**Peer Review File**

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**Reviewer Comments**

1. Title: Consider changing this to “Laser ablation for thyroid nodules has come of age”.
2. Line 31-32: “results in scarring, and frequently requires subsequent thyroid hormone replacement”.
3. Line 33: Would suggest using the abbreviation “LA” for laser ablation.

**Reply: We modified our text as advised.**

1. Line 42: I’m not sure the disclaimer “at variance with large hyperfunctioning nodules” is necessary.

**Reply: We deleted the sentence.**

1. Line 57: “asymptomatic”
2. Line 59: “some nodules” instead of part of the nodules.

**Reply: We modified our text as advised.**

1. Line 71: HIFU is the least invasive technique. Since fibers are inserted percutaneously in case of laser ablation, the technique is as invasion as RFA or MWA. It may be easier to learn how to do however.

**Reply: We modified the sentence, focusing on the possible faster learning curve of LA.**

1. Line 86: Is the laser energy not absorbed in cases of non-perfused organs?

**Reply: We added the word *especially* to underline the better transmission of energy to liquid rich tissue, not excluding the absorption of energy in non-perfused organs**

1. Line 94-97: The explanation of how laser causes a defined area of coagulative necrosis is described, however other thermal ablation techniques e.g. RFA also produce an area of coagulative necrosis with predictable size and defined margins. This doesn’t really explain why laser ablation delivers less total energy compared to other methods.

**Reply: We modified the sentence, underlying the fact that even if working at lower W, the temperature achieved is the same respect to RFA and MWA.**

1. Line 99: This may need to be re-worded. The procedure will always be performed under ultrasound-guidance (and the full word for ultrasound should be used with US in brackets as this is the first time it has been used in the paper) however a “needle-guide” may be used as opposed to inserting the fibers "free hand" parallel to the plane of the transducer.

**Reply: We modified the sentence, specifying that the procedure is always performed under US guidance, possibly being either US-guided or US-assisted.**

1. Line 101 -102: This is a repetition.

**Reply: We modified the sentence removing the repetition.**

1. Line 108 - 112: Any local anesthetic agent can be used. Similarly, any benzodiazepine can be used – would not be so specific to allow for a wider range of practices. Line 112 can be stated better – the patient needs to remain awake and able to speak/answer questions.
2. Line 113: Consider describing the needle gauge and length for the first time rather than using the term “spinal needle” to avoid confusion, and then just referring to it as the needle for the rest of the paper – I am assuming the needle is a 21 G, 2 inch long needle.
3. Line 126: “near”

**Reply: We modified our text as advised.**

1. Line 128: Please define an “illumination”

**Reply: We modified our text in order to make it clearer.**

1. Line 136: Is assessment by contrast-enhanced US necessary immediately post-procedure?

**Reply: Contrast-enhanced US is useful for a better demarcation of the area of coagulative necrosis but is not strictly necessary. Thus, we modified our text.**

1. Line 139: Are parenteral anti-inflammatory drugs commonly given after the procedure in Europe? (they are not after laser ablation of thyroid nodule in centers in the United States).

**Reply: Most centers performing thyroid thermal ablation in Italy and Europe administer a single dose of anti-inflammatory drugs after the procedure the procedure. Of course, this is not strictly necessary but prevent the otherwise inevitable discomfort during the hours immediately following the procedure.**

1. Line 158: If a benign nodule has already been biopsied before and found to be benign does the biopsy need to be repeated? And no biopsy is needed for a proven autonomously functioning thyroid nodule? I’m assuming the proof of function is an uptake and scan – if so, this needs to be mentioned. The risk of malignancy is low in autonomously functioning nodules but it is not 0%.

**Reply: According to latest European guidelines, two consistently benign cytology are suggested prior to thermal ablation procedure. In case of nodules with clear benignity features (EU-TIRADS Class II), a single benign FNA is considered as adequate. FNA is not considered mandatory for well-identified hyperfunctioning nodules because, though not totally absent, the risk of malignancy is extremely low.**

1. Line 162: Is there any role for molecular markers? I don’t believe there is specific data available for thermal ablation – but benign molecular markers may be lower risk to ablate than nodules with indeterminate cytopathology and suspicious molecular markers. Some references should be given with regards to the statement about the inappropriateness of treating Bethesda III and Bethesda IV nodules.

