November 2014

ECHOLASER News

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Consideration of a surgeon in the percutaneous treatment of volume reduction of **symptomatic benign thyroid nodules** with laser energy

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Nodular thyroid disease is common in the adult population, with prevalence increasing with age. Most nodules are benign and remain small, stable, and asymptomatic, requiring no treatment. Nevertheless, some nodules can grow over time and can cause pressure symptoms in the neck and/or cosmetic complaints. These nodules embody the real challenge in surgical practice: is traditional open surgery the right choice or might this be considered overtreatment? Do partial or total ablation of the thyroid and its loss of function make sense given the benignity of the thyroid disease? Not to mention possible adverse events such as vocal cord palsy or hypoparathyroidism, or clinical conditions that contraindicate general anaesthesia. For these reasons, over the last decade, nonsurgical, minimally invasive US-guided debulking techniques have been proposed to reduce the volume of thyroid nodules when surgery is contraindicated or refused.

Laser ablation (LA) has been proposed as a safe outpatient procedure that effectively reduces the volume of large cold solid nodules and the clinical outcomes in patients followed for more than 5 years that have been reported indicate that LA results in a satisfactory mild-to long-term clinical response in the majority of patients.

Furthermore, the opportunity to ablate only the thyroid nodule causing the pressure or cosmetic issues, leaving the thyroid parenchyma intact, solves the dilemma every surgeon has, i.e. whether open surgery of a benign disease is the right choice, with the consequent need to take replacement therapy for life or, in the worst cases, whether it is right to expose the patient to significant complications such as the IX nerve impairment or the onset of hypoparathyroidism.

Based on these considerations, we started treating a cohort of patients with symptomatic benign solid thyroid nodules referred to the Oncological Institute of Bari at the Cervico-Facial Ultrasound Diagnostic and Interventional Unit in the Ear, Nose and Throat Unit (ENTU).

All patients reported pressure symptoms and/or cosmetic complaints. Entry criteria were: a) both sexes; b) presence of a single or dominant palpable nodule, solid or predominantly solid (with a fluid component less than 20% of total volume at US examination), and any size between 1.0 and 95 mL; c) benign cytology at two consecutive US-guided FNA biopsy; d) hypoactive appearance at 99 mTc thyroid scintiscan; e) free thyroid hormones, TSH, and antithyroid antibodies within normal range; f) age between 18 and 85 years; g) refusal of surgery; h) untreated thyroid disease. None had suspicion of or a family history of thyroid cancer and none had had previous neck or trunk external beam radiotherapy. No patient had previously undergone surgery, radioiodine, or LT4 treatment for thyroid disease. All euthyroid patients had normal serum calcitonin levels, as well as normal platelet count and clotting function. Although all patients were suitable for traditional surgery and none exhibited any contraindications to traditional cervicotomic-access surgery, all refused this option as first-line therapy. Before LA procedure, all patients underwent direct laryngoscopy with video recording: those with laryngeal motility disorders and/or dysphonia from other origins were excluded from the study.

After being fully informed, 45 of 95 eligible patients (35 women; median age 52 years, range 22-81) gave their consent and entered the study. We stratified the nodule population into four classes according to baseline volume: those ≤ 5 mL were classified as small, those with volume between 5.1 to 13.0 mL as medium, those with volume between 13.1 to 30.0 mL as intermediate, and those > 30 mL as large.

Nodule size was assessed at baseline and at 6 and 12 months by bi-dimensional ultrasound with multi-frequency linear probe 5-12.5 MHz. The nodule volume was calculated before treatment at baseline and during follow up at 6 and 12 months according to the ellipsoid formula (the three main largest perpendicular diameters in thickness, width, and length multiplied by a factor of 0.525).

