For this reason, for application in the thyroid a specific RFA devices with 17/18 gauge caliber and short length

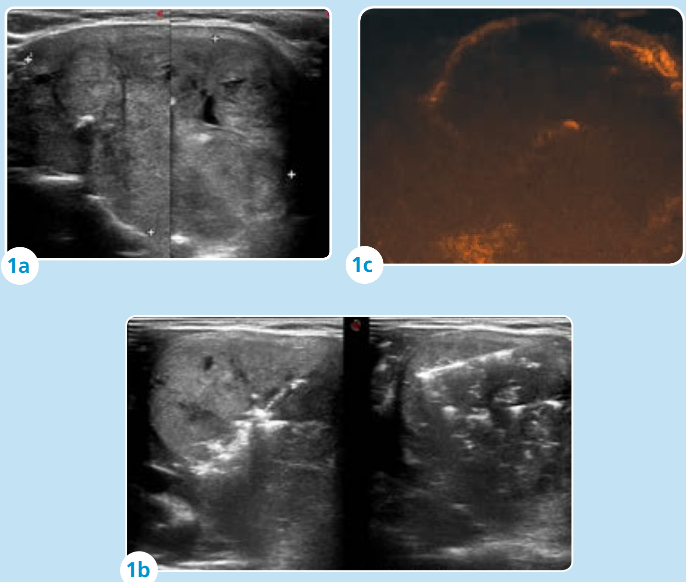

Figure 1. Representative case of 6.0 cm thyroid nodule treated by RF ablation **a)** before ablation **b)** during the treatment the applicator is positioned in different units of the nodule; **c)** after the treatment.

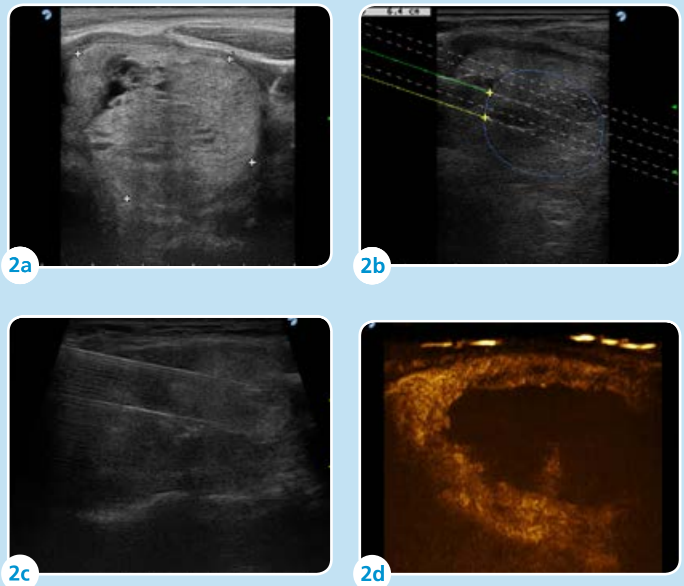

Figure 2. Representative case of 4.1 cm thyroid nodule treated by LA ablation **a)** before ablation; **b)** during the treatment in the planning phase; **c)** during the treatment with the needle inserted; **d)** after the treatment

of exposed tip (0.5 to 1.5 cm) have to be used, and the so called "moving-shot technique" is generally used [1].

With this technique, the electrode is continuously moved into the nodule under constant ultrasound monitoring, performing fast energy applications, covering with subsequent ablations the majority of the nodule.

Differently, **Laser** is characterized by high spatial and temporal coherence, which allows energy to be focused to a small focus with a very collimated beam. Thanks to these characteristics, with laser it is possible to deliver a precisely established amount of energy in a well-defined region, to determine necrotic areas of highly reproducible size. For tumor ablation, laser is applied through a very small optic fiber, which can be introduced into the tumor to be treated through a small needle (21G caliber), generating zone of coagulation necrosis up to 2 cm with a single fiber. For obtaining larger zone of ablation, multiple fibers may be simultaneously inserted using a dedicated needle guidance system. With this technique a single insertion of one or eventually multiple needles with subsequent pullbacks may be enough to achieve the ablation of the majority of the nodule.