**Reply: There are no relevant data in literature. It could be assumed that with the use of last generation genetic panels, with high negative predictive value, the risk of malignancy is markedly decreased. However, the ablation of a cytologically indeterminate thyroid nodule, that is also supposed to be large and symptomatic, hampers a definitive histological diagnosis and makes the post-surgical staging uncertain in case of malignant disease. For these reasons we would prefer not to comment on the issue.**

1. Line 172: The INR is not a percentage – it’s a ratio.

**Reply: We modified our text as advised.**

1. Line 174: Is it necessary to perform a laryngoscopy in all patients? Several practitioners do not.

**Reply: Laryngoscopy is routinely recommended in patients with prior neck surgical history or with any voice impairment at physical evaluation. In any other case, laryngoscopy is simply suggested since the voice assessment through anamnesis and clinical evaluation may not be adequate to elicit a minor vocal cord impairment. This is also relevant for preventing potential post-treatment controversies from those patients who have a professional use of their voice. We tried to better explain this issue.**

1. Line 187: one year “after” laser ablation
2. Line 193: nodule volume rather than size
3. Line 201: “volume reduction” rather than volume reduction rate as this is not being expressed per unit of time.
4. Line 228: “beginning”, “recurrent laryngeal nerve”

**Reply: We modified our text as advised.**

1. Line 237: Not sure what is meant by hyperlactation in this context. Assuming this sentence means that radioactive tracer uptake disappeared on thyroid scintigraphy.

**Reply: “Hypercaptation”. we have modified our text as advised.**

1. Line 262: Pretty much all patients with overt hyperthyroidism will require anti-thyroid medications. Only younger patients with subclinical hyperthyroidism won’t. Is this what it meant?

**Reply: Hyperfunctioning nodules associated with subclinical hyperthyroidism, or with hyperthyroidism requiring low doses of anti-thyroid medication, had in the large Italian study a higher probability of thyroid function normalization after thermal ablation. We modified the text in order to make its meaning clearer.**

1. Line 271: Would just say little data exists or something along those lines.

**Reply: We modified our text as advised.**

1. Line 297-298: Two of these citations are clinical statements rather than papers on primary data for laser treatment of unresectable tumor and distant metastases so it’s a bit ambitious of the authors to call them their previously dedicated publications. Also, I don’t believe there is any published data on laser ablation of distant metastases from thyroid cancer (though if there is it should be cited).

**Reply: We are sorry not to have cited the favorable experience of our group on a series of unresectable and radioiodine-refractory bone metastasis (Pacella CM, Di Stasio E, Guglielmi R, Baroli A, Pedrazzini L, Misischi I, et al. Role of laser ablation in multimodal treatment of radioiodine-refractory bone metastases of thyroid cancer: a retrospective study. Endocrine. 2020;70:338–47, <http://dx.doi.org/10.1007/s12020-020-02314-4>) and on an unresectable liver metastasis from thyroid follicular cancer (Guglielmi R, Pacella CM, Dottorini ME, et al. Severe thyrotoxicosis due to hyperfunctioning liver metastasis from follicular carcinoma: treatment with 131I and interstitial laser ablation. Thyroid 1999; 9:173–177). Since 1999, we also reported (mostly in Italian language) the treatment of liver metastasis from medullary cancer.**

**The pertinent references were added to bibliography.**

1. Line 300: How much of a margin is needed? Please specify.

**Reply: We added this information.**

1. Line 311: Is there any evidence the neoplastic seeding can occur during the procedure and that this technique prevents it? Or is this a hypothesis?

**Reply: Implantation of tumor cells in the subcutaneous layer or in ribbon-like muscles is reported in the literature: 0.14% of papillary thyroid carcinomas in one case series. It seems to be more likely in the case of aggressive or poorly differentiated variants (Ito Y et al. Needle tract implantation of papillary thyroid carcinoma after fine-needle aspiration biopsy. World J Surg. 2005;29(12):1544-1549. The reference was added to the bibliography. A similar recommendation is always provided when treating primary or secondary liver tumors.**

1. Line 312: If it was just one patient then it was case report rather than a feasibility study.

**Reply: We modified our text as advised.**

1. *Line 326-327: Which 2 patients had the recurrence in cervical lymph nodes? The laser ablation group, or the RFA or MWA group? And what groups did the patients have complication in?*

**Reply: A cervical lymph node metastasis was observed in two patients, from different studies, after laser ablation. They were surgically treated 24 and 30 months after thermal ablation. This sentence was added to the text.**

1. Line 357-385: Please give a range of recurrence rates of PTC (should be spelled papillary thyroid carcinoma the first time in the paper) managed by active surveillance (should be spelled out when used for the first time) over a period of time so that an assessment can be made as to whether treating micro-PTC may be clinically relevant.