Ablation technique

We have applied a variant of multiple fine-needle LA technique proposed in the past elsewhere[1-3] that uses needles with calibre less than 1 millimetre. The patient was placed on an operating table in the supine position with hyperextended neck. The procedure was performed using a commercially available ultrasound system (EchoLaser X4, Esaote, Italy) equipped with a dedicated linear transducer operating at 13-4 MHz and with a needle-guided attachment with adjustable angle selection. Each treatment was performed under conscious sedation by IV diazepam infusion (2-10 mg) in fractionated boli and local anaesthesia with a combination of 2% Lidocaine (2-5 mg) and 3 mL of Ropivacaine (Naropine©, Fresenius Kabi, USA). The number of introducer needles to be inserted was determined based upon nodule size and shape. We usually inserted only one introducer needle for small nodules with baseline volume ≤5 mL and from two to three introducer needles for medium, intermediate and large nodules, increasing the number of applications as the size of nodules increased. Under US guidance, the introducer needles were inserted into thyroid nodule along its longest axis. Subsequently a 300 μm plane-cut quartz optical fiber was introduced and advanced up to introducer needle tip. The introducer needle was then withdrawn to expose the fiber tip by at least 5 mm. Care was taken to maintain a safety distance of 10 mm between the needle-fiber tips and surrounding cervical structures and to leave interneedle spacing of 1.0 cm. The needle-fiber positions were confirmed with two-plane US images. The optic fibers were then connected with a multi-source continuous-wave laser operating at 1064 nm wavelength. The optical fibers, which should be positioned on planes as parallel as possible to the horizontal plane of the nodule, were always activated simultaneously. Each treatment was performed with a fix-power protocol (3 W), changing the application time case by case according to target size and shape. Each application time ranged from a minimum of 400 seconds to a maximum of 600 seconds to maintain the total energy applied between 1,200 and 1,800 Joules per fiber. Depending on the size of the nodule, one to three applications with a pull-back technique (with this technique the needle-fibers are generally withdrawn of around an 1 cm with overlapping of the areas of coagulation induced during the treatment) were performed in each session (by application or illumination, we mean the activation or switching of the laser source for the time necessary to deliver the energy planned i.e. 1,200 or 1,800 Joules in the case of a single application. In the case of two or three applications, instead, the time doubles or triples).

Results

Total energy used during each session ranged from 1,200 to 14,418 (mean, 3,736 ± 3,231), corresponding to 221 ± 187 J/mL nodule tissue (range, 33-952). The mean nodule volume decreased from 24.2 mL ± 19.4 to 6.2 ± 6.6 at 6 months ($p < 0.001$) and to 4.5 ± 5.2 at 12 months ($p < 0.001$). Overall, the mean nodule volume reduction at the end of the study, expressed in percentage of baseline volume, was 84% ± 13. The table (see at the end of the text) also shows mean percentage of volume changes in the four classes according to their initial volume. There was a significant correlation between energy delivered per nodule and baseline volume of the nodules ($p < 0.032$): the smaller the baseline volume of nodule, the less energy was released. No significant correlation between initial volume size and the degree of reduction was detected ($p = 0.088$). Of the 45 laser sessions, we used a single laser source in 17 (37.7%), two laser sources in 25 (55.5%), and three (6.8%) laser sources in 3 cases. The number of applications during a single procedure for the 45 cases were: a single application in 16 (35.6%), two applications in 23 (51.1%), and three applications in 6 (13.3%). The mean treatment duration was 12.6 ± 5.9 minutes (see table included at the end of the text).

Regarding cosmetic signs and pressure symptoms, we achieved a significant decrease in the ranking score. Cosmetic signs were completely resolved in 38 out of 44 subjects (87%), reduced in 4 (9%), and unchanged in 2 (2%), and pressure symptoms were resolved in 15 (88%) out of 17 patients. The serum levels of the thyroid hormones did not present significant changes during the follow-up period. We did not observe any changes in TgAb and TPOAb levels and all patients were euthyroid.

Side effects and complications

Only one patient (2.5%) experienced dysphonia immediately after the LA session, with vocal cord palsy at direct laryngoscopy. A course of corticosteroids (oral prednisone 25 mg daily for 2 weeks) was administered and the patient recovered completely (confirmed by direct laryngoscopy) after 8 weeks. Mild to moderate local pain occurred during treatment in 12 (26.7%) patients, lasting for 2-4 days after the procedure and alleviated with analgesics. Of the three patients treated with three laser sources, one experienced intense local pain during and immediately after the LA session and was effectively treated with analgesics, while another experienced hyperpyrexia (39.5 °C) lasting 1 day after the procedure, with concurrent pronounced increase in nodule size due to perinodular edema the day after treatment; the patient was effectively treated with antipyretic and corticosteroids. None developed hypocalcemia, local infection, perinodular hematoma, or hypothyroidism.