Thus, laser seems to be particularly useful when a small lesion has to be treated and high precision is required, such as when performing ablations in a critical area as the neck. Moreover, with this technique it is not necessary to have an electronic circuit including the patient, and the deployed energy is better concentrated in the area of treatment. As a consequence, lower energy may be delivered to the patient using this technique.

Materials and Methods

At our centre we started performing image-guided ablations of thyroid nodules using both RFA and LA in 2010. We used an internally cooled electrode with 17-18 gauge calibre and 0.5-1.5-cm active tip (AMICA, HS Hospital Service, Aprilia, Italy) and the moving-shot technique for RFA ablation. We used a continuous-wave Nd-YAG laser operating at 1.064 mm (EchoLaser X4©, Esaote, Genoa, Italy) for LA.

From the beginning of our experience we treated 63 patients (12 males, 41 females) with a benign thyroid nodule. 32 (4 males, 28 females) underwent treatment with RFA, and 31 (8 males, 23 females) were treated with LA under ultrasound guidance.

Results

No major complications occurred in our series. Mean volume reduction at 1 month, 6 months and 12 months was similar between the two groups. Mean time for ablation was longer in LA group, while mean energy deployment was higher in RFA group. Data of volume reduction at different time points, ablation time and energy deployed in the two groups are reported in table 1.

Conclusions

From our experience, LA and RFA appear to be safe procedures, similar in terms of volume reduction at 1, 6 and 12 months.

RFA requires operators with high experience in performing image-guided thermal ablation, as the moving-shot technique is based on several subsequent electrode free-hand positioning during constant ultrasound guidance.

Moreover, this technique requires larger devices than LA, and thus may be theoretically burdened with a higher risk of complications for not experienced operator. On the contrary, LA can be performed using small calibre needle, with needle guidance, and performing fewer needle insertions and movements into the thyroid. In our centre, we perform RFA ablation of different organs (e.g liver, kidney, and bone) for more than 20 years.

The long experience in performing RFA ablation may be one of the reason of shorter ablation time in the RFA group in our experience in comparison with the LA group.

Requiring multiple free hand insertion of a larger device, we think RFA should be reserved for high experienced operators. If on one hand RFA required shorter procedural time than LA, on the other hand with RFA a higher energy is delivered to the patient.

No data are nowadays available about impact on patients' health of energy delivered through image-guided thermal ablations. However, this aspect could not be neglected, and further study are needed to better clarify the topic.

In conclusion, RFA and LA are feasible, safe and effective modality for treating benign thyroid nodules, with similar results in terms of volume reduction at 1, 6 and 12 months.

	LA Group (31 pts)	RFA Group (32 pts)	P Value
Volume Reduction			
1 Month	46% ± 20%	49% ± 15%	0.275
6 Months	66% ± 18%	51% ± 13%	0.409
12 Months	65% ± 15%	54% ± 19%	0.440
Ablation Time	21.1 ± 7.2 min.	14.9 ± 7.2	<0.001
Deployed Energy	5493 ± 2579 J	18726 ± 9478 J	<0.001
Values are expressed as mean ± standard deviaton			

Table 1. Comparision of volume reduction, ablation time and deployed energy in 63 patients treated with image-guided thermal ablation with radiofrequency ablation and laser ablation for a benign thyroid nodule.

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SonoVue® in Liver Imaging and Ablation Procedures

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Medical imaging techniques are important in the management of many patients with liver disease. Unenhanced US examinations sometimes identify focal abnormalities in the liver that may require further investigation, primarily to distinguish liver cancers from benign abnormalities.

One of the most important factors in selecting an imaging test is the ability to provide a rapid diagnosis. Options for additional imaging investigations include CT and/or MRI and biopsy when the diagnosis remains uncertain.