**Reply: Clinically detectable lymph node metastasis during AS were detected in a minority of patients. Their occurrence ranged from 1.5% at 10 years (Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid. 2014 Jan; 24(1): 27–34.) to 8.6% at 3 years (Oh HS, Ha J, Kim HI, et al. Active surveillance of low-risk papillary thyroid microcarcinoma: A multi-center cohort study in Korea. Thyroid 2018; 28:1587-94). References were added to Bibliography section.**

**We changed the abbreviations according to the Editor advice.**

1. Line 372-374: Why is it the first proposed technique? And as pointed out before; it’s more invasive than HIFU, so it’s not the least invasive. RFA and MWA generally give more volume reduction – so a stronger argument will need to be given.

**Reply: We modified our text as advised.**

1. Line 375: How long is the learning curve?

**Reply: We added this useful information.**

1. Line 377: This is better stated as two benign biopsies are needed (the original sentence assumes a biopsy has always been done on a solid nodule which is not true).

**Reply: We modified our text as advised.**

1. Line 379: Please give a range of what percentage of patients experience improvement in symptoms from the literature.

**Reply: We added this information.**

1. In Table 1 is the follow-up in months? This should be clarified. Where the volume reduction is a median instead of a mean – this should be represented by an asterisk. Is there any difference in outcomes between the two laser sources? This should be mentioned somewhere in the paper. Does RCT stand for randomized controlled trial? This column should indicate type of study. The abbreviations should be explained in the legend.

**Reply: We modified the table as required. We specified that no difference is demonstrated among laser sources.**

1. In Table 2, what does amelioration rate mean? Studies for which energy is not reported should be marked as such. The “N” used for normalization of results is confusing – No usually stands for “no” so it appears that table states no TSH changes when there is in fact improvement. The reader shouldn’t have to read the superscript to figure out the procedure was successful. Would change the name of the column from “TSH changes” to “achieved euthyroidism”. What is the difference between TSH changes and hormone changes? I’m assuming the authors mean circulating thyroxine levels but the column should say that.

**Reply: We modified the table, in order to make relevant data easier to catch.**

1. Revision of grammar and syntax of the paper would also improve readability. Some errors have been pointed out in the comments but not all.

**Reply: We revised the grammar and syntax as requested.**

1. In addition - since the paper is proposing laser ablation as a treatment modality more discussion should focus on how it compares to the more conventional treatments of surgery and radioactive iodine in terms of outcomes, complications, and efficacy - as well as comparative costs.

**Reply: The following paragraphs were added:**

**Lines: ………. 386 Radioiodine therapy remains the treatment of choice of hyperfunctioning nodules because control of hyperthyroidism is obtained in over 90% of cases and the reduction of nodule volume ranges from 30 to 50% at 2 years (Bonnema SJ, Hegedus L. Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. Endocrine Rev 2012; 33: 1 -61). Advantages of radioiodine therapy are its low cost and ease of application as an outpatient procedure while the major disadvantage is the frequent (up to 60% at 20 years) development of hypothyroidism (Ceccarelli C, Bencivelli W, Vitti P et al. Outcome of radioiodine-131 therapy in hyperfunctioning thyroid nodules: a 20 years’ retrospective study. Clin Endocrinol 2005; 62: 331-5). Thus, LTA may be mainly considered for the management of small size hyperfunctioning thyroid nodules with subclinical hyperthyroidism. Particularly in young patients, thyroid function normalization is obtained with no irradiation or risk of late hypothyroidism.**

**Lines: Future perspectives. The available evidence on clinical outcomes of LA is mostly based on short and medium term prospective randomized studies and on large retrospective series. Controlled head-to-head prospective trials of LA vs surgery or radioiodine therapy are lacking. Thus, long-term investigation is required to better define a few relevant areas, including the appropriate role of LA vs. surgery in cytologically benign thyroid nodules, the prognostic factors for successful ablation, and the appropriate indications of LA for PTMC and local cancer recurrences. Finally, the cost effectiveness for LA vs. the traditional surgical or radioiodine treatment is still to be established. The 2022 Italian National Guidelines for the management of symptomatic thyroid nodules defined the costs of surgical lobectomy and thyroid LA as high as € 4.211 and € 1.560, respectively. However, several variables, like the need of repeat treatment in case of nodule regrowth after LA or the management of surgical complications, may strongly influence this calculation.**