Discussion

Our study shows that there is a direct correlation between the amount of energy delivered and the baseline volume of the nodule, i.e., less energy is delivered to small nodules, and more to large nodules. Further, the study does not demonstrate any significant correlation between the initial size of the nodule and the degree of volume reduction after LA treatment. Small nodules do not achieve better results than do large ones, as some authors have reported, not even in nodules smaller than 10 mL[4,5]. In our study the volume reduction at 12 months varied between 51% and 100%, with an average of 84% and thus higher than average values reported so far by other authors. In addition, we did not find statistically significant differences between small, medium, intermediate, or large nodules (see table included at the end of text). These good results can, in our opinion, be explained by our way of treating nodules, which takes into account their baseline volume and morphology. The laser energy, in fact, is applied in a very precise and predictable way with a fixed power protocol, with application times determined by the baseline volume and shape of the nodule. Thus, the amount of thermal energy deposited is correlated to the baseline volume of the nodule to be treated, with the destruction of the thyroid tissue thus being proportional. More in detail, multiple fine needles with a calibre under 1 mm allow us to vary the number of light sources and the number of applications (pull-back) based on the shape and volume of the nodule. Therefore, the need to insert multiple optic fibres, which some authors consider a drawback of the laser technique, is, based on our experience and on the results we have observed, a significant advantage.

For the most part we used one or two sources, in one or two applications, in one single treatment session. Using one or two sources made it possible to accurately and constantly US-monitor of the position of diffusers (needles and fibers) throughout the entire treatment. To be noted, in our patients with small volume nodules (≤5 mL), the nodule was in a superficial isthmic or paraisthmic location, with obvious cosmetic damage. These patients had refused surgery and had requested mini-invasive LA treatment. In these cases we obviously used one single source. Of note, we positioned the needle-fiber along long axis of the nodule in these cases as well. We never positioned the laser applicators with trans-isthmic approach along the short axis of the nodule as is commonly done with the radiofrequency technique. This type of approach does not allow for the pullback technique and/or more applications during the same treatment session.

There was only one case of vocal cord paralysis, likely due to incorrect positioning of the laser source. This adverse event was caused by positioning one of the needles too closely to the recurrent nerve area, which was reached by excessive heat. To avoid the risk of vocal cord injury it is necessary to check that the fibre tips are positioned at a safety distance of at least 10 mm from adjacent cervical vital structures with two-plane US images. The results of our experience demonstrate that LA is a safe and effective way to obtain volume reduction of benign solid thyroid nodules and provides significant improvement in cosmetic and pressure symptoms, avoiding the consequences and the possible issues of traditional open surgery. In fact, the prudent use of laser application for surgical procedures performed by highly experienced professionals most likely explains the low percentage of complications observed in this series of patients. Therefore, from a strictly surgical point of view, the possibility of solving the aesthetical and mechanical issues arising from the volume of a thyroid nodule in this kind of minimal invasive way can be considered an alternative and not a substitutive technique that can be offered to patients who refuse traditional open surgery.

Table 1. Clinical and demographic findings of the population under study before and 12 months after LA treatment.

	Total population (n = 45)	**Nodule volume**				**P value**
		≤ 5 mL (n = 6)	5.1-13.0 mL (n = 6)	13.1-30.0 mL (n = 19)	> 30 mL (n = 14)	
Gender (male/female)	10/35	0/6	2/4	2/17	6/8	0.069
Initial volume (ml) (range)	24.2 ± 19.4 (1.4-92.6)	3.3 ± 1.2 (1.4-4.5)	7.5 ± 1.8 (5.3-10.1)	19.2 ± 5.6 (13.5-29.7)	47.1 ± 17.3 (32.0-92.6)	< 0.001
Volume reduction (%) (range)	84 ± 13 (48-100)	93 ± 11 (72-100)	86 ± 18 (51-99)	85 ± 13 (48-97)	78 ± 8 (67-94)	0.088
Total Joules	3,736 ± 3,231	1,257 ± 95	1,602 ± 969	4,448 ± 3,060	4,747 ± 3,902	0.032
Joule/ml	221 ± 187	455 ± 257	220 ± 125	239 ± 169	97 ± 68	< 0.001
Joule/Fiber	1,304 ± 161	1,256 ± 59	1,205 ± 10	1,320 ± 179	1,346 ± 180	0.278
Fiber number (1/2/3)	17/25/3	6/0/0	4/2/0	7/10/2	0/13/1	0.198
Application number (1/2/3)	16/23/6	6/0/0	5/1/0	5/11/3	0/11/3	0.012
Total time (min)	12.6 ± 5.9	7.6 ± 0.6	7.1 ± 0.7	13.6 ± 4.5	15.5 ± 7.3	0.010

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The corner of the engineer

MIT Volume Chart
How does it works?