CT and MRI usually require referral with associated waiting time and are sometimes contraindicated. The use of US contrast agents may improve the ability of US in characterizing lesions and, because it can be performed at the same appointment as unenhanced US, more rapid diagnoses may be possible.

SonoVue-CEUS may improve the ability of US to differentiate liver cancer lesions from benign abnormalities. Furthermore, it can provide important information across the interventional procedures in the management of patients with liver malignancies, both HCC and metastases. Unenhanced US is commonly used to guide ablation. However, it is unable to assess tissue vascularization which is crucial to differentiate necrotic from viable tissue.

SonoVue-CEUS can be used for pretreatment staging and assessment of target lesion vascularity, in order to define the eligibility of the patient for treatment and the best ablation strategy. In the post procedure phase, SonoVue-CEUS can be used for evaluating the immediate treatment effect after ablation and eventually in supporting decision for immediate re-treatment of residual unablated tumor.

After thermal ablations, completely necrotic tumors may remain unchanged in size, whereas tumors that shrink may still be partially viable. It is often difficult to depict local tumor recurrence after ablation using unenhanced US alone.

Here, CEUS is useful to identify the viable tumor adjacent to the ablated volume and it plays a role in planning an additional treatment. Used alone SonoVue-CEUS may be extremely useful to define local recurrence in a treated nodule and to assess local tumor progression when follow-up CECT or CEMRI are contraindicated or not conclusive.

SonoVue-CEUS could provide similar diagnostic performance to other imaging modalities (CECT and CEMRI) for the assessment of FLLs and it may be used in follow-up protocols. Economic analyses indicated that CEUS is a cost-effective imaging enhanced modality.

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February
2015

The attractiveness of ModìLite, the thermal laser ablation treatment, pushes patients to transcontinental flights

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Very recently, two patients a male from Australia and a female from Brazil came to Perugia to treat their thyroid nodules by means of thermal laser ablation. In their countries, for both patients had been initially recommended total thyroidectomy for the presence of two bulky solid nodules with compressive symptoms. However, the patients consulted more endocrinologists to verify the possibility of an alternative treatment. ModìLite is a safe and non-invasive solution for benign nodules of the thyroid, is simple and short running with a fast disappearance of the symptoms. The efficacy and the safety of laser thermal ablation of thyroid nodules has been reported by a growing number of papers over the last years and the endocrinologists of countries where the methodology is not yet used are becoming aware of this alternative solution. Our Thyroid Unit of Perugia was suggested to the patients among the international referral centers because of the methodological papers we have published on the ablation technique over the last 10 years.

The man coming from Sydney had a large nodule (13 cm) of the left thyroid lobe and was previously treated for a nodular goiter with a partial resection of the right lobe. We treated the patient by inserting along the longitudinal axis three optic fibers and delivering a total energy of 15000 Joules. The patient will come back to Perugia on the next summer to verify if a second treatment will be needed, considering the initial volume of the nodule.

The woman coming from San Paolo do Brazil had a 5 cm central thyroid nodule with esthetic disfigurement. In this case we used two optical fibers and a total energy delivery of 7800 Joules. Based on the experience gained from hundreds of cases already treated, it is expected that the nodule of the patient will get a volume reduction of 60% percent, after 6 months.

Both patients were treated in a Day Surgery regimen, they did not experience relevant side effects and returned to their home the day after the intervention. The patients reported that the main reasons to deal with such a long journey were the hope to reduce the nodule size without anesthesia without scars and loss of thyroid function. The Australian patient did not pay for the treatment because there is a treaty between Australia and Italy that covers the expenses of those procedures not performed in one of the two countries. The Brazilian patient was charged by the Perugia Hospital for the day surgery admission with 1560 euros. Other foreigner patients are contacting our center in these days suggesting that a sanitary tourism is starting thanks to the innovative methodology of the laser ablation of thyroid nodules.

A photo of the patient with the medical team (Umbria Journal 27 January 2015)

Please note that from February 2015 the Echolaser News will be bimonthly.

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