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Volume reduction parameter is one of the most important indicator of efficacy for MIT (Minimal Invasive Therapy). Are they all agree?

When we are looking for a parameter able to quantify in a single value the efficacy of an ablation technique in shrinking thyroid nodules, the percentage volume reduction seems to play a key role in targeting the ablation technique effectiveness instead of reporting variations on the three dimensional axis of nodule dimension or even the absolute volume reduction. This is almost true generally speaking but some troubles arise when comparisons are attempted using this parameter alone and forgetting the basal volume of the population of the treated nodule.

In order to clarify all these aspects and overcome some pitfalls that can arise in the comparison process we introduce in this paper the Volume Reduction Chart as helpful tool for assessing the relationship between nodule diameters, nodular volume, nodular volume reduction (absolute and percentage). For simplicity we will consider spherical nodules in order to characterize nodules with just one dimension i.e. the diameter.

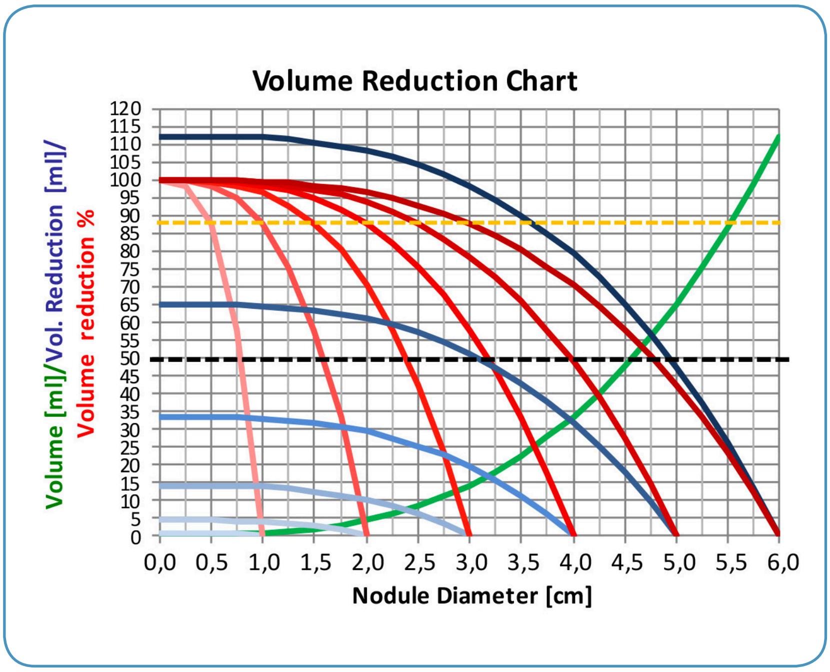
The chart reports:

- Volume-diameter curve computed by $\frac{4}{3}\pi\left(\frac{D}{2}\right)^3 \rightarrow \frac{\pi}{2*3}D^3 \rightarrow 0.52 * D^3$ (green line)
- Percentage Volume Reduction (red curve group) related to basal volume
- Removed nodular tissue from basal volume (blue curve group)

- 50% of volume reduction from basal volume (black dotted line)
- 87,5% of Percentage Volume Reduction which corresponds to a half basal diameter in reduction (yellow dotted line)

Basically the green curve represents the cubic relationship between diameter and volume. That means that a fixed increase in diameter induces different increases in volume if we consider small medium and big diameter values. Just for example, a half centimeter between 1.5 and 2 cm induce about 2 ml in volume variation in spite of a half centimeter between 4 and 4.5 cm that induces 15 ml in volume variation.

Almost all the following considerations will arise from this basic starting point.



Several scientific papers in literature deal with populations of nodules with basal volume of 5-7 ml that means that dimension ranges from 2 to 2.3 cm other papers deals with bigger nodules in the range 12-16 ml that means that radius is about 3 cm. For big nodules with mean volume of about 30 ml we obtain a mean basal volume of 4 cm.

The following discussion will highlight how nodule shrinkage (in terms of volume percentage) is simpler to be induced in small nodules with respect to bigger ones just for a geometric reasons.

Let us suppose that we want to achieve a target reduction of 50% in volume. If we consider a 2 cm (5 ml) nodule we can achieve this result removing just 2.5 ml of nodular volume. But if we consider a nodule of 4 cm (33 ml) we need to remove 16.5 ml of nodular tissue that is more than six times the previous quantity!

Even worse if we require a target reduction of 75%: for a 2 cm nodule we have to remove 4ml of nodular volume in spite of 25 ml for a 4 cm nodule that is 6 times the previous value! **It would be 12 times for a nodule of 5 cm with a removed nodular volume of 48 ml.**

Now suppose that we want to achieve a reduction of 75%. For a 2 cm nodule it happens when it shrinks to 1.3 cm (reduction of 7 mm in diameter) but for a 4 cm nodule it happens when it shrinks to 2.5 cm that is it reduced for 1.5 cm in diameter (double diameter reduction than previous!).

Now it is clear how quantities we are dealing with, are very different for small, medium and big nodules and this is due to the cubic relationship between diameter and volume. Then it is worth noting how the percentage volume reduction cannot be addressed as unique factor for assessing the efficacy of ablative technique if information of basal volume dimension are missing or omitted. From my point of view the percentage volume reduction is used too carelessly when considered as single parameter to highlight the effectiveness of a thermo ablative technique. The Volume Reduction Chart can be a useful tool aimed to increase awareness of doctors with expertise in thermo ablative treatment and clarify some points in comparison of different procedures.

How to use Nodule Reduction Chart

Fig. 1. Example for a nodule of 4 cm (basal dimension). A nodule of 4 cm in diameter is has a volume of 33 ml (green curve). If we supposed to have 75% in volume reduction we follow the red curve up to the intersection with 75% ordinate level. The abscissa value represent the achieved final diameter (2,5 cm). In the process of reduction, 25 ml of nodular tissue is removed (blue curve intersection) and 8 ml of nodular tissue are still present (green curve intersection)

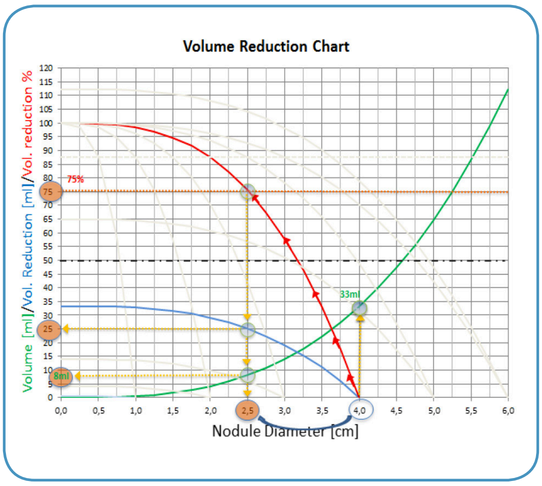
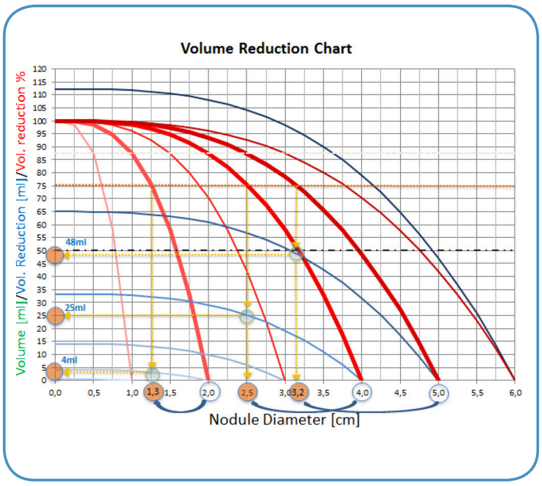


Fig. 2. Example for a nodule of 2,4 and 5 cm (basal dimension) with fixed percentage reduction of 75%. Nodules shrink respectively to 1,3 2,5 and 3,2 cm. Nodular volume removed as consequence of shrinkage are respectively 4, 25 and 48 ml.



ECHOLASER News

Meetings at a Glance Multidisciplinary conference on hepatocellular carcinoma

Held on October 3-4, 2014, in Naples, Italy

The incidence of hepatocellular carcinoma (HCC) is rising in the West. Among European countries, one of the highest mortality for HCC is registered in Italy and the peak is reached in Campania. To fight this cancer, a network of Campania's hospitals is under construction (*"Progetto Epatocarcinoma Campania"*), the first step has been the collection of all incident HCC cases diagnosed in Campania from January 2013.

The preliminary results have been shown during the "Multidisciplinary conference on HCC" which was held in the beautiful *Museo Diocesano* of Naples, 3-4 October 2014. The objectives of the conference were to present new achievements and to discuss about cutting edge topics in the field of HCC.

Participating stakeholders: researchers and opinion leaders, specialists and general practitioners, representative of patients and institutions. The faculty included many of the leading experts in this area. Most of them are using various local thermal ablative techniques for the treatment of unresectable hepatocellular carcinoma (HCC).

According to internationally endorsed guidelines, percutaneous thermal ablation is the mainstay of treatment in patients with small HCC who are not candidates for surgical resection or transplantation.

Laser ablation (LA) represents one of currently available loco-ablative techniques. During the congress the general principles, technique, image guidance, and patient selection have been reported with high interest and some presentations confirmed MIT (Minimally Invasive Therapy) is also cost-effective if compared to surgical treatments because it destroys only a minimal amount of liver parenchyma whilst reducing the number of hospitalizations.

Primary effectiveness, long-term outcome, and complications are also discussed. During the conference it was presented the first randomized control trial of Laser Ablation versus Radio Frequency Ablation that has validated the use of laser ablation for the treatment of HCC in cirrhosis.

Echolaser was presented with the new Abdominal Biopsy probe well appreciated for the Biopsy and for multi fiber laser Therapy receiving high interest from the participants.

Due to the success of the Conference a second edition has been planned for October 2015.

Several presentations will be shown via webcast on the site <u>www.epatocarcinomacampania.com</u>.

ECHO LASER News

November 2014

1st Scientific Meeting of Asia-Pacific Association of Imaging-guided Therapy in Oncology

Held on November 6-9, 2014, in Shanghai, China

With the constant and substantial advancements of the technology of image-guided minimally invasive therapies, the concept of cancer therapy is undergoing revolutionary changes, heading towards humanization, personalization, and constructiveness. Combination therapies with image-guided minimally invasive treatments as their core are likely to be an important direction of future development.

The Conference held on November 6-9, 2014 in Shanghai, China, combined the 10th Chinese Conference of Minimally Invasive Therapy in Oncology and the 1st Scientific Meeting of Asia-Pacific Association of Imaging-guided Therapy in Oncology.

About 200 experts from all over the world gave lectures on vascular and non-vascular interventional therapies in Oncology: tumor ablation (with radiofrequency, microwaves, laser, cryo, HIFU, and irreversible electroporation), brachytherapy, minimally invasive pain alleviation, molecular targeted therapy, endoscopic tumor treatment, minimally invasive surgery in Oncology, and techniques of image guidance. Board members of the Asia-Pacific Association of Imaging-guided Therapy in Oncology will also be elected at the Conference.

Definitely this conference is a valuable summit for promoting the latest concepts of minimally invasive therapies,-featuring a constructive model of cancer treatment that we have been proposing and developing, with emphasis on a humanistic, rational, and personal approach.

During the Conference we had the opportunity to collect the impressions of Dr. Luigi Solbiati, worldwide renowned expert of image-guide minimally invasive therapies and Echolaser Member. Dr. Solbiati, participated in the Conference as invited Speaker and member of Asia-Pacific Association of Imaging-guided Therapy in Oncology. His lecture was really successful and appreciated by the international audience.

Dr. Solbiati Point of View

Dr. Solbiati, you were a pioneer of Interventional Oncology in the world. What is your opinion about Chinese Interventional Oncology?
Our Chinese colleagues, thanks to their huge number of patients with different pathologies, are quickly increasing their experience and expertise in Interventional Oncology. Literature reports of Western world offer them good basic knowledge and starting from this basis they daily increase their clinical potentiality.

Your participation in this Congress is considered very important for them.
Chinese Interventional Oncology specialists recognize the work done by European and American experts and are open to collaborate with us. This 1st Scientific Meeting of Asia-Pacific Association confirms the need to create a World Association of imaging-guided therapy in Oncology. Our Chinese colleagues are willing to play an important role in this future Society.

What are the main applications of minimally invasive therapies and the most used technologies in China?
Hepatocellular carcinoma (HCC) is the most frequent cause of cancer-related death in China and the most common malignancy treated with ablation. For liver ablations microwaves are more popular and more diffusely employed than radiofrequency in China.
In addition to liver malignancies, minimally invasive image-guided treatments of thyroid goiters and breast and prostate tumors are increasingly performed in China also with new-technologies, such as laser and new cool-tip radiofrequency electrodes.

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